META-ANALYSIS

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A Network Meta-analysis of the Efficacy of Drug Therapy in First-line Treatment of Advanced Hepatocellular Carcinoma

Xinchou Wang[1,2], Gaoyao Peng[1,2], Jiangfa Li[1]

1) Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Guilin Medical University, Guilin;
2) Department of Breast Surgery, Guilin Women's and Children's Hospital, Guilin, China

Address for correspondence:
Jiangfa Li
Department of Hepatobiliary and Pancreatic Surgery, Affiliated Hospital of Guilin Medical University, No. 15, Lequn Road, Xiufen District, Guilin 541001, Guangxi, China.
247546160@qq.com

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ABSTRACT

Background & Aims: Systemic therapy is mainly recommended for advanced hepatocellular carcinoma (HCC). Considering the variety of treatments available for HCC, there is a need to understand their relative benefits and risks, especially for the newly approved combination of immune checkpoint inhibitors and vascular endothelial growth factor inhibitors represented by atezolizumab in combination with bevacizumab. A reticulated meta-analysis was used to evaluate the efficacy and safety of atezolizumab-bevacizumab combination therapy compared with other first-line systemic therapies for the treatment of patients advanced HCC.

Methods: PubMed, The Cochrane Library, Web of Science, and Embase databases were searched from the time of library construction to 01 December 2022, and the data were extracted and analyzed using Stata16.0 for Meta-analysis. The data were extracted separately, and a meta-analysis was performed using the software Stata16.0.

Results: 16 clinical studies with 8,779 subjects were identified from 13,417 records and were used to build the evidence network for all trials. TThe combination therapy of atezolizumab and bevacizumab has the advantage of prolonging the OS of patients when treating advanced HCC [HR=5.71, 95%CI (4.30, 7.12), p<0.05] Also, the combination therapy has the advantage of prolonging the patient's progression free survival [HR=1.60, 95%CI (0.89, 2.49), p<0.05].

Conclusions: Atezolizumab-bevacizumab combination therapy can improve clinical outcomes such as OS and PFS in patients with advanced HCC.

Key words: hepatocellular carcinoma – drug therapy – first-line treatment – network meta-analysis.

Abbreviations: AE: adverse event; CI: confidence interval; HCC: hepatocellular carcinoma; HR: hazard ratio; OS: overall survival; PFS: progression free survival; RCT: randomized controlled trial; ROB: risk of bias; SAE: severe adverse event; SMD: standard mean difference; TACE: transcatheter hepatic arterial chemoembolization, WMD: weighted mean difference.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a malignant tumor caused by malignant transformation of liver cells. It accounts for about 90% of primary liver cancers and is more common in men with a higher degree of malignancy [1]. Globally, HCC incidence has been significantly reduced in middle-aged adults aged 30-59 years, regardless of gender [2]. However, HCC mortality continues to rise, especially due to non-alcoholic liver disease caused by the obesity pandemic, and it is estimated that the global HCC mortality rate will increase by another 41% by 2040 [3]. Most patients have no obvious clinical symptoms in the early stage of the disease, and most of the patients have been diagnosed in the advanced stage, at which time there is no indication for surgery [4]. Middle and advanced HCC is mainly treated by transcatheter hepatic arterial chemoembolization (TACE) and tyrosine kinase inhibitor (TKI). TKI therapy and immunotherapy are used to treat HCC, while systemic therapy is recommended for advanced HCC [5]. With multiple treatments available for HCC, it is necessary to understand their relative benefits and risks. In clinical application, the number of studies on treating advanced HCC patients with atezolizumab combined with bevacizumab is still tiny, and

the efficacy of the combination is still not completely clear. In this study, a mesh meta-analysis was used to quantitatively and systematically evaluate the efficacy of the combination therapy of atezolizumab and bevacizumab in the treatment of advanced HCC compared with the currently used regimen, to provide scientific guidance for clinical drug selection, and to compare therapies approved for unresectable HCC indirectly or reported first-line treatment data.

METHODS

Literature Search

Relevant literature was searched by computer in the databases: Pubmed, The Cochrane Library, Web of Science, Embase, and the search terms mainly included Carcinoma, Hepatocellular, Sorafenib, Nivolumab, atezolizumab, Bevacizumab, lenvatinib, Linifanib, Brivanib, Sunitinib, Donafenib, Fluorouracil, Oxaliplatin, Sintilimab, TACE, Radiotherapy, Immune Checkpoint Inhibitors, Drug Targeting, randomised controlled trial, Survival, first-line, etc. The search time limit was set from the time of library construction to 1 December 2022, and the search terms are shown in Supplementary file.

