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Review Article

Efficacy and safety of atezolizumab combined with bevacizumab, arterial chemoembolization, and hepatic artery infusion chemotherapy for advanced hepatocellular carcinoma: a meta-analysis

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Abstract: Objective: Although the combination of atezolizumab and bevacizumab (A+B) shows promise for advanced hepatocellular carcinoma (HCC), its response rate is still inadequate. Previous studies indicate that the integration of FOLFOX-based hepatic arterial infusion chemotherapy (HAIC) with transarterial chemoembolization (TACE) is advantageous for the management of HCC. This meta-analysis aims to assess the safety and efficacy of the A+B+TACE or HAIC therapy protocol in patients with advanced HCC. Method: We collected pertinent studies from databases such as PubMed, Cochrane Library, Web of Science, and Embase, all published prior to August 1, 2024. We used Stata MP 14.0 software for data analysis, incorporating data extraction and quality assessment procedures. Results: Data synthesis employed a fixed-effects model in certain contexts and a random-effects model where significant variability was present. A total of 405 patients were involved over ten trials. The overall objective response rate (ORR) was 57.2% (95% CI, 46.9-67.6%), and the disease control rate (DCR) was 85.9% (95% CI, 82.0-89.7%), as determined by the modified response assessment criteria in solid tumors (mRECIST). The rates for complete response (CR) and partial response (PR) were 10.8% (95% CI, 5.0-16.6%) and 45.5% (95% CI, 38.0-53.0%), respectively. The median progression-free survival (mPFS) was 10.9 months, with a 95% confidence interval (CI) of 8.0 to 13.8. 91.0% (95% CI: 84.9-97.1%) of patients experienced adverse events (AEs) of any severity during therapy, with 24.8% (95% CI: 8.8-40.9%) reporting AEs of grade 3 or higher. Conclusion: The A+B+TACE-HAIC therapy demonstrates promising efficacy and tolerance for the management of advanced HCC.

Keywords: Immune checkpoint inhibitor, tyrosine hormone inhibitor, hepatocellular carcinoma, systemic therapy

Introduction

In hepatocellular carcinoma (HCC), a minimal fraction of patients (under 30%) are eligible for therapeutic interventions, including surgical resection, local interventional therapy, or transplantation [1]. Unfortunately, the majority of HCC cases have a poor prognosis, mostly because of the tumors' limited response to chemotherapy and the existence of underlying cirrhosis [2, 3]. Consequently, most patients are ineligible for surgical resection.

Recent pivotal data from the IMbrave150 research have demonstrated the superiority of the immune checkpoint inhibitors (ICIs) combination of atezolizumab and bevacizumab (A+B) in the first-line treatment of unresectable locally advanced or metastatic HCC. Several studies conducted between 2022 and 2023, including those by Kim et al., Su et al., Casadei et al., and Rimini et al., also reported similar results [4-6]. Although immunotherapy has revolutionized cancer treatment, the combination of ICIs with targeted therapies has shown a moderate objective response rate (ORR) of 30% and a median progression-free survival (mPFS) of 6.9 months. Despite these combinations surpassing sorafenib, they remain inadequate in fulfilling all clinical requirements. Currently, the com-

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bination therapy of A+B with transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) (A+B+TACE-HAIC) represents a significant advancement in the treatment of advanced HCC, showing substantial improvements in both overall survival (OS) and progression-free survival (PFS) among patients [7].

In the treatment of locally advanced HCC unsuitable for surgical resection, HAIC represents a crucial therapeutic alternative [8]. Sung et al. demonstrated that it can prolong patient survival [9]. Ueshima et al. found that HAIC has a better overall survival rate than sorafenib in cases of large vessel invasion without extrahepatic metastasis [10]. Hatooka et al. indicated that HAIC may be more effective than sorafenib as a first-line treatment [11]. Given the limited literature summarizing the treatment of advanced HCC with A+B combined with TACE-HAIC, this study conducted a meta-analysis to thoroughly evaluate its efficacy and safety in this patient population.

Methods

Data sources and search strategy

PRISMA was followed, and PROSPERO was used to register the study (CRD42024583159). We performed a network meta-analysis to evaluate the efficacy of first-line systemic treatments for advanced hepatocellular carcinoma. The study includes the following features: (1) Assessment of both the effectiveness and safety profiles of A+B+TACE-HAIC, as well as its potential synergy when combined with ICIs; (2) Evaluation of the OS or PFS as the primary endpoint; (3) Inclusion of individual or combined local treatments and not allowing for systemic treatment.

We conducted literature searches across several esteemed databases, including PubMed, Cochrane Library, Web of Science, and Embase to ensure a thorough and uniform method in assessing the efficacy and safety of treatments for advanced HCC. These searches were extensive, ranging from the foundation of these databases up until August 1, 2024. The methodology used conforms to established reporting methods, assessments, and meta-analysis techniques, with the objective of delivering a thorough and evidence-based evaluation of the existing knowledge concerning therapy alternatives for this complex ailment. This search keyword or medical topic keyword (MESH) term is as follows: ("atezolizumab" OR "anti-PDL1" OR "MPDL3280A" OR "Tecentriq" OR "RG7446") AND ("bevacizumab" OR "Avastin" OR "Mvasi" OR "Bevacizumab awwb") AND ("Chemotherapy") AND ("Liver cancer" OR "Hepatocellular carcinoma" OR "Hepatoma" OR "HCC"). The identification of other potentially qualified personnel for research, references in research, or related reviews was manually reviewed. Articles not written in English are not included in literary searches.

