Efficacy and safety of different angiogenesis inhibitors combined with PARP inhibitors in the treatment of ovarian cancer: A systematic review and meta-analysis

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Abstract. Ovarian cancer is a leading cause of mortality among women with gynecological malignancies, largely due to its asymptomatic nature in early stages and frequent late diagnosis. Targeted therapies, such as angiogenesis inhibitors and poly(ADP-ribose) polymerase inhibitors (PARPi), have emerged as promising treatments by disrupting tumor vasculature and impairing DNA repair mechanisms, particularly in patients with BRCA mutations. The objective of the present study was to comprehensively evaluate the combined use of different angiogenesis inhibitors and PARPi in ovarian cancer treatment by meta-analysis. This included assessing their impact on objective response rate (ORR) and progression-free survival (PFS), understanding the role of BRCA mutation status, and comparing the effects of various angiogenesis inhibitors when used in combination with PARPi. The PubMed, Embase and Cochrane databases were searched from inception to February 2024. Only studies on the combined treatment of ovarian cancer with angiogenesis inhibitors and PARPi were included. Duplicate studies, studies with incomplete data, animal studies, literature reviews and systematic studies were excluded. The results underscored a noteworthy improvement in the ORR and median PFS (mPFS) among patients receiving combination therapy compared with those on monotherapy. Specifically, the pooled ORR for combination therapy was significantly higher than that of monotherapy, indicating a substantial benefit in terms of tumor response. Furthermore, combination therapy was found to significantly prolong PFS, offering patients a longer duration without disease progression. Subgroup analyses of patients treated with angiogenesis inhibitors combined with PARPi provided deeper insights, revealing that patients with BRCA mutations exhibited an ORR of 90% compared with 61% in those without BRCA mutations. Additionally, when different angiogenesis inhibitors were compared, patients treated with anti-VEGF agents combined with PARPi showed a longer mPFS (15.53 months) than those treated with TKIs combined with PARPi (7.49 months). In conclusion, the present study demonstrates that combinations of angiogenesis inhibitors and PARPi show great potential for improving treatment outcomes in ovarian cancer, particularly in patients with BRCA mutations. The observed differences in efficacy between various angiogenesis inhibitors highlight the importance of personalized treatment approaches. Further research is warranted to explore the long-term benefits of these combination strategies and refine them to obtain optimal patient outcomes.

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Introduction

Ovarian cancer is one of the leading causes of mortality among women with gynecological malignancies worldwide, primarily due to its asymptomatic nature in the early stages, which typically leads to a late diagnosis (1). The introduction of targeted therapies represents a major breakthrough in the treatment of ovarian cancer, as it has the potential to improve the survival rates and quality of life of patients (2). Among these targeted therapies, angiogenesis inhibitors and poly (ADP-ribose) polymerase inhibitors (PARPi) have played a leading role, targeting specific molecular pathways implicated in cancer progression and DNA repair, respectively (3,4). Different angiogenesis inhibitors and PARPi have been utilized due to their distinct mechanisms of action and varying effectiveness in targeting specific pathways involved in ovarian cancer progression (5). For example, anti-vascular endothelial growth factor (VEGF) agents such as bevacizumab specifically target the VEGF pathway and inhibit the formation of new blood vessels essential for tumor growth, while tyrosine kinase inhibitors (TKIs) such as anlotinib offer a broader inhibition of angiogenesis by targeting multiple receptors (6). These differences may account for the variability in clinical outcomes observed for combinations with PARPi, which impair the DNA repair mechanisms of cancer cells. Understanding these mechanisms provides a rationale for the selection of particular combinations based on the unique clinical and molecular context of each patient.

Angiogenesis plays a pivotal role in tumor growth and metastasis, as it facilitates the supply of nutrients and oxygen

to the tumor (7). Anti-angiogenic therapies, particularly those targeting the VEGF pathway, have shown promise in the inhibition of tumor vascularization (8). Conversely, PARPi exploit the concept of synthetic lethality to selectively kill cancer cells with homologous recombination deficiencies by further impairing their DNA repair capabilities (9). This approach has been demonstrated to be particularly effective in BRCA-mutated ovarian cancer, in which the DNA repair mechanisms are already compromised (10).

Mutations of the BRCA1 and BRCA2 genes are known to impair homologous recombination, a critical DNA repair pathway. Patients with these mutations are more susceptible to DNA damage, making them particularly responsive to PARPi therapy, which further disrupts the already weakened DNA repair mechanisms. Therefore, the presence of BRCA mutations has become an important predictive biomarker for the efficacy of PARPi, which can be used to guide personalized treatment approaches in ovarian cancer (11).

Recent research has posited the potential for synergistic effects when angiogenesis inhibitors and PARPi are combined. The rationale is that inhibiting angiogenesis while simultaneously blocking DNA repair pathways may lead to enhanced tumor regression (12). However, the evidence to date has been mixed, with a significant heterogeneity in outcomes across studies, which has prompted the suggestion that a more comprehensive analysis is necessary to obtain an improved understanding of the efficacy and safety of these combination therapies (13).

Patient-specific factors, such as BRCA mutation status, have emerged as crucial determinants of the response to these treatments (14). A recent systematic review and meta-analysis by Wei *et al* (15) focused on the overall efficacy and safety of PARP inhibitors combined with antiangiogenic agents in ovarian cancer and analyzed the general effects of such combinations. By contrast, the aim of the present study was to investigate the efficacy of different types of antiangiogenic agents when used in combination with PARP inhibitors. Furthermore, the impact of BRCA mutation status on the effectiveness of these combined treatments were explored. By addressing these two aspects, the present study provides a more comprehensive and personalized understanding of how the type of antiangiogenic agent and the BRCA mutation status both influence treatment outcomes in ovarian cancer. Through this approach, it is hoped to obtain a granular understanding of treatment efficacy and safety profiles, ultimately guiding clinical decision-making and contributing to personalized medicine strategies.

Materials and methods

Literature inclusion and exclusion criteria

Inclusion criteria. The inclusion criteria were as follows: i) Study design: Randomized controlled trials (RCTs) and single-arm trials on the combined treatment of ovarian cancer with anti-angiogenic agents combined with PARPi. The language was limited to English. ii) Study subjects: Patients with a confirmed diagnosis of ovarian cancer were included without restrictions on race or age. iii) Interventions: In the control group, if included, the patients received monotherapy with anti-angiogenic agents or PARPi, and in the experimental group, patients received combination therapy using anti-angiogenic agents and PARPi. iv) Outcome measures: The objective response rate (ORR), disease control rate (DCR), median progression-free survival (mPFS) and incidence of adverse events (grade >3) were assessed.

Exclusion criteria. The exclusion criteria were as follows: i) Case reports, review articles and duplicates of previously published studies. ii) Studies on animals and basic research. iii) Literature not meeting the inclusion criteria. iv) Studies with flawed research designs or treatment measures unrelated to the experiment. v) Literature without valid information and data.