Inclusion criteria were 1) advanced HCC that is not amenable to surgical treatment; 2) to include an existing first-line drug or interventional therapy control group; 3) randomized controlled trial (RCT); 4) to report data in interval or numerical form; 5) to use at least one standardized outcome indicator; 6) to allow calculation of a large effect size; 7) exclusion of other interventions that affected the outcome.

Exclusion criteria were 1) clinical trials in patients with HCC after undergoing surgical treatment; 2) the treatment used was not a first-line treatment; 3) clinical trials that did not have a control group; 4) animal experiments, case reports, reviews, meta-analyses, and studies in non-randomized groups, repetitive publications, and literature with duplicated data.

Literature Screening and Data Extraction

The studies that were included in the meta-analysis were reviewed by two independent researchers, and the relevant literature was searched in the database according to the search formula in English and Chinese respectively. All the retrieved literature was imported into the Endnote X9 literature management system. Duplicates, reviews, systematic evaluations, syntheses, animal experiments, meta-analyses, were eliminated. The two researchers initially screened the literature by reading the title and abstract and deleted the studies that did not meet the inclusion criteria. Then the carefully read the full text of the remaining literature, and further screened the literature that met the requirements according to the inclusion and exclusion criteria, of which the full text of the literature could not be obtained by contacting the authors via e-mail or obtaining the full text of the medical forum. Finally, the two people discussed the results, and the third researcher resolved the disagreement of any relevant literature to reach consensus.

Primary effect metric was overall survival (OS). The secondary effect metric were progression-free survival (PFS), time elapsed to substitute TTP as a secondary outcome in trials that did not report PFS as an endpoint, complications and adverse events (AEs). Severe adverse events (SAEs) classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4 (grade 1, mild; grade 2, moderate; grade 3, severe or medically significant; grade 4, life-threatening) were defined as the proportion of grade 3 or worse.

The literature included in this retrospective meta-analysis were all RCTs, of which 14 used the randomized table of numbers method, and 2 only mentioned random allocation without specifying the exact method. The risk of bias was assessed using the risk of bias (ROB) assessment tool, recommended by the Cochrane Collaboration for the included literature.

Statistical Analysis

The extracted data were analyzed and processed using Stata16.0 software, and the combined effect sizes of dichotomous variables were analyzed using hazard ratio (HR) and 95% confidence interval (CI), and the combined effect sizes of continuous variables were analyzed using weighted mean difference (WMD) or standard mean difference (SMD) and 95% CI. Heterogeneity analysis was performed on the statistics of the included literature, and the p-value and I^2 value of the statistics were usually used to test the heterogeneity, such as $p \geq 0.1$ or $I^2 < 50\%$, which indicated that there was less heterogeneity among the results of the studies, and the choice of a fixed effects model. On the contrary, random effects model should be selected, and further subgroup analysis or sensitivity analysis should be used to study the source of heterogeneity [6]. The mean value of each index before and after treatment of each study was recorded by Excel, and then the difference between the pre-and post-intervention measurements was used as the index to be evaluated for the integrated analysis. Forest plots were used to represent the results, and funnel plots indicated the presence or absence of publication bias; if the funnel plots were symmetrical on both sides, it indicated less publication bias, and vice versa, more bias.

RESULTS

By searching in various databases according to the search formula respectively, 13,417 articles were initially obtained, and reviews, basic type of studies, irrelevant articles, duplicate published literature, and literature that did not conform to the present analysis were deleted, 495 articles remained, and the full text was read through to exclude literature that could not be accessed to the data, data errors, and subgroups that did not conform to the presentanalysis. Finally, 16 English-language articles were included, including 16 clinical trials involving 8,779 subjects, which constituted a network of evidence for all trials, and the process was as follows in Fig. 1. The k (kappa) value of agreement between the two reviewers was 0.997.

After literature inclusion was completed, the 2 researchers then independently extracted and organized baseline data on patients within the included literature: 1) sample size; 2) age; 3) gender; 4) tumor score as rated by the Eastern Cooperative Oncology Group (ECOG); 5) whether the tumor had metastasis or vascular infiltration; 6) intervention and control groups included (Table I). The Network map of all comparisons in this study was shown in the Supplementary file (Fig. S1).