Inclusion and exclusion criteria

The inclusion criteria for this study were: (1) Participants: All patients diagnosed with HCC; (2) Intervention measures: Patients received treatment with A+B+TACE-HAIC; (3) In the literature, at least one clinical tumor outcome must have been reported, such as the ORR, disease control rate (DCR), complete response (CR), partial response (PR), mPFS, or adverse events (AEs); (4) Modified Response Evaluation Criteria in Solid Tumors (mRECIST) must have been used to assess tumor response, while the Common Terminology Criteria for Adverse Events (CTCAE) must be used to assess toxic effects; (5) Our research included exclusively English-language prospective clinical and retrospective studies, spanning a diverse range of designs, including cohort studies, single-arm studies and randomized controlled trials. The exclusion criteria were: (1) Pathological studies, animal experiments, case reports, reviews, letters, and conference abstracts; (2) Incomplete or other language literature; (3) Absence of original literature. The eligibility of each article was independently assessed by two researchers, adhering to predefined inclusion and exclusion criteria. In cases where there were discrepancies, a third researcher was consulted to resolve any inconsistencies and ensure a consistent approach to article selection.

Data extraction and quality assessment

Data were extracted independently from selected articles by X. Y., P. G. and R. C. joined the discussion to resolve any ambiguities that arose during the process. The extracted information included the first author's name, the year of publication, the research type, the coun-

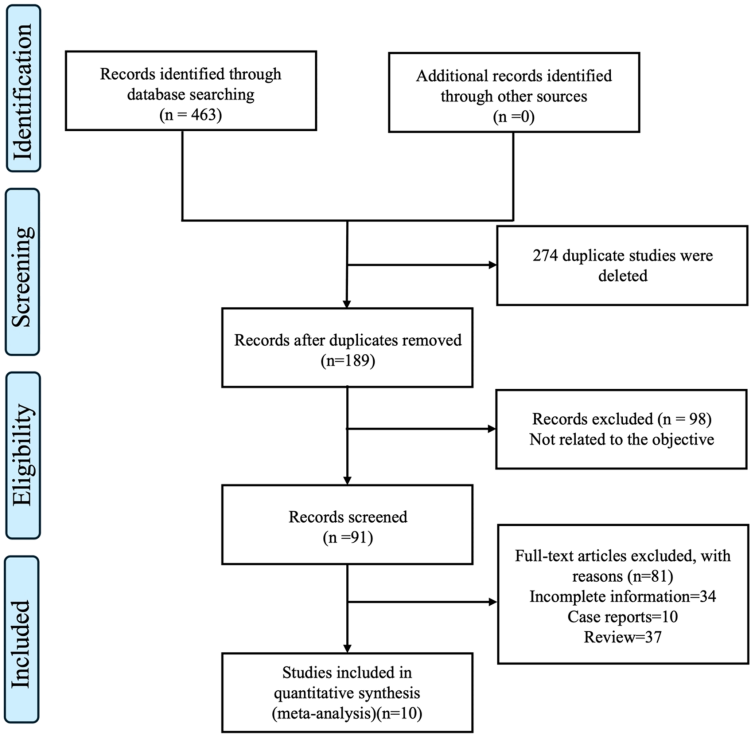

Figure 1. Flow chart of the study selection process.

try of origin, the sample size, the age of participants, the intervention method, and the endpoint event. Besides the clinical and safety outcomes, mPFS, ORR, DCR, CR, PR AEs, and grade 3 AEs were also recorded. Retrospective single-group studies were assessed using the Joanna Briggs Institute (JBI) Case Series Critical Evaluation Checklist.

Statistical analysis

Statistical analyses were conducted using Stata MP 14.0 software. This meta-analysis primarily aimed to assess PFS, with the impact magnitude quantified by the hazard ratio (HR) and its corresponding 95% confidence interval. A 95% confidence interval was also used for binary variables. Heterogeneity was assessed by the Cochran's Q test and the I^2 index, with a *p*-value below 0.1 signifying heterogeneity. In cases of significant heterogeneity, a random-effects model was used for data integration. Conversely, when heterogeneity was minimal, a fixed-effects model was employed. The probable existence of publication bias was evaluated using Begg's and Egger's tests. Statistical significance was established as a *p*-value below 0.05.

Ethical approval and consent to participate

This meta-analysis adhered to the Helsinki Declaration and was executed with informed consent from all participants in the included trials. Additionally, the research obtained permission from the relevant institutional ethics committees supervising those studies. This meta-analysis of existing published data did not necessitate extra informed consent.

Results

Bibliography retrieval

An initial search encompassing four databases - PubMed (87 studies), Embase (124 studies), Cochrane Library (19 studies), and Web of Science (233 studies) - identified a total of 189 relevant and published studies for further consideration. After meticulous screening and removal of duplicates, 10 studies were selected for inclusion, which collectively encompassed a total of 405 patients [12-17]. The detailed research screening approach used in our study is illustrated in **Figure 1**. Furthermore, **Tables 1** and **2** delineate the principal characteristics and quality evaluation results of the 10 incorporated studies, respectively.