Literature search. The literature search was conducted using Embase (https://www.embase.com/), PubMed (https://pubmed.ncbi.nlm.nih.gov/) and The Cochrane Library (https://www.cochranelibrary.com/) databases. The publication dates searched for were from database inception until February 2024. The search terms were a combination of MeSH terms and entry terms. The search terms included: ((((((((((‘ovarian neoplasms’[Mesh]) OR (ovarian neoplasm[Title/Abstract])) OR (ovary neoplasms[Title/Abstract])) OR (ovary neoplasm [Title/Abstract])) OR (ovary cancer[Title/Abstract])) OR (ovary cancers[Title/Abstract])) OR (ovarian cancer [Title/Abstract])) OR (ovarian cancers[Title/Abstract])) OR (cancer of ovary[Title/Abstract])) OR (cancer of the ovary[Title/Abstract])) AND ((((niraparib[Title/Abstract]) OR (olaparib[Title/Abstract])) OR (veliparib[Title/Abstract])) OR (rucaparib[Title/Abstract]))) AND (((((anlotinib [Title/Abstract]) OR (cediranib[Title/Abstract])) OR (bevacizumab[Title/Abstract])) OR (sorafenib[Title/Abstract])) OR (apatinib[Title/Abstract])).

Data extraction. Two researchers independently conducted the screening and data extraction based on the inclusion and exclusion criteria. In case of discrepancies between the two researchers, disagreements were resolved through discussion or, if needed, with the judgement of the third researcher.

Literature quality assessment. Two independent researchers used the Methodological Index for Non-Randomized Studies (MINORS) (16) to evaluate the quality of evidence for each study. This index includes 12 items, each with a mean score of 0-2, giving a maximum total of 24 points. The studies are categorized by score as ‘moderate quality’, defined as a score of 9-16, and ‘high quality’, defined as a score of 17-24. For RCTs, Review manager 5.3 software risk assessment tool was used to evaluate the included literature according to random sequence generation, allocation concealment, blinding, whether research results were blinded to review, completeness of outcome data, selection of reported research outcomes and other biases. The meta-analysis was performed in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement (17).

Data synthesis and statistical analysis. Data were analyzed using STATA 15.1 (StataCorp LLC) (18). The forest plots generated in this analysis visually represent the summary of individual study results, including key parameters such as the relative risk (RR), hazard ratio (HR) and effect size

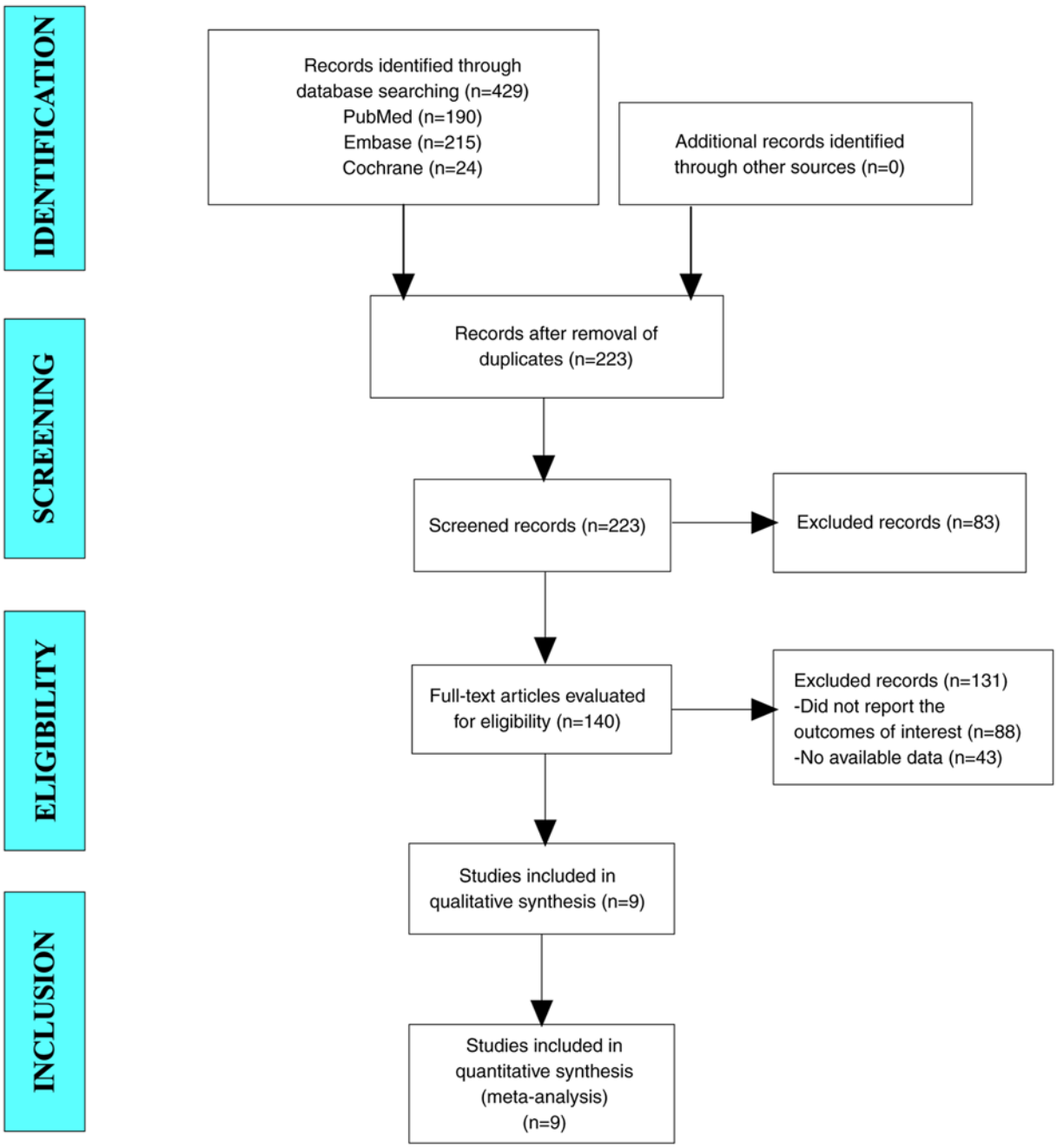

Figure 1. Flow diagram for the selection of studies.

(ES), and the associated 95% confidence interval (95% CI). I^2 was used to evaluate heterogeneity. If the test yielded $P<0.1$ and $I^2>50\%$, significant heterogeneity was indicated. If heterogeneity was indicated, whether any specific study was the source of the heterogeneity was identified using sensitivity analysis. In the sensitivity analysis, every trial was excluded individually and a combined analysis of the remaining trials was performed. Additionally, the contribution of each study to the pooled result was indicated by its %weight, which reflects the influence of the study based on its sample size and variability. Studies with larger sample sizes or lower variability provide a greater contribution to the overall estimate; thus, they contribute more heavily to the meta-analysis. A random-effects model was used for the pooling effect in all meta-analyses. Publication bias was analyzed using funnel plots and Egger's test, with $P>0.05$ indicating no publication bias.

Results

Literature search results. A total of 429 articles were initially identified for potential inclusion in the present study. After the exclusion of duplicate studies, 223 articles remained. After reading the titles and abstracts, a total of 140 articles were selected for further evaluation. Ultimately, 9 studies were integrated into the meta-analysis (Fig. 1) (19-27).

Baseline characteristics and quality assessment of the included studies. The 9 studies included in the study were conducted in various countries, namely the USA, Korea, Canada, China

Table I. Baseline characteristics and quality assessment of the included studies.

