Efficacy and safety of immune checkpoint inhibitors combined with anti-angiogenic agents for advanced cervical cancer: A systematic review and meta-analysis

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Abstract. Combining anti-angiogenic agents with immune checkpoint inhibitors (ICIs) may improve clinical outcomes in patients with advanced cervical cancer. However, the majority of available evidence is derived from small-sample single-arm trials. The present systematic review and meta-analysis aimed to evaluate the efficacy and safety of this combination regimen in patients with advanced cervical cancer. A systematic search was conducted across eight major databases, including PubMed, the Cochrane Library, Embase, Web of Science, Chinese National Knowledge Infrastructure, Chinese Biological Medicine Database, Wanfang Data and VIP Database, with a retrieval cutoff date of April 14, 2026. Sensitivity analysis and heterogeneity testing were subsequently performed. A total of five clinical trials encompassing 336 patients fulfilled the predefined inclusion criteria. Pooled analyses were conducted for several endpoints, namely objective response rate (ORR), disease control rate (DCR), median progression-free survival (PFS), overall survival (OS), 1-year overall survival rate (1-y OSR) and the incidence of adverse events (AEs). A total of five independent trial cohorts comprising 336 patients were ultimately included in the pooled analysis. The synthetic results revealed a pooled ORR of 37% and a DCR of 80%. The pooled PFS and OS were 8.05 months and 20.24 months, respectively, with a pooled 1-y OSR of 62%. For grade 1-2 AEs, the most common were proteinuria (42%), increased aspartate aminotransferase (38%), increased alanine aminotransferase (33%), diarrhea (30%) and decreased platelet count (30%). Only two grade ≥3 AEs had an incidence >10%, while all others had an incidence <3%. These two events were anemia and hypertension with incidences of 14 and 13%, respectively. Treatment-related mortalities were reported in two trials, involving a total of five cases. The present meta-analysis indicates that combination therapy with anti-angiogenic agents and ICIs confers potential survival benefits alongside a tolerable and manageable safety profile for patients with advanced cervical cancer. Nonetheless, these findings should be interpreted with caution, due to the limited number of included studies and the occurrence of treatment-related mortalities.

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Introduction

Cervical cancer remains a major global health challenge, ranking as the 4th leading cause of cancer incidence and mortality among women worldwide, with an estimated 604,000 new cases and 342,000 mortalities reported annually (1). The development of metastatic, persistent or recurrent disease, which is not amenable to curative local therapy, leads to a particularly worse prognosis, with limited treatment options available (2). Despite the emergence of novel treatment regimens in previous years, patients diagnosed with recurrent or metastatic cervical cancer continue to face a worse prognosis (3). Thus, the development of innovative therapeutic strategies represents a key unmet need in this field.

The incorporation of the anti-angiogenic agent bevacizumab into platinum-based chemotherapy as a standard first-line treatment regimen, based on the GOG 240 trial,

marked a major advancement, demonstrating notable improvement in overall survival (OS) (4-6). Despite this progress, the median OS remains unsatisfactory, underscoring the persistent urgent need for more effective therapeutic approaches (6). The integration of immune checkpoint inhibitors (ICIs) has begun to transform the treatment landscape for advanced cervical cancer. For instance, pembrolizumab monotherapy received approval for programmed death-ligand 1 (PD-L1)-positive advanced cervical cancer based on modest yet notable objective response rates (ORRs) (7).

However, the limited efficacy of ICI monotherapy has prompted exploration of combination strategies, particularly with anti-angiogenic agents, due to their complementary mechanisms of action. The scientific rationale for combining immunotherapy with anti-angiogenic agents stems from the intricate bidirectional interplay between the tumor vasculature and the immune microenvironment. VEGF-mediated angiogenesis not only drives tumor growth and metastasis but also creates a profoundly immunosuppressive state by impairing T cell infiltration, proliferation and effector function (8,9). Concurrently, PD-L1 is frequently expressed in cervical cancer tissues, facilitating immune evasion. Preclinical models and clinical studies in other types of cancer suggest that VEGF inhibition can enhance the efficacy of ICIs by normalizing tumor vasculature and reversing immunosuppression (10,11).

This therapeutic combination has been successfully validated in other solid tumor types, which has stimulated a growing number of clinical trials investigating ICI-anti-angiogenic regimens specifically in cervical cancer (12-14). Initial studies (15-18), such as a phase II trial of atezolizumab combined with bevacizumab, explored this combination in previously treated patients; however, the results indicated that the addition of bevacizumab to PD-L1 blockade did not notably improve the ORR in patients who had received prior bevacizumab therapy (18). By contrast, different combinations have shown greater promise. The phase II trial of camrelizumab [an anti-programmed cell death protein 1 (PD-1) antibody] plus famitinib (a multi-targeted tyrosine kinase inhibitor) demonstrated promising antitumor activity with an ORR of 39.4% and a median progression-free survival (PFS) of 10.3 months in patients with pretreated recurrent or metastatic cervical squamous cell carcinoma (15). Similarly, sintilimab combined with anlotinib yielded an ORR of 54.8% and a median PFS of 9.4 months when administered as second-line or later therapy for patients with PD-L1-positive disease (17). Most notably, the phase III BEATcc trial suggested that the addition of atezolizumab to bevacizumab combined with platinum-based chemotherapy resulted in notable improvements in both PFS and OS (19).

