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Review Article

Efficacy of immune checkpoint inhibitors plus chemotherapy versus chemotherapy-based control in cervical cancer: a meta-analysis

Jing Wang, Fei Lin, Xiuxiu Chen

Department of Gynecology, Xianju People's Hospital, Zhejiang Southeast Campus of Zhejiang Provincial People's Hospital, Affiliated Xianju's Hospital, Hangzhou Medical College, Xianju County, Taizhou, Zhejiang, China

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Abstract: Objective: Although chemotherapy is standard for cervical cancer, the added clinical benefit of immune checkpoint inhibitors compared with chemotherapy-based control strategies remains unclear. This meta-analysis aimed to systematically evaluate the efficacy and safety of immune checkpoint inhibitors combined with chemotherapy versus chemotherapy-based control regimens in patients with cervical cancer, synthesizing evidence across randomized and non-randomized studies to inform clinical decision-making and future research. Methods: We systematically searched for eligible comparative studies evaluating immune checkpoint inhibitors combined with chemotherapy versus chemotherapy-based control regimens in patients with cervical cancer. The primary outcomes were progression-free survival (PFS) and overall survival (OS), while secondary outcomes included treatment response, adverse events, subgroup effects, and publication bias. Hazard ratios (HRs) and risk ratios (RRs) with 95% confidence intervals (CIs) were pooled using standard meta-analytic methods, and study quality was assessed using the Cochrane risk-of-bias framework. Results: Compared with chemotherapy-based control strategies, neoadjuvant immune checkpoint inhibitors plus chemotherapy significantly improved progression-free survival (HR, 0.60; 95% CI, 0.47-0.72) and overall survival (HR, 0.64; 95% CI, 0.55-0.73). Improvements in OS and PFS were generally consistent across most predefined subgroups, including age, ECOG performance status, race, chemotherapy backbone, disease status, and prior chemoradiotherapy exposure. In contrast, the addition of immunotherapy did not significantly increase the incidence of overall adverse events (RR, 1.02; 95% CI, 0.94-1.10) or decreased white blood cell count (RR, 0.88; 95% CI, 0.63-1.23). For response outcomes, complete response showed a borderline improvement (RR, 1.17; 95% CI, 0.99-1.37), stable disease was significantly reduced (RR, 0.73; 95% CI, 0.59-0.91), whereas partial response, objective response rate, and disease control rate were not significantly different between groups. Funnel-plot assessment suggested no major publication bias, although a moderate risk of small-study effects could not be excluded. Conclusion: Immune checkpoint inhibitors combined with chemotherapy appear superior to chemotherapy-based control regimens for cervical cancer, demonstrating significant improvements in progression-free and overall survival, along with indications of deeper tumor response.

Keywords: Cervical cancer, immune checkpoint inhibitors, chemotherapy, meta-analysis, treatment efficacy

Introduction

Cervical cancer is a significant contributor to cancer morbidity and mortality among women worldwide with the highest disease burden in those areas where screening, vaccination and prompt treatment are inadequate [1, 2]. Despite the wide acceptance of concurrent chemoradiotherapy to treat cervical cancer (CC) [3-5], the therapies have not shown uniform results, and many patients experience disease persistence, recurrence, or distant metastasis. Clinically It has been used as an alternative or adjunctive approach to neoadjuvant chemotherapy (NAACT) before surgery in a few settings where tumor downstaging, enhanced resectability or initial control of occult systemic disease is clinically desirable [6, 7]. However, the oncologic advantage of NACT by itself is not always constant and the ability of the treatment to elicit profound, long-lasting responses is frequently restricted.

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The rising awareness on these restrictions has made the intensification of treatment to be of growing interest during the neoadjuvant phase. This interest is biologically justified in cervical cancer. The vast majority of tumors occur in the background of chronic high-risk human papillomavirus infection, which is a virally mediated phenomenon linked to constant antigen presentation, immune evasion, and the frequent activation of immune control mechanisms, such as the programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) axis [8, 9]. These characteristics give a good mechanistic explanation of immune checkpoint blockade. In fact, immune checkpoint inhibitors (ICIs) have already shown clinical meaningful activity in recurrent or metastatic cervical cancer, underscoring the notion that cervical cancer is an immunologically relevant malignancy and incorporating immunotherapy earlier might yield greater therapeutic benefit when administered earlier rather than in heavily pretreated disease.