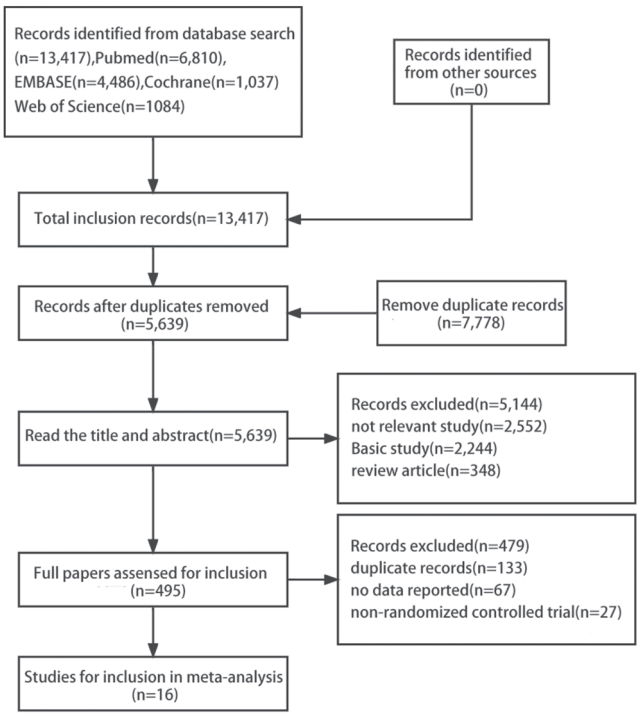


Fig. 1. The process of study selection.

The evaluation of the study quality included is shown in Fig. 2; two researchers used the ROB tool.

Indirect survival comparisons of atezolizumab and bevacizumab combination therapy versus TACE could not be done because OS was not reported in the 2 clinical trials involving TACE, and OS was not reported in the ORIENT-32 trial, which involved sintilimab and bevacizumab combination therapy. Therefore, in a meta-analysis of OS, a total of 13 clinical trials were included comparing atezolizumab and bevacizumab combination therapy with lenvatinib, sorafenib, nivolumab, linifanib, SIRT, HAIO+FO, sunitinib, brivinib, donafinib, and placebo or the primary measure of treatment. As p>0.1 and I^2<50%, indicated less heterogeneity between the results of the studies, the fixed-effect model was used; the results were HR=5.71, 95%CI: 4.30, 7.12, p<0.05, and the difference was statistically significant, indicating that the combination therapy of atezolizumab and bevacizumab has the advantage of prolonging the OS of patients when treating advanced HCC. The results are shown in Fig. 3.

Subsequently, to clarify the ranking of each treatment's recommendation against the patient's OS, we assessed it using the surface under the cumulative ranking curve (SUCRA), which is a metric that summarizes the cumulative ranking probability and is calculated by the formula

$$\text{SUCRAj} = \frac{\sum_{b=1}^{a-1} cumj,b}{a-1}$$

where j is the intervention, b is the ranking, a is the total number of interventions, and cumj,b is the cumulative probability of intervention j in ranking b [24]. Based on the size of the SUCRA value the ranking of the interventions as superior or inferior can be performed [25]. The calculated SUCRA value for the atezolizumab and bevacizumab combination therapy group was 93.8% (Fig. 4).

Indirect survival comparisons between atezolizumab and bevacizumab combination therapy and theirs could not be done because some of the trials did not report on the PFS status of the patients. In a meta-analysis of progression-free survival PFS, a total of 10 clinical trials included atezolizumab and bevacizumab therapy with lenvatinib, sorafenib, nivolumab, SIRT, linifanib, sunitinib, donafinib, sindilimab plus bevacizumab and placebo or primary treatment measures were compared. As p>0.1, I^2<50%, indicated less heterogeneity between the results of the studies, a fixed-effects model was used, and the result was HR=1.60, 95%CI: 0.89-2.49, p<0.05, a statistically significant difference, suggesting that the combination therapy of atezolizumab and bevacizumab has the advantage of prolonging the patient's PFS (Fig. 5). To clarify the recommended ranking of each treatment against the patient's PFS, we calculated a SUCRA value of 84.3% for the atezolizumab and bevacizumab combination therapy group (Fig. 6).