Despite the therapeutic advances achieved with the incorporation of bevacizumab into standard chemotherapy regimens, the prognosis for patients with recurrent or metastatic cervical cancer remains poor (5). Concurrently, several phase II trials of ICIs combined with anti-angiogenic agents have reported encouraging but fragmented results (15-18), and no prior meta-analysis has systematically pooled these data across different ICI-anti-angiogenic combinations in advanced cervical cancer. Therefore, the present systematic review and meta-analysis aimed to comprehensively synthesize and evaluate the efficacy and safety of ICIs combined with anti-angiogenic therapy for patients with advanced cervical cancer, with the goal of providing evidence-based guidance for clinical decision-making and informing the design of future clinical trials.

Materials and methods

The present systematic review and meta-analysis was performed and reported in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (20).

Search strategy and registration. A comprehensive literature search was systematically conducted across eight databases including PubMed (https://pubmed.ncbi.nlm.nih.gov), the Cochrane Library (https://www.cochranelibrary.com), Embase (https://www.embase.com), Web of Science (https://www.webofscience.com), Chinese National Knowledge Infrastructure (CNKI; https://www.cnki.net), Chinese Biological Medicine Database (CBM; https://www.sinomed.ac.cn), Wanfang Data (https://www.wanfangdata.com.cn) and VIP Database (https://www.cqvip.com) to identify all relevant clinical studies published up to April 14, 2026. The search strategy was developed based on the Population, Intervention, Comparison and Outcome framework with the following components: Population (advanced cervical cancer), intervention (ICIs combined with anti-angiogenic agents) and outcomes (efficacy and safety) (21). The full search terms were: 'Angiogenesis Inhibitors' OR 'Angiostatic Agents' OR 'Neovascularization Inhibitors' OR 'Angiogenesis Factor Inhibitors' OR 'Anti-Angiogenesis Effects') AND ('Immunotherapy' OR 'Immune Checkpoint Inhibitors' OR 'Nivolumab' OR 'Opdivo' OR 'Pembrolizumab' OR 'PD-1 inhibitors' OR 'PD-L1 inhibitors') AND ('Uterine Cervical Neoplasms' OR 'Cervical Cancer' OR 'Cancer of the Cervix'). The present meta-analysis was registered with PROSPERO (registration no. CRD420251036185). As only published statistical data were utilized, ethical approval was deemed unnecessary for the present systematic review.

Inclusion and exclusion criteria. Studies were eligible for inclusion if they met all the following criteria: i) Patients with advanced or metastatic cervical cancer; ii) treatment regimens consisting of ICIs combined with anti-angiogenic agents; iii) phase I, II or III clinical trials; and iv) the outcome indicators included ORR, PFS and adverse events (AEs). The exclusion criteria encompassed: i) Duplicate publications, review articles, animal trials, case reports and retrospective studies; and ii) incomplete or statistically inconsistent outcomes. Two independent investigators performed the initial title and abstract screening against the predefined eligibility criteria. Full-text articles of potentially relevant studies were subsequently retrieved and assessed for final inclusion. Any discrepancies between the two investigators were resolved through consensus or by adjudication with a third senior researcher. Following the screening process, six articles met all the inclusion criteria. Notably, these six articles reported findings from five independent clinical trial cohorts; therefore, only five unique cohorts were included in the final meta-analysis.

Data extraction and quality assessment. Two investigators independently extracted data from the final study set, capturing the following key information: First author, registration number, treatment regimens and efficacy/safety outcomes (including PFS, OS, ORR, AEs and ≥3 AEs). Since the present meta-analysis was designed as a single-arm study, non-comparative data from individual treatment arms were exclusively extracted. Consequently, regardless of whether the original study employed a randomized or single-arm design, the analyzed data were evaluated as non-randomized studies of interventions. The Jadad scale was not applied, as it is designed exclusively for randomized controlled trials, whereas the majority of the included studies were single-arm, non-randomized trials. Accordingly, the quality of these studies was evaluated by employing the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) (22). The present risk-of-bias evaluation covered six core domains: Participant selection, confounding variables, measurement of exposure, blinding of outcome assessors' assessments, incomplete data and selective outcome reporting. Two reviewers independently assigned risk-of-bias ratings (low, moderate or high) to each study, with inconsistencies being resolved through discussion with a third researcher.