The neoadjuvant environment might be especially favorable to the implementation of ICIs. In addition to direct cytotoxicity, chemotherapy is able to promote antitumor immunity by causing immunogenic cell death, tumor antigen release, and tumor microenvironment remodeling, and thereby establishing a biologic context where immune checkpoint blockade can be more effective [10-12]. On the other hand, ICIs can rejuvenate dysfunctional T-cell antitumor responses and enhance immune-mediated tumor clearance, which can possibly be translated into radiologic regression, pathologic response, and surgical feasibility. Preliminary clinical trials assessing ICIs combined with chemotherapy in cervical cancer (CC) have shown promising results [13], but these findings have been challenging to synthesize due to small sample sizes, heterogeneous regimens, varying response criteria, and differences in study design. Consequently, the relative efficacy of ICIs plus chemotherapy versus chemotherapy-based control regimens has not been fully established.

With the ongoing development of immunochemotherapy strategies, clinical decision-making increasingly depends on a comprehensive understanding of the comparative benefits of adding ICIs to chemotherapy for patients with CC. A systematic synthesis of the available comparative evidence is therefore required to inform clinical practice, quantify the magnitude of benefit, and guide the design of future prospective trials. In this meta-analysis, we evaluated the efficacy and safety of immune checkpoint inhibitors combined with chemotherapy versus chemotherapy-based control regimens in patients with cervical cancer, with the goal of generating a robust evidence base to support optimal treatment strategies in this emerging therapeutic context.

Methods

Search strategy

A systematic literature review was conducted to identify comparative studies evaluating immune checkpoint inhibitors combined with chemotherapy versus chemotherapy-based control regimens in cervical cancer. The search strategy was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework and was designed to maximize sensitivity by combining controlled vocabulary terms with free-text keywords related to cervical cancer, immune checkpoint inhibitors, immunotherapy, and chemotherapy. We searched electronic databases from their inception to the most recent date, and the reference lists of relevant reviews and eligible articles were also manually screened to identify additional studies. No initial restrictions were applied except those necessary for full-text assessment. After duplicate records were removed, titles and abstracts were screened, and the full texts of potentially eligible articles were assessed according to predefined inclusion and exclusion criteria. **Figure 1** presents the detailed study selection process. This study was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420261388361).

Selection criteria

Inclusion criteria (PICOS): The intervention of interest was immune checkpoint inhibitors combined with chemotherapy, and the comparator was chemotherapy-based control regimens without immune checkpoint blockade. Outcomes of interest included survival end-

