Systematic Review and Meta-Analysis

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Trans-catheter arterial chemoembolization plus Sorafenib, an unsuccessful therapy in the treatment of hepatocellular carcinoma?

A systematic review and meta-analysis

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Abstract

Background: Trans-catheter arterial chemoembolization (TACE) plus Sorafenib is recommended as one of the primary means for treating hepatocellular carcinoma (HCC). This updated meta-analysis focuses on identifying the efficacy and safety of TACE plus Sorafenib versus TACE, which remains controversial despite years of exploration.

Method: PubMed, Medline, Embase, China Journal Full-text Database, Wanfang Database, and Weipu Database were used to retrieve the studies which are about comparing the clinical efficacy and safety of TACE+Sorafenib with TACE alone. The Review Manager (Version 5. 3) software was used to perform a meta-analysis of the results of studies which met the inclusion criteria recommended by the Cochrane Collaboration.

Result: Compared with TACE for treating primary HCC, TACE combined with Sorafenib can improve the 1 year, 2 years, 3 years, and 5 years overall survival rate (OS) of patients, respectively, and also improve disease control rate (DCR) and objective response rate (ORR). In terms of adverse reactions, the treatment group can lead to more complications significantly, such as hand-foot skin reaction, hypertension, diarrhea, rash, hair loss, and so on, most of which are relevant to Sorafenib related adverse reactions, but most patients have a good prognosis after symptomatic treatment.

Conclusion: The clinical efficacy of TACE combined with Sorafenib in treating primary hepatocellular carcinoma is better than TACE, and the safety is acceptable.

Abbreviations: CR = complete remission, DCR = disease control rate, HCC = hepatocellular carcinoma, HFSR = hand-foot reaction, ORR = objective response rate, OS = overall survival rate, PD = disease progression, PR = partial response, SD = disease stabilization, TACE = trans-catheter arterial chemoembolization, TTP = time to progress, VEGF = vascular endothelial growth factor.

Keywords: hepatocellular carcinoma, liver tumor, meta-analysis, Sorafenib, transcatheter arterial chemoembolization

1. Introduction

Hepatocellular carcinoma (HCC) is a blood-rich tumor originating from hepatocytes, and 90% of blood supply is from the hepatic artery.[1] In the early stage, this disease was more insidious, with a high degree of malignancy and rapid progress. Most patients with HCC had already been in the middle and late stages at the time of initial diagnosis.[2] In severe cases, even metastasis had occurred. For patients with advanced HCC, they have lost the opportunity for surgery, and only 15% to 20% of patients were suitable for surgery.[3,4]

At present, trans-arterial chemoembolization (TACE) is recognized as one of the commonly used non-surgical treatments for hepatocellular carcinoma.[1] Using TACE for the treatment of hepatocellular carcinoma has the advantages of small trauma and high targeting, which can inhibit the progression of tumor tissue significantly, and its short-term efficacy is evident.[5] However, in many cases, tumor cells can adapt to the highly anaerobic microenvironment due to the negative feedback effect produced by TACE and incomplete embolization. Hypoxic and ischemia caused by embolism can increase the expression of HIF-1α, which could increase the expression of vascular endothelial growth factor (VEGF) and stimulate tumor neovascularization so that eventually leads to tumor recurrence and metastasis.[5]

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Sorafenib is the first Food and Drug Administration-approved targeted therapy for systemic therapy for HCC that inhibits the activity of RAF-1 serine/threonine kinase and VEGF receptors-mediated tyrosine kinase. Previous studies have shown that Sorafenib could prolong the overall survival of HCC.[6] It is because of the complementary effect of Sorafenib and TACE that the combination of them has become a hot spot in treating advanced HCC. Peng et al[7] obtained a retrospective multicenter study of 260 patients in order to observe the outcomes of TACE combined with Sorafenib in treating HCC, in which they found that the objective response rate (ORR), disease control rate (DCR), 1-year overall survival rate (OS), 3-year OS, and 5-year OS were 72.3%, 87.3%, 73.9%, 39.9%, and 25.3%, respectively, which were significantly higher than the 50.0%, 80.6%, 50.3%, 28.5%, and 16.9% in the control group (TACE). So Peng et al proposed TACE combined with Sorafenib has a high clinical efficacy compared with TACE alone. However, Lei et al,[8] in a retrospective study of 67 patients, found that the 1 year OS of TACE combined with Sorafenib in treating HCC was 94.7%, which was lower than that of TACE (96.6%). Many studies suggested that combination therapy could lead to many adverse reactions associated with Sorafenib, such as hand-foot reaction (HFSR), diarrhea, high blood pressure, rash and hair loss, etc. In summary, there are still uncertainties in the clinical efficacy and safety of TACE combined with Sorafenib in treating HCC, which are also the reasons for the current controversy. Therefore, more comprehensive researches are still needed to provide more useful information and theoretical basis for the clinic.

