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Efficacy and safety of PD1/PDL1 inhibitors combined with radiotherapy and antiangiogenic drugs for hepatocellular carcinoma: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: The triplet regimen based on the programmed cell death 1 (PD1)/ programmed cell death ligand 1 (PDL1) inhibitors combined radiotherapy and antiangiogenic drugs is a novel therapeutic strategy for hepatocellular carcinoma. We conducted a meta-analysis to evaluate the efficacy and safety of the triplet therapeutic regimen in the treatment of hepatocellular carcinoma.

MATERIALS AND METHODS: We searched scientific literature databases and clinical trial databases through October 31, 2022, for required studies. The pooled hazard ratio (HR) was used to analyze the of overall survival (OS), progression-free survival (PFS), and the pooled relative risk (RR) was used to analyze the of objective response rate (ORR), disease control rate (DCR), mortality rate (MR), and adverse events (AEs) through random or fixed effects model, 95% confidence interval (CI) was determined for all outcomes. Qualities of the included literature were assessed by MINORS Critical appraisal checklist. Funnel plot was used to assess publication bias in the included studies.

RESULTS: Five studies (3 single-arm and 2 non-randomized comparative trials), including 358 cases were enrolled. Meta-analysis showed that the pooled ORR, DCR, and MR were 51% (95% CI: 34%-68%), 86% (95% CI: 69-102%), and 38% (95% CI: 18-59%), respectively. Compared with triplet regimen, the single or dual-combination treatments had shorter OS (HR=0.53, 95%: 0.34-0.83 *via* univariate analysis; HR=0.49, 95%: 0.31-0.78 *via* multivariable analysis) and PFS (HR=0.52, 95%: 0.35-0.77 *via* univariate analysis; HR=0.54, 95%: 0.36-0.80 *via* multivariable analysis). Common AEs to triplet regimens included skin reaction (17%), nausea/vomiting (27%), fatigue (23%), while severe AEs (10%), fever (18%), diarrhea (15%), and hypertension (5%) without statistically significant differences.

CONCLUSIONS: In the treatment of hepatocellular carcinoma, PD1/PDL1 inhibitors combined radiotherapy and antiangiogenic drugs achieved better survival benefits than alone or dual-combination regimens. In addition, the triple-combination therapy has tolerable safety.

Key Words:
PD1/PDL1 inhibitors, Antiangiogenic drugs, Radiotherapy, Hepatocellular carcinoma, Meta-analysis.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors and the mortality of the disease ranking third among malignant tumors worldwide[1]. Most patients are in the advanced stage of cancer and miss the chance to be surgically removed when HCC are diagnosed. However, the efficacy of non-excision treatment options is unsatisfactory, such as chemotherapy, radiotherapy, and immune checkpoint inhibitors. Therefore, it is pivotal to explore a novel clinical therapeutic strategy for HCC[2].

The PD-1 and PD-L1 axis is one of the most common immune systems and plays an important role in facilitating immune evasion[3]. Recent years, PD1 and PDL1 inhibitors are the backbone of systemic therapies in clinical practice for HCC[4]. The PD1/PDL1 inhibitors have shown unequivocal signs of activity in the treatment of HCC after sorafenib failure or unacceptable toxicity and produce a 15-20% rate of objective response that are durable and associated with prolonged survival[5]. It has been demonstrated

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that the patients with HCC achieve long-survival benefits from PD1/PDL1 inhibitors. For example, the CheckMate 459 has provided confirmation of the capacity of PD1/PDL1 inhibitors *vs*. sorafenib to increase the overall survival (OS) (29% *vs*. 21% at 33 months)[6].

Although the majority of patients with HCC derive benefit from PD1/PDL1 inhibitors, the general response rate remains unsatisfactory. Evidence suggests that targeting both the tumor vessels and immune cells could increase the effectiveness in HCC[6]. Increasing studies[7] have indicated that the PD1/PDL1 inhibitors combined with antiangiogenic drugs can improve OS, progress-free survival (PFS), disease response, and tolerable safety. Immunotherapy and antiangiogenic therapy have synergistic anticancer effects, angiogenic inhibitors can regulatory T cells and restore their anti-tumor immune function[8].Therefore, anti-PD1/PDL1 drugs combined angiogenic inhibitors can inhibit the tumor growth through reprogramming the immunosuppressive microenvironment to immunostimulatory microenvironment[8]. However, still nearly half of the patients remain unresponsive to the dual-combination therapy. Therefore, the addition of another treatment approach, particular radiotherapy (RT) which can lead the tumor microenvironment to immune-reactive, could further augment the antitumor efficacy of antiangiogenic drugs plus PD1/PDL1 inhibitors. Besides, the angiogenic drugs enhance the efficacy by normalizing tumor vessels[9,10].