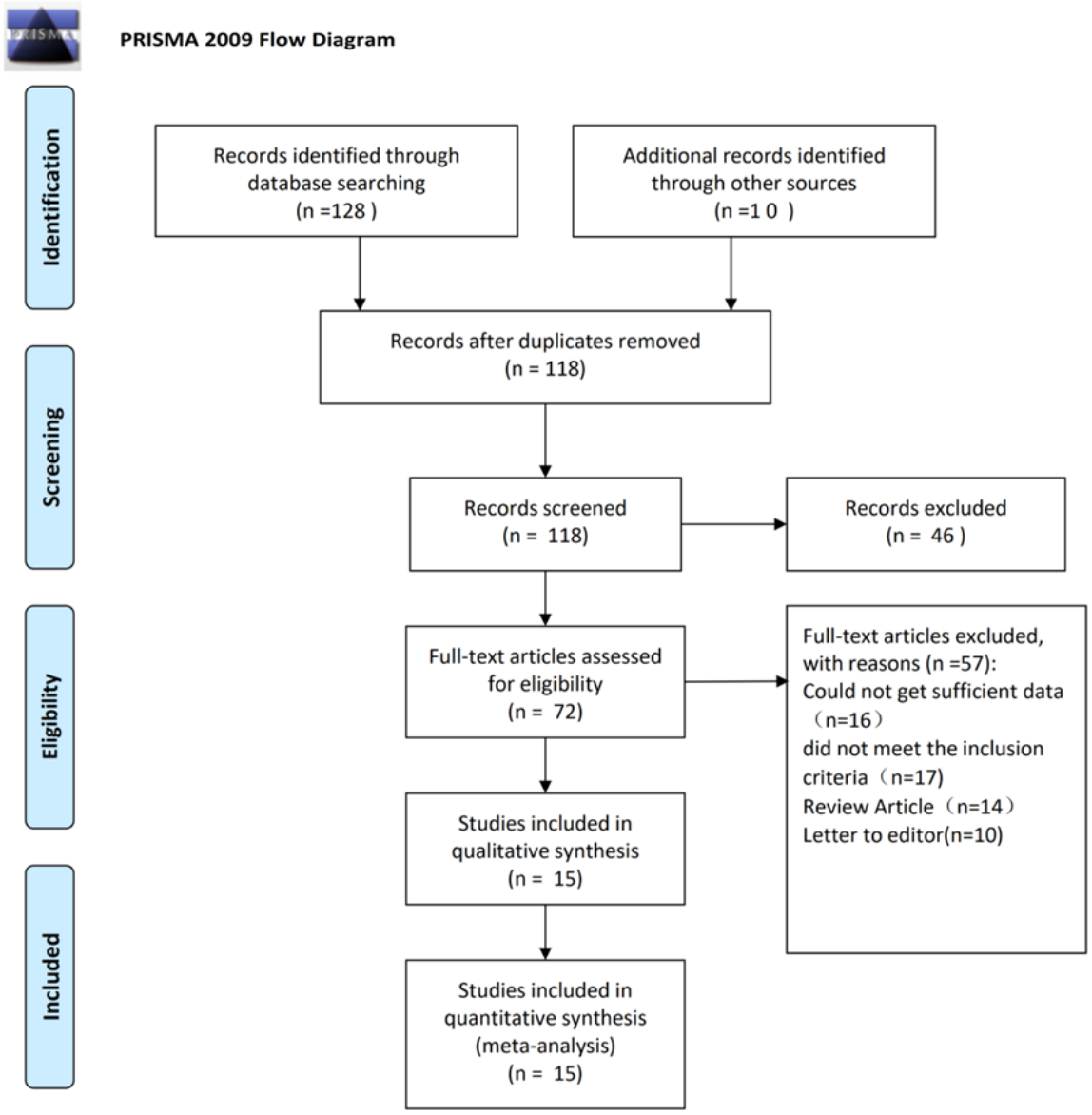

Figure 1. Flow chart.

points, specifically progression-free survival and overall survival, as well as treatment response and safety outcomes, including adverse events and response-related efficacy measures. Eligible study designs included prospective or retrospective comparative studies, including phase I-III clinical trials, that provided sufficient data to extract or estimate effect sizes. Reviews, letters, conference abstracts without usable data, duplicate publications, non-comparative studies, and reports lacking extractable outcome data were excluded. When multiple reports described overlapping populations, the most comprehensive or most recent report was included in the analysis.

Data extraction

Two reviewers independently extracted the data using a predefined standardized form and any differences were resolved through discussion until a consensus was obtained. The following data were obtained with regard to each eligible study: first author, year of publication, study phase, treatment group and comparator, sample size, age of patients, treatment regimen, and follow-up period. In the case of quantitative synthesis, time-to-event data regarding progression-free survival and overall survival were preferredly extracted in terms of hazard ratios (HRs) with respective 95% confidence

intervals (CI). In case of dichotomous results such as adverse events and treatment responses the number of events and total number of participants in each group was noted to obtain the pooled risk ratios (RR) with 95% CIs. Moreover, when possible, subgroup-specific estimates of effects were also derived based on prespecified clinical variables such as age, ECOG performance status, race category, chemotherapy backbone, disease status, and prior chemoradiotherapy. In cases where several reports included the same study population, the most comprehensive and non-overlapping data were used in the analysis.