Numbers Q1-Q10 in heading signified

Q1, were there clear criteria for inclusion in the case series? Q2, was the condition measured in a standard, reliable way for all participants included in the case series? Q3, were valid methods used for identification of the condition for all participants included in the case series? Q4, did the case series have consecutive inclusion of participants? Q5, did the case series have complete inclusion of participants? Q6, was there clear reporting of the demographics of the participants in the study? Q7, was there clear reporting of clinical information of the participants? Q8, were the outcomes or follow up results of cases clearly reported? Q9, was there clear reporting of the presenting site(s)/clinic(s)

Table 1. Baseline clinical characteristics of the included studies

Study	Country	Design	Period	Sample size (male/female)	Intervention	End points
Zhenkun Huang 2024	China	Retrospective	From March 2021 to July 2023	82 (78/4)	A 1200 mg + B 15 mg/kg plus transarterial chemoembolization	Effectiveness and Safety
Hongjie Cai 2024	China	Retrospective	From September 2019 to September 2022	30 (28/2)	A 1200 mg + B 15 mg/kg plus transarterial chemoembolization	Effectiveness and Safety
Yujing Xin 2022	China	Retrospective	From October 2020 to September 2021	52 (46/6)	A 1200 mg + B 15 mg/kg plus transarterial chemoembolization	Effectiveness and Safety
Hiroyuki Suzuki 2024	Japan	Retrospective	From November 2020 to September 2022	27 (24/3)	A 1200 mg + B 15 mg/kg plus transarterial chemoembolization	Effectiveness and Safety
Cao Fei 2023	China	Retrospective	From April 2021 to October 2022	62 (52/10)	A 1200 mg + B 15 mg/kg plus transarterial chemoembolization	Effectiveness and Safety
Yitao Zheng 2024	China	Retrospective	From June 2021 to March 2022	46 (8/38)	A 1200 mg + B 15 mg/kg plus transarterial chemoembolization	Effectiveness and Safety
Jae-sung Yoo 2024	Japan	Retrospective	From January 2022 to September 2023	16 (14/2)	A 1200 mg + B 15 mg/kg plus transarterial chemoembolization	Effectiveness and Safety
Qiu J. 2023	China	Retrospective	From March 2022 to March 2022	35	A 1200 mg + B 15 mg/kg plus transarterial chemoembolization	Effectiveness
Chenghao Zhao 2023	China	Retrospective	From October 2020 to October 2022	34 (29/5)	A 1200 mg + B 15 mg/kg plus transarterial chemoembolization	Effectiveness and Safety
Kang Wang 2023	China	Retrospective	From March 2021 to September 2021	21 (19/2)	A 1200 mg + B 15 mg/kg plus transarterial chemoembolization	Effectiveness and Safety

A, Atezolizumab; B, Bevacizumab.

Table 2. Quality assessment of the studies included in the meta-analysis

JBI Critical Appraisal Checklist for Case Series for included retrospective studies											
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	TOTAL
Hongjie Cai 2024	2	0	2	2	2	0	2	2	2	2	16
Hiroyuki Suzuki 2024	2	0	2	2	2	0	2	2	2	2	16
Zhenkun Huang 2024	2	0	2	2	2	0	2	2	2	2	16
Yujing Xin 2022	2	0	2	2	2	0	2	2	2	2	16
Cao Fei 2023	2	0	2	2	2	0	2	2	2	2	16
Yitao Zheng 2024	2	0	2	2	2	0	2	2	2	2	16
Jae-sung Yoo 2024	2	0	2	2	2	0	2	2	2	2	16
Qiu J. 2023	2	0	2	2	2	0	2	2	2	2	16
Chenghao Zhao 2023	2	0	2	2	2	0	2	2	2	2	16
Kang Wang 2023	2	0	2	2	2	0	2	2	2	2	16

JBI, Joanna Briggs Institute.

demographic information? Q10, was statistical analysis appropriate?

Tumor response

10 studies reported the efficacy of A+B+TACE-HAIC in the treatment of advanced HCC [12-21]. The ORR and DCR of A+B+TACE-HAIC treatment were evaluated using the mRECIST, with a summary ORR rate of 57.2% (95% CI, 46.9-67.6%, I^2 = 76.8%, P = 0.00, **Figure 2A**) and a summary DCR rate of 85.9% (95% CI, 82.0-89.7%, I^2 = 32.7%, P = 0.157, **Figure 2B**). The CR and PR rates were evaluated using mRECIST, with CR and PR rates of 10.8% (95% CI, 5.0-16.6%, I^2 = 65.6%, P = 0.003, **Figure 2C**) and 45.5%, respectively (95% CI, 38.0-53.0%, I^2 = 53.5%, P = 0.022, **Figure 2D**).

Survival

6 studies reported complete mPFS data, with a total mPFS of 10.9 months (95% CI, 8.0-13.8, I^2 = 82.5%, P = 0.00, **Figure 3**).

