Regorafenib plus programmed death-1 inhibitors vs. regorafenib monotherapy in second-line treatment for advanced hepatocellular carcinoma: A systematic review and meta-analysis

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Abstract. The present study compared the efficacy and safety of regorafenib plus programmed death-1 inhibitors (R-P) with regorafenib monotherapy as second-line therapies for advanced hepatocellular carcinoma (HCC). A systematic search of relevant literature published in PubMed, Embase, Web of Science and Cochrane Library databases until October 2023 was conducted. Two authors independently performed data extraction and screening using standardized protocols. Stata/MP 17.0 was used for the meta-analysis to evaluate the impact of R-P treatment on major outcome indicators, including overall survival, progression-free survival (PFS), tumor response and adverse reactions, in patients with advanced HCC. The results indicated that five cohort studies involving 444 patients with advanced HCC were included. The results revealed that R-P treatment improved overall survival [hazard ratio (HR), 0.61; 95% confidence interval (CI) 0.48-0.77; I^2=0.0%; P=0.663] and PFS (HR, 0.51; 95% CI 0.41-0.63; I^2=17.5%; P=0.303). Additionally, it increased the objective response rate (risk ratio, 2.33; 95% CI, 1.49-3.64; I^2=0.0%; P=0.994) and disease control rate (HR, 1.40; 95% CI, 1.20-1.63; I^2=0.0%; P=0.892) compared with those of regorafenib. However, R-P treatment was associated with an increased incidence of adverse events, such as hypothyroidism, thrombocytopenia and rash, compared with that in regorafenib. In conclusion, R-P is superior to regorafenib monotherapy in terms of survival benefits and tumor response.

Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of global cancer-related mortality, and its associated death rate is anticipated to increase persistently over the next decade (1). HCC typically manifests as a latent progression with inconspicuous symptoms, often resulting in diagnosis at an advanced stage (2). Currently, the internationally endorsed first-line therapies for advanced liver cancer include sorafenib, lenvatinib and other pharmaceutical drugs. The results of the IMbrave150 trial revealed that the combination of atezolizumab and bevacizumab was more clinically significant than sorafenib alone in terms of life, function and disease symptoms, making it an important current first-line treatment option (3). Nevertheless, the efficacy of these primary interventions is limited, frequently culminating in the emergence of drug resistance shortly after treatment (4). In cases where patients exhibit intolerance or encounter failure with first-line approaches, secondary options such as regorafenib, cabozantinib, or nivolumab monotherapy may be considered (5).

Regorafenib, an innovative oral multi-kinase inhibitor, has demonstrated inhibitory effects on diverse protein kinases, including those implicated in tumor angiogenesis and tumorigenesis. It exhibited antiproliferative, antiangiogenic, antitumor and anti-metastatic activities in rat models (6). A pivotal randomized, double-blind, placebo-controlled phase 3 trial (7) substantiated the significant enhancement of overall survival (OS) in patients with progressive HCC after sorafenib treatment. Consequently, it was approved as a pioneering second-line targeted therapy, with subsequent clinical trials corroborating its efficacy in patients with late-stage HCC (8).

Research posits that regorafenib plus programmed death-1 (PD-1) inhibitors augment survival benefits for patients with late-stage HCC compared with that for those undergoing regorafenib monotherapy (9). The underlying mechanism lies in regorafenib's facilitation of the antitumor immune response of PD-1 inhibitors by modulating the IFN-γ/NSDHL/SREBP1/TGF-β1 axis (10). In a murine liver cancer model, this combined approach substantially elevated the expression of CXCL10 in HCC cells, fostering the normalization of the tumor vascular system and amplifying the infiltration of $CXCR3^+CD8$ T cells, thereby effectively impeding tumor growth (11).

In practical clinical settings, the amalgamation of regorafenib with PD-1 inhibitors is progressively gaining traction as a second-line treatment for late-stage HCC. However, reported cases remain limited (12), and comprehensive investigations examining the relative efficacy and safety of these treatment modalities are currently lacking. Therefore, the objective of the

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present meta-analysis was to compare the efficacy and safety of regorafenib with or without PD-1 inhibitors as second-line therapy in advanced-stage HCC. The present study aimed to provide a thorough basis for clinical decision-making.

Materials and methods

Search strategy. To gather the pertinent literature, a thorough investigation of PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com), Web of Science (https://webofscience.com) and Cochrane Library (https://www.cochranelibrary.com/) databases was conducted in October 2023. The search strategy was not limited by language or other factors (Table SI). The utilized keywords encompassed 'liver neoplasms', 'hepatocellular carcinoma', 'regorafenib'. 'Stivarga', 'immune checkpoint inhibitors', 'programmed death-1', and 'PD-1'. The research design and implementation adhered to the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (13).