Statistical analysis. Study quality assessments were performed using Review Manager software (version 5.4; The Cochrane Collaboration) and all statistical analyses were conducted using STATA software (version 15.0; StataCorp LLC). Due to the inherent heterogeneity expected across studies from different populations and settings, a random-effects model was applied for all meta-analyses, regardless of the I^2 value. For binary outcomes [ORR, disease control rate (DCR) and AEs], Freeman-Tukey double arcsine transformation was applied to stabilize the variance and approximate normality, and a random-effects meta-analysis was then performed on the transformed scale using the random-effects model [DerSimonian-Laird (DL) estimator] for between-study heterogeneity, with inverse-variance weighting; the pooled estimates and their 95% CIs were subsequently back-transformed to the original proportion scale for presentation (23). For time-to-event outcomes (PFS and OS), reported median times were first natural-log-transformed, then pooled on the log scale using DL estimator with inverse-variance weighting and finally exponentiated back to the original month scale (24). Heterogeneity across studies was evaluated using Cochran's Q test (with a significance threshold of α=0.10) and the I^2 statistic. Forest plots were generated to visually present the pooled effect estimates. A leave-one-out sensitivity analysis was conducted by sequentially omitting each individual study to assess the robustness of the primary outcome (ORR) results. Publication bias for ORR was evaluated using Begg's funnel plot (25).

Results

Study selection. A total of 2,011 records were initially identified through eight electronic databases: PubMed (n=151), Cochrane Library (n=9), Embase (n=1,490), Web of Science (n=215), CNKI (n=5), CBM (n=12), Wanfang (n=96) and VIP Database (n=33). After 210 redundant entries were removed via deduplication, 780 records were excluded as they represented meta-analyses or review articles. Subsequently, a thorough screening of titles and abstracts was conducted, resulting in the exclusion of 942 irrelevant records. Full-text articles of the remaining potentially eligible studies were then retrieved and assessed, with 73 articles excluded for failing to meet the predefined eligibility criteria. Ultimately, six eligible articles encompassing a total of 336 patients were selected for the final meta-analysis. The complete flow of this selection procedure is outlined in Fig. 1.

The baseline characteristics of the included studies are presented in Table I. Notably, these six publications reported findings from five independent trial cohorts (15-19,26), as Lan *et al* (16,26) reported a short-term analysis and a long-term survival analysis; therefore, the present study combined their data for the pooled analyses. All meta-analytic calculations were performed based on these 5 independent cohorts.

Quality assessment. Methodological quality and risk of bias were evaluated using the RoBANS tool, with results shown in Fig. 2. The majority of assessed domains, including participant selection, exposure measurement, outcome data completeness and selective reporting, were rated as low risk. By contrast, the domains of confounding variables and blinding of outcome assessors were primarily judged as moderate risk. This moderate risk for outcome assessors blinding was largely unavoidable, as the majority of included studies were phase II single-arm trials that did not incorporate blinding procedures. However, the reliance on objective evaluation criteria (such as RECIST version 1.1) was deemed to have reduced the potential for detection bias. As such, researchers identified a moderate-risk rating for this domain. Regarding confounding variables, although most studies lacked a control group, researchers conducted thorough identification, measurement and reporting. Thus, a low-to-moderate risk of bias rating was assigned for this domain.

Tumor response. All included trials reported ORR and four of the studies reported DCR. The pooled ORR across all five studies was 47% (95% CI: 21.0-74.0%) using a random-effects model (I^2=94.55%; P<0.001). Due to the high heterogeneity observed, a sensitivity analysis was performed, which identified the study by Oaknin *et al* (19) as the primary source of heterogeneity. This study was therefore excluded, and a reanalysis of the remaining four studies yielded a final pooled ORR of 37% (95% CI: 17-60%) using a random-effects model (I^2=83.49%; P<0.001; Fig. 3A). The combined DCR was 79% (95% CI: 67-89%) using a random-effects model (I^2=40.72%; P=0.113; Fig. 3B). A formal subgroup meta-analysis stratified by PD-L1 expression could not be performed because only one study Xia *et al* (15) reported outcomes separately for PD-L1-positive and PD-L1-negative subgroups, while another study performed by Xu *et al* (17) exclusively enrolled patients with PD-L1-positive tumors. Consequently, the current evidence is insufficient to quantitatively compare the efficacy of this combination regimen between PD-L1 expression subgroups.

Survival outcomes. All included studies reported PFS, however the study by Xia *et al* (15) did not reach the median

