Translational Oncology 14 (2021) 101238

Contents lists available at ScienceDirect

Translational Oncology

journal homepage: www.elsevier.com/locate/tranon

Optimal timing of combining sorafenib with trans-arterial chemoembolization in patients with hepatocellular carcinoma: A meta-analysis

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ARTICLE INFO

Keywords:
Hepatocellular carcinoma
Trans-arterial chemoembolization
Sorafenib
Survival
Safety
Meta-analysis

ABSTRACT

Background: The combination therapy of trans-arterial chemoembolization (TACE) and sorafenib were proved to be one of the effective methods for intermediate and advanced hepatocellular carcinoma (HCC). Although it has been confirmed that the combination therapy can prolong survival for advanced HCC effectively, the therapeutic efficacy and safety are still controversial and the clinical value has not been determined. This meta-analysis aims to evaluate the efficacy and safety of combination therapy and discuss the optimal timing of combination for better clinical benefits.

Data sources: PubMed, EMBASE, the Cochrane Library, MEDLINE, and Web of Science were systematically reviewed to search for relevant studies published before May 15, 2021. Studies comparing the efficacy and safety of TACE + sorafenib with TACE + placebo / alone were adopted. Two reviewers independently extracted study outcomes. The data were analyzed through fixed/random-effect meta-analysis models with Review Manager (Version 5. 3) software.

Results: 7 randomized controlled trials (RCTs) were included with 1464 patients with unresectable HCC (734 in TACE + sorafenib group and 730 in TACE + placebo or alone group). Meta-analysis showed that objective response rate (ORR) and disease control rate (DCR) were slightly improved in TACE + sorafenib group (ORR: risk ratio = 1.24; 95% confidence interval: 1.08–1.42; $P = 0.002$; DCR: risk ratio = 1.09; 95% confidence interval: 1.01–1.18; $P = 0.02$). The combination therapy obviously improved time to progression (TTP) (hazard ratio: 0.73; 95% confidence interval: 0.55–0.96; $P = 0.03$) and progression-free survival (PFS) (hazard ratio 0.62; 95% confidence interval: 0.52–0.73, $P < 0.00001$) but not overall survival (OS) (hazard ratio: 0.93; 95% confidence interval: 0.59–1.46; $P = 0.75$) or time to untreatable progression (TTUP) (hazard ratio: 0.76; 95% confidence interval: 0.31–1.89; $P = 0.56$). In addition, the incidence of adverse reactions (AEs) in combination group were higher than TACE + placebo / alone group. Furthermore, the subgroup analysis showed that the heterogeneity of TTP was notably decreased (pre-TACE: $P = 0.12$, $I^2 = 48\%$; post-TACE: $P = 0.58$, $I^2 = 0\%$), and the hazard ratio was 0.59 (95% confidence interval: 0.51–0.68; $P < 0.00001$) in pre-TACE subgroup which indicated that combination before TACE significantly prolonged TTP but not in combination after TACE (hazard ratio: 0.88; 95% confidence interval: 0.62–1.24; $P = 0.46$). In term of AEs, sensitivity analysis indicated that the risk ratio for hand-foot skin reaction, diarrhea, rash/desquamation, and hypertension was 7.41, 2.58, 2.14, 1.55 in pre-TACE subgroup respectively and was 11.34, 3.26, 3.61, 4.11 in post-TACE subgroup respectively (All $P < 0.05$).

Conclusion: The combination of TACE and sorafenib significantly can improve TTP and PFS, and reduce the level of risk of adverse reactions of unresectable HCC, especially in the combination before TACE.

Abbreviations: AEs, adverse events; BCLC, Barcelona clinic liver cancer; CI, confidence intervals; CR, complete response; DCR, disease control rate; DEB-TACE, trans-arterial chemoembolization with drug-eluting beads; ECOG, Eastern cooperative oncology group; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HFSR, hand-foot skin reaction; HR, hazard ratio; mRECIST, modified RECIST; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease; PD-L1, programmed death ligand 1; PR, partial response; RCT, randomized controlled trial; RECIST, response evaluation in solid tumors; RR, risk ratio; SD, stable disease; TTP, time to progression; TTUP, time to untreatable progression; VEGF, vascular endothelial growth factor.

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https://doi.org/10.1016/j.tranon.2021.101238
Received 26 August 2021; Received in revised form 30 September 2021; Accepted 2 October 2021