Toxicity

A comprehensive analysis was conducted on the safety of the combination of A+B and TACE-HAIC in aHCC (**Table 3**). Most patients experienced mild to moderate side effects. Specifically, 91.0% of patients (95% CI, 84.9%-97.1%, I^2 = 57.9%, P = 0.05) reported all grades of AEs. The incidence of severe AEs (grade 3 or higher) was 24.8% (95% CI, 8.8%-40.9%, I^2 = 91.6%, P = 0.00) (**Figure 4A**, **4B**). The three most prevalent AEs across all grades were elevated aspartate transaminase (AST) levels (61.9%, 95% CI: 38.1%-85.7%, I^2 = 95.2%, P = 0.00), alanine transaminase (ALT) levels (50.7%, 95% CI: 39.6%-61.8%, I^2 = 68.4%, P = 0.01), and nausea (37.4%, 95% CI: 28.8%-45.9%, I^2 = 52.6%, P = 0.05). These findings highlight the critical need for regular liver function monitoring and hematologic assessments during treatment. The most frequently observed grade 3 or higher AEs were elevated AST levels (10.3%, 95% CI: 5.8%-14.8%, I^2 = 78.1%, P < 0.001), blood bilirubin increase (7.7%, 95% CI: 2.1%-13.3%, I^2 = 0.00%, P = 0.67), and ALT levels (7.5%, 95% CI: 3.4%-11.7%, I^2 = 0.00%, P = 0.63). Thus, while serious AEs occurred, they were infrequent and manageable with appropriate clinical oversight.

Sensitivity analysis

Sensitivity analysis was employed to individually eliminate each study and evaluate its effect on the total aggregate results. No individual study significantly influenced the pooled data, indicating that the results of this investigation were relatively robust and reliable (**Figure 5**).

Publication bias

Both Egger's and Begg's tests were applied to the meta-analysis in order to assess publication bias. The evaluation outcomes revealed that for the mRECIST criteria, no significant publication bias was detected in the assessment of ORR (P = 0.592 for Egger's test and P = 0.986 for Begg's test), DCR (P = 0.091 for Egger's test and P = 0.090 for Begg's test), PR (P = 0.881 for Egger's test and P = 1.000 for

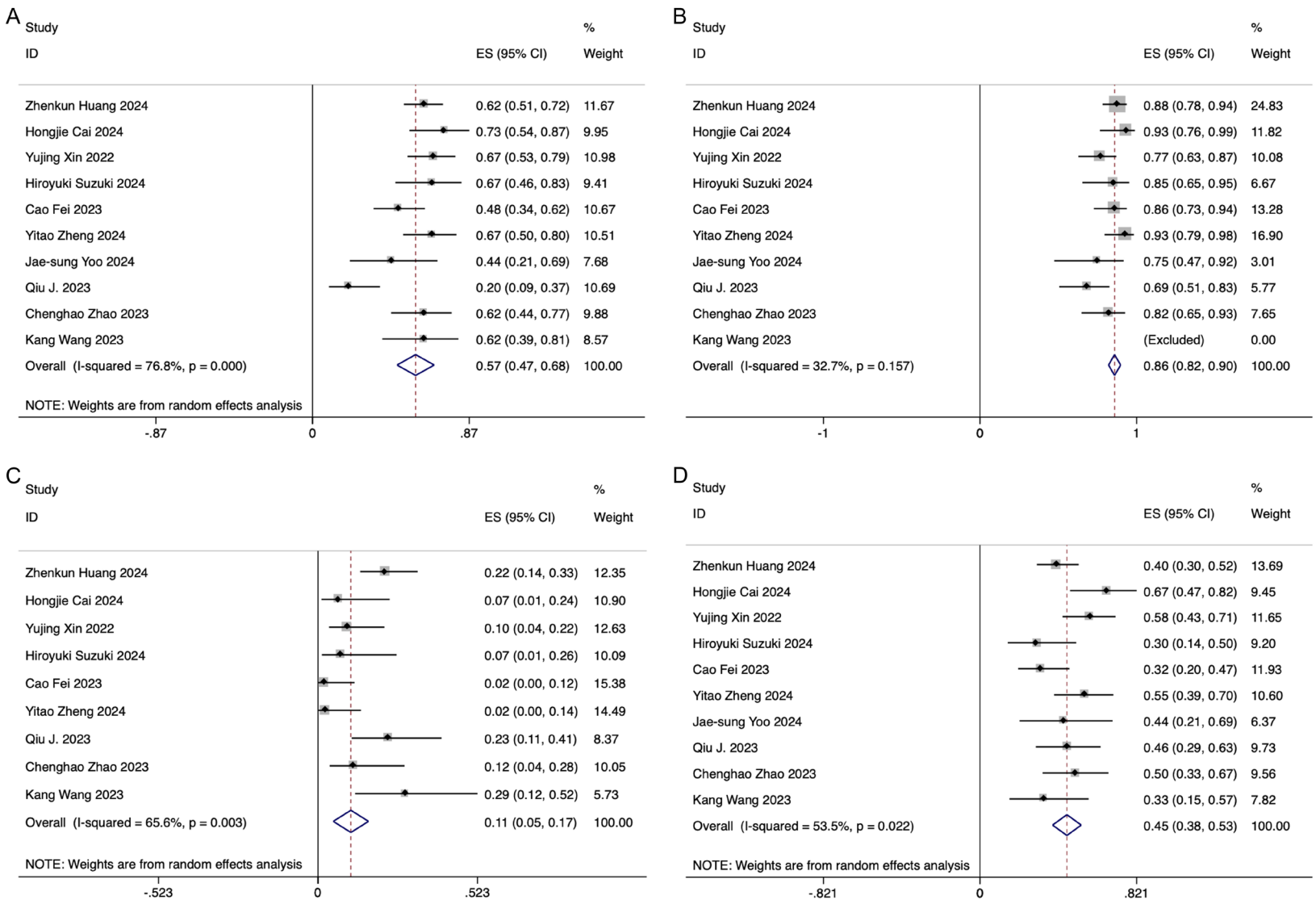

Figure 2. A. ORR of A+B+TACE-HAIC based on mRECIST; B. DCR of A+B+TACE-HAIC based on mRECIST; C. PR of A+B+TACE-HAIC based on mRECIST; D. CR of A+B+TACE-HAIC based on mRECIST. ORR, objective response rate; A+B+TACE-HAIC, A+B with transarterial chemoembolization and hepatic arterial infusion chemotherapy; DCR, disease control rate; PR, partial response; CR, complete response; mRECIST, modified response evaluation criteria in solid tumors.