First author, year	NCT registration no.	Country	Study design	Sample size	Age, years, median (range)	Treatments	BRCA mutation, status n with/n without	MINORS score	(Refs.)
Lee *et al*, 2022	NCT02889900	USA	Single-arm	60	64.5 (42-80)	Cediranib + olaparib	-	19	(19)
Lee *et al*, 2022	NCT03699449	Korea	Single-arm	16	58.0 (47-76)	Cediranib + olaparib	-	18	(20)
Lheureux *et al*, 2020	NCT02681237	Canada	Single-arm	34	-	Cediranib + olaparib	-	17	(21)
Liu *et al*, 2022	NCT02446600	USA	RCT	189[a]/189[b]	-	Cediranib + olaparib/olaparib	45/144[a], 45/144[b]	-	(22)
Liu *et al*, 2022	NCT04376073	China	Single-arm	40	54.0 (37-69)	Anlotinib + niraparib	5/35	18	(23)
Liu *et al*, 2014	NCT01116648	USA	RCT	44[a]/46[b]	57.8 (41.9-85.6)[a]/ 58.1 (32.7-81.9)[b]	Cediranib + olaparib/plaparib	23/21[a], 24/22[b]	-	(24)
Mirza *et al*, 2019	NCT02354131	USA	RCT	48[a]/49[b]	67 (59-70)[a]/ 66 (58-70)[b]	Bevacizumab + niraparib/niraparib	15/33[a], 18/31[b]	-	(25)
Hardesty *et al*, 2022	NCT03326193	USA	Single-arm	105	60.0 (54-67)	Bevacizumab + niraparib	-	18	(26)
Ray-Coquard *et al*, 2023	NCT02477644	Germany	RCT	537[a]/269[b]	61 (32-87)[a]/ 60 (26-85)[b]	Bevacizumab + olaparib/bevacizumab	-	-	(27)

[a]Combination therapy; [b]monotherapy. NCT, National Clinical Trial; MINORS, Methodological Index for Non-Randomized Studies; RCT, randomized controlled trial.

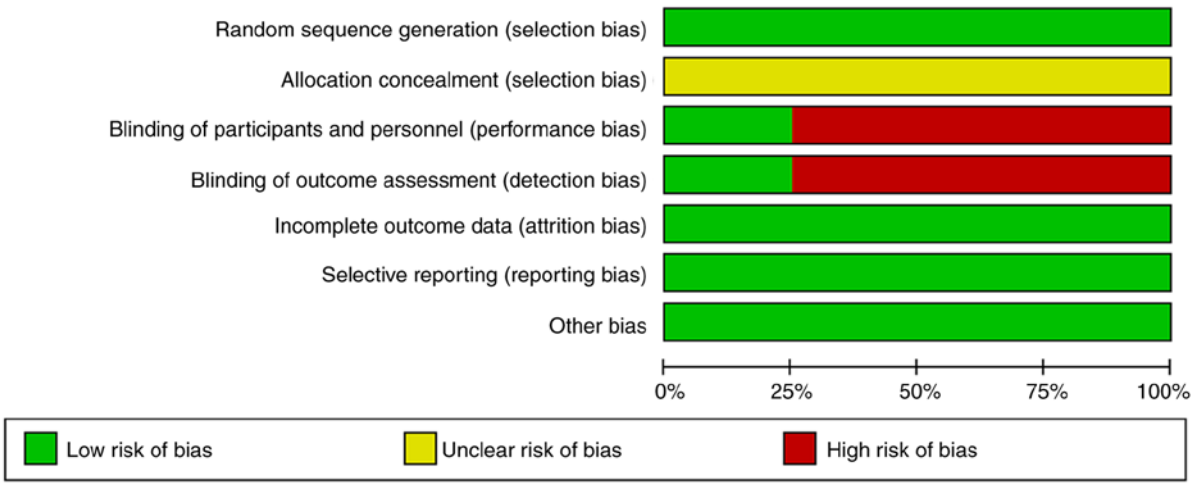

Figure 2. Risk of bias graph for the randomized controlled trials.

and Germany. They comprised 5 single-arm trials and 4 RCTs, with sample sizes ranging from 16 to 537 participants in the combination therapy groups. The interventions investigated were cediranib plus olaparib, anlotinib plus niraparib, and bevacizumab plus niraparib or olaparib, which reflect a diverse approach to the targeting of ovarian cancer. Age data, where available, indicate the participants ranged broadly from their 30 to 80s. However, 5 of the studies omitted specific data on BRCA mutation status, suggesting a gap in the genetic characterization of study populations. Quality assessment scores calculated using the MINORS criteria indicate that the included studies are of moderate to high quality, with scores between 17 and 19 (Table I).

The findings of quality assessment showed that the 4 RCT studies included in this review used random sequence generation. However, none of the studies described allocation concealment, and only one study used a double-blinding method (Figs. 2 and 3).

Meta-analysis results

ORR. Two studies compared the ORR of combination therapy with monotherapy in the treatment of ovarian cancer. Meta-analysis of the aggregated results using a random-effect model indicates that the ORR in the combination therapy group was significantly higher than that in the monotherapy group (RR, 1.41; 95% CI, 1.15-1.73; P<0.001; Fig. 4).

HR of PFS. Three studies documented the differences in PFS between combination therapy and monotherapy in the treatment of ovarian cancer. Significant heterogeneity was observed (I^2, 66.7%, P=0.049), and a random effects model was used. The pooled results indicate that combination therapy significantly prolongs PFS for ovarian cancer treatment compared with monotherapy (HR, 0.48; 95% CI, 0.32-0.73; P<0.001; Fig. 5).

ORR of combination therapy. Six studies reported the ORR for the treatment of ovarian cancer with angiogenesis inhibitors combined with PARPi. Significant heterogeneity was observed (I^2, 95.38%; P<0.001), and a random effects model was used. The pooled results indicate that the ORR for the treatment of ovarian cancer with anti-angiogenic agents combined with PARPi was 44% (95% CI, 20-70%; Fig. 6).

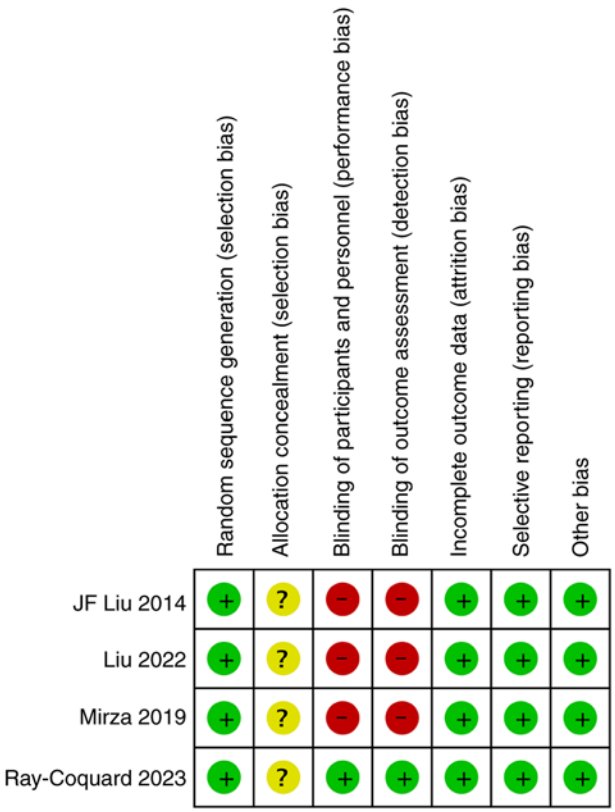

Figure 3. Risk of bias summary for the randomized controlled trials.