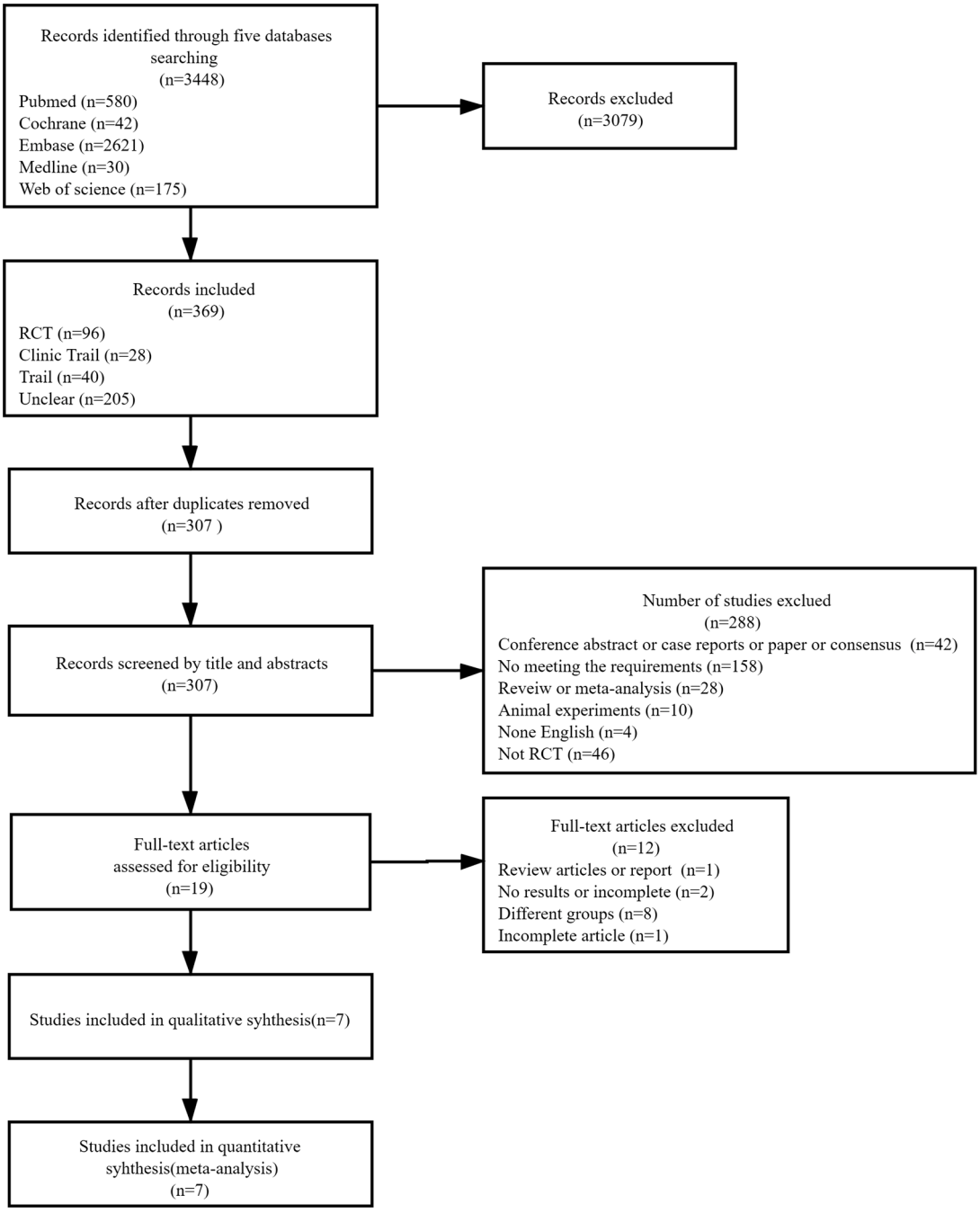

Fig. 1. Flowchart of the selection of included studies.

Introduction

Hepatocellular carcinoma (HCC) is the seventh most common cancer in the world and the second most common cause of cancer-related death [1]. The highest incidence rates in the world are in Asia and Africa due to the high prevalence of hepatitis B virus infection [2]. As of 2018, there were approximately 930,000 new cases of HCC and 850,000 deaths worldwide each year [1]. Most HCC patients are mostly in the intermediate and advanced stages when they are clinically discovered, and have lost the opportunity of radical surgical resection so that to choose loco-regional therapy.

Clinically, personalized treatment methods are often selected according to Barcelona Clinic Liver Cancer (BCLC) staging. According to the American Association for the Study of Liver Diseases (AASLD) guidelines, trans-arterial chemoembolization (TACE) is the only recommended treatment method for patients with HCC in intermediate stage (BCLC stage B) [3]. Compared with the best supportive therapy, TACE can prolong the overall survival of patients to a certain extent [4]. However, repeated TACE therapy can promote drug resistance, and increase the chance of tumor recurrence and metastasis [5]. In addition, it will increase side effects and aggravate liver damage [6]. Among these, the high recurrence rate may be related to the increased expression of vascular endothelial growth factor (VEGF) [7].

Fortunately, as an antiangiogenic drug, sorafenib can inhibit tumor cell proliferation and angiogenesis by restraining VEGF, and increase tumor cell apoptosis as well [8]. Furthermore, a recent study [9] has pointed out that the programmed death ligand-1 (PD-L1) inhibitor atezolizumab combined with bevacizumab has better efficacy than

Table 1
Baseline characteristics of 7 RCTs and patients.

References	Country	Group	Number of cases	Etiology (HBV/HCV/Other) (%)	Mean age (years) (%)	Male (%)	AFP (ng/mL) (≦400/>400)	ECOG (0/1) (%)	BCLC stage (A/B/C) (%)	Child-Pugh class (A/B/C) (%)
Hoffmann et al.[17]	Germany	TACE+sorafenib vs. TACE+placbo	50	12.5/45.8)/41.6 vs. 12.5/26.9/61.5	58.5(44.0–66.0) vs. 58.0 (43.0–69.0)	NA	NA	NA	NA	58.3/37.5/4.2 vs. 76.9/23.1/NA
Kudo et al. [15]	Japan, USA, South Korea	TACE+sorafenib vs. TACE+placbo	458	20.5/60.7/18.8 vs. 22.7/64.6/12.7	69 vs. 70	76.0 vs. 73.4	NA	87.8/12.2 vs. 88.2 / 11.8	NA	All class are A
Kudo et al. [20]	Japan, UK	TACE+sorafenib vs. TACE alone	156	12.5/47.5/340.0 vs. 2.6/69.7/27.6	72.0(36–85) vs. 73.0(53–86)	78.8 vs. 72.4	NA	88.8/11.3 vs. 88.2/11.8	33.8/55.0/11.3 vs. 43.4/44.7/11.8	98.8/1.3 vs. 93.5/5.6
Lencioni et al. [18]	USA, Italy, Spain, China, France, UK, South Korea,	DE-TACE+sorafenib vs. DE-TACE+placbo	307	35.7/25.3/39.0 vs. 32.7/26.8/40.5	64.5 vs. 63.0	87.7 vs. 82.4	73.4/26.8 vs. 73.2/26.8	All status are 0	All stage are B	99.4/0.6 vs. 99.3/0
Liu et al. [21]	China	TACE+sorafenib vs. TACE alone	118	NA	56.31±9.87 vs. 58.11±10.44	62.7 vs. 54.2	76.3/23.7 vs. 83.1/16.9	57.6/42.4 vs. 66.1/33.9	0/50.8/49.2 vs. 0/61.0/39.0	72.9/27.1 vs. 81.4/18.6
Meyer et al. [19]	UK	DE-TACE+sorafenib vs. DE-TACE+placbo	313	5.0/12.0/83.0 vs. 5.0/7.0/88.0	65(57–71) vs. 68 (63–74)	89 vs. 88	NA	62/62/1 (NK) vs. 37/37/1 (NK)	NA	93/4/0/4 (NK) vs. 95/2//0/3(NK)
Sansonno et al. [16]	Italy	TACE+sorafenib vs. TACE alone	62	All hepatitis are C	73 ± 4 vs. 72.8 ± 6.4	58.1 vs. 61.3	NA	86 /24 vs. 77 /23	All stage are B	All class are A

TACE: Trans-arterial chemoembolization; DE-TACE: Trans-arterial chemoembolization with drug-eluting beads; AFP: alpha-fetal protein; NK: Not known.

sorafenib monotherapy in the initial treatment of patients with unresectable HCC, in which both two drugs have synergistic activity, and bevacizumab has immunomodulatory effects. Atezolizumab combined with bevacizumab may reverse VEGF-mediated immunosuppression, leading to increased *T*-cell tumor infiltration and further improving the efficacy of atezolizumab [10]. However, the treatment of sorafenib for HCC is currently discussed as the most common in most randomized controlled trials (RCTs). Therefore, combining sorafenib with TACE may be an effective strategy to decrease the recurrence rate of tumors and improve the treatment efficacy compared to TACE alone therapy [11]. In addition, a recent RCT study [12] comparing the effects on liver function after selective internal radiation therapy (SIRT) + sorafenib and sorafenib alone groups in patients with unresectable HCC found that only in a specific subgroup of patients, the combined group can achieve a longer survival time or better liver function scores. Previous RCTs designed the different time of combination of sorafenib including before TACE and after TACE. However, when combining sorafenib for the longest survival and lowest side effects remains an important issue which few studies have reported.

The purpose of this meta-analysis is to analyze the safety and efficacy of sorafenib combined with TACE in patients with unresectable HCC and discuss the best timing to combine sorafenib with TACE.