This study conducted a meta-analysis of several studies comparing the clinical efficacy of TACE with Sorafenib + TACE in treating primary HCC, including the latest research from 2018 and 2019, to explore the better choice in treating HCC.

2. Methods

2.1. Study selection

The literature should involve: the comparison of the efficacy of TACE + Sorafenib and TACE alone; more complete information (type of trial, number of cases, treatment plan, RECIST or mRECIST criteria evaluation results: complete remission [CR], partial response [PR], disease stabilization [SD], disease progression [PD], objective response rate [CR + PR = ORR], disease control rate [CR + PR + SD = DCR]), OS, and the adverse reactions related to the therapy, etc. In order to ensure the statistical significance of the included studies, the number of patients in each study should not be <100 cases.

2.2. Search strategy

PubMed, Medline, Embase, China Journal Full-text Database, Wanfang Database, and Weipu Database were used to retrieve the studies on comparing the clinical efficacy and safety of TACE + Sorafenib with TACE. English search terms "trans-arterial chemoembolization" or "TACE" and "Sorafenib" and "hepatocellular carcinoma" or "HCC" or "liver cancer" or "liver tumor" were used. Review Manager (Version 5.3) (The Nordic Cochrane Centre, Copenhagen, Denmark) software was used to perform a meta-analysis of the results of the literature that met the inclusion criteria, as recommended by the Cochrane Collaboration. The indicators included were OS, ORR, DCR, and complications, including hand-foot reaction, diarrhea, hypertension, rash and hair loss, fatigue, gastrointestinal reactions, elevated transaminases, and myelosuppression, etc. Various outcomes of combined treatment and TACE treatment were compared comprehensively, and thus the best treatment was finally got.

2.3. Data acquisition

Two reviewers screened the literature, extracted the data, and cross-checked independently to ensure consistent data extracted from the literature. The literature was screened strictly following the inclusion criteria. The randomized controlled trials (RCT) was scored according to the Jadad quality criteria, and the non-randomized controlled trials (NRCT) was scored according to Newcastle-Ottawa Scale (NOS) quality criteria.

2.4. Statistical methods

Statistical processing was performed using the Review Manager (version 5.3) Software. Before the meta-analysis, the heterogeneity test was performed. The test results of $I^2 < 50\%$, $P > .1$ suggest that the homogeneity of each test was good; thus the meta-analysis was performed using the fixed-effect model; in contrast, the random effects model was used. Finally, the forest plots was obtained, and the risk ratio (RR) and 95% CI of it were described and discussed. $P > 0.05$ was considered no statistical significance.

2.5. Ethical approval

The ethical approval was not necessary for this article because this study did not involve the patient's informed consent or any animal experiments, but a second calculation of the known research results. The ethics of the articles it has included had been already approved by the review board of the corresponding ethics committee or institution.

3. Result

3.1. Literature search results and document characteristics

The meta-analysis included a total of 15[7,9–22] studies on comparison of TACE + Sorafenib and TACE in treating primary hepatocellular carcinoma, including 5 RCT and 10 NRCT. According to the Jadad score, RCT had 4 articles with scores of at least 3 and 1 articles with low scores. According to the NOS score, NRCT had 6 articles with 8 stars, 1 article with 7 stars, and 3 articles with 6 stars. The literature inclusion criteria and search process are showed in Fig. 1. The study included 3104 patients with primary HCC (Table 1).

3.2. ORR and DCR

There were 11 reports include ORR and DCR from patients with HCC, according to heterogeneity test (ORR $I^2 = 0\%$, $\chi^2 = 7.88$, $P = .64$; DCR $I^2 = 82\%$, $\chi^2 = 56.75$, $P < .00001$), the ORR were combined and analyzed using fixed-effects model, and the DCR were combined and analyzed using random-effects model. Meta-analysis showed that the ORR and DCR of TACE combined with Sorafenib in patients with primary HCC was slightly superior to those treated with TACE (ORR RR = 1.49, 95% CI 1.32–1.69, $P < .00001$; DCR RR = 1.21, 95% CI 1.06–1.38, $P = .006$) (Fig. 2).