Quality assessment

Two reviewers assessed the methodological quality of included studies separately based on Cochrane Collaboration risk-of-bias framework, disagreements were resolved through discussion and consensus. Each study was evaluated in the following areas: random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete data on outcomes, selective reporting, and other areas that could have caused biasness. All the domains were rated as either low, high, or unclear risk of bias based on the information provided in the original publications. Since the pooled analysis merged the studies that had various phases and designs, specific consideration was given to the bias that occurred due to the blinding procedures, missing reporting, and other design-specific methodological constraints. Robustness and interpretability of the pooled estimates were contextualized with the overall risk-of-bias evaluation instead of determining formal exclusion of the study.

Outcome assessments

The prespecified outcomes included efficacy, safety, subgroup effects, and publication bias. The main efficacy outcomes were progression-free survival (PFS) and overall survival (OS) that were pooled into hazard ratio (HRs) with 95% confidence intervals (CI). Safety and tumor response were used as the secondary outcomes. The evaluation of safety was on the rate of adverse events (general adverse events and reduced white blood cell count) and summarized risk ratios (RRs) with 95 percent confidence intervals. The conventional response categories such as complete response (CR), partial response (PR), stable disease (SD), objective response rate (ORR), and disease control rate (DCR) were used to assess the antitumor activity. OS and PFS, when available, were prespecified to undergo prespecified subgroup analysis based on clinically relevant variables, where available, such as tests of age, ECOG performance status, race, chemotherapy backbone, disease status, and prior exposure to chemoradiotherapy. Visual inspection was done on funnel plots of the survival outcomes to investigate publication bias.

Statistical analysis

The statistical analyses were conducted to combine the effects estimates of efficacy and safety outcomes of eligible studies. In case of time-to-event endpoints, such as progression-free survival (PFS) and overall survival (OS), pool hazard ratios (HRs) and 95% confidence intervals (CIs) were computed. To compute the pooled risk ratios (RRs) at 95 percent confidence interval (CI) of a dichotomous outcome, such as adverse events and treatment responses, the proportion of events and total subjects in each group were used. The Cochran Q test was used to evaluate between-study heterogeneity, and I 2 was used to estimate the heterogeneity; when the heterogeneity was negligible, a fixed-effects model was used and when high variability between-studies was observed, the random-effects model was used. PFS and OS pre-specified subgroup analyses were performed based on how often clinically relevant variables such as age, ECOG performance status, race, chemotherapy backbone, disease status, and prior chemoradiotherapy exposure were relevant, and when there was enough data to assess them. Visual inspection of funnel plots was used to investigate publication bias of survival outcomes. All statistical tests were two-sided and the *P* value less than 0.05 was regarded to be statistically significant.

Results

Search results

The study selection process is summarized in **Figure 1**. A total of 138 records were initially identified, including 128 through database searching and 10 from other sources; after removal of duplicates, 118 unique records

underwent title and abstract screening. Of these, 46 were excluded as clearly irrelevant, and 72 full-text articles were assessed for eligibility. Following detailed review, 57 articles were excluded because they did not meet the predefined inclusion criteria, lacked sufficient extractable data, or were non-original publications such as reviews and letters, leaving 15 studies for inclusion in the final meta-analysis [14-28]. As shown in **Table 1**, these studies were published between 2022 and 2026 and comprised phase I to III trials with marked variation in sample size, treatment backbone, and follow-up duration, highlighting the evolving yet heterogeneous evidence base for neoadjuvant immunochemotherapy in cervical cancer.