Methods

Search strategy

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [13]. All studies in PubMed, EMBASE, the Cochrane Library, MEDLINE, and Web of Science were searched (until 15 May 2021) using combinations of the following terms: "Carcinoma, Hepatocellular" or "Hepatocellular Carcinomas" or "Liver Cancer" AND "Chemoembolization, Therapeutic" or "Therapeutic Chemoembolization" AND "Sorafenib" (Details in Supplementary S1).

Selection criteria

Inclusion criteria

(a) patients diagnosed with HCC according to the diagnostic criteria; (b) the studies were RCTs; (c) treatments included TACE and sorafenib; (d) English articles and adult patients; (e) study endpoints involved the hazard ratio (HR) and its corresponding 95% confidence interval (CI) for overall survival (OS), time to progression (TTP), time to untreatable progression (TTUP), progression-free survival (PFS) which were available or could be calculated, and tumor response, objective response rate (ORR), disease control rate (DCR), and adverse events (AEs).

Exclusion criteria

(a) reviews, meta-analysis, abstracts, letters, consensus, editorials, papers, as well as case reports; (b) animal experiments; (c) none-English articles; (d) incomplete information.

Data extraction and quality assessment

Two independent reviewers extracted the data, and a third reviewer was consulted if there was uncertainty regarding eligibility. The quality assessment of studies was evaluated according to assessing the risk of bias in the Cochrane Handbook for Systematic Reviews of Interventions [14].

Statistical analysis

All statistical meta-analysis was performed using the Review Manager (version 5.3) Software. The hazard ratio (HR) with 95% confidence interval (CI) was calculated for OS, TTP, TTUP, and PFS among patients treated with TACE + sorafenib compared to those with TACE + placebo or TACE alone. The risk ratio (RR) with 95% CI was calculated for the ORR, DCR, and AEs. Heterogeneity between studies was evaluated by the I^2 value. An $I^2 < 50\%$, $P > 0.1$ suggests that there is no or low heterogeneity that can be ignored, and the meta-analysis was used the fixed-effect model; otherwise, the random-effect model was adopted.

Table 2
Summary of study participants and study outcomes.

References	Treatment type	Number of cases	Chemoembolization	The order of sorafenib	Dose of sorafenib	Using of sorafenib	Tumor response, CR/PR/SD/PD (%)	Median TTP (months)	Median TTUP (months)	Median PFS (months)	Median OS (months)
Hoffmann et al. [17]	TACE+sorafenib vs. TACE+placbo	24 vs.26	carboplatin	three days before TACE	400 mg/ twice daily	Discontinued: three days before TACE, Resumed: three days after each TACE.	4.3/17.4/47.8/ 30.4 vs. 0/26.9/ 46.2/26.9	2.4 vs.2.8	NA	NA	NA
Kudo et al. [15]	TACE+sorafenib vs. TACE+placbo	229 vs. 229	epirubicin, cisplatin, doxorubicin, mitomycin	after TACE treatment	400 mg/ twice daily	Adverse events were investigator-assessed and graded according to NCI CTCAE version 3.0	62.0/NA/NA/NA vs. 62.0/NA/NA/ NA	5.4 vs. 3.7	NA	NA	29.7 vs. NA
Kudo et al. [20]	TACE +sorafenib vs. TACE alone	80 vs.76	epirubicin or miriplatin	2, 3 weeks prior to first TACE	400 mg/ day	Discontinued: 2 days before and 2 days after each TACE session, Resumed:3 days after TACE.	28.8/42.5/12.5/ 2.5/13.8(NE) vs. 27.6/34.2/15.8/ 3.9/18.4(NE)	26.7 vs. 16.4	26.7 vs. 20.6	25.2 vs. 13.5	NA
Lencioni et al. [18]	DE-TACE+sorafenib vs. DE-TACE+placbo	154 vs.153	doxorubicin	sorafenib or placebo was initiated on day 1 and the first DEB-TACE session was performed 3–7 days later	400 mg/ twice daily	Adverse events were investigator-assessed and graded according to NCI CTCAE version 3.0	13.0/22.7/33.8/ 13.0/17.5(NE) vs. 11.1/17.0/36.7/ 22.5/11.8(NE)	5.6 vs. 9.1	3.2 vs. 7.5	NA	9.0 vs. 9.1
Liu et al. [21]	TACE +sorafenib vs. TACE alone	59 vs. 59	oxaliplatin, epirubicin, 5-fluorouracil	1 week after TACE	400 mg/ twice daily	Discontinued: Resumed:	6.8/49.2/30.5/ 13.5 vs. 1.7/35.6/ 30.5/32.2	NA	NA	NA	25.3 ± 2.6 vs. 22.5 ± 2.5
Meyer et al. [19]	DE-TACE+sorafenib vs. DE-TACE+placbo	157 vs. 156	doxorubicin	within 24 h of randomization	400 mg/ twice daily	continued until disease progression	29/25/21/8/17 (NE) vs. 23/29/ 25/10/14(NE)	10.9 vs. 10.7	NA	7.9 vs. 7.8	20.0 vs. 19.9
Sansonno et al. [16]	TACE+sorafenib vs. TACE alone	31 vs. 31	doxorubicin, mitomycin	30 days after TACE treatment	400 mg/ twice daily	Adverse events were investigator-assessed and graded according to NCI	NA	9.2 vs. 4.9	NA	NA	NA

NE:Not evaluated.

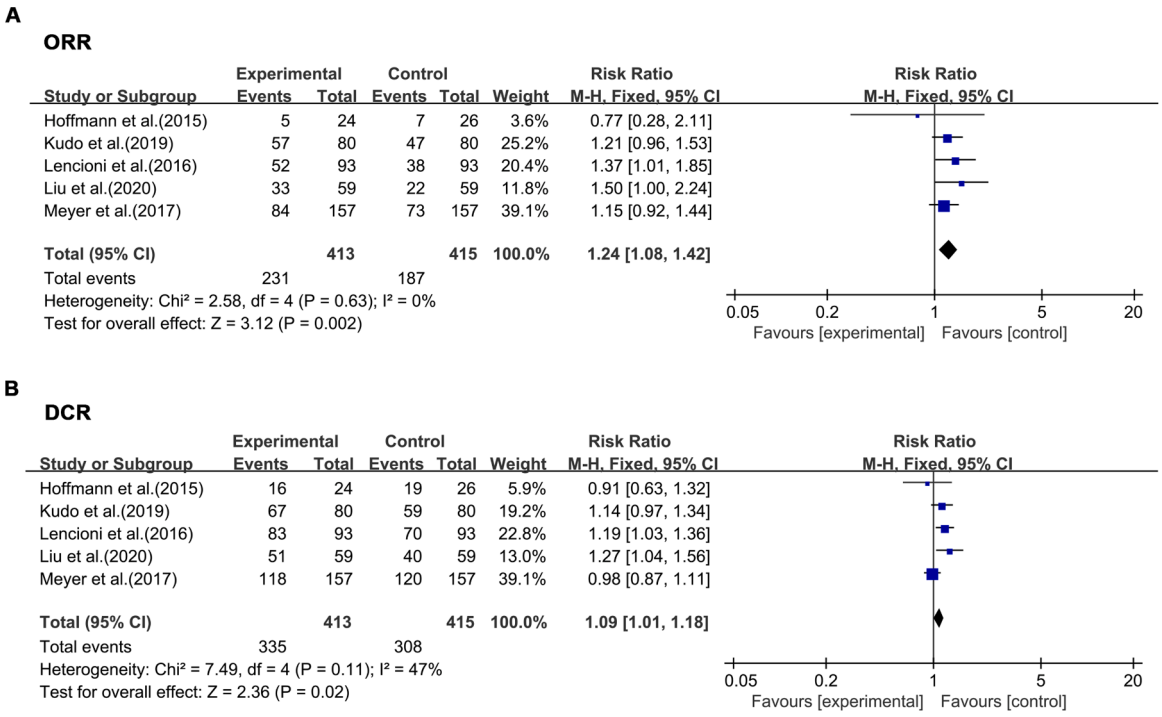

Fig. 2. Forest plot of ORR and DCR.