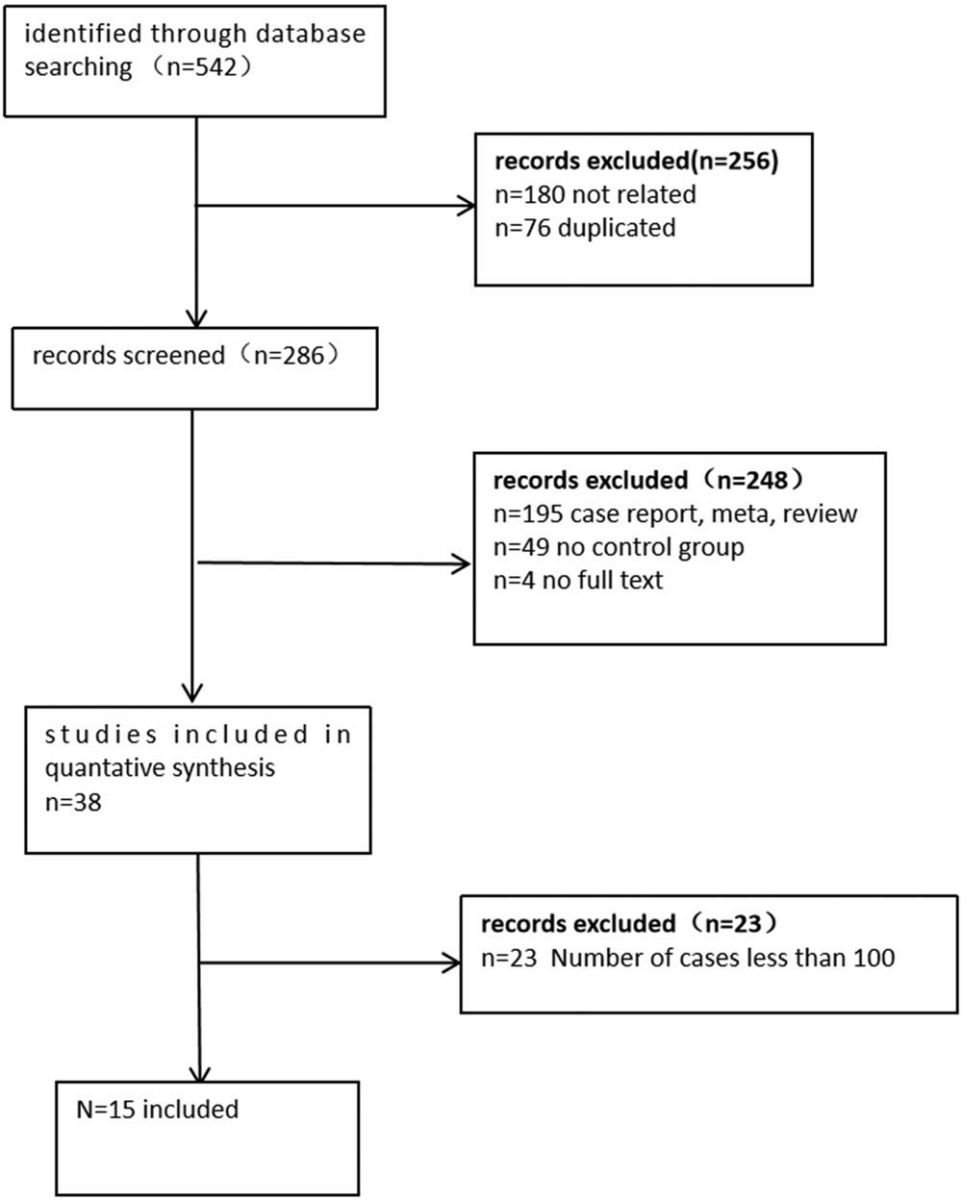

Figure 1. Flow diagram of the selection process.