Inclusion and exclusion criteria. Inclusion criteria were as follows: i) Population: Patients with advanced HCC who failed first-line therapy (sorafenib, lenvatinib, pabolizumab, atezolizumab + bevacizumab). These patients had Eastern Cooperative Oncology Group Performance Status scores ranging from 0 to 1; ii) the study encompassed either prospective or retrospective clinical investigations; and iii) the intervention administered to the participants in blue could be regorafenib or a treatment referred to as R-P.4. The outcomes assessed included OS, progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and occurrence of adverse events (AE).

Exclusion criteria were as follows: i) Any malignant tumor other than HCC, current or historical; ii) use of alternative targeted medications aside from regorafenib in second-line therapy; iii) non-clinical studies, including case reports, reviews, meta-analyses, systematic reviews, letters, guidelines and basic experiments; and iv) studies lacking sufficient resulting data or in which data extraction is not feasible.

Data extraction. The authors Zhao Li and Jie Wang individually reviewed the literature, collected data and cross-verified the data using a standardized protocol after obtaining the relevant articles. Endnote X9 software was used for literature review. Disagreements were resolved through discussion or by referring to the opinions of a third author. The extracted information included the first author's name, publication year, racial composition of the study population, study design, sample size, patient numbers, and clinical outcomes, such as survival, tumor control and adverse reactions. If crucial information was missing, the corresponding author was contacted via email to obtain unpublished data.

Literature quality assessment. The cohort studies included in this meta-analysis were independently assessed by two authors using the Newcastle-Ottawa Scale. Subsequently, they engaged in discussions to establish a consensus. The scores assigned to the Newcastle-Ottawa Scale ranged from zero to nine, where scores between one and five were indicative of low quality and scores between six and nine signified high quality.

Statistical analysis and bias assessment. Stata/MP software version 17.0 (StataCorp LP) was used for statistical analysis. Hazard ratios (HR) and their corresponding 95% confidence intervals (CI) were used as the primary outcome measures (OS and PFS), with the log HR and its variance summarized using inverse variance-weighted averages. Secondary outcome measures (ORR, DCR and AE) were represented using relative risk (RR) and their corresponding 95% CI. To assess the heterogeneity of the included studies, Q-tests and I^2-tests were used (14). If there was no heterogeneity ($P>0.05$ or $I^2<50\%$), a fixed-effects model was used for meta-analysis. Otherwise, a random effects model was used. Sensitivity analysis was conducted by sequentially excluding each study. Potential publication bias was evaluated using Egger's and Begg's tests.

Results

Literature search and selection. A preliminary search of these four databases yielded 974 articles. After automated and manual checks, 365 duplicate studies, 136 meta-analyses, systematic reviews and case reports were excluded. The remaining articles underwent independent title and abstract reviews by two authors, resulting in a detailed examination of the full text of the 27 studies that aligned with the research criteria. A total of 16 studies were excluded with inconsistent content and six studies without sufficient outcome data. Finally, the meta-analysis included five articles (15-19). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart illustrating the process of including the studies in the analysis is displayed in Fig. 1.

Study characteristics and quality assessment. All five studies included in the analysis were conducted in China and were retrospective cohort studies. These studies encompassed a total of 444 patients with advanced HCC. The regorafenib plus programmed death-1 inhibitors (R-P) and regorafenib groups comprised 270 and 174 patients, respectively. The decision to use monotherapy or combination therapy for regorafenib is primarily determined by the attending physician in consultation with the patient, taking into consideration the patient's condition. There was no statistical difference in baseline clinical characteristics between the two groups in the five studies, which was comparable. Except for the study by Tu *et al* (19), which included two patients with Child-Pugh class C HCC in both the regorafenib and R-P groups, all other patients had a Child-Pugh score of A-B. The basic characteristics of the included studies are summarized in Table I. In terms of quality assessment, all five retrospective cohort studies were rated as high-quality (Table II).

Survival. All the included studies reported differences in OS and PFS between the two groups. Heterogeneity between studies was extremely low and using a fixed-effect model analysis revealed that, compared with regorafenib monotherapy, patients with late-stage HCC receiving R-P treatment had an extension in OS (HR, 0.61; 95% CI, 0.48-0.77; $I^2=0.0\%$; $P=0.663$) (Fig. 2A). Similarly, R-P treatment improved PFS in