Causes of heterogeneity were identified through subgroup and sensitivity analyses. The risk of publication bias was evaluated with funnel plots. $P < 0.05$ was considered statistically significant. Furthermore, subgroup analysis and sensitivity analysis were performed to explain the possible causes of heterogeneity.

According to the Cochrane Handbook for Systematic Reviews of Interventions [14], we did not evaluate publication bias because the number of studies included in the meta-analysis was too small to assess for publication bias using a funnel plot.

Results

Literature search results

Our initial search strategy from five databases identified 3448 potentially relevant studies, of which 369 studies were selected by RCTs, Trials, Clinic trials, and unclear type studies (Fig. 1). After the removal of duplicates, a total of 307 studies were identified for selection. According to titles and abstracts, there were 288 studies excluded, and the full texts of the remaining 19 studies were examined. Finally, 7 RCTs [15–21] were eligible for inclusion criteria in the final meta-analysis.

Characteristics of the included studies

The 7 RCTs included 1464 patients with unresectable HCC, with 734 patients treated with TACE + sorafenib and 730 treated with TACE + placebo or TACE alone. The mean age across the studies ranged from 56.3 to 73.0 years, and a higher percentage of patients were male. For both two groups, patients with hepatitis B and C virus (HBV, HCV) and infection, BCLC stage B and C, Child-Pugh class A, and Eastern Cooperative Oncology Group (ECOG) score of 0 were more common. The detailed baseline characteristics of patients are displayed in Table 1.

Among 7 RCTs, 5 RCTs were conventional TACE, which chose carboplatin, oxaliplatin, epirubicin, cisplatin, doxorubicin, mitomycin, 5-fluorouracil as chemotherapeutics, and gelatin sponge or iodipin as embolization; 2 RCTs were TACE with doxorubicin-eluting beads. In terms of sorafenib, the dosage was 400 mg twice a day in 6 RCTs and was 400 mg once a day in 1 RCT. Furthermore, sorafenib was combined before TACE in 4 RCTs, and combined after TACE in 3 RCTs. In these studies, the exact timing of administration of sorafenib varied. According to the occurrence of AEs, patients of all studies were undergone medication adjustment of sorafenib, including dosage reduction or discontinuation required (Table 2). The quality assessments of all RCTs are shown in Figs. S1, S2.

Tumor response, ORR and DCR

In terms of tumor response, the 5 RCTs [17–21] were assessed according to the response evaluation in solid tumors (RECIST) or modified RECIST (mRECIST) which were classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). ORR was calculated as (CR + PR) / total cases × 100%, and DCR was calculated as (CR + PR + SD) / total cases × 100%. According to heterogeneity test (ORR: $\chi^2 = 2.58$, $P = 0.63$, $I^2 = 0\%$; DCR: $\chi^2 = 7.49$, $P = 0.11$, $I^2 = 47\%$), both risk ratio (RR) of ORR and DCR were combined and analyzed using fixed-effects model. Meta-analysis demonstrated that ORR and DCR of TACE + sorafenib group was slightly superior to those treated with TACE + placebo / alone group (ORR: RR = 1.24, 95% CI 1.08–1.42, $P = 0.002$; DCR: RR = 1.09, 95% CI 1.01–1. 18, $P = 0.02$) (Fig. 2). For the 2 RCTs [15,16], the assessment of tumor response was different. In the study of Kudo et al. [15], tumor response was classified as complete response (CR) and non-CR which rate of the two was 142 (62.0%) / 87 (38.0%) both in TACE + sorafenib group and TACE + placebo group. In the study of Sansonno et al. [16], intrahepatic tumor progression occurred in 21 (68%), 31 (100%) patients in TACE + sorafenib group and the TACE + placebo / alone group, respectively. These 2 RCTs were not analyzed the ORR and DCR.

OS, TTP, TTUP and PFS

OS

There were 3 RCTs [15,18,19] that involved OS with HR and 95% CI (Fig. 3A). The median OS time ranged from 9.0 to 29.7 months for patients in TACE + sorafenib group and 9.1 to 22.5 months in TACE +