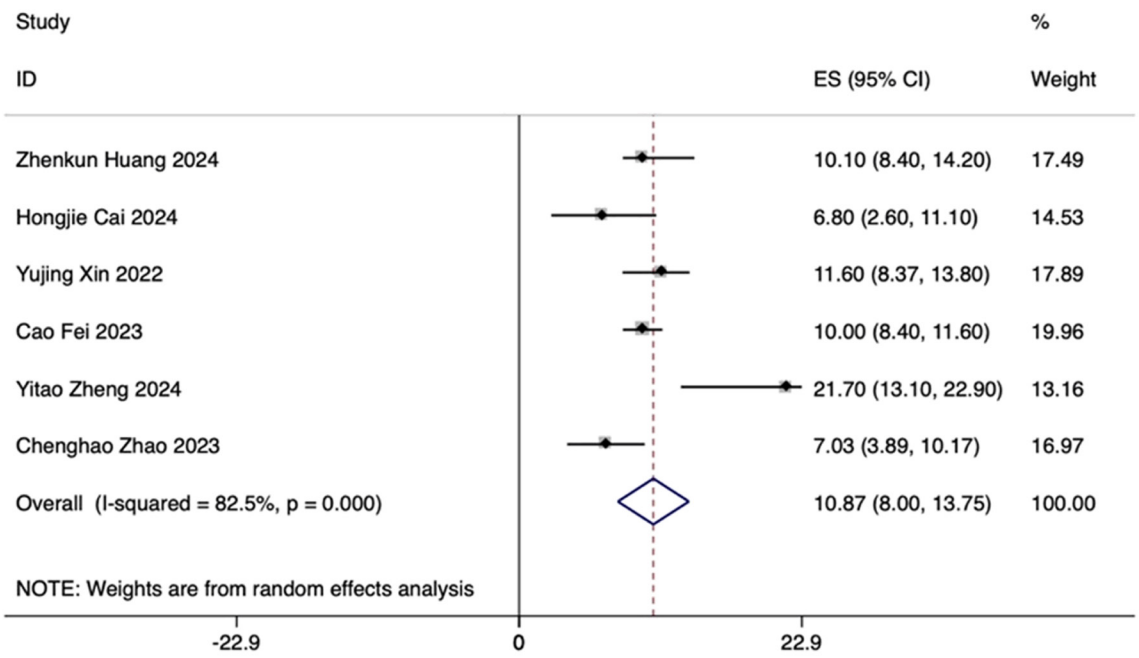

Figure 3. Pooled results of the mPFS with A+B+TACE-HAIC. mPFS, median progression-free survival; A+B+TACE-HAIC, A+B with transarterial chemoembolization and hepatic arterial infusion chemotherapy.

Table 3. Pooled results of common adverse events

Adverse Event	All Grades		≥ Grade 3	
	ES, % (95% CI)	I^2, %	ES, % (95% CI)	I^2, %
AST increase	61.9 (38.1-85.7)	95.2	10.3 (5.8-14.8)	78.1
ALT elevation	50.7 (39.6-61.8)	68.4	7.5 (3.4-11.7)	0
Proteinuria	20.8 (9.9-31.6)	66.0	5.6 (0.5-10.7)	0
Hypertension	27.4 (21.6-33.2)	0.0	6.6 (2.7-10.5)	0
Fatigue	28.3 (13.2-43.4)	87.7	3.9 (0.3-7.5)	0
Thrombocytopenia	25.5 (20.1-30.9)	46.6	5.2 (0.7-9.7)	0
Appetite loss	21.7 (16.1-27.2)	19.8	2.2 (0-5.8)	0
Pyrexia	34.7 (20-49.5)	85.9	3 (0-7.2)	0
Nausea	37.4 (28.8-45.9)	52.6	4.8 (0.7-8.9)	0
Blood bilirubin increase	34.9 (22-47.8)	81.6	7.7 (2.1-13.3)	0
Thyroid dysfunction	13.8 (9-18.7)	0.0	3.3 (0-12.8)	0
Gastrointestinal hemorrhage	4.6 (1.2-7.9)	0.0	3.7 (0-9.4)	0
Bellyache	34.1 (18.2-50)	85.5	2.9 (0-6.6)	0
Diarrhea	14.9 (8.9-20.9)	50.3	2.9 (0-6)	0
Lose weight	12 (7.4-16.6)	32.5	0 (0-0)	0

AST, aspartate transaminase; ALT, alanine aminotransferase.