3.3. OS

There were respectively 6, 2, 2, and 2 studies involved 1 year, 2 years, 3 years, and 5 years OS (Fig. 3). Based on heterogeneity test (1 year OS $I^2=89\%$, $\chi^2=45.12$, $P<.00001$; 2 years OS $I^2=0\%$, $\chi^2=0.66$, $P=.42$; 3 years OS $I^2=45\%$, $\chi^2=1.82$, $P=.18$; 5 years OS $I^2=25\%$, $\chi^2=1.33$, $P=.25$), the fixed effect model was used for 2 years, 3 years, and 5 years OS, and the 1-year OS was analyzed by random effect model. The results showed that the efficacy of TACE combined with Sorafenib in treating primary HCC in 1 year, 2 years, 3 years, and 5 years OS were all slightly superior to that of TACE (1 year OS RR=1.29, 95% CI 1.00–1.67, $P=.05$; 2 years OS RR=1.54, 95% CI 1.27–1.88, $P<.0001$; 3 years OS RR=1.38, 95% CI 1.07–1.78, $P=.01$; 5 years OS RR=1.66, 95% CI 1.11–2.48, $P=.01$).

3.4. Adverse effects of TACE combined with Sorafenib versus TACE

In all 15 studies,[7,9–22] the main adverse reactions involved were: hand-foot reaction, nausea, and vomiting, fever, fatigue, diarrhea, abnormal liver function, hypertension, myelosuppression, stomatitis, rash, and hair loss, etc. The outcomes of the meta-analysis showed that the combined group have a higher risk of hand-foot skin reaction, hypertension, diarrhea, rash, hair loss, but other adverse reactions were not statistically significant compared with the control group. After research and analysis, none of the patients died of treatment-related adverse reactions,[7,9–22] and after the corresponding symptomatic treatment, patients were effective for their safety and tolerance (Table 2).

Table 1

Various information included in the study.

Study	Research design	Country	Etiology	Group	Number of cases	Age (treatment/control)	Gender (male/female)	ECOG (0/1/2/3)	BCLC (A/B/C/D)	Child-Pugh (A/B/C)
Huang 2017	RCT	China	NA	TACE + sorafenib TACE alone	120	65.17 ± 8.41/65.22 ± 8.37	87/33	NA	NA	NA
Bi 2016	RCT	China	NA	TACE + sorafenib TACE alone	114	58.7 ± 6.6/58.9 ± 6.5	68/46	NA	NA	NA
Lv 2019	RCT	China	NA	TACE + sorafenib TACE alone	120	51.42 ± 9.61/50.80 ± 9.58	78/42	NA	0/70/30/0	86/34/0
Wang 2019	Retrospective	China	NA	TACE + sorafenib TACE alone	102	52.9 ± 6.2/52.4 ± 7.0	63/39	7/72/23/0	0/73/29/0	71/31/0
Wu 2015	RCT	China	HBV: 106 Other: 9	TACE + sorafenib TACE alone	115	NA	70/45	41/45/29/0	NA	66/49/0
Xu 2015	Retrospective	China	HBV: 192 HCV: 14 No Infection:22	TACE + sorafenib TACE alone	228	60 ± 12/61 ± 12	194/34	NA	NA	149/79/0
Zhang 2016	Retrospective	China	NA	TACE + sorafenib TACE alone	120	53.8 ± 8.1/54.6 ± 7.6	105/15	25/88/7/0	0/66/54/0	97/23/0
Bai 2013	Retrospective	China	HBV (219) HCV (11) no infection (16)	TACE + sorafenib TACE alone	246	54 ± 13/52 ± 12	219/27	0/64/182/0	78/139/27/1	178/68/0
Varghese 2017	Retrospective	India	HBV (39) HCV (26) Ethanol (13) Cryptogenic/non-alcoholic steatohepatitis (51)	TACE + sorafenib TACE alone	124	NA	112/12	0/59/65/0	NA	63/61/0
Kudo 2011	RCT	Janpan and Korea	Alcohol (31) HBV (99) HCV (287) other (27)	TACE + sorafenib TACE + Placebo	458	NA	342/116	NA	378/80/0/0	NA
Lencioni 2016	Phase II, Randomized, Double-Blind SPACE Trial	Global Cooperation	HBV(105) HCV(80) Alcohol use (57) Other (65)	TACE + sorafenib TACE + Placebo	307	NA	261/46	NA	NA	NA
Peng 2019	Retrospective	China	HBV (218) HCV (13) Alcohol (10)	TACE + sorafenib TACE alone	260	55 ± 7.6/56 ± 8.3	217/43	198/62/0/0	NA	NA
Ren 2019	Retrospective	China	HBV (242) HCV (18) No infections(48)	TACE + sorafenib TACE alone	308	NA	257/51	0/180/128/0	NA	274/34/0
Zheng 2017	Retrospective	China	HBV (16) other (220)	TACE + sorafenib TACE alone	236	53.88 ± 12.25/57.35 ± 11.88	205/31	153/83/0/0	127/91/18/0	172/58/5
Hu 2014	Retrospective	China	HBV (207) HCV (16) no infection (23)	TACE + sorafenib TACE alone	246	61 ± 11/60 ± 11	209/37	NA	NA	161/85/0