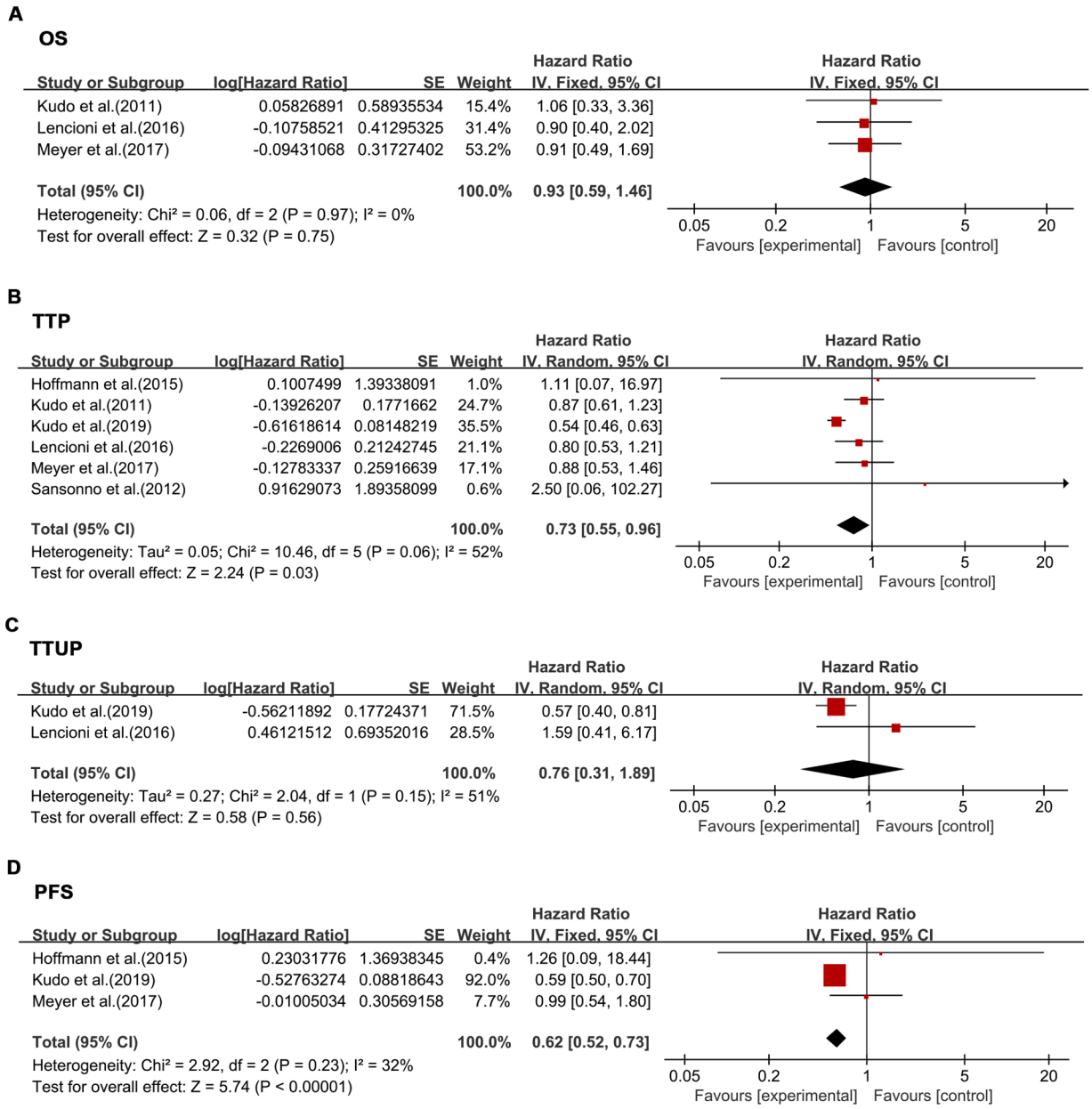

Fig. 3. Forest plot of OS, TTP, TTUP and PFS.

placebo / alone group. Based on heterogeneity test ($\chi^2 = 0.06$, $P = 0.97$, $I^2 = 0\%$), the fixed effect model was adopted. The forest plot demonstrated that the HR for OS was 0.93 (95% CI 0.59–1.46, $P = 0.75$), suggesting that combination therapy may not improve OS.

TTP

There were 6 RCTs [15–20] that involved TTP with HR and 95% CI (Fig. 3B). The median TTP time ranged from 2.4 to 26.7 months and 2.8 to 16.4 months for patients with TACE + sorafenib and those with TACE + placebo / alone, respectively. According to heterogeneity test ($\chi^2 = 10.46$, $P = 0.06$, $I^2 = 52\%$), the random effect model was used. The forest plot displayed that the HR for TTP was 0.73 (95% CI 0.55–0.96, $P = 0.003$), indicating that combination therapy significantly prolonged TTP.

TTUP

There were 2 RCTs [18,20] that involved TTP with HR and 95% CI (Fig. 3C). The median TTUP time was 3.2 and 26.7 months for patients with TACE + sorafenib group and was 7.5 to 20.6 months for patients with TACE + placebo / alone group. In accordance with heterogeneity test ($\chi^2 = 2.04$, $P = 0.15$, $I^2 = 51\%$), the random effect model was used. The forest plot showed that the HR for TTUP was 0.76 (95% CI 0.31–1.89, $P = 0.56$), implying that combination therapy may not remarkably prolonged TTUP.

PFS

There were 3 RCTs [17,19,20] that contained PFS with HR and 95% CI (Fig. 3D). Based on heterogeneity test ($\chi^2 = 2.92$, $P = 0.23$, $I^2 = 32\%$), the fixed-effect model was used. The forest plot expressed that the HR for PFS was 0.62 (95% CI 0.52–0.73, $P < 0.00001$), suggesting that combination therapy extended PFS.

Adverse effects (AEs)

In all 7 RCTs, the main AEs were displayed in Table 3. Among these, HFSR, diarrhea, fatigue, hypertension, nausea, and rash/desquamation

Table 3
Comparison of complications between TACE combined with Sorafenib and patients with TACE alone.

Adverse reactions	Inclusion study	Events/Total TACE+sorafenib	TACE+placebo/alone	RR (95%CI)	Heterogeneity	*P*
Abdominal pain	2	185/310	182/307	1.01(0.88, 1.15)	$\chi2 = 0.21$, $P = 0.64$, $I^2 = 0\%$	0.92
Alopecia	4	160/563	32/559	4.9(3.41, 7.02)	$\chi2 = 20.1$, $P = 0.0002$, $I^2 = 85\%$	<0.00001
Amylase	2	80/306	37/298	2.07(1.47, 2.93)	$\chi2 = 2.34$, $P = 0.13$, $I^2 = 57\%$	0.01
Anorexia	4	114/427	95/418	1.18(0.94, 1.49)	$\chi2 = 2.73$, $P = 0.43$, $I^2 = 0\%$	0.16
Constipation	2	52/310	73/307	0.71(0.51, 0.97)	$\chi2 = 5.19$, $P = 0.02$, $I^2 = 81\%$	0.03
Diarrhea	7	289/739	102/729	2.95(1.84, 4.72)	$\chi2 = 21.6$, $P = 0.001$, $I^2 = 72\%$	<0.00001
Elevated ALT	3	143/459	91/449	1.50(1.24, 1.80)	$\chi2 = 24.94$, $P<0.00001$, $I^2 = 92\%$	<0.0001
Elevated AST	3	167/459	105/449	1.52(1.29, 1.79)	$\chi2 = 86.39$, $P<0.00001$, $I^2 = 98\%$	<0.00001
Elevated lipase	2	139/306	36/298	3.72(2.68, 5.16)	$\chi2 = 10.51$, $P = 0.001$, $I^2 = 90\%$	<0.00001
Fatigue	5	226/451	187/443	1.19(1.06, 1.35)	$\chi2 = 12.11$, $P = 0.02$, $I^2 = 67\%$	0.004
Fever	3	94/289	94/281	0.98(0.78, 1.23)	$\chi2 = 1.85$, $P = 0.40$, $I^2 = 0\%$	0.85
HFSR	7	395/739	42/729	9.10(6.76, 12.25)	$\chi2 = 8.64$, $P = 0.19$, $I^2 = 31\%$	<0.00001
Hemorrhage/bleeding	3	67/350	38/347	1.74(1.20, 2.50)	$\chi2 = 2.23$, $P = 0.33$, $I^2 = 10\%$	0.003
hyperbilirubinaemia	3	83/254	55/247	1.43(1.11, 1.83)	$\chi2 = 1.46$, $P = 0.48$, $I^2 = 0\%$	0.006
Hypertension	5	177/558	75/548	2.33(1.28, 4.24)	$\chi2 = 19.28$, $P = 0.0007$, $I^2 = 79\%$	0.006
Nausea	5	179/433	164/431	1.08(0.93, 1.27)	$\chi2 = 2.49$, $P = 0.65$, $I^2 = 0\%$	0.32
Rash/desquamation	5	220/638	78/633	2.80(2.22, 3.53)	$\chi2 = 7.48$, $P = 0.11$, $I^2 = 47\%$	<0.00001
Thrombocytopenia	3	137/330	72/323	1.82(1.50, 2.20)	$\chi2 = 51.33$, $P<0.00001$, $I^2 = 96\%$	<0.00001
Vomiting	3	90/369	90/366	0.99(0.79, 1.26)	$\chi2 = 5.16$, $P = 0.08$, $I^2 = 61\%$	0.96
Weight loss	4	60/411	17/403	3.94(1.03, 15.08)	$\chi2 = 10.62$, $P = 0.01$, $I^2 = 72\%$	0.05

HFSR: Hand–foot skin reaction.