Begg's test), mPFS (P = 0.833 for Egger's test and P = 1.000 for Begg's test), and AEs incidence (P = 0.210 for Egger's test and P = 0.613 for Begg's test). Except for the incidence of CR and grade 3 or above adverse events, no significant publication bias was observed in the overall analysis. Despite this, upon scrutinizing the occurrence of severe AEs graded 3 or higher and CR, a notable publication bias was identified, AEs graded 3 or higher (P = 0.036 for Egger's test and P = 0.260 for Begg's test) and CR (P = 0.009 for Egger's test and P = 0.076 for

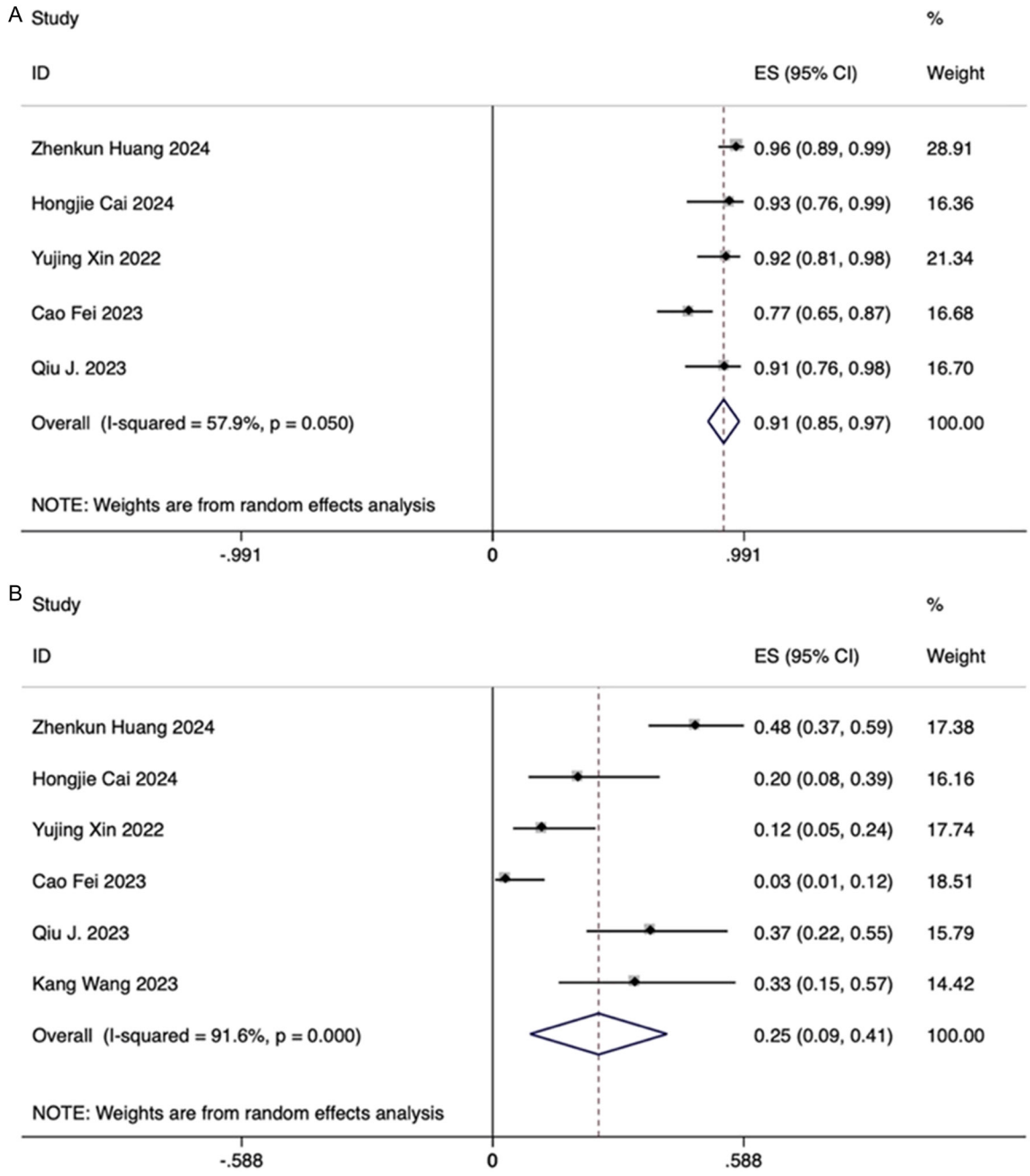

Figure 4. Combined incidence of all-grade AEs and those of grade 3 or higher. A. Combined incidence of all-grade AEs; B. Combined incidence of grade 3 and higher AEs. AEs, adverse events; A+B+TACE-HAIC, A+B with transarterial chemoembolization and hepatic arterial infusion chemotherapy.

Begg's test). Publication bias may have arisen because the two results contained too few data. The insufficient sample size hampered the ability of statistical analysis to accurately capture true effects, thereby increasing the risk of bias.