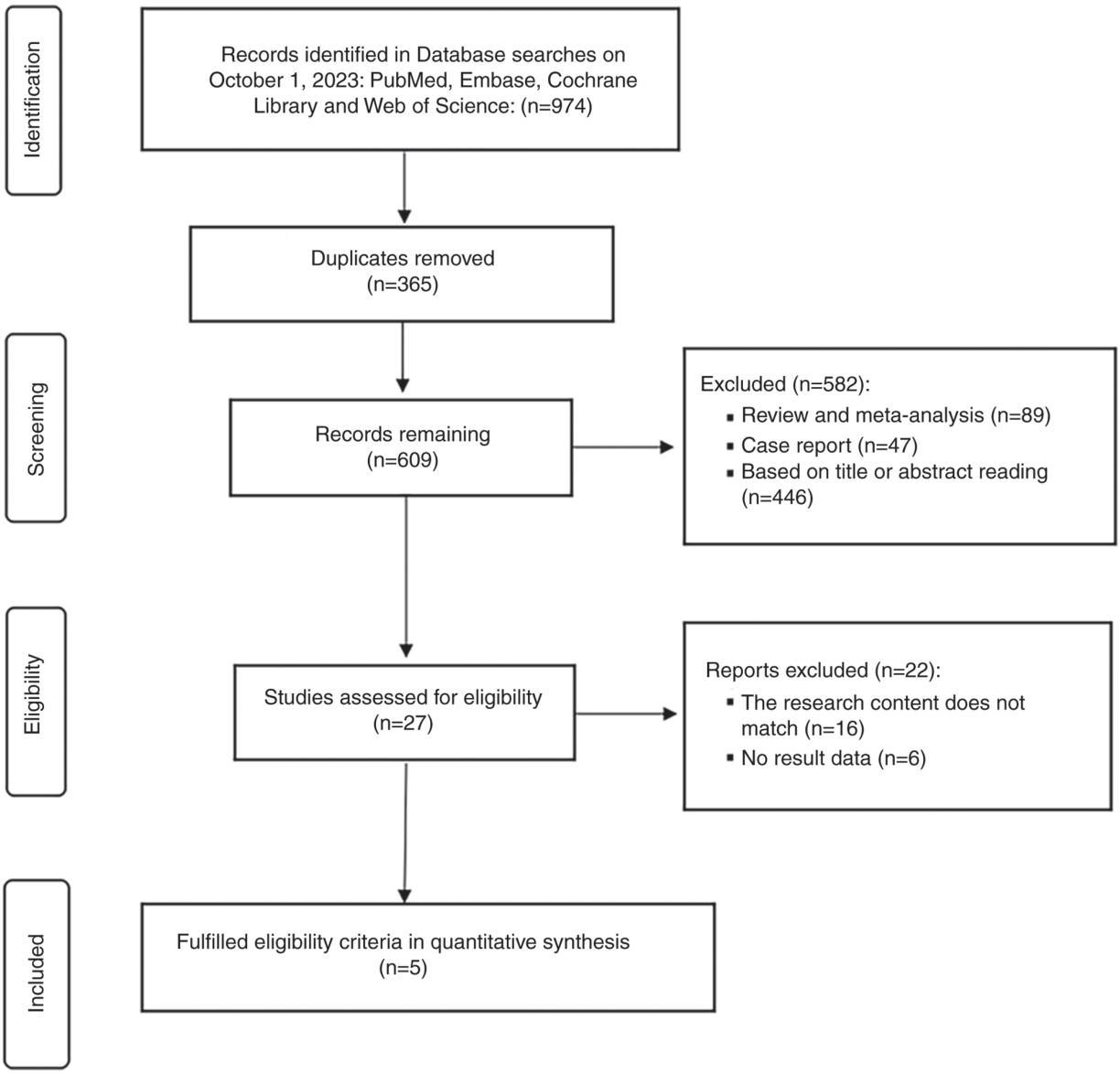

Figure 1. PRISMA flow diagram of the process for the identification of eligible studies.

late-stage HCC compared with regorafenib monotherapy (HR, 0.51; 95% CI, 0.41-0.63; I^2 =17.5%; P=0.303) (Fig. 2B).

Tumor response. All five studies reported differences in objective response and DCRs between the two treatment methods. Based on heterogeneity test results, a fixed-effect model analysis revealed that the ORR in the R-P group was higher than in the regorafenib group (RR, 2.33; 95% CI, 1.49-3.64; I^2=0.0%; P=0.994) (Fig. 3A). Similarly, the DCR in the R-P group was higher than in the regorafenib group (RR, 1.40; 95% CI, 1.20-1.63; I^2=0.0%; P=0.892) (Fig. 3B). These results indicated that, compared with regorafenib monotherapy, R-P treatment can significantly improve tumor response in patients with late-stage HCC.

Safety. In terms of AE, the risk of hypothyroidism, rash and thrombocytopenia was higher with R-P treatment than with regorafenib monotherapy. The most common AE for both regorafenib monotherapy and R-P treatment was hand-foot skin reaction, with a similar risk of occurrence (RR, 1.05; 95% CI, 0.80-1.38; I^2=0%; P=0.632) (Table III).

Sensitivity analysis and publication bias. Sensitivity analyses were conducted for the primary outcome measures (OS and PFS). The meta-analysis results remained stable when each study was sequentially excluded as there were no significant changes in the effect size for OS, PFS, or 95% CI (Fig. 4). The OS and PFS tests for publication bias indicated that there was no potential publication bias since the P-values for Egger's test were 0.160 and 0.710, respectively, and the P-values for Begg's test were 0.226 and 1.000, respectively (Fig. 5).