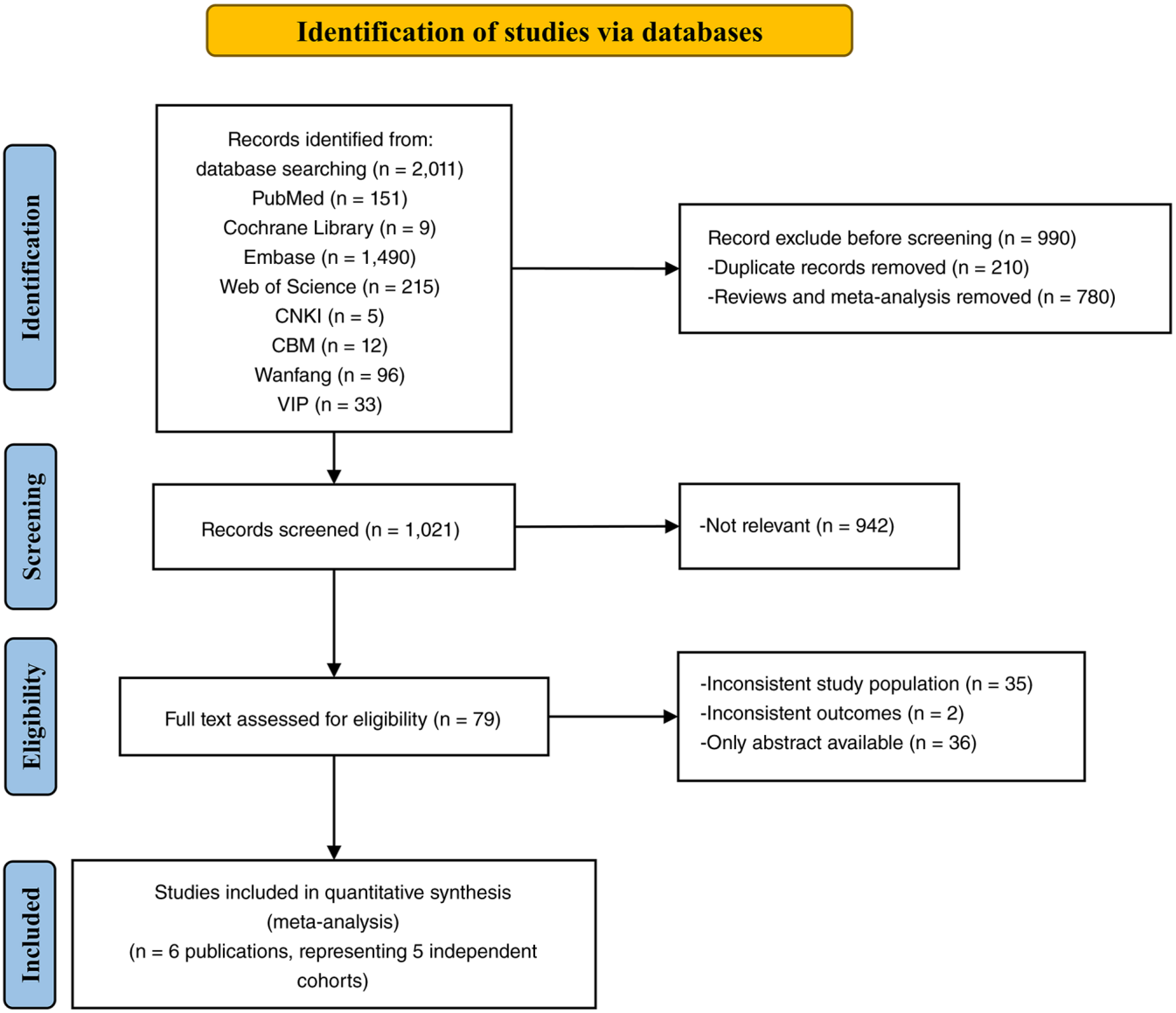

Figure 1. Flow chart for the inclusion and exclusion of articles. CNKI, Chinese National Knowledge Infrastructure; CBM, Chinese Biological Medicine Database.

PFS endpoint, so PFS analyses were performed using data from the remaining four studies. The pooled PFS was 8.05 months (95% CI: 4.75-13.64 months) according to the random-effects model (I^2=89.2%; P<0.001; Fig. 4A). Three of the studies reported OS and one-year OS rate (1-y OSR). According to the random-effects model (I^2=75.8%; P=0.016), the pooled OS was 20.24 months (95% CI: 10.16-40.29 months; Fig. 4B). The combined 1-y OSR was 62% (95% CI: 45.0-87.0%) according to the random-effects model (I^2=63%; P=0.067; Fig. 4C).

Safety. All selected studies reported AEs. However, the specific AEs documented varied across trials due to differences in the therapeutic regimens employed. Therefore, the present meta-analysis focused exclusively on AEs that were reported in at least three individual studies. Overall, the combined incidence of ≥3 AEs was 58% (95% CI: 31-82%; I^2=94.03%; P<0.001). This pooled figure aggregates data across heterogeneous regimens; notably, the incidences of most individual grade ≥3 AEs were <3%, with only anemia and hypertension exceeding 10% (Table II; Fig. S1). The pooled analysis of grade 1-2 AEs identified five events with an incidence >30%: Proteinuria at 42% (95% CI: 18-67%), increased aspartate aminotransferase (AST) at 38% (95% CI: 24-53%), increased alanine aminotransferase (ALT) at 33% (95% CI: 19-47%), diarrhea at 30% (95% CI: 17-44%) and decreased platelet count (PLT) at 30% (95% CI: 0-78%). Corresponding grade ≥3 AEs were moderate: 3% for proteinuria, 2% for diarrhea, 1% for increased AST, 1% for increased ALT and 1% for decreased PLT (Table III; Fig. S2).

Sensitivity analysis and publication bias. To evaluate the influence of individual studies on overall heterogeneity, leave-one-out sensitivity analysis was performed by sequentially omitting each trial. Due to the limited number of included trials (n=5), sensitivity analysis could only be performed for ORR, as it was the only outcome with complete data available from all five studies. Sensitivity analyses for other endpoints

Table I. Characteristics of included studies.