Table I. Basic features of the included literature

Study, reference	Patients		Age		Gender, male, n (%)		ECOG 0/1–2, n (%)		MVI positive or EHS positive or both, n (%)		Treatments	
	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator
IMbrave 150 [7, 8]	336	165	64	66	277 (82)	137 (83)	209 (62)	103 (62)	258 (77)	120 (73)	Ate + Bev#	Sorafenib
Kim YJ 2022 [9]	44	83	58	59	40 (90.9)	144 (88.9)	23 (71.9)	99 (61.1)	31 (70.5)	111 (68.5)	Lenvatinib	Sorafenib
SHARP [10]	299	303	64.9	66.3	140 (87)	264 (87)	161 (54)	164 (54)	159 (53)	150 (50)	Sorafenib	placebo
REFLECT [11]	478	476	63	62	314 (85)	317 (85)	304 (64)	301 (63)	291 (61)	295 (62)	Lenvatinib	Sorafenib
CheckMate 459 [12]	371	371	65	65	314 (85)	317 (85)	271 (73)	261 (70)	222 (60)	207 (56)	Nivolumab	Sorafenib
Asia-Pacific [13]	150	76	51	52	66 (86.8)	127 (84.7)	38 (25.3)	21 (27.6)	103 (68.7)	52 (68.4)	Sorafenib	placebo
NCT00699374 [14]	530	544	59	59	436 (82.3)	459 (84.4)	278 (52.5)	288 (52.9)	418 (78.9)	415 (76.3)	Sunitinib	Sorafenib
NCT01009593 [15]	521	514	59	60	444 (86.4)	436 (83.7)	323 (62.8)	344 (66.2)	307(59.7)	296 (56.8)	Linifanib	Sorafenib

ECOG: Eastern Cooperative Oncology Group, rated by the Eastern Oncology Collaborative Group; #Ate+Bev: Atezolizumab + Bevacizumab; HAIO+FO: oxaliplatin - fluorouracil arterial chemotherapy; SIN+ Bev: Sintilimab + Bevacizumab; SIRT: Selective in vivo radiation therapy; TACE: Hepatic arterial chemoembolization; NA: not reported; EHS: extrahepatic spread; MVI:macrovascular invasion

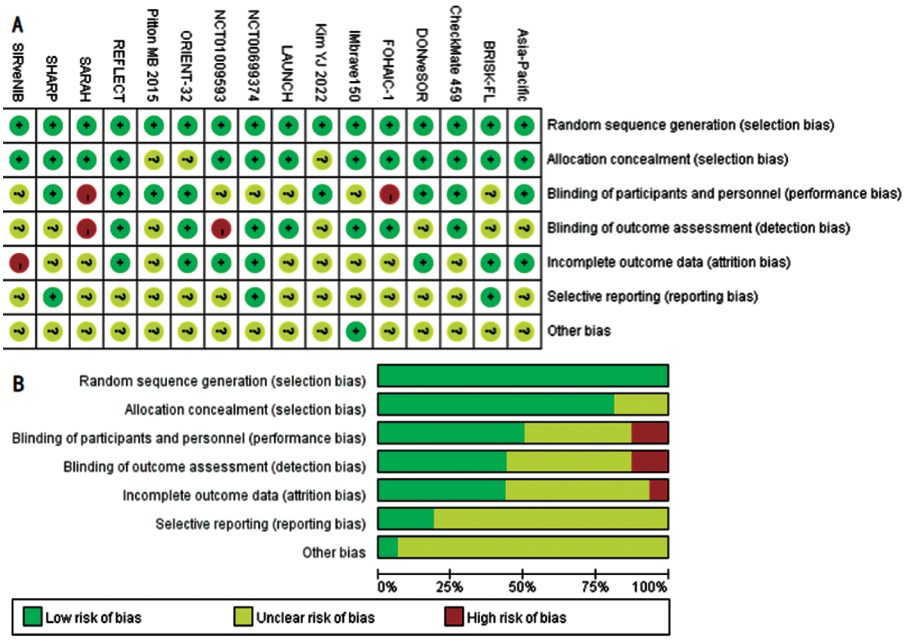


Fig. 2. Methodological quality of the studies included (QUADAS-2 results). A: bias risk assessment diagram of the included literature; B: risk contribution of bias in the included literature.

The available safety information for test CheckMate 459 was insufficient for comparison (only grade 3-4 treatment-related AE and AEs leading to treatment interruption were reported). Rates of any adverse event were similar for atezolizumab-bevacizumab, lenvatinib, and sorafenib; in IMbrave150 and REFLECT studies, patients receiving atezolizumab and bevacizumab or lenvatinib experienced more SAEs of any grade than patients receiving sorafenib. Compared with sorafenib, atezolizumab-bevacizumab and lenvatinib reported more AEs leading to treatment modification. Some SIRT or TACE treatment groups reported fewer adverse events than systemic therapy. The differences between the SIRT and sorafenib studies were inconsistent in all-grade serious adverse events. SIRTACE reported fewer SAEs in patients randomized to TACE than SIRT. In trials comparing SIRT with sorafenib, patients randomized to SIRT were more likely to have a SAE than those randomized to sorafenib. Patients assigned to sorafenib had fewer AEs which resulted in treatment interruption. Safety outcomes were not reported by the subgroup, and the most common grade 3-4 AEs was elevated aspartate aminotransferase (Table II).