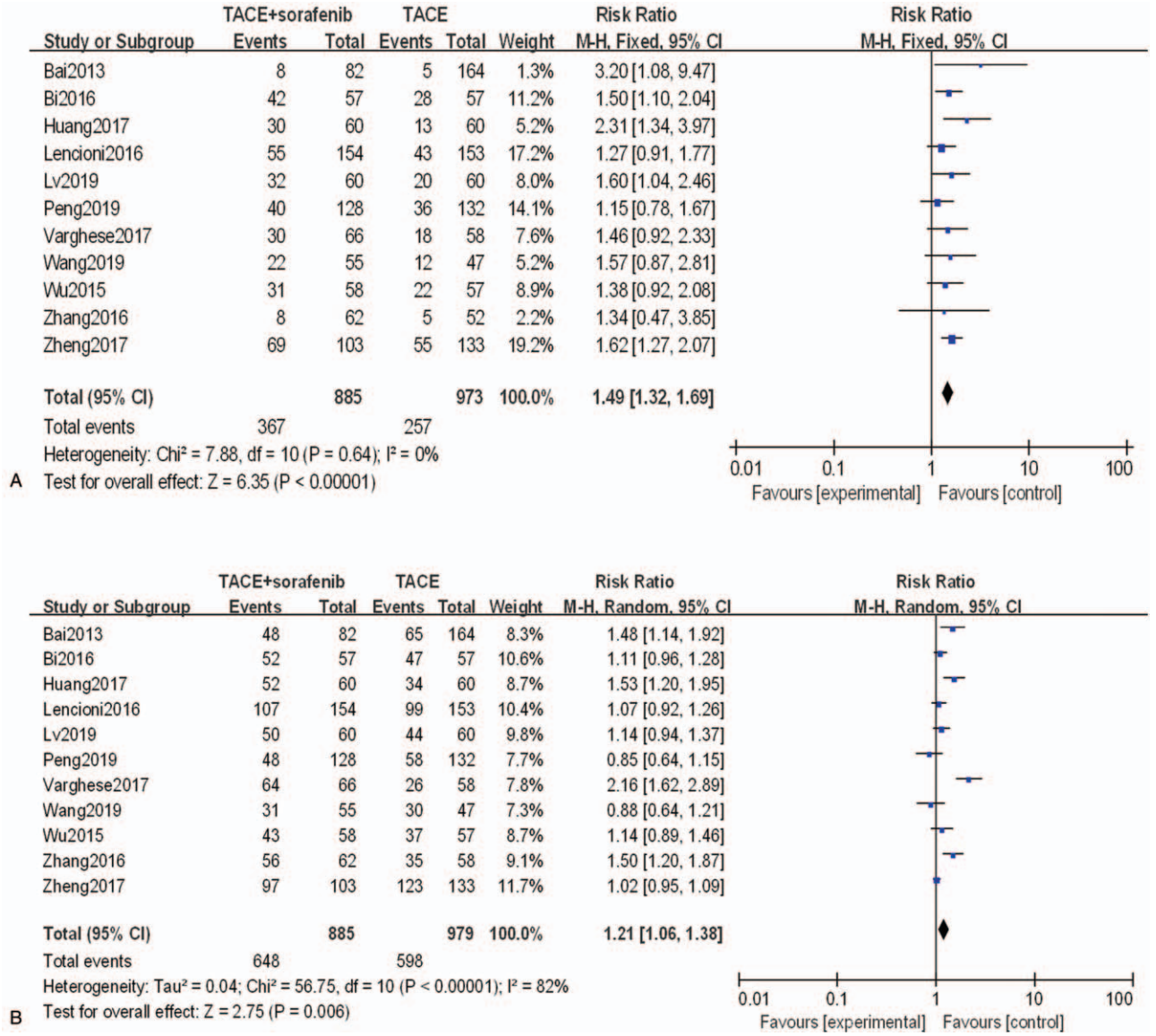

Figure 2. Objective effective rate (A) and disease control rate (B) of patients with TACE combined with Sorafenib compared with TACE alone or with placebo. TACE = trans-catheter arterial chemoembolization.