Study	First author, year	Study	Total samples	Arms and treatment	Anti-angiogenesis drugs	Immune checkpoint inhibitors	Age, years (range)	Key eligibility criteria	Histology	(Refs.)
NCT02921269	Friedman *et al*, 2020	Phase II, single arm	10	Bevacizumab 15 mg/kg IV Q3W + atezolizumab 1,200 mg IV Q3W	Bevacizumab	Atezolizumab/ PD-L1	48 (31-55)	Patients with advanced cervical cancer	Mixed	(18)
NCT03827837	Xia *et al*, 2022	Phase II, single arm	33	Camrelizumab 200 mg IV day 1, Q3W + famitinib 20 mg PO QD	Famitinib	Camrelizumab/ PD-1	50 (43-55)	Recurrent or metastatic cervical squamous cell carcinoma	Squamous cell carcinoma	(15)
ChiCTR1900023015	Xu *et al*, 2022	Phase II, single arm	42	Sintilimab 200 mg IV day 1, Q3W + anlotinib 10 mg PO QD (days 1-14, Q3W)	Anlotinib	Sintilimab/PD-1	53 (36-67)	Recurrent or metastatic cervical cancer	Mixed	(17)
NCT03816553	Lan *et al*, 2020	Phase II, single arm	45	Camrelizumab 200 mg IV Q2W + apatinib 250 mg PO QD	Apatinib	Camrelizumab/ PD-1	51 (33-67)	Advanced cervical cancer	Mixed	(16)
NCT03556839	Oaknin *et al*, 2024	PhaseIII, RCT	206	i) Cisplatin 50 mg/m^2 IV day 1, Q3W+ paclitaxel 175 mg/m^2 IV day 1, Q3W + bevacizumab 15 mg/kg IV day 1, Q3W + atezolizumab 1,200 mg IV day 1, Q3W (chemotherapy for up to 6 cycles, then atezolizumab + bevacizumab maintenance) ii) or carboplatin AUC 5 IV day 1, Q3W + paclitaxel 175 mg/m^2 IV day 1, Q3W + bevacizumab 15 mg/kg IV day 1, Q3W + atezolizumab 1,200 mg IV day 1, Q3W (chemotherapy for up to 6 cycles, then atezolizumab + bevacizumab maintenance)	Bevacizumab	Atezolizumab/ PD-L1	51 (43-60)	Metastatic (stage IVB), persistent or recurrent cervical cancer	Mixed	(19)

RCT, randomized controlled trials; PD-L1, programmed death-ligand 1; IV, intravenous; PO, per os (oral); QD, once daily; Q2W, every 2 weeks; Q3W, every 3 weeks; AUC, area under the curve.

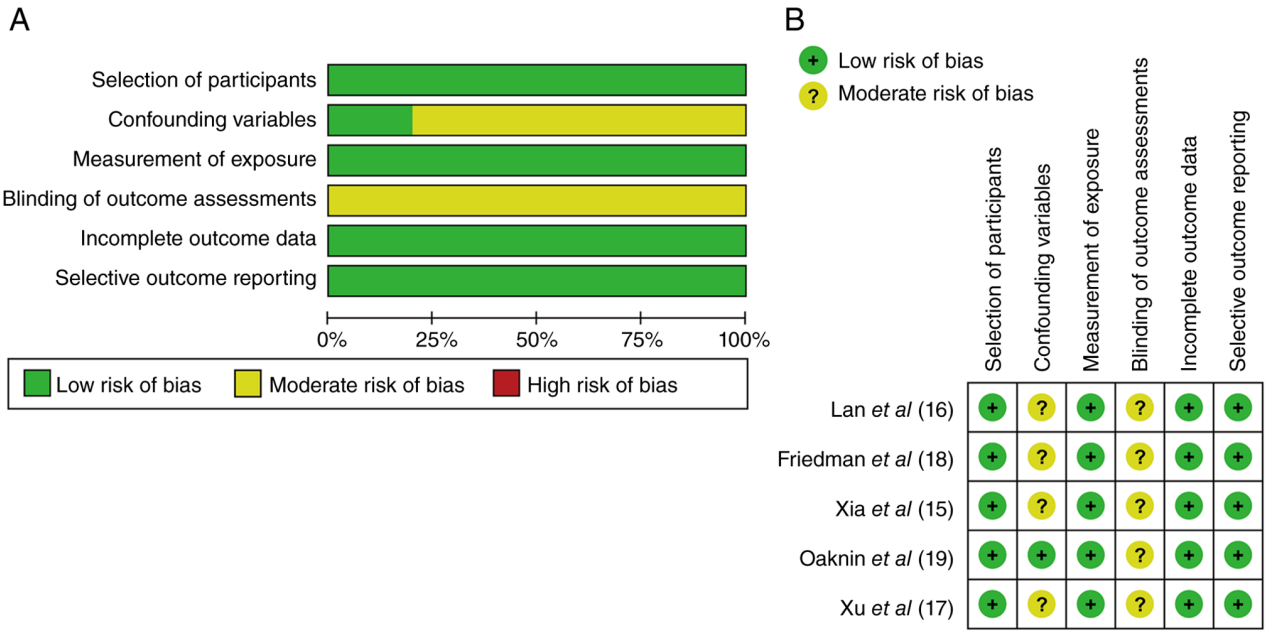

Figure 2. Quality assessment of studies included in the present meta-analysis. (A) Risk of bias graph by domains and (B) risk of bias summary by studies and domains.