Here, we conducted the meta-analysis of clinical trials to summarize the clinical safety and efficacy of the triplet regimens based on PD1/PDL1 inhibitors combined RT and antiangiogenic drugs for patients with HCC.

Materials and Methods

Search Strategy

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (**Supplementary Table I**)[11,12].

Two investigators independently searched for articles in the PubMed, Web of Science, Cochrane Library, Embase from inception to October 31, 2022. We used the following search terms: "immune checkpoint inhibitors, PD1 inhibitors, PDL1 inhibitors, nivolumab, pembrolizumab, camrelizumab" "radiotherapy, Stereotactic body radiation therapy, SBRT" "angiogenesis inhibitors, bevacizumab, apatinib, sorafenib" "cancer, carcinoma, tumor". **Supplementary Table II** shows the detailed search strategy for each database.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: Original papers of human clinical trials that reported the outcomes of the triplet regimen based on PD1/PDL1 inhibitors combined RT and antiangiogenic drugs in patients with HCC. There were no restrictions on publication date, tumor stage, study population, and study design.

The exclusion criteria were as follows: (1) Studies that reported HCC concomitant with other cancers, (2) data could not be extracted, (3) duplicate reports, (4) studies published as conference abstracts, reviews, comments, case reports, letters.

Two researchers independently screened and confirmed which articles should be included in the meta-analysis. Any inconsistency was resolved by consulting a third investigator.

Data Extraction

The two investigators independently extracted the following information from each trial: the first author's name, year of publication, study design, median follow-up time, disease status, sample size, median age, treatment, and main outcomes. The main outcomes included objective response rate (ORR), disease control rate (DCR), mortality rate (MR) and complete response rate (CRR). The following data were also extracted if the study contains: overall survival (OS), progression free survival (PFS), and adverse events (AEs).

Methodological Quality Assessment

The collected nonrandomized studies were evaluated using nonrandomized study methodological (MINROS)[13]. Single-arm trials with scores ≥8 were considered high-quality reports, while scores <8 were considered low-quality reports. Nonrandom comparative studies with scores ≥13 were considered high-quality reports, otherwise the studies were low-quality. Two independent reviewers completed the above tasks, and discordance was solved through consultation.

Statistical Analysis

All data analyses were performed using the Review Manager 5.1.7 software (Review manager Web, The Cochrane collaboration, Copenha-

gen, Denmark). The pooled rates used a random effect model or a fixed effect model. The pooled HRs were used to analysis of OS, PFS, and RR were used to analysis of ORR, DCR, MR, and AEs, the effect size of all combined results is represented by the 95% confidence interval (CI). Cochran's Q test and I^2 statistics were used to assess the heterogeneity between studies, with a threshold of $p<0.1$. The fixed-effects model was used for pooled results with low heterogeneity ($I^2<50\%$); otherwise, the random-effects model was used for analysis. Funnel plot was used to assess publication bias in the included studies. In addition, if the p-value is no more than 0.05, the results above all can be regarded as statistical significance.

Results

Study Selection

A total of 1,032 studies were included from the primary electronic database search: 184 from PubMed, 399 from Web of Science, 112 from Cochrane Library, and 337 from Embase. After eliminating duplicates and browsing the titles and abstracts, the remaining 42 studies were screened in full text, and 5 articles[14-18] were finally included according to the inclusion criteria. The literature review and identification process are shown in Figure 1.