3.5. Publication bias

The funnel plot was applied to resolve the publication bias for this meta-analysis.

Figure 4 indicates that the comparison of ORR and DCR was among the 95% confidence intervals. In addition, the scatter points were distributed symmetrically in the inverted funnel. All the evidence indicates that the probability of publication bias is low.

4. Discussion

This meta-analysis evaluates the efficacy of TACE alone or TACE + Sorafenib in treating patients with advanced HCC. Compared with TACE alone in treating primary HCC, TACE combined with Sorafenib can improve the OS of patients in 1 year, 2 years, 3 years, and 5 years respectively, and can also improve the DCR and ORR. In terms of adverse reactions, the treatment group can lead to more complications significantly, such as hand-foot skin reaction, hypertension, diarrhea, rash, hair loss, etc. and most of them are adverse reactions associated with Sorafenib. After symptomatic treatment, most patients had a good prognosis.

Kudo et al[11] in a Phase III study of Sorafenib after TACE has shown that Sorafenib did not significantly prolong time to progress (TTP) in patients who responded to TACE, which means that this combined therapy doesn't have potential efficacy. However, he subsequently explained that this might have been due to delays in starting Sorafenib after TACE and/or low daily Sorafenib doses (200 mg twice daily used in their study vs 400 mg twice daily in the other trials),[11] therefore, in order not to affect the accuracy and reliability of the experimental results, in subsequent clinical trials, the use of sorafenib should be as soon as possible after TACE, and the adequate dosage of the drug