DCR of combination therapy. Five studies reported the DCR for the treatment of ovarian cancer with angiogenesis inhibitors combined with PARPi. Significant heterogeneity was observed (I^2, 96.16%; P<0.001), and a random effects model was used. The pooled results indicate that the DCR for the treatment of ovarian cancer with anti-angiogenic agents combined with PARPi was 74% (95% CI, 37-98%; Fig. 7).

mPFS. Six studies reported the mPFS for the treatment of ovarian cancer with angiogenesis inhibitors combined with PARPi. Significant heterogeneity was observed (I^2, 93.6%; P<0.001), and a random effects model was used. The pooled

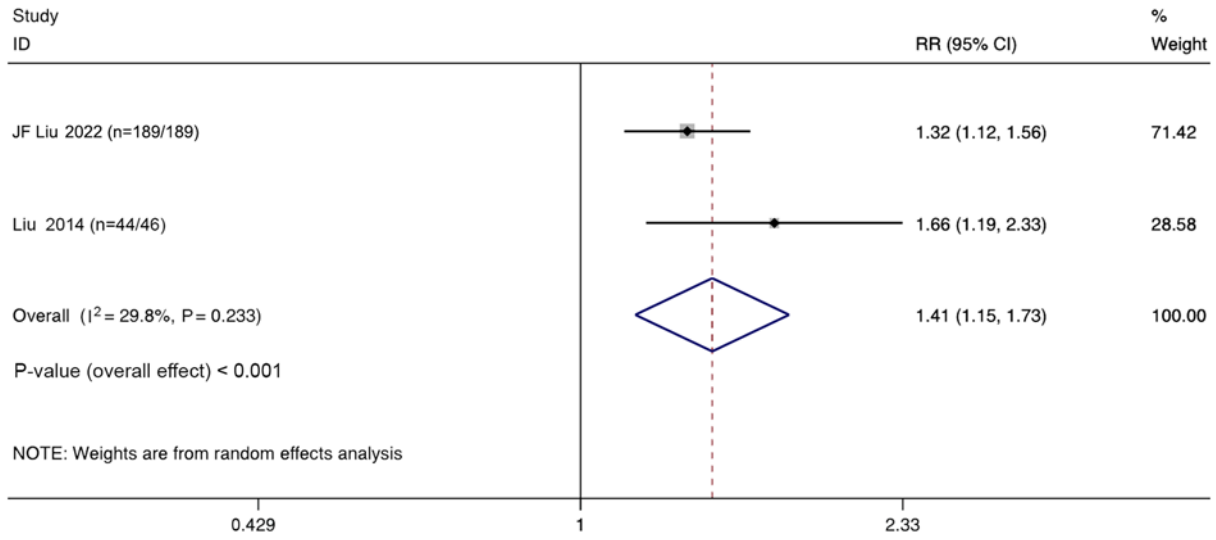

Figure 4. Comparison of the objective response rate between combination therapy and monotherapy in the treatment of ovarian cancer. RR, relative risk; CI, confidence interval.

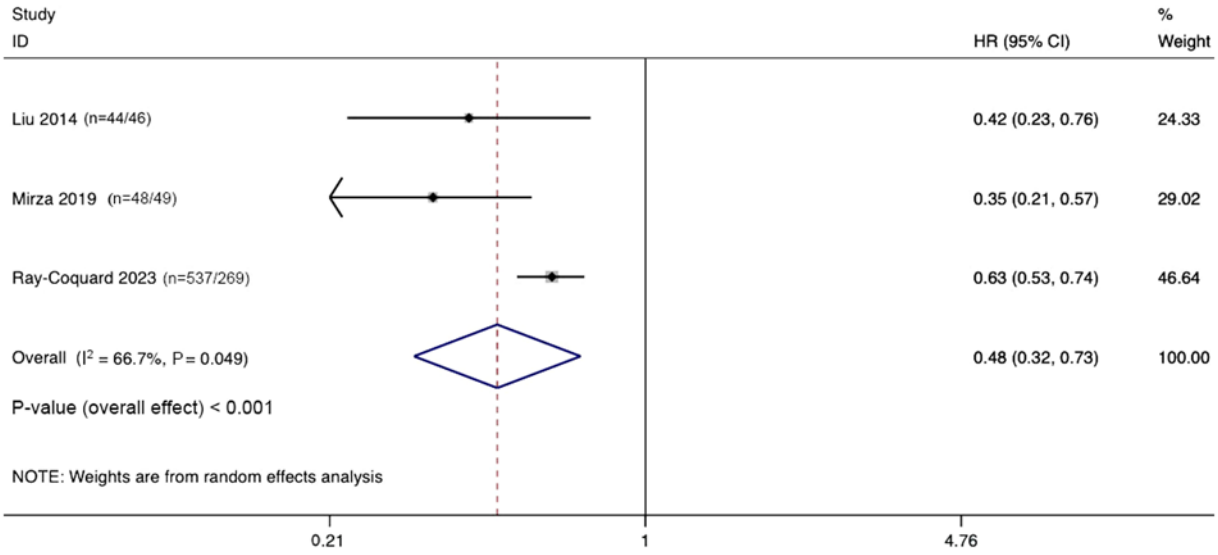

Figure 5. Comparison of progression-free survival between combination therapy and monotherapy in the treatment of ovarian cancer. HR, hazard ratio; CI, confidence interval.

results indicate that the mPFS for the treatment of ovarian cancer with anti-angiogenic agents combined with PARPi was 9.53 months (95% CI, 6.27-14.47 months; Fig. 8).

Incidence of adverse events (grade >3). Six studies reported the incidence of adverse events (grade >3) after the treatment of ovarian cancer with angiogenesis inhibitors combined with PARPi. Significant heterogeneity was observed (I^2, 87.42%; P<0.001), and a random effects model was used. The pooled results indicate that the incidence of adverse events after the treatment of ovarian cancer with anti-angiogenic agents combined with PARPi was 57% (95% CI, 39-73%; Fig. 9).

Subgroup analyses

ORR of combination therapy. Subgroup analysis based on BRCA mutation status using a random effects model showed that the ORR for patients with ovarian cancer and BRCA mutations treated with angiogenesis inhibitors combined with PARPi was 90% (95% CI, 81-97%), whereas the ORR for patients without BRCA mutations was only 61% (95% CI, 44-76%) (Fig. 10).

mPFS. A random effects model was used to perform a subgroup analysis, based on the type of angiogenesis inhibitor used for the combination therapy of patients with ovarian cancer. The analysis showed that the mPFS for patients treated with TKIs combined with PARPi was 7.49 months (95% CI, 5.08-11.03 months), while the mPFS for patients treated with anti-VEGF agents combined with PARPi was 15.53 months (95% CI, 9.53-25.30 months) (Fig. 11).