Discussion

HCC is one of the most common types of cancer worldwide, typically diagnosed at advanced stages, necessitating systemic treatment (20). Current first-line therapeutic options include sorafenib, lenvatinib and combinations of atezolizumab and

Table I. Demographic characteristics of included studies.

Study	Country	Study type	Treatment	Sample size	Age, years	Male	HBV positive	AFP (<400 ng/ml)	Child-Pugh class A	BCLC stage B	ECOG PS 0	PVTT	EHM	(Refs.)
Huang *et al* 2022	China	RCS	R-P	58	54 (41-62)[a]	51	48	NA	37	NA	35	40	37	(15)
			R	55	51 (47-63)[a]	50	49	NA	35	NA	27	31	29	
Li *et al* 2023	China	RCS	R-P	38	51.2±10.3[b]	28	30	17	NA	8	23	27	14	(16)
			R	32	53.3±13.1[b]	26	27	30	NA	11	17	19	15	
Liu *et al* 2022	China	RCS	R-P	48	54 (47-60)[a]	39	33	29	NA	8	29	11	39	(17)
			R	30	55 (47-61)[a]	27	23	15	NA	7	20	6	23	
Yan *et al* 2023	China	RCS	R-P	94	55.5 (48.0-62.7)[a]	85	NA	NA	65	16	37	46	47	(18)
			R	39	58 (51.5-63.0)[a]	34	NA	NA	27	5	16	15	22	
Tu *et al* 2022	China	RCS	R-P	32	50.3 (34.4-69.0)[a]	29	30	16	23	4	9	10	28	(19)
			R	18	53 (34.4-71.0)[a]	14	18	4	7	0	2	7	15	

[a]Data presented as median (range); [b]data presented as the mean ± SD. HBV, hepatitis B virus; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group Performance Status; PVTT, portal vein tumor thrombus; EHM, extrahepatic metastasis; RCS, retrospective cohort study; R-P, Regorafenib plus programmed death-1 inhibitors; R, Regorafenib.

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Table II. Assessment of cohort studies using Newcastle-Ottawa scale.

Selection				Comparability	Exposure/outcome				
Represent activeness of cohort	Selection of control cohort	Ascertainment of exposure	Outcome not present at start	Comparability of cohorts	Assessment of outcome	Length of follow-up	Adequacy of follow-up	Total score	Study
*	*	*	*	**	*	*		8	Huang *et al* 2022 (15)
*	*	*	*	**	*	*		8	Li *et al* 2023 (16)
*	*	*	*	**	*	*	*	9	Liu *et al* 2022 (17)
*	*	*	*	**	*	*	*	9	Yan *et al* 2023 (18)
*	*	*	*	**	*			7	Tu *et al* 2022 (19)

* represents a project score of 1 and ** represents a project score of 2.