Discussion

The IMbrave150 trial established the use of A+B in advanced HCC treatment, but the representativeness of high-risk HCC patients was insufficient, and the efficacy of A+B was limit-

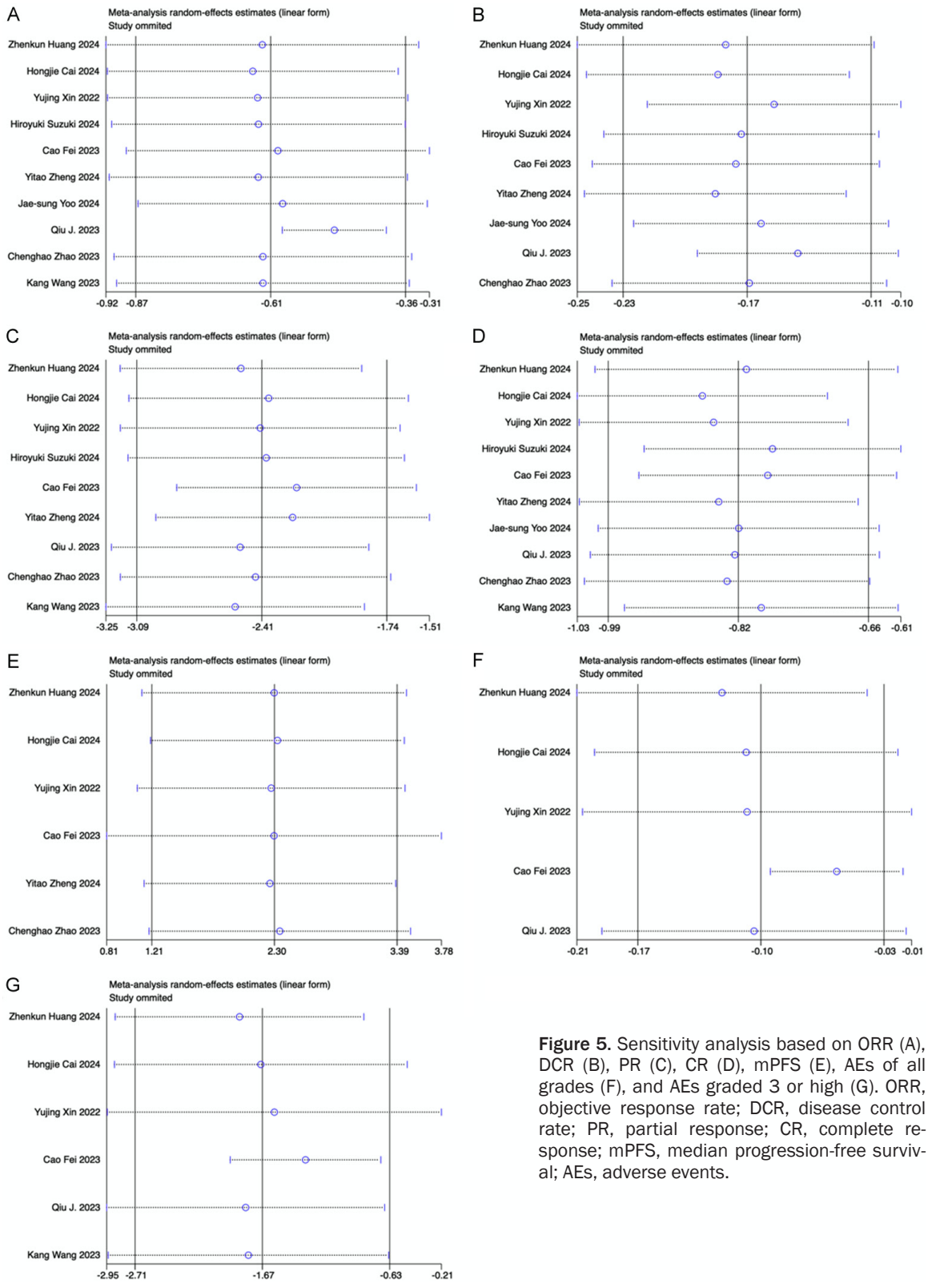

Figure 5. Sensitivity analysis based on ORR (A), DCR (B), PR (C), CR (D), mPFS (E), AEs of all grades (F), and AEs graded 3 or high (G). ORR, objective response rate; DCR, disease control rate; PR, partial response; CR, complete response; mPFS, median progression-free survival; AEs, adverse events.

ed, with a mOS of 7.6 months [7, 22, 23]. For high-risk HCC patients with a diameter over 8 cm, monotherapy has limited efficacy, and it is advisable to integrate local and systemic thera-

pies [23]. The LAUNCH trial showed that TACE + lenvatinib had promising prospects compared to monotherapy [24]. The TACTICS trial explored the therapeutic effect of the combination of TACE and sorafenib, and the results showed that the PFS of patients in the combination treatment group was as high as 25.2 months, significantly higher than the 13.5 months of patients receiving TACE treatment alone [25]. The integration of systemic therapy with HAIC was effective; however, the effectiveness of A+B+TACE had not been examined [26]. This meta-analysis aimed to evaluate the efficacy and tolerability of the A+B+TACE-HAIC treatment for advanced HCC, leveraging the HAIC-TACE therapies to address the shortcomings of combined immune-targeted therapies.

In contrast to the RECIST 1.1 criteria, the mRECIST standard stood out by specifically targeting the assessment of the enlarged (or active) section of the targeted lesion. This approach confineed the quantification to the viable tumor area, thus excluding necrotic tissues from consideration. In the comprehensive treatment of HCC, necrosis is often caused by embolism, while TACE-HAIC treatment often leads to significant necrosis. Therefore, RECIST 1.1 may have underestimated the efficacy of A+B+TACE-HAIC, while mRECIST was more accurate and reasonable.