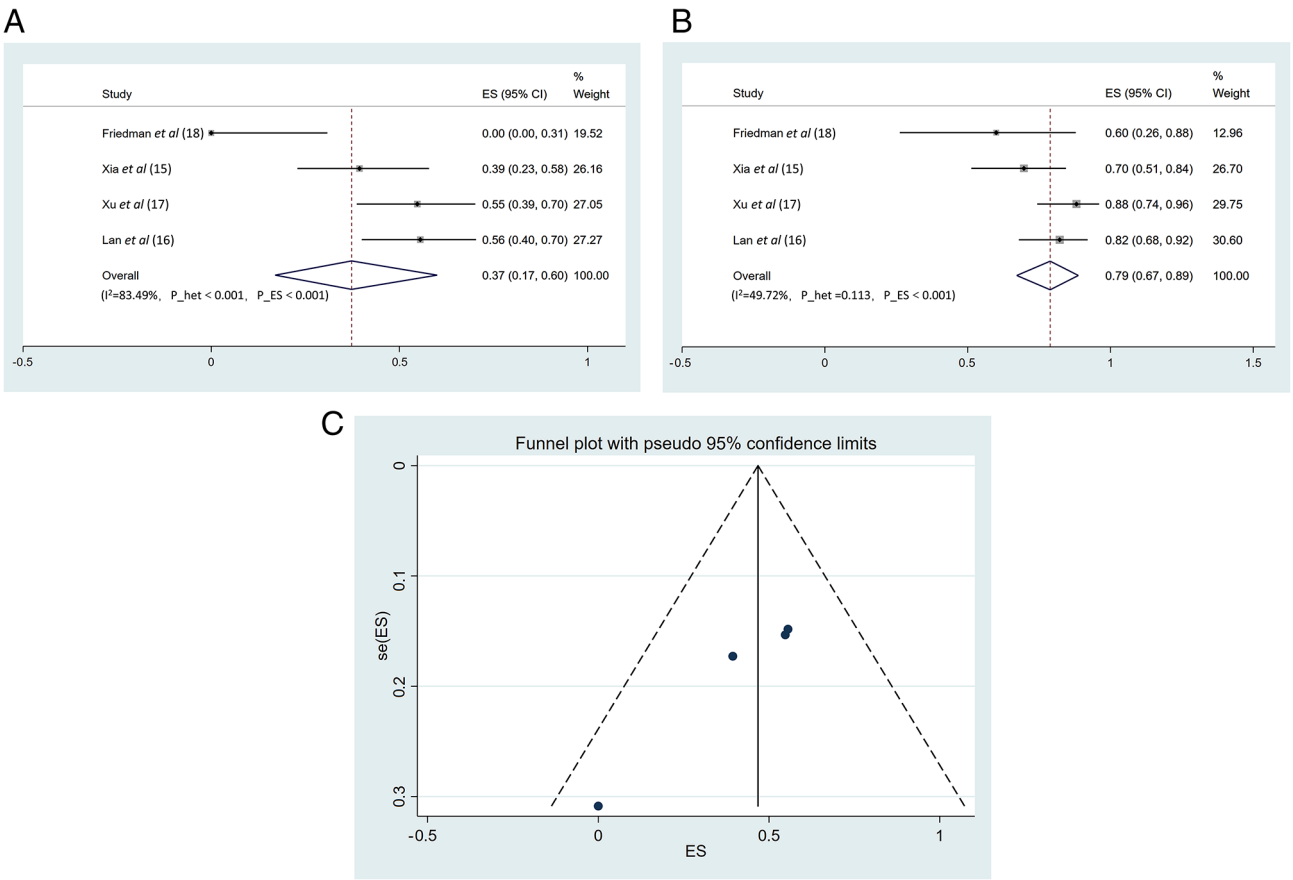

Figure 3. Forest plot of tumor response and assessment of publication bias. (A) Objective response rate. (B) disease control rate. (C) Begg's funnel plot for assessment of publication bias in the pooled objective response rate. P_het, P-value for heterogeneity; ES, effect size.

were precluded by insufficient data. Similarly, publication bias assessment was only conducted in the analysis of ORR and Begg's funnel plot symmetry analysis demonstrated there was no publication bias in the pooled result of ORR (Fig. 3C).