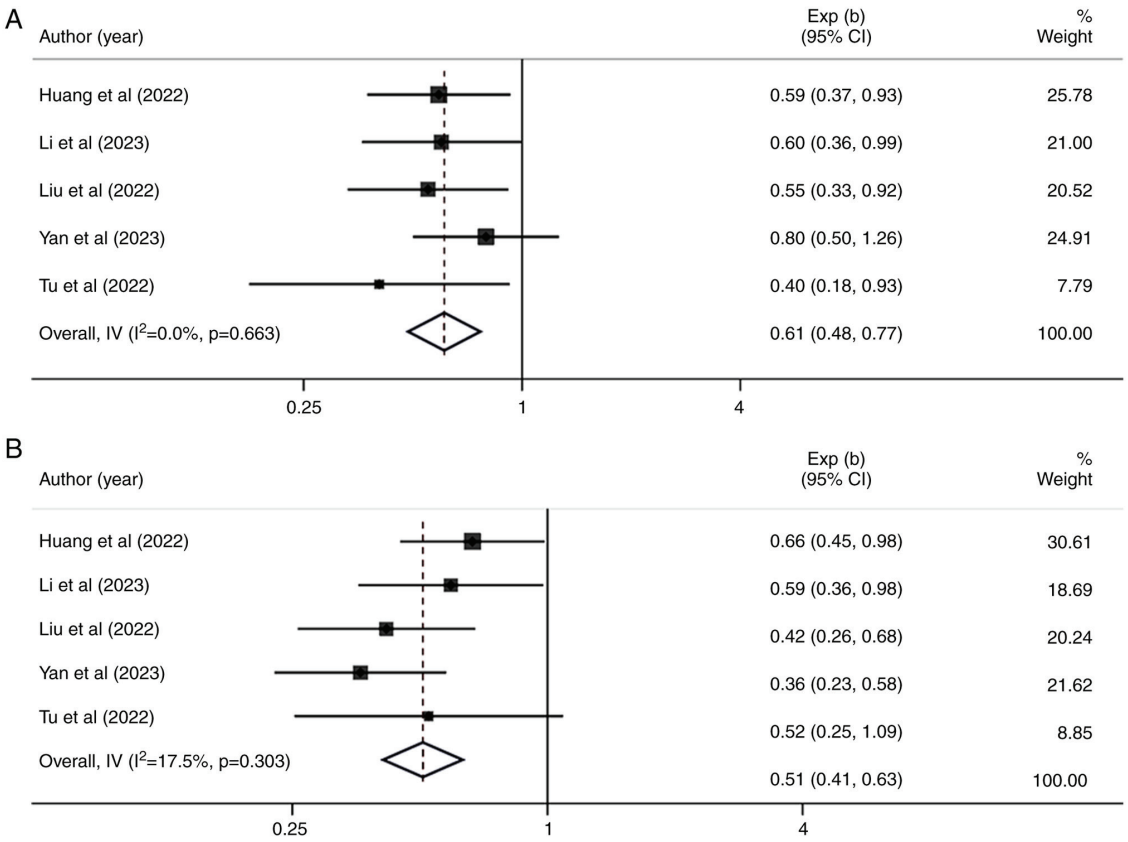

Figure 2. Forest plots for the comparison of (A) overall survival and (B) progression free survival. CI, confidence interval.

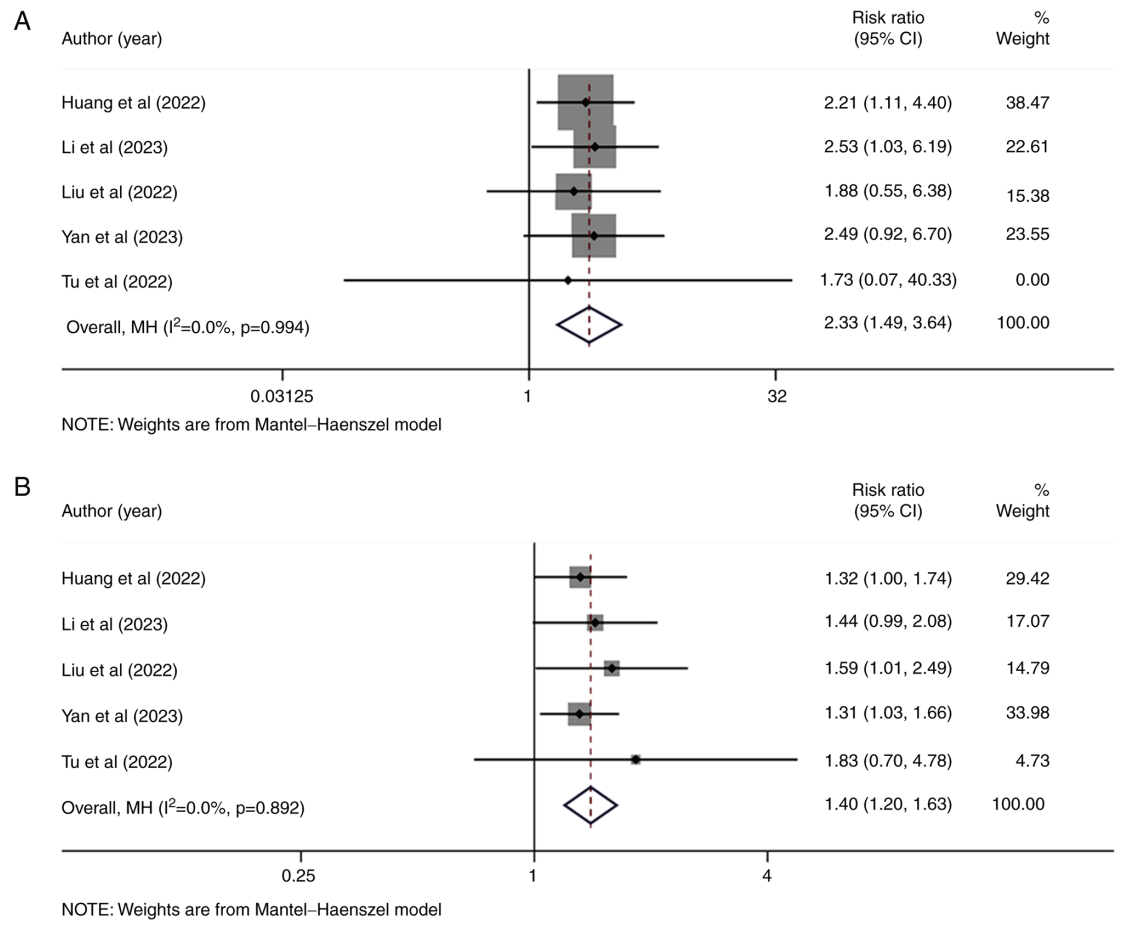

Figure 3. Forest plots for the comparison of (A) objective response rate and (B) disease control rate. CI, confidence interval.

Table III. Summary of treatment-related adverse events.