The funnel plot and Egger's test results were used to determine the publication bias of the literature, and the results of the funnel plot and Egger's test are shown in Fig 7. The symmetry of the funnel plot of OS, PFS, complications and AEs was fair, and there was no evidence of publication bias because the difference was not statistically significant at p>0.05 by Egger's test.

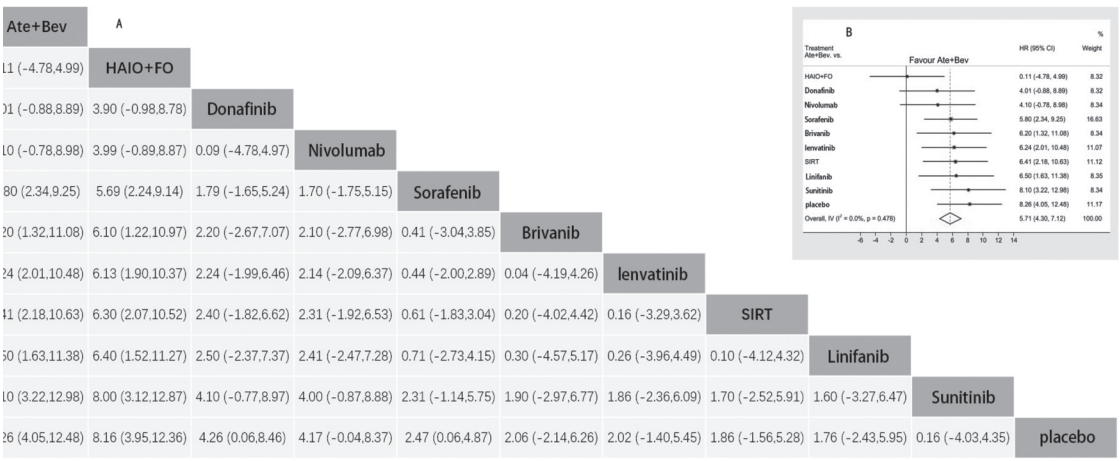


Fig. 3.Overall survival comparison. A:This is a league table showing the comparative efficacies of indirect evidence across all trial evidence networks. The comparison results were expressed using [HR (95%CI)]. An HR value greater than 1 indicated that the drug on the right of the two drugs was relatively less effective. B: Forest map of fixed effects network meta-analysis model for overall survival. Ate+Bev: atezolizumab + bevacizumab; HAIO+FO: oxaliplatin - fluorouracil arterial chemotherapy; SIRT: Selective in vivo radiation therapy