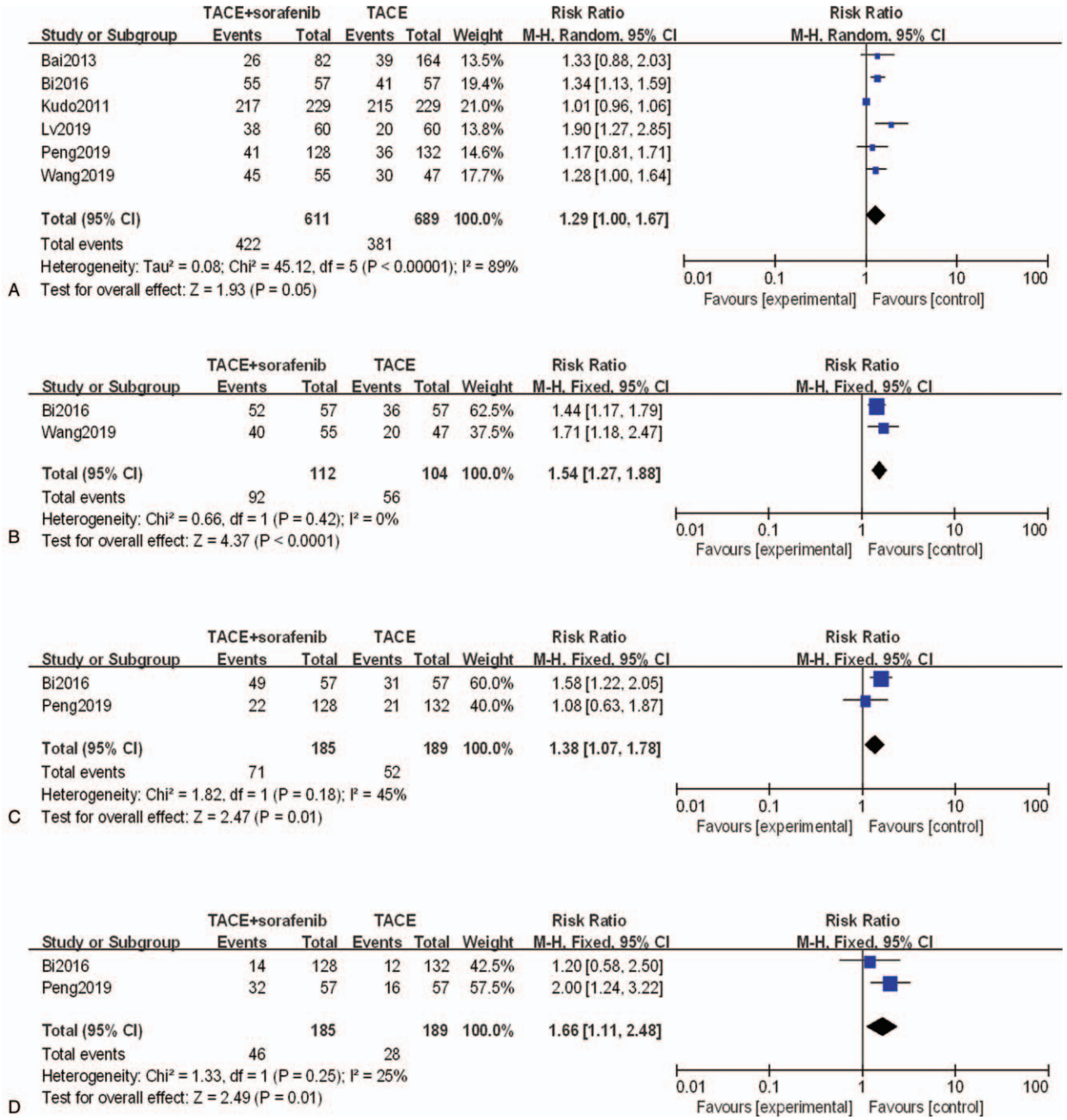

Figure 3. Overall survival at 1 year, 2 years, 3 years, and 5 years in patients with TACE plus Sorafenib compared with TACE alone or with placebo. TACE = transcatheter arterial chemoembolization.

should also be guaranteed. It is also doubtful that, Meyer[23] showed the treatment of Sorafenib combined with TACE is not a successful means of therapy, without any convincing meta-analysis, but meta-analysis is considered as one of the most reliable statistical methods in evidence-based medicine. So it is necessary for us to prove whether this conclusion is reliable or not.

The information in this article is more comprehensive than similar studies by Li et al[24] and Hu et al.[25] because we had analyzed the clinical efficacy of this combination therapy from more perspectives. Not only that, we also added a lot of relevant researches from 2018 and 2019, including more large-scale studies, which makes our article more time-efficient and persuasive. More importantly, the number of patients in each study we included exceeded 100, ensuring a large sample size and effectively avoiding publication bias due to the small sample size, which is also a point that has not been achieved by similar meta-analysis previously.

This study also had some shortcomings: among these 15 documents, more than half of the studies are non-randomized

Table 2

Comparison of complications between TACE combined with Sorafenib and patients with TACE alone.

Adverse reactions	Inclusion study	Heterogeneity	RR	95% CI	*P*
Hand-foot skin reaction	11	$P=.0009$, $I^2=66\%$	62.23	22.43–172.60	<.00001
Hypertension	10	$P<.0001$, $I^2=74\%$	11.20	3.76–33.41	<.0001
Diarrhea	10	$P<.00001$, $I^2=87\%$	12.95	4.12–40.78	<.0001
Weak	5	$P<.0001$, $I^2=84\%$	1.78	0.89–3.52	=.10
Abnormal liver function	6	$P<.0001$, $I^2=81\%$	1.76	0.89–3.50	=.11
Myelosuppression	2	$P=.68$, $I^2=0\%$	1.26	0.52–3.03	=.61
Rash	8	$P=.004$, $I^2=66\%$	4.40	2.25–8.63	<.0001
Hair loss	7	$P<.00001$, $I^2=90\%$	10.62	2.31–48.93	=.002
Fever	5	$P=.55$, $I^2=0\%$	1.01	0.91–1.13	=.80
Feel sick and vomit	5	$P=.87$, $I^2=0\%$	1.08	0.93–1.25	=.30

TACE = trans-catheter arterial chemoembolization.

controlled trials, and this study included some low-quality articles, which may have potential publication bias; in some indicators, such as the 5-year survival rate, the number of studies involved is small, which can also induce some potential publication bias; there is a lack of longer-term survival rate indicators, which allowed us to include limited information and cannot be drawn how the 2 treatment regimens perform in the long-term, for example, 10 and 20 years of clinical outcomes.