Additionally, a subgroup analysis based on the presence of BRCA mutations showed that ovarian cancer patients with BRCA mutations treated with angiogenesis inhibitors combined with PARPi had a mPFS of 17.38 months (95%

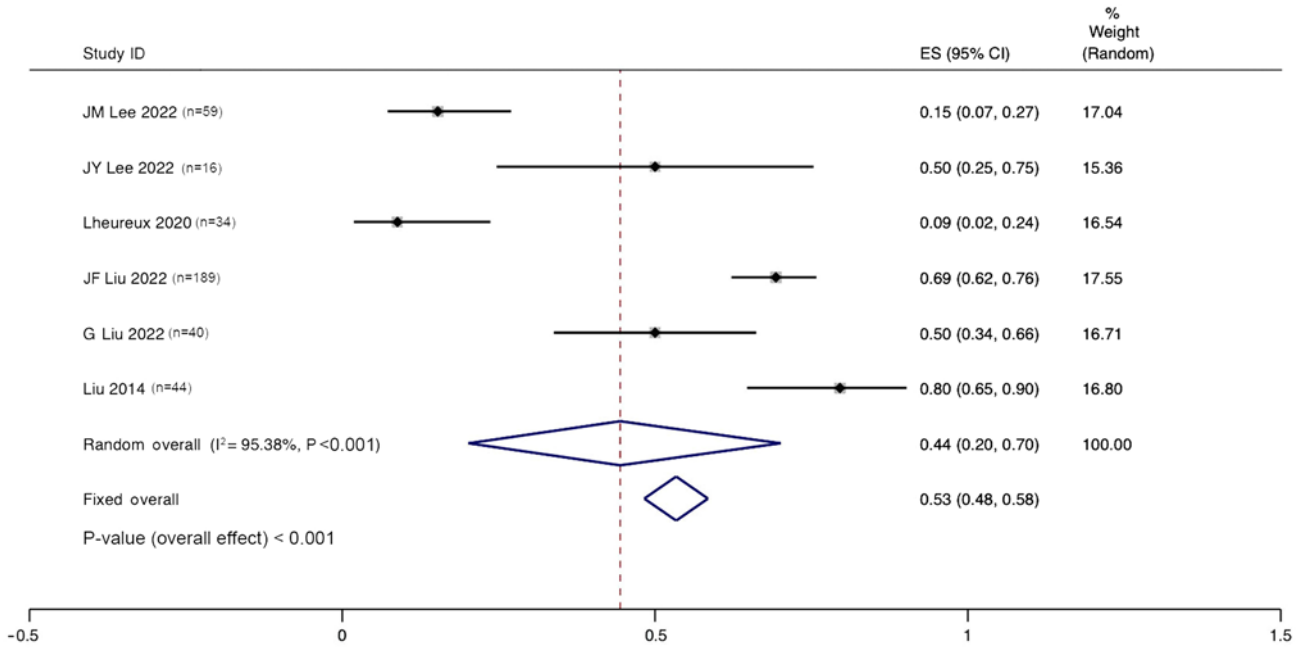

Figure 6. Pooled objective response rate for the treatment of ovarian cancer with anti-angiogenic agents combined with poly (ADP-ribose) polymerase inhibitors. ES, effect size; CI, confidence interval.

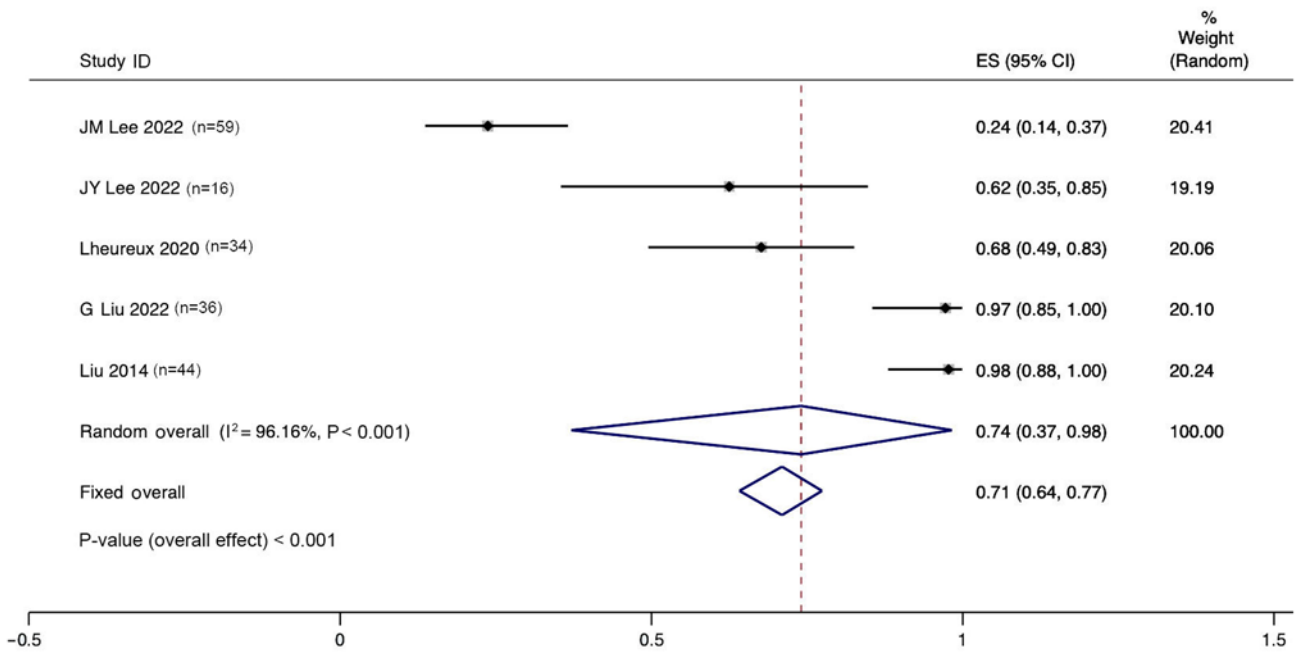

Figure 7. Pooled disease control rate for the treatment of ovarian cancer with anti-angiogenic agents combined with poly (ADP-ribose) polymerase inhibitors. ES, effect size; CI, confidence interval.

CI, 13.43-22.49 months). By contrast, the mPFS for patients without BRCA mutations was only 9.00 months (95% CI, 8.06-10.04 months) (Fig. 12).

Sensitivity analysis. The sensitivity analysis indicated that no study had a great influence on the results, suggesting that the results of the present study are reliable and stable (Fig. S1-S5).

Publication bias. A funnel plot was constructed for the present meta-analysis (Fig. 13). It is largely symmetrical, with P=0.330 from Egger's test, indicating that there was no significant publication bias in the present meta-analysis.

Discussion

The present meta-analysis provides a critical evaluation of the efficacy and safety of different angiogenesis inhibitors combined with PARPi in the treatment of ovarian cancer. The results demonstrate a significant improvement in ORR and mPFS when combination therapy is employed compared with