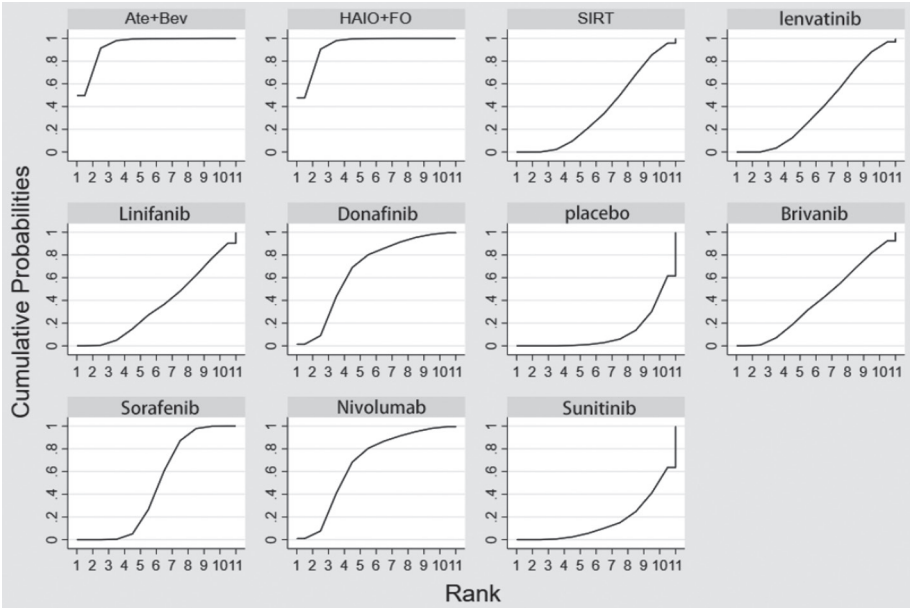


Fig. 4. SUCRA of overall survival for different treatment regimens SUCRA, which was a metric that summarizes the cumulative ranking probability, had a value between 0 and 1 (0 ≤ SUCRA ≤ 1). A SUCRA of 1 indicated that the intervention was absolutely effective, while a SUCRA of 0 indicated that the intervention was absolutely ineffective. Interventions could be ranked according to the size of SUCRA values. After calculation, the SUCRA value of Ate+Bev group was 93.8%, that of HAIO+FO group was 93.6%, that of Donafenib was 67.4%, that of opdivo group was 47.8%, that of sorafenib was 47.8%, and that of Brinib was 39.9%. The SUCRA value of lenvatinib was 39.8%, that of Linivanib was 36.2%, that of Sunitinib was 16.3% and that of placebo was 11.6%. Note: Ate+Bev: Atezolizumab + Bevacizumab; HAIO+FO: oxaliplatin - fluorouracil arterial chemotherapy; SIRT: Selective *in vivo* radiation therapy; SUCRA:The surface under the cumulative ranking curve.

DISCUSSION

A total of 16 clinical trials were included in this retrospective meta-analysis to evaluate atezolizumab in combination with bevacizumab in treating patients with advanced HCC from an evidence-based medical perspective. Atezolizumab in combination with bevacizumab had the highest SUCRA score of the OS superiority probability ranking curve compared with multiple therapies. Atezolizumab in combination with bevacizumab had the second highest SUCRA score after lenvatinib of the PFS superiority probability ranking curve compared with multiple treatments. This article analyzed the occurrence of SAEs; there were differences in reporting SAEs across groups, but the overall disparity was not significant; the spectrum, incidence, and severity of AEs observed are consistent with the known safety profile of the single-agent medication and the underlying disease for atezolizumab and bevacizumab combination. Approximately 15% of patients in the atezolizumab and bevacizumab group discontinued treatment due to AEs, with gastrointestinal bleeding being the most common reason for discontinuation, which showed consistency with common comorbid symptoms in patients with HCC and underlying cirrhosis. Therefore, it is important to assess patients for the presence of esophageal and gastric varices and intervene as appropriate before administering combination therapy.

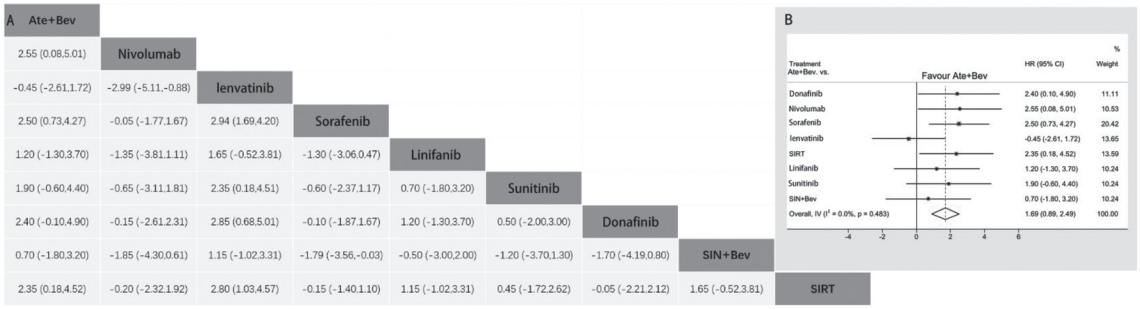


Fig. 5. Progression-free survival comparison. A: This is a league table showing the comparative efficacies of indirect evidence across all trial evidence networks. The comparison results were expressed using [HR (95%CI)]. An HR value greater than 1 indicated that the drug on the right of the two drugs was relatively less effective. B: Forest map of the progression-free survival fixed-effect network meta-analysis model. Note: Ate+Bev: Atezolizumab + Bevacizumab; SIN+Bev: Sintilimab + Bevacizumab; SIRT: Selective in vivo radiation therap.