Characteristics of Studies

Five studies were included to analyze, including two non-randomized comparative studies and

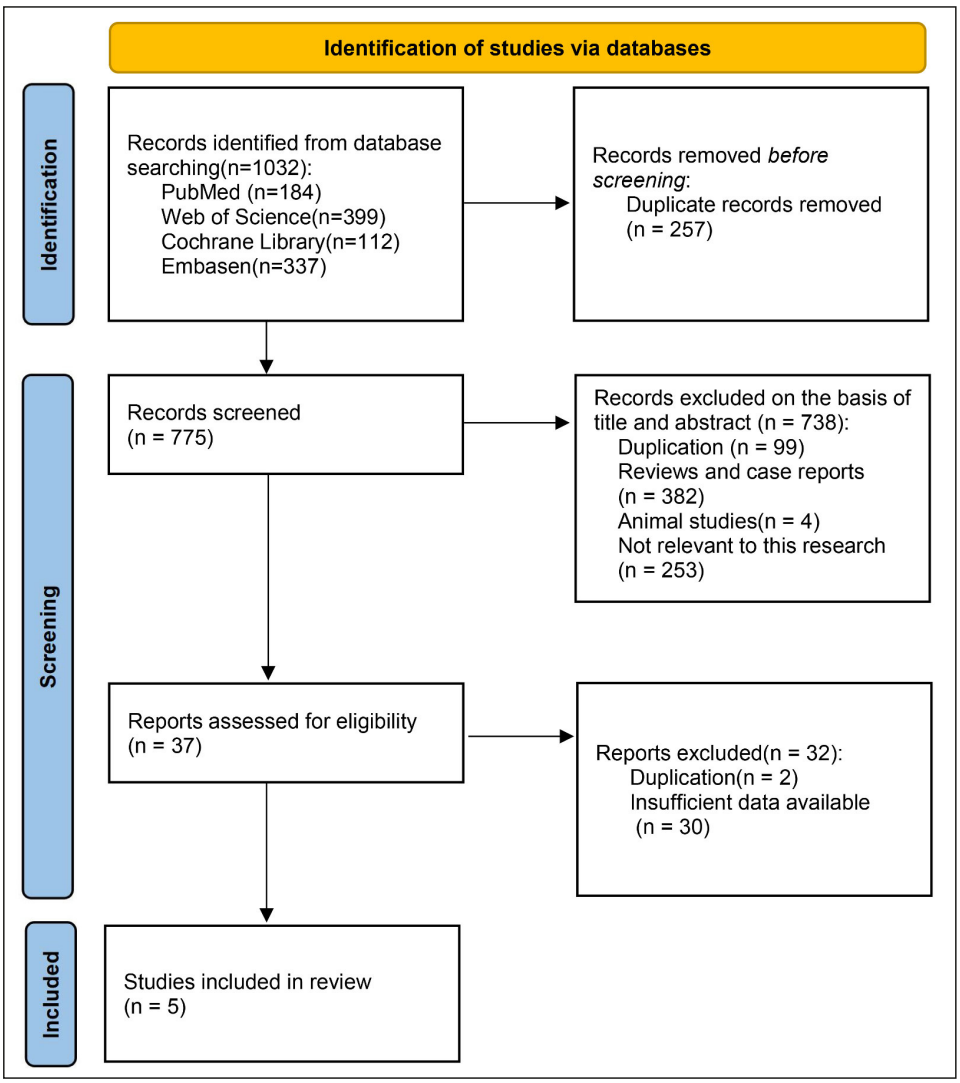

Figure 1. PRISMA flow chart of literature search and study selection.

Table I. Basic characteristics of included studies.

Study	Year	Country	Caner type	Trail design	Sample size (years)	Interventions			
						Median age	Experiment group	Control group	End-points
Huang et al[14]	2020	China	HCC	Single arm	12	54.5	SBRT+sorafenib +camrelizumab +TACE	None	ORR, DCR, AEs
Manzar et al[15]	2022	USA	HCC	Single arm	21	68	RT (2/3 IMRT+ 1/3 underwent proton therapy) +atezolizumab +bevacizumab	None	ORR, DCR, AEs, MR
Su et al[16]	2022	China	HCC	Retrospective comparative	54	NR	IMRT+anti-PD1 +antiangiogenesis	Anti-PD1+ antiangio-genesis	OS, PFS, ORR, DCR, AEs, MR
Zhang et al[17]	2022	China	HCC	Retrospective comparative	30	52	SBRT+camreli-zumab/tisleli-zummab+ sorafenib+TACE	Sorafenib+ TACE	OS, PFS, ORR, AEs
Zhong et al[18]	2021	China	HCC	Single arm	16	51.5	SBRT+anti-PD1/ PDL1+TA	None	ORR, DCR, AEs, MR

three single-arm trials, all published between 2020 and 2022. The basic characteristics of the included studies are shown in Table I. All included studies were high quality reports as the MINORS[13].