Discussion

The prognosis for patients with metastatic, recurrent or persistent cervical cancer remains poor, with limited treatment

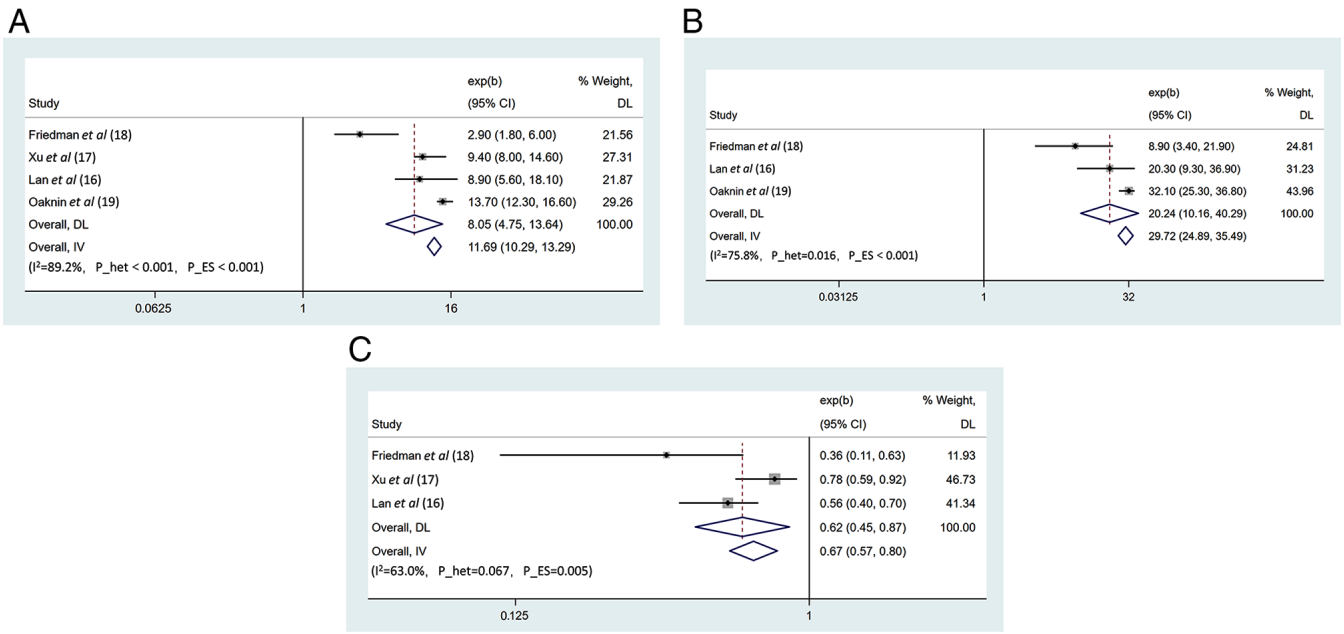

Figure 4. Forest plot of survival outcomes. (A) Progression-free survival. (B) Overall survival. (C) One-year overall survival rate. P_het, P-value for heterogeneity; ES, effect size.

options available for patients. Platinum-based chemotherapy remains the main treatment for advanced cervical cancer. The addition of the anti-angiogenic agent bevacizumab to platinum-based chemotherapy received regulatory approval from the U.S. Food and Drug Administration based on data from the randomized phase III GOG 240 study, which demonstrated that bevacizumab notably improved survival outcomes (5). Furthermore, with the development of ICIs, a growing body of literature has investigated ICI monotherapy for advanced cervical cancer (7,27,28). Although these agents showed improved survival outcomes compared with chemotherapy alone, their effectiveness remained minimal. Owing to the limited benefits of monotherapies, substantial efforts have been directed toward investigating innovative combination therapeutic strategies. In particular, there is a strong rationale for combining ICIs with anti-angiogenic agents. Mechanistically, anti-angiogenic therapy induces vascular normalization, which reconditions the immunosuppressive tumor microenvironment. This shift improves the recruitment and function of cytotoxic T cells and reduces immunosuppressive cell populations. Consequently, the reinvigorated immune response produces more IFN-γ, thereby triggering the adaptive upregulation of PD-L1 expression on tumor cells, known as adaptive immune resistance (29,30). This elevated PD-L1 expression may thereby increase tumor vulnerability to anti-PD-1/PD-L1 agents.

Despite this mechanistic rationale, clinical trials investigating the combination of ICIs and anti-angiogenic agents in advanced cervical cancer remain limited. In the present study, only 5 trials were identified that met the inclusion criteria. Pooled analysis of 336 patients demonstrated that the combination of ICIs and anti-angiogenic therapy could yield promising efficacy with a manageable safety profile. Concerning the pooled tumor response results, the pooled ORR was 37% and the pooled DCR was 80%. It is noteworthy that one study reported an ORR of 0%, which may be attributed to its extremely small sample size (only 10 patients were recruited in the trial) (18). Furthermore, the pooled survival outcomes showed that the PFS was 8.05 months, the OS was 20.24 months and the 1-y OSR was 62%. Notably, the combination therapy evaluated in the present study yielded a superior median OS (20.24 months compared with 12.0 months) and a >2-fold higher ORR (37% compared with 16.4%) in the NCT03257267 trial which investigated mono-immunotherapy in advanced cervical cancer (27). Additionally, compared with the chemotherapy-plus-bevacizumab regimen evaluated in the GOG 240 trial, the present pooled analysis also showed a longer median OS (20.24 months compared with 16.8 months) (5). These findings collectively suggest that the combined regimen may offer a clinically notable advantage over either ICI monotherapy or anti-angiogenic therapy alone.