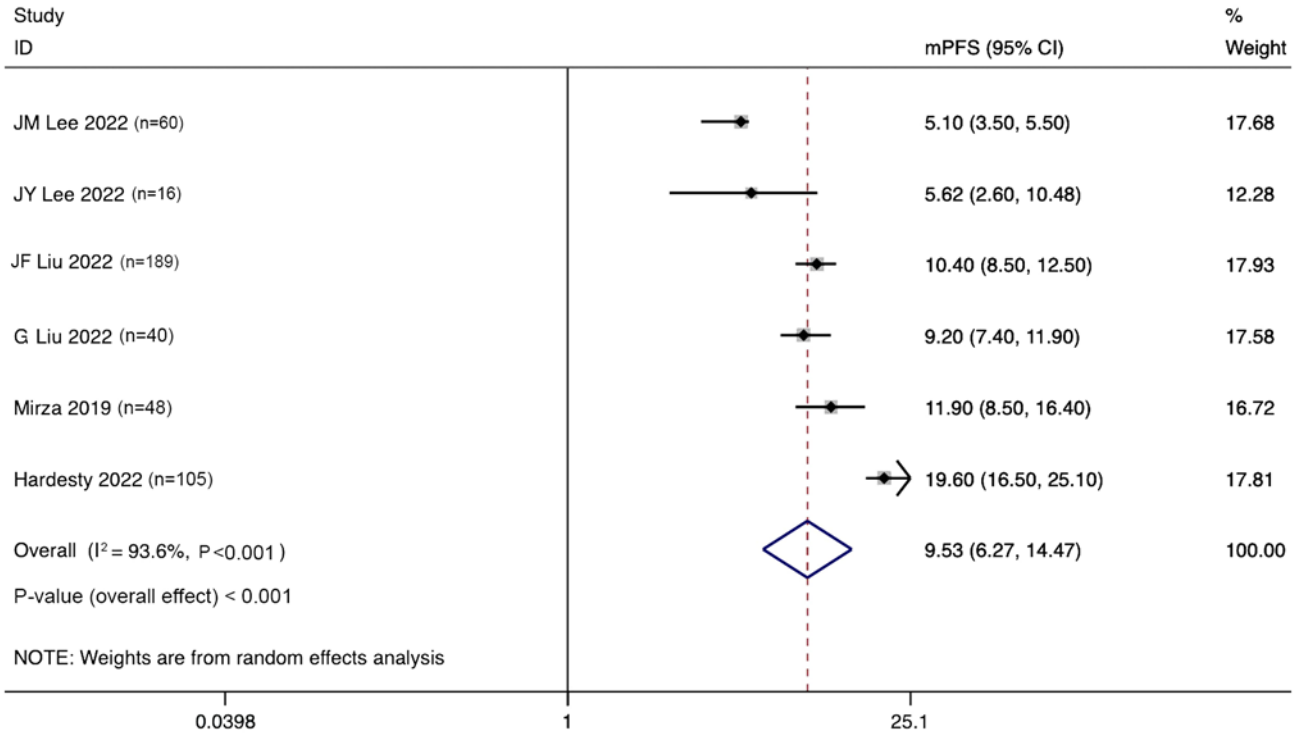

Figure 8. Pooled mPFS for the treatment of ovarian cancer with anti-angiogenic agents combined with poly (ADP-ribose) polymerase inhibitors. mPFS, median progression-free survival; CI, confidence interval.

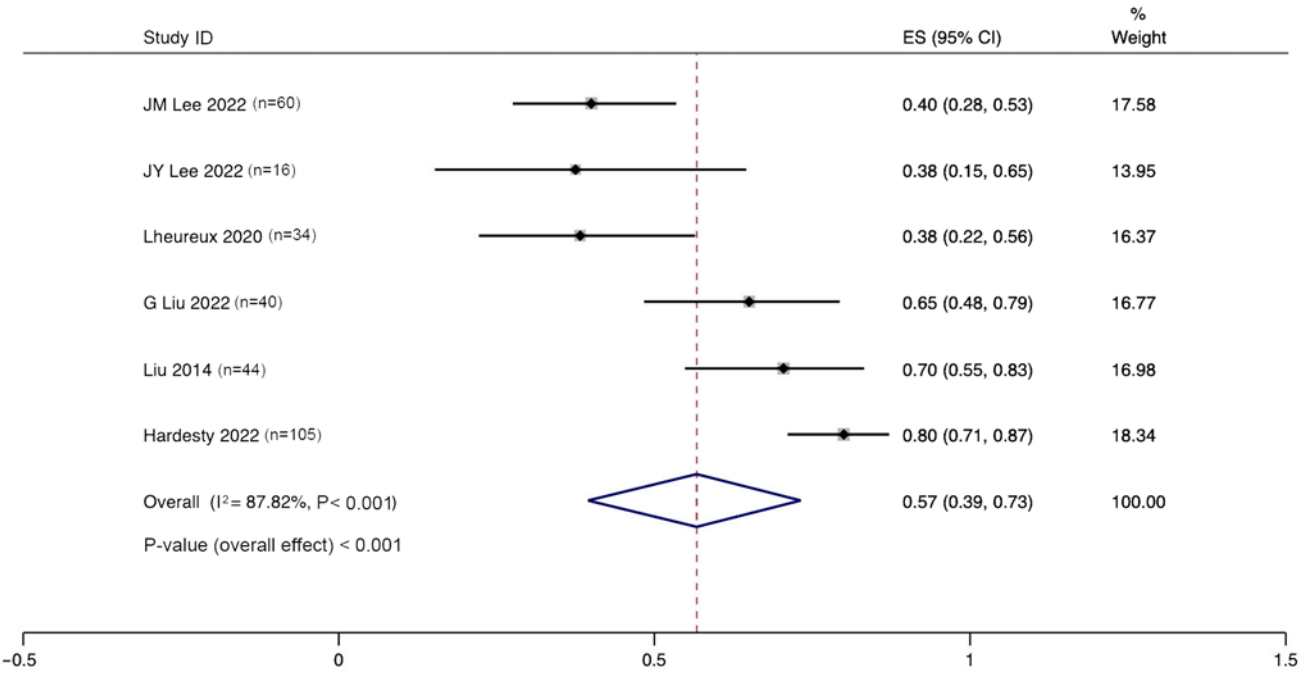

Figure 9. Incidence of adverse events after the treatment of ovarian cancer with anti-angiogenic agents combined with poly (ADP-ribose) polymerase inhibitors. ES, effect size; CI, confidence interval.

monotherapy. Notably, the subgroup analysis revealed distinct differences in efficacy between TKIs and anti-VEGF agents when combined with PARPi, highlighting the complexity involved in the optimization of combination therapy for patients with ovarian cancer.

Combination therapy had a pooled ORR of 44%, and induced a marked improvement in mPFS, underscoring the therapeutic potential of this strategy. Such findings align with previous research suggesting that the simultaneous inhibition of angiogenesis and DNA repair pathways can synergistically hinder tumor growth (28,29). In present study, the superior performance of anti-VEGF agents over TKIs in the treatment of ovarian cancer, as indicated by a mPFS of 15.53 months compared with 7.49 months, respectively, suggests that the