Response Rate of Triplet Regimens

All included studies reported ORR, DCR. The pooled ORR of patients received the triplet regimens was 51% (95% CI: 34-68%, $p<0.00001$; $I^2=0\%$, $p=0.49$) and the pooled DCR was 86% (95% CI: 69-102%, $p<0.00001$; $I^2=0\%$, $p=0.67$). While there were three studies reported MR[15,16,18], and the pooled MR was 38% (95% CI: 18-59%, $p=0.0002$; $I^2=0\%$, $p=0.57$) (Figure 2A-C).

Survival of Triplet Regimens

Two studies[16,17] reported the OS and PFS. The relevant results showed that the OS in patients treated with monotherapy or dual-combination therapy was shorter than patients treated with triplet regimens (HR=0.53, 95%: 0.34-0.83, $p=0.006$; $I^2=0\%$, $p=0.93$) by univariate analysis and (HR=0.49, 95%: 0.31-0.78, $p=0.002$; $I^2=0\%$, $p=0.89$) by multivariable analysis (Figure 3A-B). Compared with triplet regimen, monotherapy or dual-combination treatment were significantly associated with a shorter PFS (HR=0.52, 95%: 0.35-0.77, $p=0.001$; $I^2=0\%$, $p=1$) by univariate analysis and (HR=0.54, 95%: 0.36-0.80, $p=0.002$; $I^2=0\%$, $p=0.52$) by multivariable analysis (Figure 3C-D).

Adverse Events

Although 15 AEs were mentioned in the five included studies, there were only 6 AEs would be analyzed to pool effects. The results showed that the pooled effects of fatigue, nausea/vomiting, and skin reaction were 23%, 27% and 17%, respectively. While the severe AEs was 10%, and fever (18%), diarrhea (15%), hypertension (5%) were analyzed, but without statistically significant differences. The pooled AEs are shown in Table II.

Publication Bias

All included studies reported overall response rate, so ORR was selected for publication bias analysis. Funnel plot results showed that there was no significant publication bias (Figure 4).