Adverse events	Number of studies	Rate of events (%)		Relative risk (95% confidence interval)	P-value	I^2 (%)
		R-P	Regorafenib			
Hypertension	5	14.8	17.8	0.99 (0.65-1.50)	0.391	2.8
Diarrhea	5	21.1	20.7	1.10 (0.77-1.59)	0.867	0
Fatigue	5	22.6	20.1	1.29 (0.90-1.85)	0.208	32
Hand-foot skin reaction	5	32.6	31.6	1.05 (0.80-1.38)	0.632	0
Elevated transaminases	5	21.5	20.1	1.26 (0.88-1.79)	0.994	0
Hypothyroidism	5	15.7	8.6	2.35 (1.36-4.05)	0.811	0
Thrombocytopenia	4	11.4	7.4	1.54 (0.74-3.23)	0.918	0
Rash	4	13.4	6.4	2.59 (1.35-4.99)	0.280	21.8

R-P, Regorafenib plus programmed death-1 inhibitors.

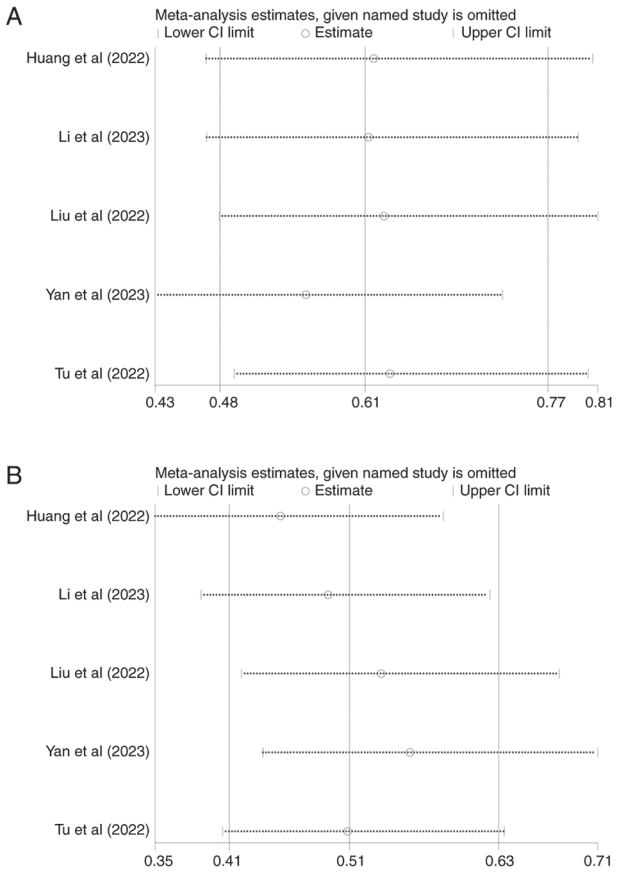

Figure 4. Sensitivity analysis plot based on (A) overall survival and (B) progression free survival.CI, confidence interval.

cizumab (21). Selecting an appropriate second-line treatment after the initial therapy fails is pivotal for enhancing patient survival outcomes.

Second-line treatments include regorafenib, cabozantinib and ramucirumab. Regorafenib, an oral tyrosine kinase inhibitor, was initially approved for treating metastatic colorectal cancer in the randomized, placebo-controlled phase 3 CORRECT trial. The trial was confirmed in an expanded Asian patient population in the randomized, placebo-controlled, phase 3 CONCUR trial (22). In the phase 3 CORRECT trial, patients with metastatic colorectal cancer randomly assigned to either regorafenib 160 mg or placebo revealed a survival benefit, with a median OS of 6.4 months in the regorafenib group and 5.0 months in the placebo group (23). Regorafenib was the first oral drug approved for patients with HCC who did not respond to sorafenib. However, owing to its lower ORR and moderate improvement in OS, there is a clear need for a more efficacious second-line treatment (24). There is growing hope for the potential of immunotherapy as a second-line treatment for liver cancer, as the results of a phase 2 clinical trial (KEYNOTE-224) revealed that pembrolizumab is effective and well-tolerated in patients with HCC who have failed in getting treated with sorafenib (25). However, PD-1 inhibitor monotherapy has a low response rate across different populations of patients with HCC. In a phase 3 clinical trial evaluating pembrolizumab as a second-line treatment for advanced HCC (KEYNOTE-240), neither OS nor PFS met the predefined primary endpoints. The publication of results from a phase III clinical trial (26) introduced the combination of targeted therapy and immunotherapy as a burgeoning option, providing a fresh outlook for the second-line treatment of advanced HCC.