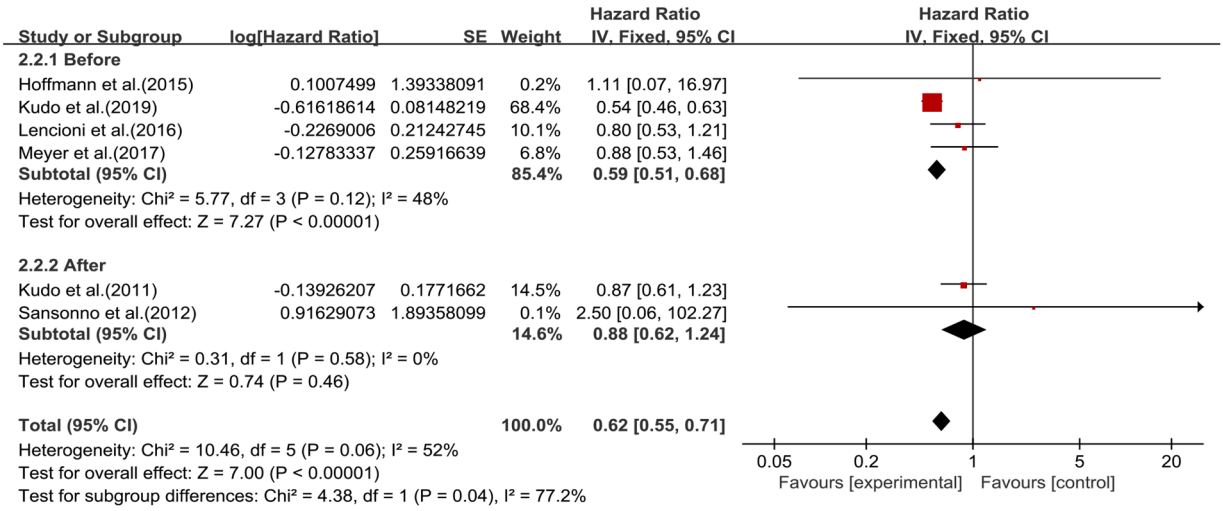

Fig. 4. Forest plot of subgroup analysis of TTP.

were reported in 7, 7, 5, 5, 5, and 5 studies, respectively. The incidence of AEs in the TACE + sorafenib group was higher than TACE + placebo/alone group. However, a meta-analysis demonstrated that the heterogeneities were discovered in alopecia, amylase, constipation, diarrhea, elevated ALT, elevated AST, elevated lipase, fatigue, hypertension, thrombocytopenia.

Subgroup analysis and sensitivity analysis

Due to the heterogeneity, we performed subgroup analysis for TTP and AEs according to combination timing of sorafenib and TACE (pre-TACE vs. post-TACE). 4 RCTs [17–20] were pre-TACE subgroup, 3 RCTs [15,16,21] were post-TACE subgroup. The forest plot demonstrated that the heterogeneity was significantly decreased after subgroup analysis (pre-TACE: $P = 0.12$, $I^2 = 48\%$; post-TACE: $P = 0.58$, $I^2 = 0\%$), and the HR for TTP was 0.59 (95% CI: 0.51–0.68, $P < 0.00001$) in pre-TACE group and was 0.88 (95% CI: 0.62–1.24, $P = 0.46$) in post-TACE group (Fig. 4.). These data may mean the positive TTP outcome of statistical significance in the pre-TACE group. Since there were only 2 studies, we did not perform subgroup analysis and sensitivity analysis for TTUP.

Among of AEs, we still performed the same subgroup analysis for diarrhea, HFSR, nausea, rash/desquamation, and hypertension, which all involved more than 2 RCTs in both subgroups. The forest plots indicated that the heterogeneity of HFSR, rash/desquamation, and hypertension was decreased to varying degrees after subgroup analysis (Fig. 5A–E). The RR for those was 7.41, 2.14, and 1.55 in the pre-TACE subgroup respectively, and was 11.34, 3.61, and 4.11 in post-TACE subgroup respectively. However, after the subgroup analyzing the heterogeneity of the diarrhea was not changed and the heterogeneity of the nausea was increased slightly in post - TACE subgroup ($P = 0.29$; $I^2 = 11\%$).

Additionally, to identify additional AEs related to the timing of the combination, we also performed a sensitivity analysis by removing the studies of the combination after TACE. The results indicated that both the heterogeneity and RR of the elevated ALT, hemorrhage/bleeding, nausea, and thrombocytopenia were significantly decreased (RR: 1.50, 1.74, 2.33, and 2.80 before sensitivity analysis; 1.15, 1.62, 1.03, and 1.13 after sensitivity analysis) (Table S1).