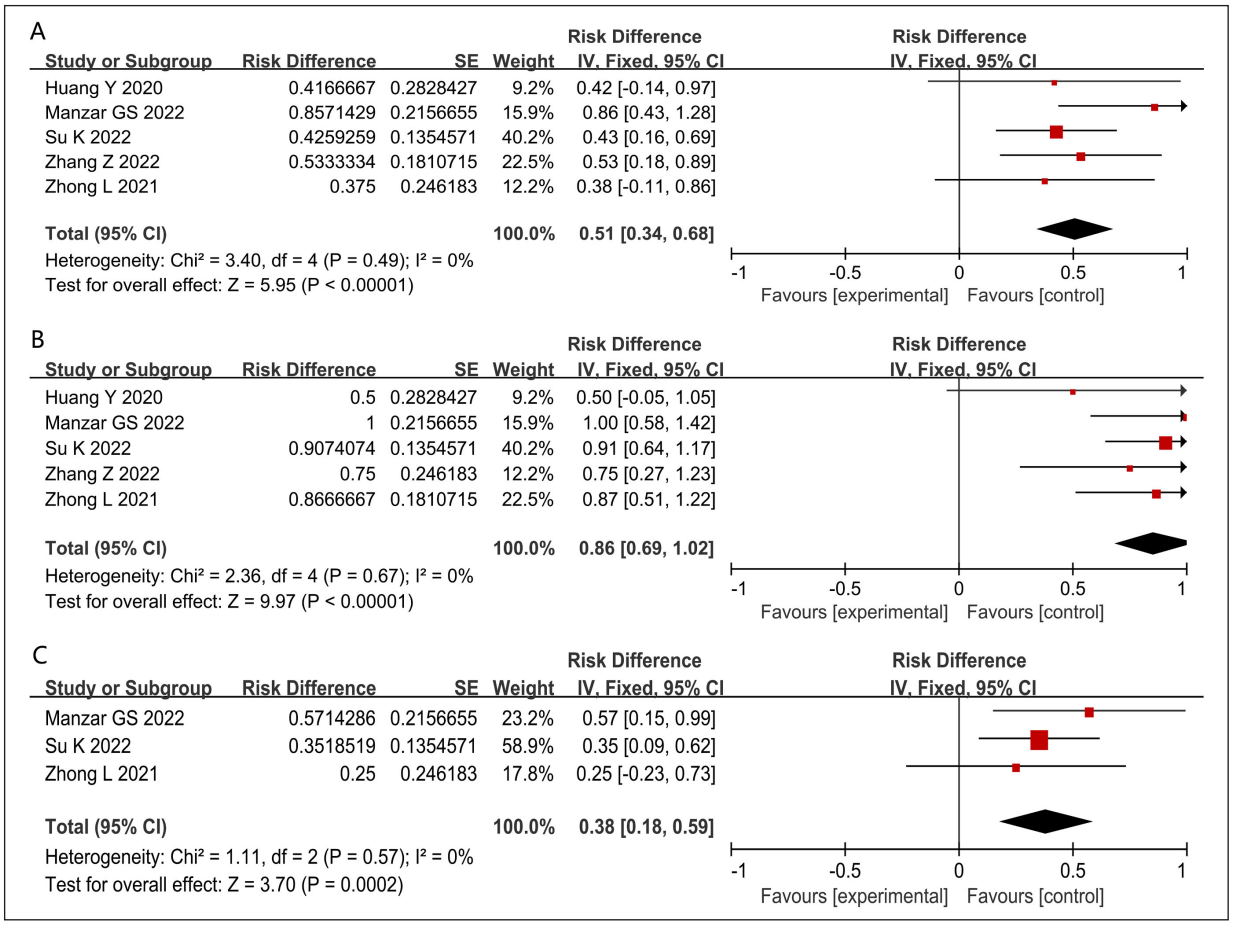

Figure 2. Forest plot of response rate for triplet regimens. (**A**), the forest plot of ORR; (**B**), the forest plot of DCR; (**C**), the forest plot of MR.

Discussion

To improve the survival benefit, the multi-approach combination therapy has become the mainstream therapeutic strategy. Several studies[7,19,20] have demonstrated that the patients achieved long-survival benefits from the combination of immune checkpoint inhibitors (ICIs) and antiangiogenic drugs, and the combination regimen was recommended as the treatment of HCC by the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Despite the dual combination therapy resulting in clearly improved patient outcomes for HCC, nearly half of patients remain unresponsive, especially those who received over two-line therapy.

All the radiotherapy, PD1/PDL1 inhibitors and antiangiogenic drugs act on tumor microenvironment, and they have synergistic effect. RT can enhance the release and presentation of tumor antigens and induce vessel normalization, drive effector T cells to infiltrate tumor tissues, and up-regulate the expression of tumor PDL1 and major histocompatibility complex 1 (MHC-1)[21]. This up-regulation can be overcome by the actions of ICIs. Antiangiogenic agents can promote transport of immune effector cells to the tumor sites and partly limit hypoxia *via* vascular re-normalization, reduce myeloid-derived suppressor cells and Tregs, and transiently increase perfusion, thus sensitizing cancer cells and enhancing the efficiency of ICIs[9,22,23]. These dynamic interactions provide a rationale for the triple combination of ICIs, RT, and anti-angiogenesis for cancer management.

In this study, we noticed that the ORR and DCR of patients treated with triple regimen were 51% and 86%, respectively. The results were satisfying in treatment of patients with HCC, and consistent with the theory that the