The exploration of combined molecular targeted drugs and PD-1 inhibitors has emerged as a research hotspot, yielding encouraging results with the combination of atezolizumab and bevacizumab (3). Regorafenib has immunomodulatory effects (27): M1 macrophage polarization, enhanced $CD8^+$ T cell proliferation and activation, other than the inhibition of STAT3 activity, and increased the expression of C-X-C motif chemokine ligand 10 in combination with anti-PD-1 agents, extending both tumor penetration and the survival of activated $CD8^+$ T cells. Moreover, JAK1/2STAT1 and MAPK signals can be effectively inhibited, and the expression of PD-L1 in tumors can be reduced, thus improving the efficacy of PD-1 inhibitors (28). Given regorafenib's unique therapeutic mechanisms targeting tumor cell proliferation and spread as well as tumor angiogenesis and tumor-associated immune evasion, combination therapy with PD-1 inhibitors is a promising new therapeutic strategy, and several clinical trials are investigating the efficacy and safety of combination therapy based on

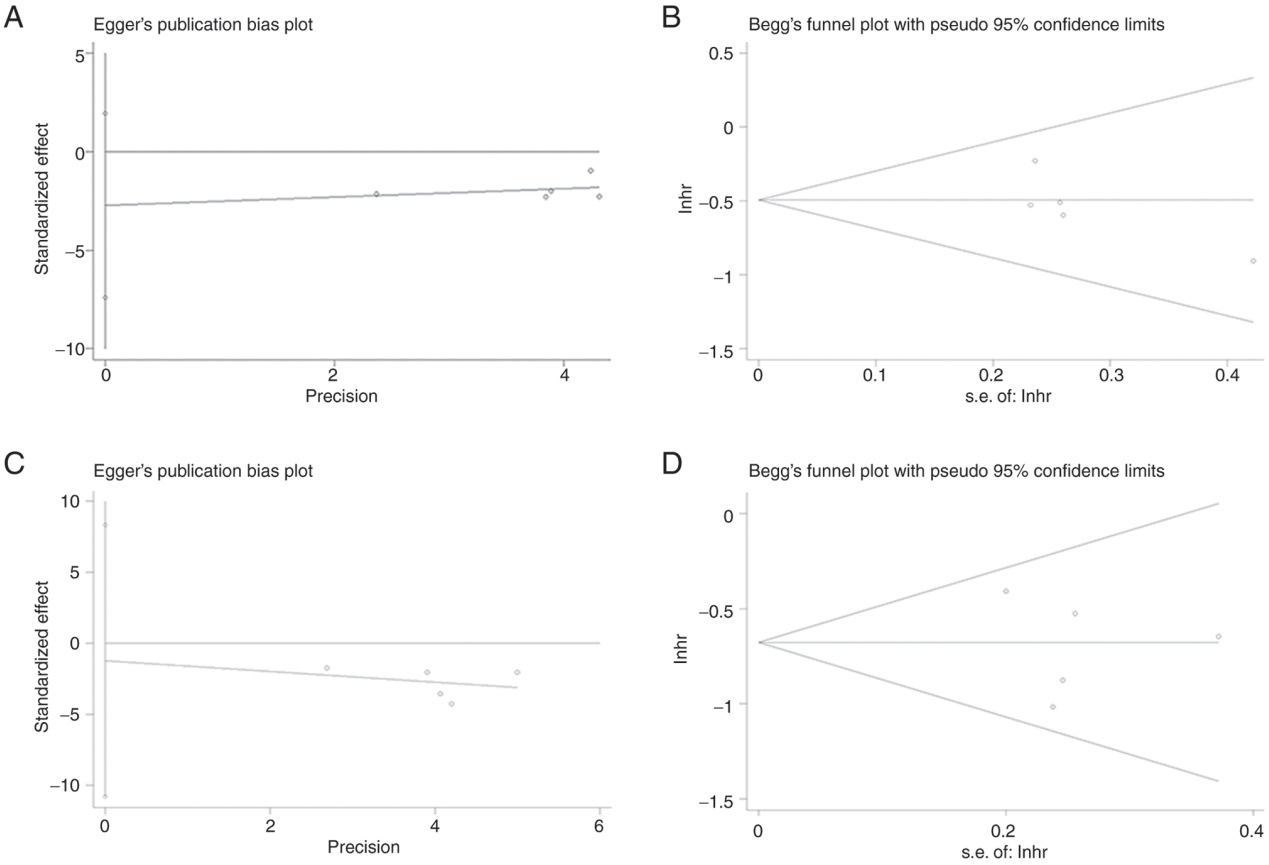

Figure 5. (A) The Egger's and (B) Begg's test for overall survival. (C) Egger's and (D) Begg's test for progression-free survival.

regorafenib plus immune checkpoint inhibitors (29). To date, no comprehensive meta-analysis has compared the effectiveness and safety of the two methods.