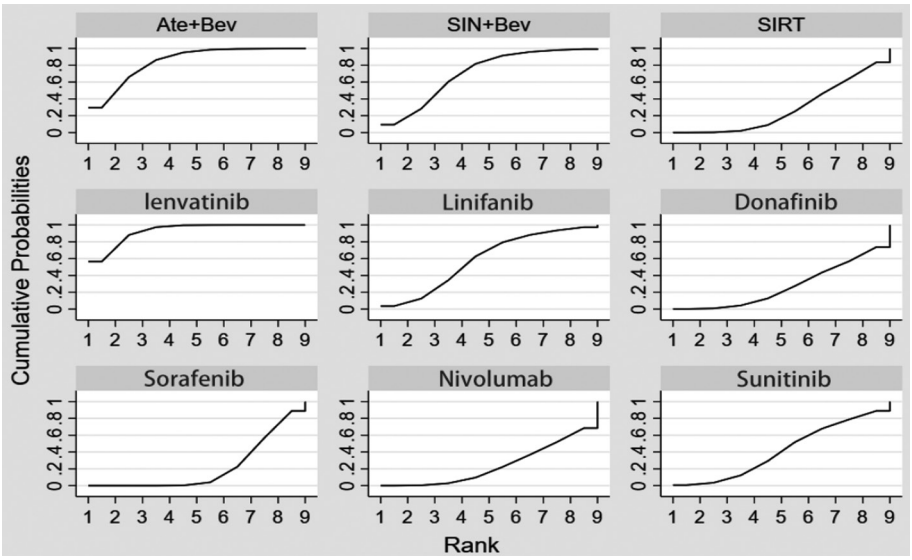
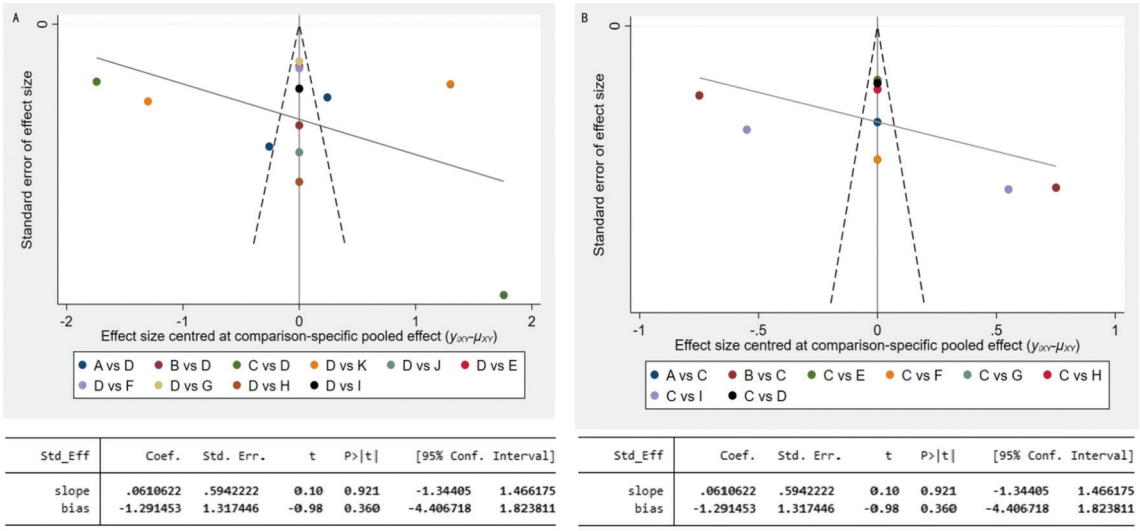


Fig. 6. SUCRA of progression-free survival with different treatment regimens SUCRA, which was a metric that summarizes the cumulative ranking probability, had a value between 0 and 1 (0 ≤ SUCRA ≤ 1). A SUCRA of 1 indicated that the intervention was absolutely effective, while a SUCRA of 0 indicated that the intervention was absolutely ineffective. Interventions could be ranked according to the size of SUCRA values. After calculation,Renvatinib SUCRA value was 92.7%, SUCRA value of Ate+Bev group was 84.3%, SIN+ Bev group SUCRA value was 70.6%. The SUCRA value of Linivanib was 59.0%, that of Sunitinib was 41.6%, and that of SIRT group was 28.7%%. The opdivo SUCRA value was 24.0%, Donafenib SUCRA value was 27.5%, sorafenib SUCRA value was 21.6%. Note: Ate+Bev: Atezolizumab + Bevacizumab; SIN+ Bev: Sintilimab + Bevacizumab; SIRT: Selective i*n vivo* radiation therap; SUCRA:The surface under the cumulative ranking curve.