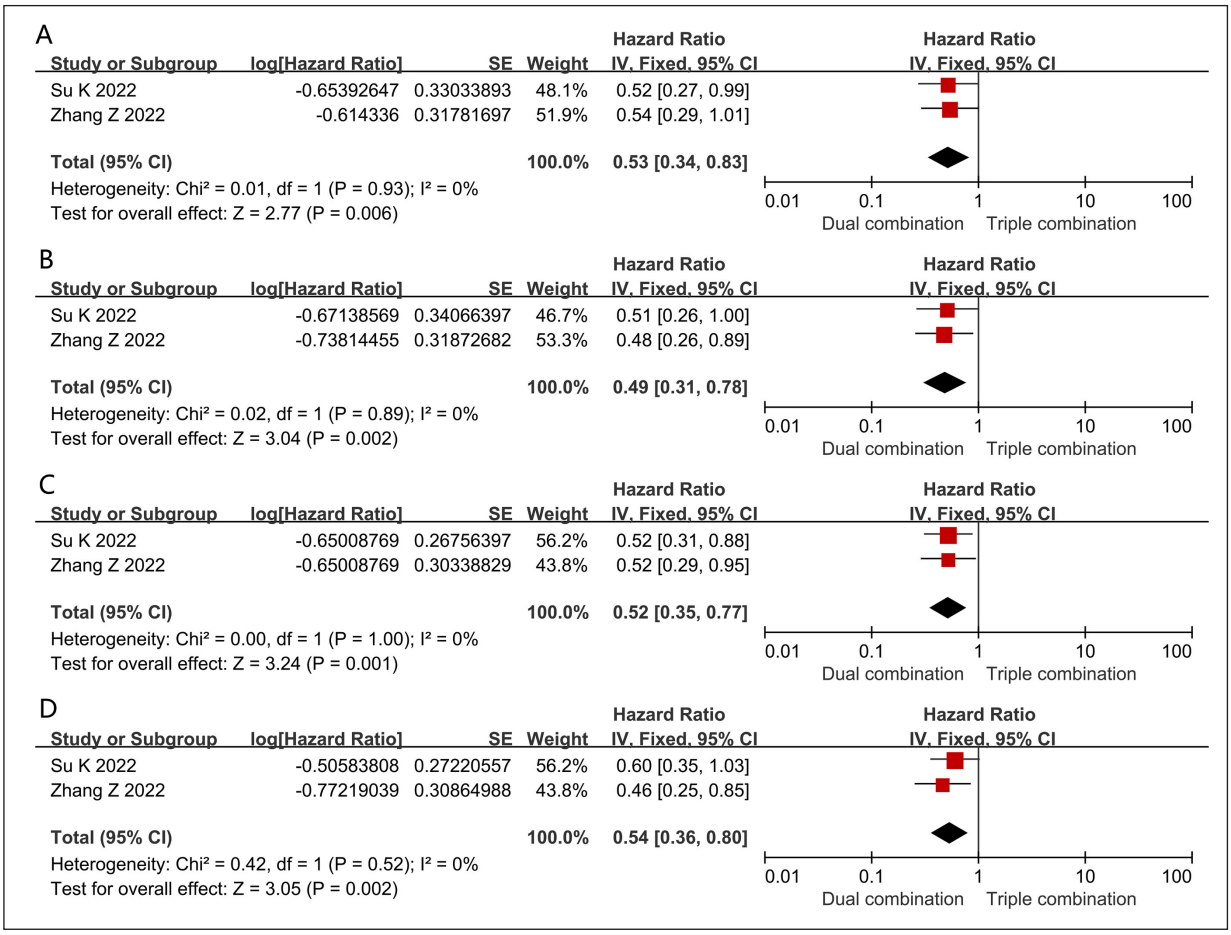

Figure 3. Forest plot of survival analysis for triplet regimens. **A**, the forest plot of OS by univariate analysis; (**B**), the forest plot of OS by multivariate analysis; (**C**), the forest plot of PFS by univariate analysis; (**D**), the forest plot of PFS by multivariate analysis.

triplet combination can improve the HCC response[24,25]. While there was a 38% mortality during the treatment of the triplet regimen, the reasons may be that the treatment strategy could not prevent the progression of HCC, besides the AEs of triplet regimen might promote the mortality of patients who were non-sensitive to treatment[26,27]. Moreover, our study pooled 6 AEs and 3-4 grade AEs, and found that the common AEs were nausea/vomiting (27%), fatigue (23%), fever (18%), skin reaction (17%), diarrhea (15%), and hypertension (5%). The results showed that nausea/vomiting and diarrhea were the most obvious symptoms, considering

Table II. Pooled effects of common AEs in patients treated with triple regimens.