A meta-analysis was performed to compare the effectiveness and safety of R-P and regorafenib in patients with advanced HCC following unsuccessful initial treatment. The results of the present analysis revealed that, compared with regorafenib, R-P significantly extends the survival period for patients with advanced HCC post first-line treatment failure, while concurrently augmenting tumor response. A recent multicenter, single-arm, phase 2 RENOBATE trial reported supportive results in treating unresectable HCC with the combination of regorafenib and nebuliumab, demonstrating efficacy and safety, with an ORR of 31.0% and a median PFS of 7.38 months (30). Notably, low heterogeneity was observed among the included studies. The investigation conducted by Yan *et al* (18) found no statistically significant differences in OS between the R-P group and the regorafenib group (OS, 12.0 months; 95% CI, 10.0-22.0) vs. 14.0 months (95% CI, 14.0-16.0; P=0.32). This lack of significance may be attributed to the study's nearly four-year duration, which resulted in varying first-line treatment strategies over different periods. For example, in the initial stages, patients mostly received single-drug treatment with molecular-targeted drugs as the first option, whereas patients in advanced stages primarily underwent combination therapy involving both molecular-targeted drugs and immune checkpoint inhibitors, which significantly affected the experimental results. This disparity was further confirmed by a subgroup analysis. In the investigation by Tu *et al* (19), the PFS of the R-P group exceeded that of the regorafenib group (3.7 months; 95% CI, 2.74-4.72; vs. 2.1 months; 95% CI, 1.12-3.01; P=0.078), although the difference did not achieve statistical significance. This lack of significance may be attributed to the continued favorable tumor response and survival outcomes demonstrated by PD-1 inhibitors when sequentially combined with molecular targeted drug therapies (31). Consequently, the administration of regorafenib within a few months of PD-1 inhibitor failure yielded synergistic effects, thereby mitigating the disparity between the two groups.

These findings indicated that the combination of molecular targeted agents with PD-1 inhibitor dual therapy surpasses molecular targeted agents' monotherapy in conferring survival benefits and eliciting a tumor response. This conclusion is consistent with the outcomes of the meta-analysis by Yu *et al* (32), in which the combination of lenvatinib with PD-1 inhibitors significantly improved survival benefits and tumor response, as opposed to using lenvatinib alone, in patients with advanced HCC. A recent single-center study conducted at a single center (33) provided additional validation that the combination of regorafenib and PD-1 inhibitors is highly effective in treating patients with advanced HCC after initial treatment failure. This treatment approach has revealed commendable results, with an increased tumor remission rate and a low incidence of severe AE. The residual liver function is a well-known limiting factor for systemic therapy and its indications/contraindications. The results of Cox univariate and multivariate analyses from three of the five included

studies indicated that Child-Pugh B is an independent risk factor for OS. However, most of the patients included in all studies were classified as Child-Pugh grade A, which may be attributed to the significant difference in the number of Child-Pugh grade A and B patients, as well as the small sample size. Therefore, a comparison between Child-Pugh grade A and B was not conducted. Given that both the current meta-analysis and the aforementioned studies were based on clinical retrospective research, these conclusions require further validation and confirmation through large-scale prospective multicenter randomized clinical trials. Fortunately, an ongoing prospective, multicenter, randomized controlled clinical trial for second-line treatment of liver cancer (34) has the potential to provide robust supportive evidence for the efficacy of R-P treatment.

Concerning treatment-related AE, the R-P regimen resulted in a higher incidence of hypothyroidism, rash and thrombocytopenia than in regorafenib monotherapy. Nevertheless, the occurrence rates of these AEs in both groups were relatively low and were successfully controlled by changing the dosage and providing supportive treatment (35). No significant differences in the risk of adverse reactions were observed between the two groups in other categories. Based on the present analysis of all included studies, there were no statistically significant differences in the occurrence of severe AE (grade 3/4) between the two groups, which further affirmed the safety profile of the R-P regimen. In summary, R-P treatment yields clinical benefits for patients with advanced HCC following first-line treatment failure, while maintaining a commendable safety profile.

However, the present study has some limitations. First, the total number of included studies was restricted, and the sample size was relatively small, potentially impacting the comprehensiveness of the results. Second, all the included studies were retrospective, introducing the potential for selection bias. Third, the PD-1 inhibitor types varied among the studies, affecting the uniformity of the treatment approach. The fact that all PD-1 inhibitors used in the present study have been recommended for treating HCC (36) further enhances the authors' trust in the dependability of the findings.

In conclusion, the findings of the present study suggested that in patients with advanced HCC after first-line treatment failure, R-P treatment demonstrates advantages in terms of survival benefit and tumor response compared with regorafenib monotherapy. In addition, the adverse reactions were manageable. Therefore, the R-P treatment regimen could emerge as a new therapeutic option. Large-scale randomized controlled studies are necessary to further validate the efficacy of this treatment approach.

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Availability of data and materials

The data generated in the present study may be found in the PROSPERO under the accession number CRD42024498866 or the following URL (www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=498866).

Authors' contributions

ZLi, JW, JZ and ZL conceived and designed the study. ZLi, JW, JZ and ZLe confirm the authenticity of all the raw data. ZLi and JZ conducted the data collection. ZLi and JW conducted statistical analysis. ZLi and JW played a role in interpreting the data. ZLi and ZLe were responsible for drafting and revising the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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