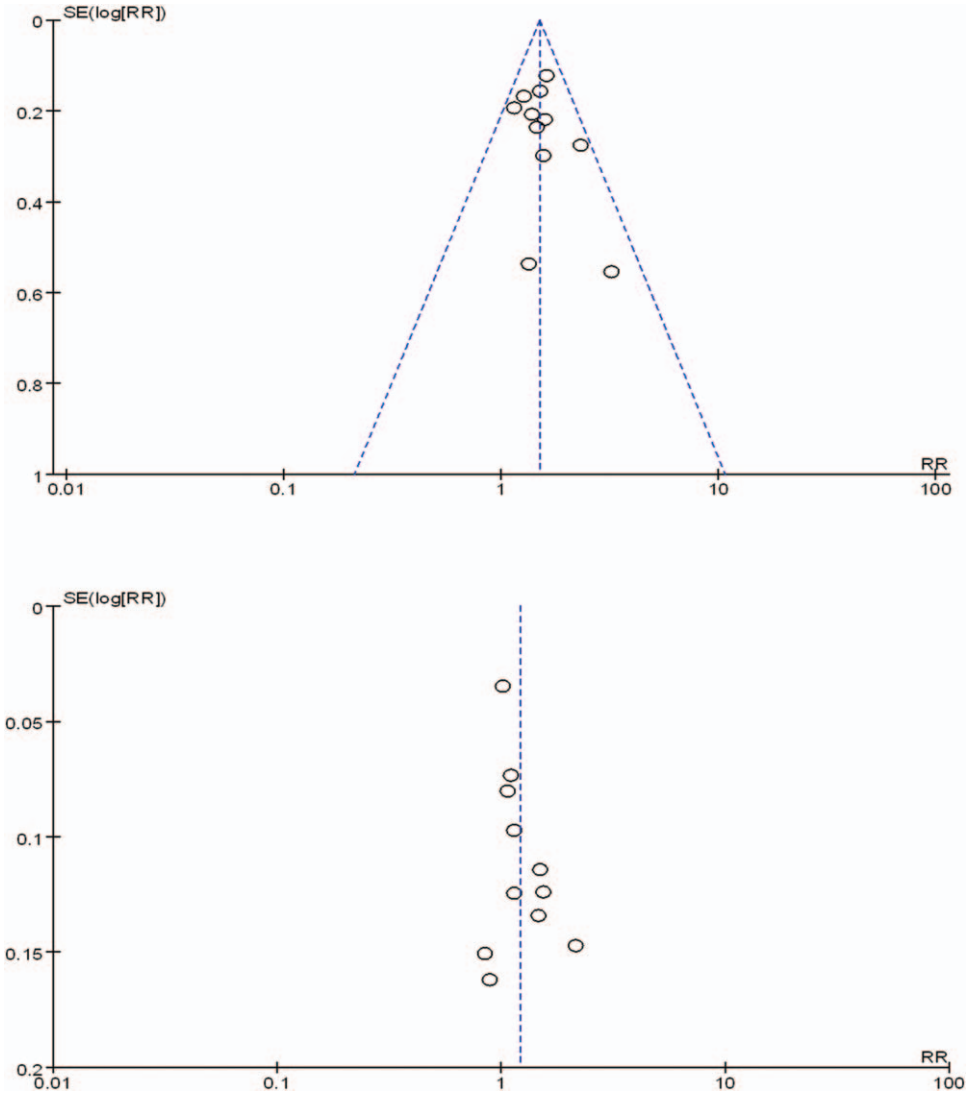

Figure 4. Funnel plots of comparison of the ORR and DCR. Combination group, TACE + sorafenib; and Control group, TACE. CI = confidence interval; DCR = disease control rate; ORR = objective response rate; RR = risk ratio; TACE = trans-catheter arterial chemoembolization.

5. Conclusion

The clinical efficacy of TACE combined with Sorafenib in treating primary HCC is slightly better than that of TACE, at least in the aspects of 1 year, 2 years, 3 years, and 5 years OS, ORR, DCR, moreover, the long-term efficacy is unknown. Although combination therapy can lead to Sorafenib-related adverse reactions, patients were well tolerated, according to many articles we included. Nevertheless, more large-scale researches are needed to verify this conclusion. It also needs more large-scale research about this combination therapy versus another to verify Meyer T's conclusion.

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Author contributions

Tao Zhang: Research design, data collection, charting, article writing, and modification.
Weisen Huang: Article evaluation, data collection, data processing.
Haorong Dong: Processing data in meta-analysis, article translation, and modification.
Yijun Chen: Co-designer of this study, assists in data processing, article writing, review and modification.

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