Alongside its promising efficacy, the combination regimen demonstrated a tolerable and manageable safety profile in the present pooled analysis. The overall incidence of grade ≥3 AEs was 58%. The most common grade ≥3 AEs were anemia and hypertension, with incidences of 14 and 13%, respectively. The pooled incidence of all other grade ≥3 AEs was <3%. Of note, treatment-related mortalities were reported in two trials: 3 cases in the study by Oaknin *et al* (19) and 2 cases in the study by Xia *et al* (15), indicating that this combination requires careful patient monitoring in clinical practice. Nevertheless, several key questions remain unresolved regarding the use of ICI-anti-angiogenic combinations in cervical cancer. Subgroup analyses were insufficiently reported in the included studies. Further investigation is therefore warranted to identify which patient subgroups derive the greatest clinical benefit from this combination regimen, and which subgroups may experience disproportionate harm without meaningful efficacy gains.

Notwithstanding these encouraging results, several limitations of the current evidence must be acknowledged.

Table II. Pooled results of most common grade ≥3 AEs.

	Grade ≥3		Grade 1-2	
AEs	Rate (95% CI)	I^2, %	Rate (95% CI)	I^2, %
Anemia	14 (4-27)	82.66	29 (19-39)	64.63
Hypertension	13 (6-22)	65.39	29 (13-47)	87.53

AE, adverse effects.

Table III. Pooled results of most common grade 1-2 AEs.

	Grade 1-2		Grade ≥3	
AEs	Rate (95% CI)	I^2, %	Rate (95% CI)	I^2, %
Proteinuria	42 (18-67)	92.17	3 (0-9)	64.96
Increased AST	38 (24-53)	61.88	1 (0-5)	0.00
Increased ALT	33 (19-47)	61.61	1 (0-5)	63.42
Diarrhea	30 (17-44)	79.82	2 (1-4)	0.00
Decreased PLT	30 (0-78)	96.39	1 (0-3)	0.00

AEs, adverse events; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLT, platelet count.

First, the present analysis exhibited notable heterogeneity, which can be attributed to the predominance of single-arm studies and small sizes of included trials, as this could introduce potential selection and reporting bias. Furthermore, differences in treatment lines, histological composition and specific anti-angiogenic agents across the included studies may also contribute to the observed heterogeneity. Second, formal quantitative subgroup analyses were not performed due to insufficient data. Among the included studies, Xia *et al* (15) reported comparable ORR and DCR between PD-L1-positive and PD-L1-negative subgroups, while Xu *et al* (17) enrolled patients with PD-L1-positive tumors and reported encouraging outcomes. Due to the limited evidence and considering the findings of Xia *et al* (15) derive from a single small phase II trial, the predictive value of PD-L1 expression status for this combination strategy remains uncertain. Nevertheless, future randomized trials with pre-specified stratification by PD-L1 expression status are warranted to identify patients most likely to benefit from this regimen. Third, one of the studies included patients only with squamous cell carcinoma, while the remaining four trials recruited patients with mixed histologies, which may represent a potential source of heterogeneity affecting patient prognosis. Finally, treatment-related mortalities were reported in two trials (5 cases), and the pooled incidence of grade ≥3 adverse events was 58%, underscoring the need for careful patient selection and monitoring in clinical practice. In addition, the relatively short follow-up duration in most included trials limits the ability to assess the durability of the observed survival benefits, highlighting the need for longer follow-up in future studies. Large-scale, well-powered randomized controlled trials are therefore urgently warranted to confirm these findings, identify predictive biomarkers and define the optimal combination regimen. Such trials may consider PFS as the primary endpoint, with OS and ORR as key secondary endpoints.

Of note, in the forest plots for proportion meta-analyses, the overall-effect diamonds are asymmetric on the original scale. This is an expected statistical characteristic because a proportion is bounded between 0 and 1 and its sampling distribution is naturally asymmetric, leading to asymmetric confidence intervals.

In conclusion, the pooled evidence from the present systematic review and meta-analysis, together with emerging clinical trial data, suggests that the combination of ICIs and anti-angiogenic agents may offer promising efficacy with a manageable safety profile in patients with advanced cervical cancer. Nevertheless, these findings must be interpreted with caution due to the limited number of included studies, the predominantly single-arm designs of most trials, and the occurrence of treatment-related mortalities. Future research efforts should focus on conducting larger, randomized trials to confirm these benefits, defining optimal combination regimens and identifying biomarkers to guide patient selection.

Based on the present findings, combination therapy with anti-angiogenic agents and ICIs exhibited promising antitumor efficacy and a clinically manageable safety profile for the treatment of patients with advanced cervical cancer. Nevertheless, the limited number and predominantly single-arm design of existing trials highlight the critical need for definitive confirmation in well-powered, large-scale phase III randomized controlled trials.

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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

HC and XY contributed to the comprehensive study design, paper revision and submission. YQ and YS were responsible for the search of articles and data extraction. YQ and YS also checked and confirmed the authenticity of the raw data. XL, YX, YQ and YS performed the statistical analysis and contributed to data interpretation. WX, MJ and FZ contributed to data interpretation and manuscript revision. 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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