An analysis of the ten studies indicated that female patients exhibited a lower incidence of HCC compared to male patients, possibly due to the higher prevalence of HCC among males [27]. This research indicated that regardless of the preceding therapeutic strategies, disease progression, and medication dosage administered, the ORR (based on mRECIST) of A+B+TACE-HAIC in the treatment of advanced HCC was 57.2%, DCR was 85.9%, CR was 10.8%, and PR was 45.5%, significantly higher than the results of the IMbrave150 trial with ORR of 35% and the LAUNCH trial with ORR of 54.1% [7, 24]. Besides demonstrating a higher tumor response rate, the mPFS of 10.9 months for HCC patients treated with A+B+TACE-HAIC was significantly longer than the mPFS of 6.9 months reported in the IMbrave150 trial and 10.6 months in the LAUNCH trial [7, 24]. The PFS did not surpass the results of the TACTICS trial, possibly due to factors such as small sample size and differences in patient selection criteria [25]. The TACTICS experiment encompassed a larger cohort with varied patient characteristics, yielding a more thorough comprehension of long-term results. Divergences in therapeutic regimens, follow-up duration, and definitions of advancement may also have accounted for these disparities. Future research should implement extensive randomized controlled trials with standardized methodologies and long-term follow-up to mitigate these limitations.

Antilizumab blocks programmed cell death-ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) and activates T cell anti-tumor activity, resulting in a 17% ORR for monotherapy in stage Ib HCC [28]. Bevacizumab inhibits angiogenesis, with a phase II monotherapy ORR of 14% [29]. The effectiveness of using two medications alone is limited due to the interaction between immune escape and angiogenesis in the tumor microenvironment (TME) [30]. Preclinical studies support the combination of the two [31], and subsequent clinical studies have confirmed their efficacy [32]. Bevacizumab not only decreases angiogenesis but also affects vascular endothelial growth factor (VEGF)-mediated Treg proliferation and inflammatory responses. When administered alongside atezolizumab, it synergistically amplifies the efficacy of CD8+ T cells and dendritic cells within the tumor microenvironment, thereby stimulating the immune response and suppressing tumor proliferation [33]. Low platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio values may indicate optimal treatment with A+B [34, 35]. HAIC could enhance the anti-tumor response of A+B by effectively reducing the intrahepatic tumor burden and increasing exposure to tumor immune antigens [36]. Following TACE treatment, a significant increase in cytotoxic T lymphocytes was observed, indicating an enhanced immune response [36-38]. This finding is further supported by research showing that TACE induced notable changes in the HCC immune microenvironment, including the upregulation of PD-L1 expression in inflammatory cells [39]. These alterations not only underscore TACE's positive effect on the tumor immune environment but also provide a theoretical foundation for combination immunotherapy strategies. Additionally, bevacizumab can overcome chemotherapy resistance by normalizing tumor neovasculariza-

tion [40]. The potential synergy of HAIC combined with VEGF and ICIs may further boost anti-cancer activity and extend response duration, thereby improving patient prognosis [38]. Similarly, the synergistic effect of A+B may normalize tumor vasculature, mitigate hypoxia, and enhance the efficacy of HAIC [41].

AEs associated with A+B+TACE-HAIC therapy were 91.0% overall, with the most common all-grade AEs occurring at over 5% frequency, namely: AST increase (62%), ALT elevation (51%), nausea (37%), blood bilirubin increase (35%), pyrexia (35%), bellyache (34%), fatigue (28%), hypertension (27%), thrombocytopenia (26%), appetite loss (22%), proteinuria (21%), diarrhea (15%), thyroid dysfunction (14%), weight loss (12%), and gastrointestinal hemorrhage (5%). 24.8% of grade 3 or higher AEs occurred, with the following being the most common: AST increase (10%), blood bilirubin increase (8%), ALT elevation (8%), hypertension (7%), proteinuria (6%), nausea (5%), thrombocytopenia (5%), fatigue (4%), gastrointestinal hemorrhage, (4%) pyrexia (3%), bellyache (3%), thyroid dysfunction (3%), and diarrhea (3%). This study revealed a significant increase in the incidence of treatment-related adverse events (TRAEs) associated with A+B+TACE-HAIC, characterized by raised AST and ALT levels; however, this can be mitigated through dose modification or cessation of therapy. In alignment with the A+B regimen TRAEs identified in the IMbrave150 research, this study similarly noted hypothyroidism and other symptoms. Given the high efficacy of combination therapy, the incidence of TACE-HAIC-related AEs such as liver damage, nausea, and abdominal discomfort was higher than in historical data [42, 43]. All included studies followed established guidelines for managing all severe TRAEs [34, 35, 44]. For cases of grade 3-4 severity, treatment was promptly discontinued, and appropriate medical intervention was administered. The combination therapy has not been shown to cause new toxicity, confirming its feasibility and safety.

This meta-analysis has certain limitations. First, the exclusion from the RCT may result in selection bias. Second, the study's inclusion criteria precluded comparisons with other conventional first-line medications. Third, there was considerable variation among the research studies. Fourth, there may have been publication bias. Ultimately, the absence of data precluded certain analysis from being performed.

Conclusion

The concurrent administration of A+B with TACE-HAIC shows effectiveness in managing advanced HCC, resulting in favorable outcomes for patients. This combination therapy had acceptable tolerance and toxicity profiles, with no novel toxicities identified. Future prospective clinical trials with larger sample sizes are necessary to confirm these findings.

Disclosure of conflict of interest

None.

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