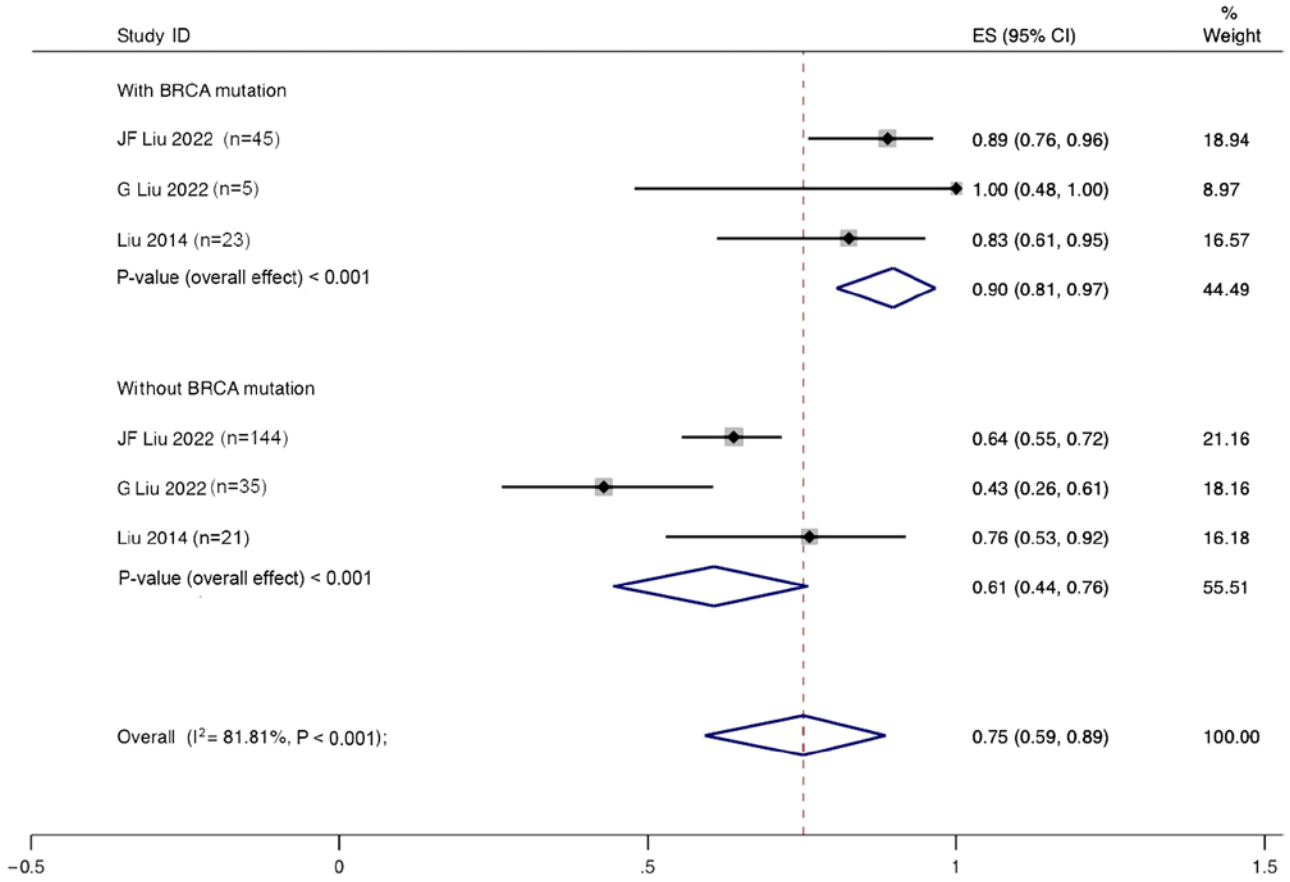

Figure 10. Subgroup analysis of the objective response rate for the treatment of ovarian cancer with anti-angiogenic agents combined with poly (ADP-ribose) polymerase inhibitors, based on the presence of BRCA mutations. ES, effect size; CI, confidence interval.

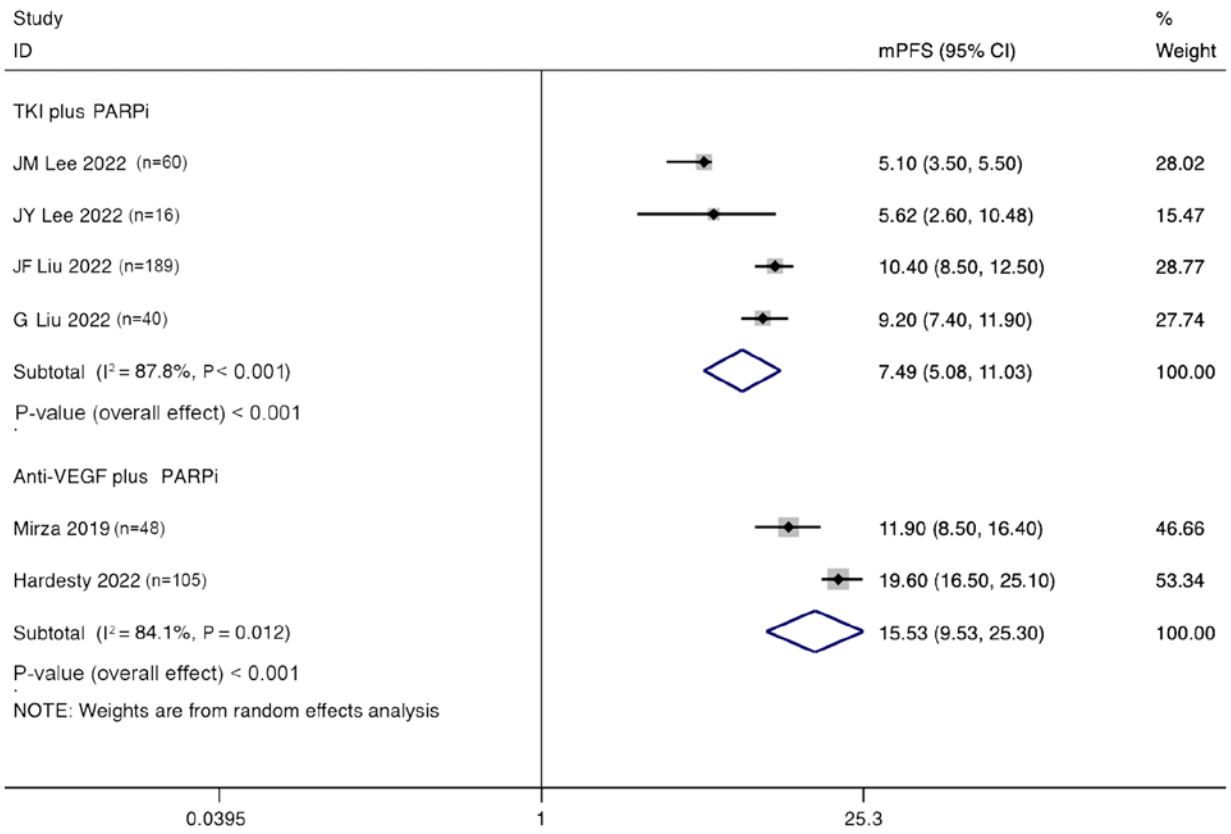

Figure 11. Subgroup analysis of mPFS in ovarian cancer treated with different angiogenesis agents combined with PARPi. mPFS, median progression-free survival; CI, confidence interval; PARPi, poly (ADP-ribose) polymerase inhibitors; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.