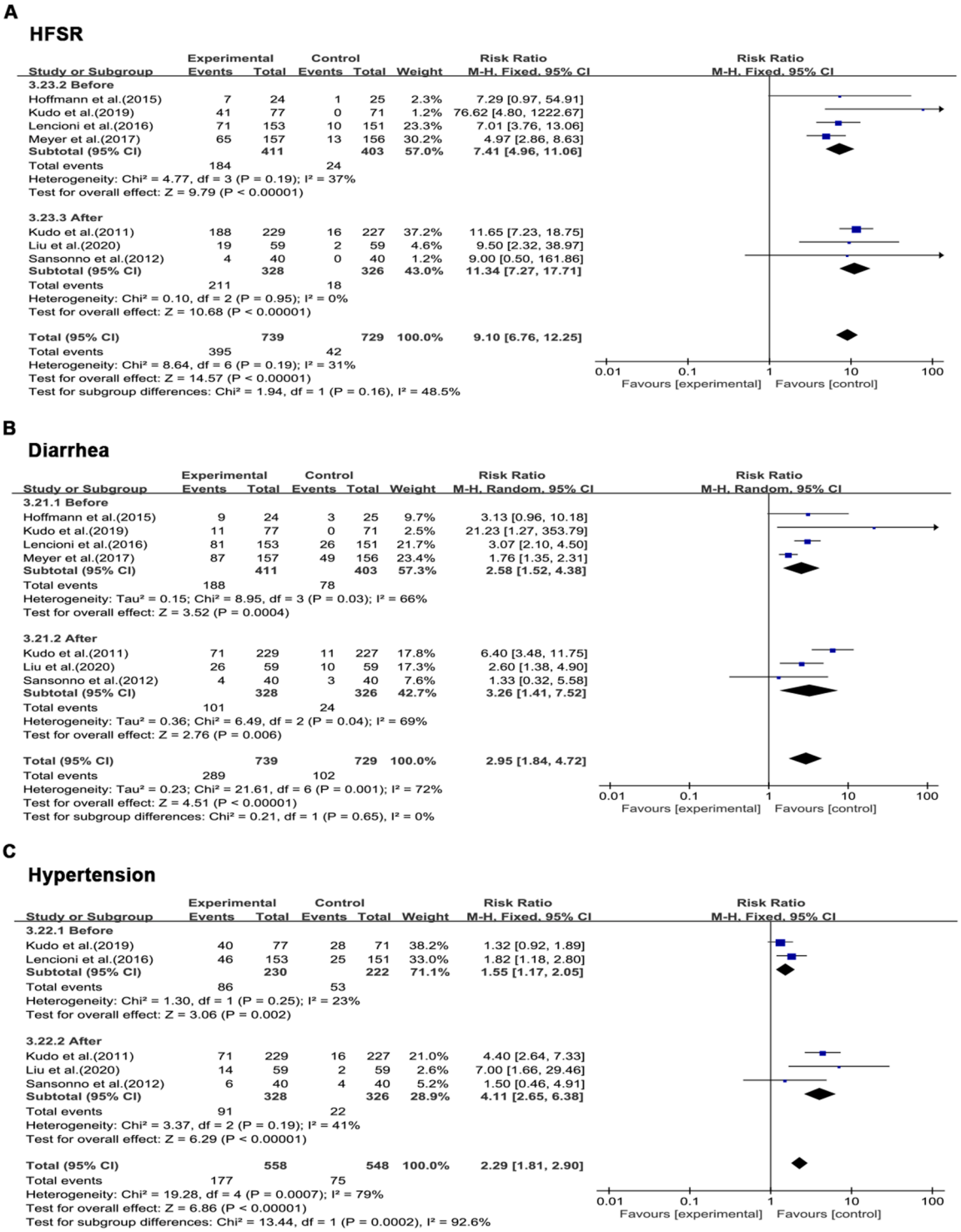

Fig. 5. Forest plot of subgroup analysis of AEs.

Discussion

This meta-analysis evaluated the efficacy and safety of TACE + sorafenib or TACE + placebo / alone in treating patients with hepatocellular carcinoma and analyzed the optimal combination timing of sorafenib and TACE. We discovered that the combination of sorafenib and TACE can prolong TTP and PFS, and can also increase the DCR and ORR. In terms of AEs, the rate of incidence in the TACE + sorafenib group was higher than that in TACE + placebo / alone significantly. After investigating we found that the timing of the combination of sorafenib is unclear and diversified, and the type and dosage of drugs for combined TACE with sorafenib have not been standardized which may be due to geographical treatment differences and physician experience differences. Thus, to achieve better efficacy and a lower incidence of AEs, while also aiming to provide an optimal dosing regimen for future studies, we questioned whether the timing of combination would have an impact on these outcomes. In majorities studies [17–20] with the design of combining before TACE, sorafenib was started on 400

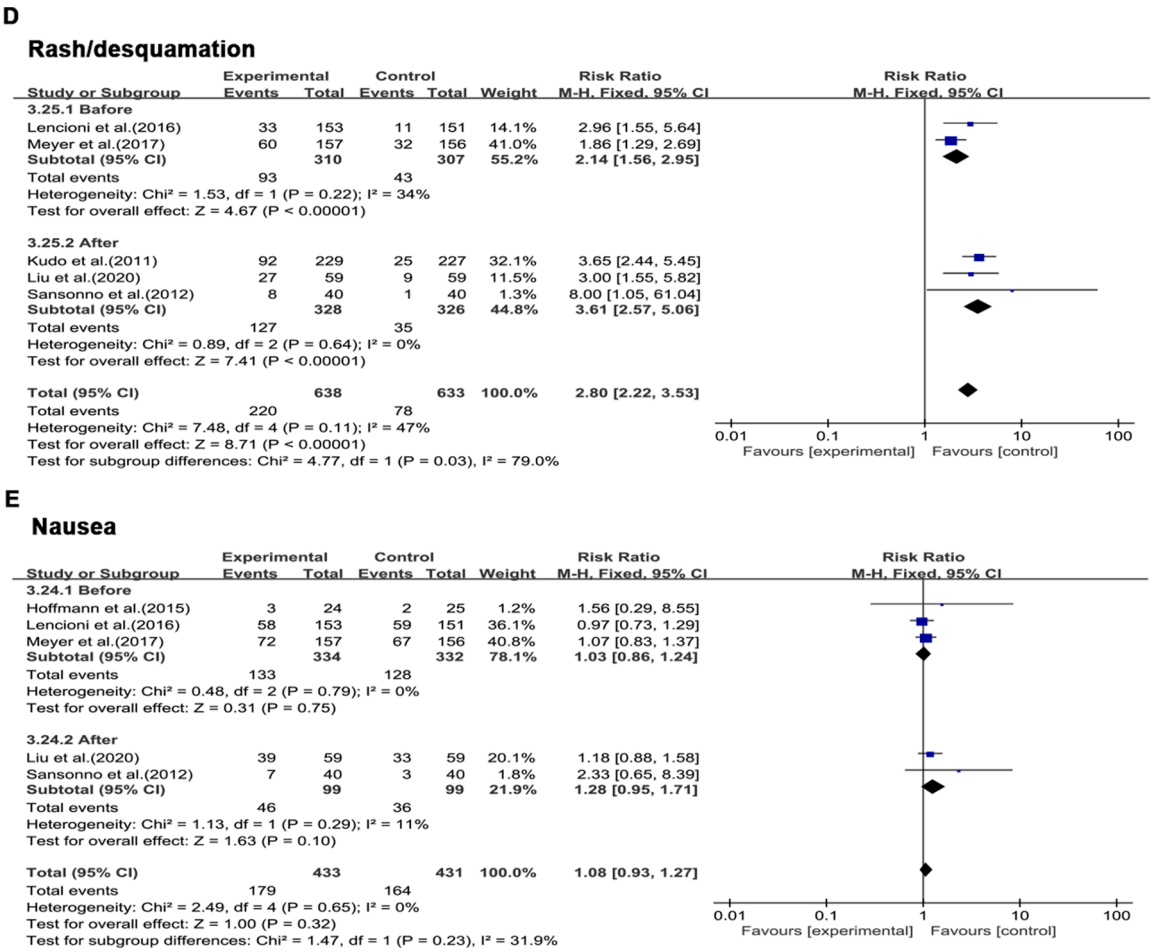

Fig. 5. (*continued*).

mg/twice a day before the first TACE to confirm tolerability to sorafenib, to normalize tumor neo-vasculature for efficient TACE response, and to suppress the VEGF increase after the TACE procedure [20]. As for the studies [15,16,21] of the combination after TACE, there is currently no corresponding explanation, which may be related to the subjectivity of clinicians or researchers. After subgroup analysis according to combination timing of sorafenib and TACE, we obtained that the heterogeneity of TTP was significantly reduced, and longer TTP was achieved with the combination of sorafenib before TACE (HR = 0.59, $P < 0.00001$) than with the combination after TACE (HR = 0.88, $P = 0.46$). As for AEs, the heterogeneity of HFSR, rash/desquamation, and hypertension was reduced to varying degrees, and RR is also significantly different (pre--TACE: 7.41, 2.14, and 1.55; post-TACE: 11.34, 3.61, and 4.11). However, this needs to be validated by more RCTs in order to develop relevant guidelines and consensus for future studies.