Table II. Occurrence of adverse events

Study	Treatment	Number of patients	Any AEs, %	Serious AEs, %	Severe AEs, %	AEs leading to treatment interruptions, %	AEs Leading to dose reduction, %
IMbrave150	Ate+Bev	329	98.2	38.0	61.1	15.5	35.0
	Sorafenib	156	98.7	30.8	60.9	10.3	32.7
DONveSOR	Donafinib	333	100	17	57	30	10
	Sorafenib	332	99	20	67	42	13
CheckMate 459	Nivolumab	367	71	7	23	NA	NA
	Sorafenib	363	94	8	50	NA	NA
NCT00699374	Sunitinib	526	97	NA	82.1	30.0	76.6
	Sorafenib	542	98	NA	74.2	35.1	58.7
NCT01009593	Linifanib	510	99.6	52.4	85.3	45.3	36.3
	Sorafenib	519	98.5	38.5	75	31.2	25.4
BRISK-FL	Brivanib	575	98	NA	67	49	33
	Sorafenib	575	99	NA	65	50	43
REFLECT	Lenvatinib	476	98.7	43.1	75.0	13.2	39.9
	Sorafenib	475	99.4	30.3	66.5	9.1	32.2
Asia-Pacific	Sorafenib	149	98.0	47.7	NA	19.5	NA
	Placebo	75	94.7	45.3	NA	13.3	NA
Llovet et al.	Sorafenib	297	98.0	51.5	NA	29.0	44.1
SHARP	Sorafenib	216	NA	81.5	NA	NA	NA
	Placebo	302	96.0	54.3	NA	29.8	30.1
IRveNIB	SIRT	130	60.0	20.8	27.7	2.3	39.9
	Sorafenib	162	84.6	35.2	50.6	9.9	32.2
SARAH	SIRT	226	NA	77.0	NA	NA	NA
SIRTACE	SIRT	13	92.3	53.8	NA	NA	NA
	TACE	15	66.7	33.3	NA	NA	NA

NA: not applicable; AEs: adverse events; SIRT: selective internal radiation therapy;TACE: transhepatic arterial chem otherapy and embolization.



Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0610622	.5942222	0.10	0.921	-1.34405	1.466175
bias	-1.291453	1.317446	-0.98	0.360	-4.406718	1.823811

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0610622	.5942222	0.10	0.921	-1.34405	1.466175
bias	-1.291453	1.317446	-0.98	0.360	-4.406718	1.823811

Fig. 7. Funnel plot and Egger test. A: Funnel plot and Egger test of the combined treatment of Atezolizumab plus bevacizumab for OS; B: Funnel plot and Egger test of Atezolizumab plus bevacizumab in combination treatment of PFS. Note: A: Nivolumab; B: Lunvatinib; C: Sorafenib; D: Linifanib; E: Sunitinib; F: Ate+ Bev; G: Donafenib; H: SIN+ Bev; I: SIRT

Otherwise, the efficacy of the treatment may be compromised or even the patient's life endangered due to drug-induced bleeding. Patients with a high risk of Child-Pugh class B-C liver function and other bleeding risks should be evaluated even more carefully before choosing combination therapy, and alternative therapies may also be considered. Overall, compared with the currently available first-line treatment options, atezolizumab and bevacizumab combination therapy has better results in improving patients' OS and PFS and provides an excellent first-line systemic treatment option for the majority of patients with metastatic and locally advanced HCC without a significant increase in the incidence of AEs.

In our meta-analysis, atezolizumab plus bevacizumab combination therapy was found to be first in OS ranking when used in patients with locally advanced or metastatic unresectable HCC, which is consistent with the results of two previous meta-analyses [25, 26]. Differently, the results of the network meta-analysis presented at the ASCO Gastrointestinal Symposium 2021 were that the combination of atezolizumab plus bevacizumab was ranked first in PFS and lenvatinib was ranked first in ORR [26]. In contrast, in our study, lenvatinib was ranked first in terms of PFS, and the combination of atezolizumab plus bevacizumab was ranked second in terms of PFS, which may be due to the inclusion of two studies involving lenvatinib in our meta-analysis [9, 11].

There are also deficiencies in this study. Firstly, the number of literature studies included in this paper is limited, and there is some heterogeneity in the quality of the studies included in the analysis; for example, the analysis included large phase III clinical trials, such as REFLECT and Checkmate 459, as well as smaller phase II clinical studies. Therefore, larger samples and large-scale clinical studies are needed to avoid publication bias. Secondly, for the reporting of OS, PFS, and complications, there were differences among clinical trials and incomplete reporting, so there may be bias in conducting the analysis. The duration of follow-up influences third, binary outcomes such as adverse events, and more patients may experience adverse events when longer time frames are used. The effect on discontinuation is difficult to assess because locoregional therapy is usually given once. The availability and categorization of trials and differences in treatment exposure and follow-up time limit descriptive safety assessments. Therefore, more RCTs with strictly regulated uniform setting criteria are required for further validation to provide more reliable and accurate evidence in evidence-based medicine.

CONCLUSIONS

This study concludes that atezolizumab and bevacizumab combination therapy can improve clinical outcomes such as OS and PFS in patients with advanced HCC.

Conflicts of interest: None to declare.

Authors' contributions: XC W, GY P and JF L conceived and designed. XC W and GY P analyzed the data. XC W and GY P wrote the manuscript. JFL conceptualized and developed an outline for the manuscript and revised the manuscript. All authors read and approved the final manuscript.

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