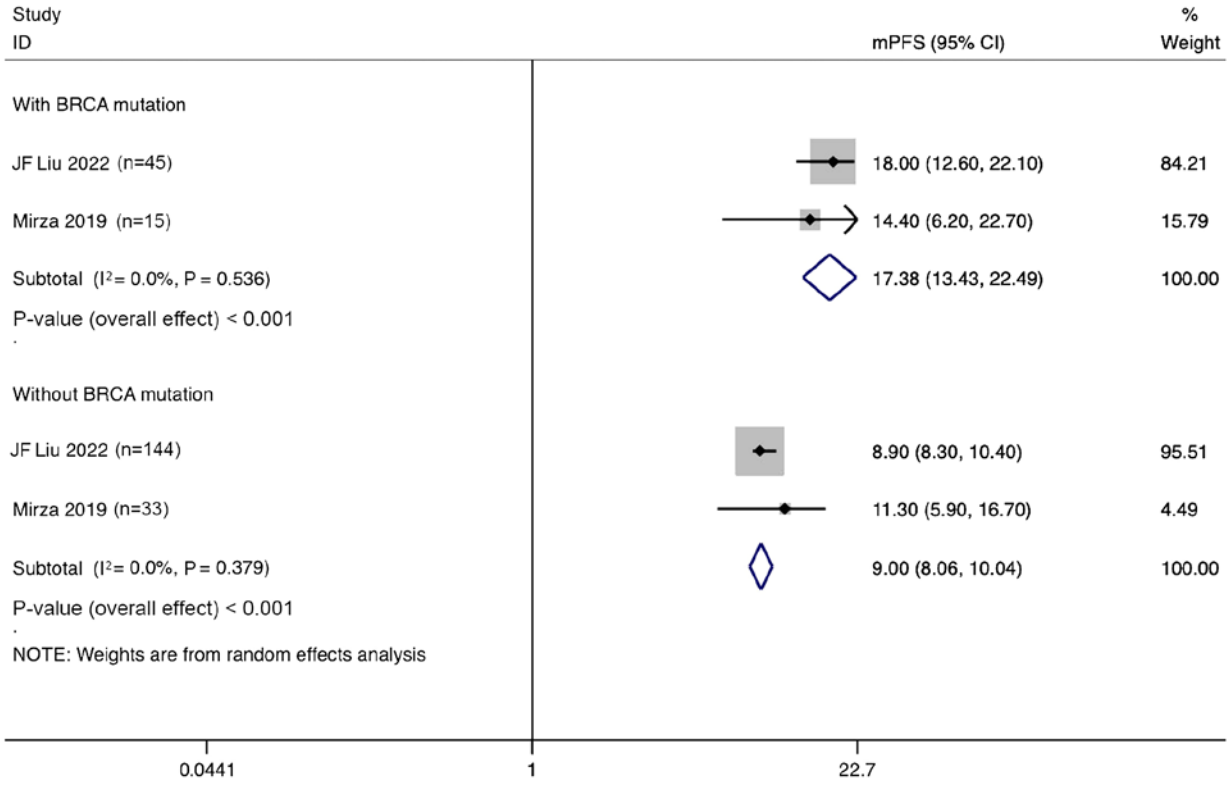

Figure 12. Subgroup analysis of the mPFS for the treatment of ovarian cancer with anti-angiogenic agents combined with poly (ADP-ribose) polymerase inhibitors, based on the presence of BRCA mutations. mPFS, median progression-free survival; CI, confidence interval.

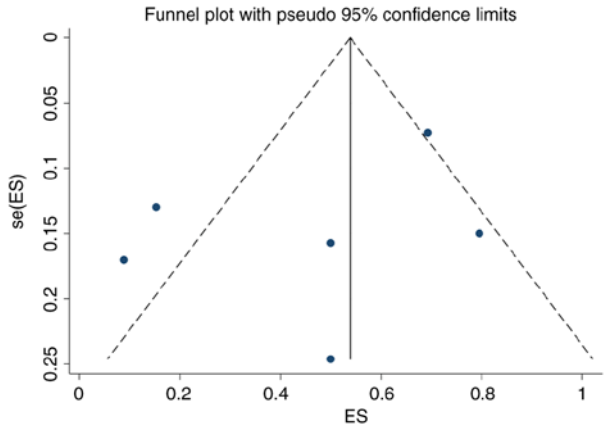

Figure 13. Funnel plot evaluating the publication bias of the present meta-analysis. ES, effect size; se, standard error.

specificity of anti-VEGF agents in targeting the VEGF pathway may confer a more potent anti-angiogenic effect, thereby enhancing the effectiveness of PARPi. Moreover, the pronounced benefit in ORR and mPFS observed in patients with BRCA mutations compared with those without BRCA mutations when treated with anti-VEGF agents and PARPi emphasizes the importance of genetic profiling in tailoring treatment strategies. This supports the notion that individuals with inherent DNA repair deficiencies are more susceptible to treatments targeting DNA repair mechanisms, a concept that is gaining traction in personalized oncology (30). The clinical translation of these insights necessitates a nuanced approach, underpinned by the principles of precision medicine. The differential treatment outcomes observed indicate that it is imperative to adopt a more individualized approach to treatment planning. This entails leveraging the comprehensive genetic and molecular profiling of tumors to discern patient-specific vulnerabilities that these combination therapies can exploit (31). For instance, the distinct advantage observed in patients with BRCA mutations when treated with this combination therapy underscores the importance of genetic markers in predicting therapeutic success (32). This stratification not only aids in the identification of candidates likely to derive the most benefit but also in the tailoring of treatment regimens to mitigate potential adverse effects, thus optimizing patient outcomes. Moreover, the variance in efficacy between different classes of angiogenesis inhibitors when used in conjunction with PARPi suggests a pivotal area for future clinical research. It beckons the design of clinical trials aimed at elucidating the underlying mechanisms of this differential response, which could, in turn, inform the development of more effective combination strategies (33). Such endeavors would not only contribute to the refinement of current treatment paradigms but also assist in the identification of novel therapeutic targets within these pathways.

Despite the promising findings of the present meta-analysis, the marked heterogeneity observed across the studies underscores the complexity of ovarian cancer treatment. This variability highlights that personalized approaches, involving the consideration of genetic and molecular tumor profiles, are necessary to optimize therapeutic outcomes. Furthermore, the 57% incidence of adverse events (grade >3) in patients treated with combination therapy indicates that cautious patient management is necessary and underscores the necessity for ongoing research into the mitigation of treatment-related toxicities.

The present study has certain limitations, Firstly, there is some heterogeneity among the studies, which might be attributed to the different PARPi used. Future studies are necessary in which more unified research designs and more consistent patient cohorts are implemented. Additionally, most of the included studies focused on short-term treatment effects, such as the ORR and mPFS, and data on long-term or OS rates, quality of life and follow-up after treatment are lacking. Therefore, our understanding of the long-term benefits of these treatment strategies remains limited. Another limitation of the present study is the relatively small sample size, as only a small number of studies met the rigorous inclusion criteria from an initial pool of 140 articles. This may affect the generalizability and consistency of the findings. Despite this, meta-analytical techniques and sensitivity analyses were employed to ensure the robustness of the results, although the small sample size remains a consideration.

In conclusion, the present study highlights the significant therapeutic potential of combining angiogenesis inhibitors with PARPi in the treatment of ovarian cancer. The findings suggest that this combination therapy can offer enhanced efficacy, particularly in patients with BRCA mutations, who are more likely to benefit from the combined effects of these agents. The comparative analysis between TKIs and anti-VEGF agents reveals distinct differences in their effectiveness, emphasizing the importance of selecting the appropriate angiogenesis inhibitor based on the molecular and genetic characteristics of the tumor.

The results underscore the critical requirement for personalized treatment strategies that leverage comprehensive genetic and molecular profiling to optimize therapeutic outcomes. While the combination of angiogenesis inhibitors and PARPi shows promise, further research is necessary to fully understand the long-term benefits and potential risks of such combinations, particularly regarding OS. Future studies should also explore the development of biomarkers to better predict patient response and refine treatment protocols, which should ultimately advance the field of ovarian cancer therapy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XH and JL made substantial contributions to conception and design. XH wrote the manuscript and JL created the figures. LG participated in the acquisition of data. XH and LG confirm the authenticity of all the raw data. All authors read and approved the final version of the 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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