Previous studies have indicated that TACE combined with sorafenib can prolong the overall survival and improve clinical outcomes of unresectable HCC patients [22,23]. Zhang et al. [24] analyzed 15 studies including 5 RCTs and 10 NRCTs in a total of 3104 patients with primary HCC and pointed that TACE + sorafenib can prolong the 1-year, 2-year, 3-year, and 5-year OS of patients, respectively, and improve ORR and DCR. Jin et al. [25] included 5 RCTs with 2538 patients and still indicated that the combination group significantly improved TTP (HR = 0.66; $P = 0.006$), OS (HR = 0.57; $P < 0.001$), and DCR (HR = 1.30; $P = 0.05$). Likewise, in our meta-analysis, the combination group remarkably prolonged TTP (HR = 0.73; $P = 0.003$) and PFS (HR = 0.62; $P < 0.00001$), and improved the ORR (RR = 1.24; $P < 0.002$) and DCR (RR = 1.09; $P = 0.02$) as well. Nevertheless, Zeng et al. [26] analyzed 4 RCTs including a total of 887 patients with early or intermediate stage HCC, and showed that the combination group significantly increased TTP (HR = 0.77; $P = 0.005$) but not OS, ORR, and DCR. Compared with the results of Zeng et al., our meta-analysis discovered that OS (HR = 0.93; $P = 0.75$) was not improved similarly but ORR and DCR in the combination group were slightly superior to TACE + placebo / alone group. In terms of OS, the possible reason is that all the included studies were high-quality RCTs in Zeng et al. and ours, with less heterogeneity and more reliable results; secondly, in terms of ORR and DCR, our analysis included more RCTs and the number of patients than those of Zeng et al., with higher reliability. Additionally, some studies [26–28] pointed out that OS was not better after TACE + sorafenib for HCC compared with TACE + placebo / alone. However, it is not clear why the combination of TACE and sorafenib did not have the desired effect. There is speculation that advanced HCC is more likely to benefit on OS than early or intermediate stage HCC from this combination therapy [29]. Moreover, although TTUP (HR = 0.76; $P = 0.56$) was analyzed in our meta-analysis, it was not significantly improved in the combination group. The probable reason is that there are only two RCTs involved and the results may not be representative.

However, as for AEs, a previous meta-analysis showed that TACE + sorafenib can lead to more complications significantly [22–24]. Our meta-analysis is consistent with the results of previous studies, in which the HFSR and diarrhea, fatigue, hypertension, nausea, and rash/desquamation were common in the combination group. This seems to be an inevitable side effect of sorafenib. Fortunately, it has been confirmed that the efficacy of immunosuppressive therapy was superior to sorafenib [9], which lower incidence of AEs was in the former. Jia et al. [30] noted that OS was significantly improved in the TACE + CIK group compared to the TACE group and that CIK treatment was a single

independent risk factor for OS in patients treated with local minimally invasive therapy (HR = 0.557, $P = 0.031$). In addition, no severe AEs associated with CIK treatment were observed in their study, except for the fever.

It has been noted [31] that sorafenib leads to a decrease in regulatory T cells and an increase in PD-1 expression on Th1 cells, which may be the result of hypoxic conditions. Similarly, anti-angiogenesis is limited by tumor hypoxia-induced immune escape [32]. Tumor hypoxia upregulates PD-L1 via hypoxia-inducible factor-1 alpha (HIF-1), thus allowing the immune system to escape [31]. These results suggest that combining antiangiogenic therapy with checkpoint inhibitors may target hypoxic immune evasion. But no statistical difference was obtained in terms of improving OS which may need a better patient selection or combination therapy [33].

Noteworthy, after sensitivity analysis, we found that most of the RCTs combined with sorafenib before TACE had varying degrees of reduction in RR for the occurrence of AEs, which may suggest that although TACE combined with sorafenib does not prolong OS, combination before TACE would be at a reduced risk of AEs. The pooled analysis for the timing of combination before TACE, rather than post-TACE, was more probably to reveal a positive HR and RR significance.

Nevertheless, there is more evidence to suggest that combination therapy with PD-1/PD-L1 inhibitors and tyrosine kinase inhibitors (TKIs) is becoming a future trend in advanced HCC [34]. We think that combination loco-regional therapy with systemic therapy in unresectable HCC patients will more mature and become standardized in the next 5 years, and we believe that more studies will be conducted in the future to compare the safety and efficacy of loco-regional therapy combined with immunosuppressive agents versus sorafenib in order to maximize the clinical benefit.

There are some limitations to our meta-analysis. First, although the studies included were RCTs, the number was still small so that the reliability of results in meta-analysis and subgroup analysis needs to be further confirmed. Second, there are the results of bias due to the number of studies involved in each primary and secondary endpoint is different. In addition, our meta-analysis did not analyze the efficacy of other systemic therapeutic agents combined with TACE (e.g., lenvatinib, immunosuppressants) in the treatment of unresectable HCC which efficacy was superior to sorafenib. Third, in our subgroup analysis, we only analyzed the timing of the combination but did not analyze whether the exact timing of administration of sorafenib in different subgroups would make a difference to the results, which needs to be analyzed and discussed in more RCTs in the future. Finally, the number of included studies was too little to carry out statistical analysis, and hence publication bias was not analyzed in our meta-analysis.

In conclusion, our meta-analysis indicated that the combination of TACE and sorafenib significantly can improve the ORR, DCR, TTP, and PFS of unresectable HCC, especially in combination before TACE. Furthermore, in terms of AEs, the combination before TACE had a lower incidence than the combination after TACE.

Supplementary Material

CRediT authorship contribution statement

Yanmei Dai: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Huijie Jiang:** Conceptualization, Writing – review & editing. **Hao Jiang:** Formal analysis, Writing – review & editing. **Sheng Zhao:** Formal analysis, Writing – original draft, Writing – review & editing. **Xu Zeng:** Formal analysis, Writing – review & editing. **Ran Sun:** Formal analysis, Writing – review & editing. **Ruoshui Zheng:** Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Funding

This study was supported by grants from the National Key Research and Development Program of China (2019YFC0118100), National Natural Science Foundation of China (81671760 and 81873910).

Acknowledgments

None.

Ethical approval

The ethical approval was not required in this article which was only a secondary calculation of the known study results and did not involve the patient's informed consent or any animal experiments.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2021.101238.

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