Adverse event	Effect size (%)	95% CI (%)	*p*-value	Heterogeneity		Reference
				I^2(%)	*p*-value	
3-4 Grade AEs	10	-7-27	0.26	0	0.87	14-18
Fever	18	-2-38	0.08	0	0.4	14, 16, 17
Skin reaction	17	1-34	0.04	0	0.97	14-18
Diarrhea	15	7-37	0.17	0	0.95	14, 15, 17, 18
Hypertension	5	-13-24	0.57	0	1	14, 16-18
Nausea/vomiting	27	10-44	0.002	0	0.55	14-18
Fatigue	23	6-39	0.009	0	0.41	14-18

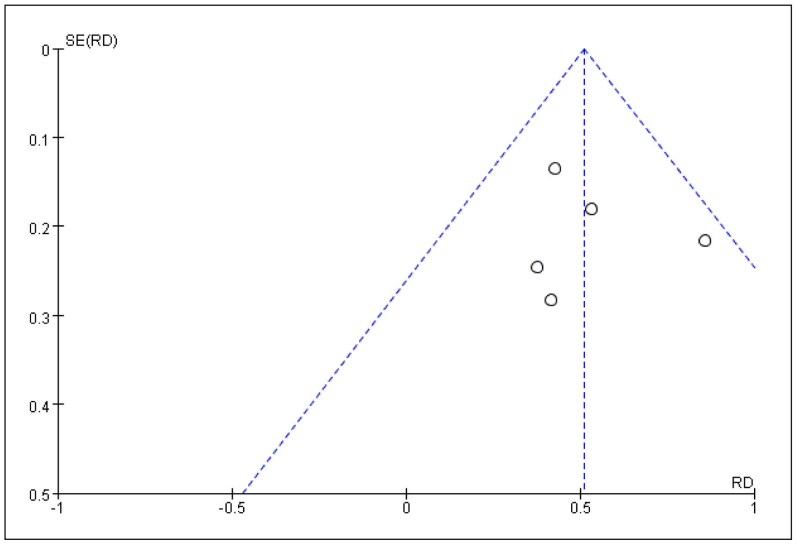

Figure 4. Funnel plot of objective response rate for triplet regimens.

the increasing AEs when adding immunotherapy to RT, as well as the enhanced RT-related gastrointestinal luminal toxicities when adding angiogenic inhibitors to RT, it is conceivable that even more pronounced AEs may be noted by adding RT to the double combination of anti-angiogenesis with ICIs[28,29]. Moreover, fatigue, skin reaction and hypertension may be mainly caused by angiogenic inhibitors[30].

Generally, meta-analysis is not performed when there are less than 3 studies, but we still pooled the OS and PFS in two trials since exploring the survival benefits of patients received the triple therapy regimen. Comparing with triple regimen, patients received single or dual-combination therapy had a shorter OS (HR=0.53, 95%: 0.34- 0.83 by univariate analysis; HR=0.49, 95%: 0.31-0.78 by multivariable analysis) and PFS (HR=0.52, 95%: 0.35-0.77 by univariate analysis; HR=0.54, 95%: 0.36-0.80 by multivariable analysis). Therefore, triplet therapeutic strategy can augment the long-survival benefits in the patients with HCC[27,31,32]. But it is necessary to further confirm those results above by more clinical trials.

Limitations

This study includes some limitations: (1) there are few relevant randomized controlled trials; (2) few studies report the survival outcomes; (3) there are too few studies to conduct subgroup analysis; (4) because of the available data in this field, we could not explore more details regarding the efficacy and safety of the triple combination treatment, such as the treatment sequences, radiotherapy method.

Conclusions

In summary, the triplet regimens based on PD1/PDL1 inhibitors, angiogenic inhibitors and radiotherapy could present excellent over response rate and survival benefits to HCC. Although the combination therapy has tolerable safety, the therapy-related gastrointestinal toxicities should be taken seriously.

Availability of Data and Materials

The original contributions presented in the study are included in the article and Supplementary Material. Further inquiries can be directed to the corresponding author.

Authors' Contribution

FX and GX designed the study. FX and JW screened the studies and extracted the data. Quality of evidence was judged by FX, JW, and JB. FX and YY analyzed and interpreted the data. FX and WJ prepared the figures and drafted the manuscript. YY and GX contributed to the review and editing. all authors approved the final version of the article, including the authorship list.

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Ethics Approval
Not applicable.

Conflict of Interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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