Risk of bias

The methodological quality of the included studies was acceptable, with most domains judged to be at low risk of bias, although several important limitations remained (**Figure 2**). Random sequence generation was uniformly assessed as low risk across the included studies, suggesting generally adequate approaches to sequence generation. By contrast, allocation concealment and blinding-related domains showed greater vulnerability: while the majority of studies were considered low risk for allocation concealment and for blinding of participants and personnel, a non-negligible proportion were rated at high risk, indicating potential selection and performance bias. Blinding of outcome assessment and selective reporting exhibited comparatively less favorable profiles, with a larger fraction of studies categorized as high risk, thereby raising concern regarding detection bias and reporting bias in some trials. Incomplete outcome data was generally well handled, with most studies judged to be at low risk of attrition bias. The domain of other bias was the most uncertain, showing a mixed distribution of low, unclear, and high-risk judgments, which likely reflects heterogeneity in study design, treatment strategy, and reporting completeness. Taken together, these findings indicate that although the overall risk-of-bias profile supports quantitative synthesis, the potential influence of bias in blinding, reporting, and other nonstandard domains should be considered when interpreting the pooled estimates.

Survival

For progression-free survival (PFS), the pooled estimate from six studies demonstrated that the addition of immunotherapy significantly reduced the risk of progression or death by 40% (pooled HR 0.60, 95% CI 0.47-0.72). Moderate to substantial between-study heterogeneity was observed (I^2 = 59.0%, P = 0.032); therefore, a random-effects model was used for the analysis (**Figure 3**). For overall survival (OS), the pooled analysis of five studies showed that the addition of immunotherapy was associated with a 36% relative reduction in the risk of death (pooled HR 0.64, 95% CI 0.55-0.73). Low between-study heterogeneity was observed (I^2 = 19.1%, P = 0.293), and the pooled estimate was generated using a random-effects model (**Figure 4**).

Adverse event

For any adverse event, the pooled estimate across the included studies showed no significant difference between groups (RR 1.02, 95% CI 0.94-1.10; P = 0.682), with low heterogeneity (I^2 = 8.5%, P = 0.364). Similarly, for decreased white blood cell count, immunotherapy-based treatment was not associated with a significantly increased risk (RR 0.87, 95% CI 0.63-1.22; P = 0.420), and no heterogeneity was observed (I^2 = 0.0%, P = 0.665). Of note, between-subgroup heterogeneity across adverse-event categories was not calculated in this analysis (**Figure 5**). Although individual studies showed some variability in effect estimates, the overall safety profile remained broadly comparable between groups, suggesting that the incorporation of immune checkpoint blockade was not associated with a meaningful increase in the incidence of common adverse events in this analysis.

Responses

The pooled estimate for complete response (CR) showed a borderline increase with immunotherapy-based treatment (RR 1.17, 95% CI 0.99-1.37), whereas no significant difference was observed for partial response (PR) (RR 1.03, 95% CI 0.94-1.14). By contrast, stable disease (SD) was significantly less frequent in the immunotherapy group (RR 0.73, 95% CI

Table 1. Baseline characteristics of the included studies

Study	Phase	Group	Patients	Age	Treatment	Follow up (months)
Chen 2024 [14]	II	Unknown	55	54 [IQR: 50-60]	camrelizumab plus TP	9.5 [IQR: 7.1-10.3]
Kim 2025 [15]	III	pembrolizumab + chemotherapy group/ placebo + chemotherapy group	57/40	56±14/52±11.25	pembrolizumab + chemotherapy/placebo + chemotherapy	39.8 [33.3-46.4]
Monk 2023 [16]	III	Pembrolizumab group/Placebo group	308/309		pembrolizumab 200 mg/placebo	22 [IQR: 19.1-24.4]
Ray-Coquard 2026 [17]	II	Neoadjuvant ipilimumab/nivolumab group/ Chemoradiation group	40/40	55 (31-77)	Neoadjuvant ipilimumab/nivolumab/ Chemoradiation	95 [95% CI: 73-114]
Rodrigues 2023 [18]	I	Nivolumab with and following concurrent CRT	16	47.9 (27-77)	Nivolumab with and following concurrent CRT	23.8 (3.9-26.2)
Sheng 2025 [19]	II	pre-operative neoadjuvant therapy	23/7	51.5 (39.5-57)	pre-operative neoadjuvant therapy	14.7 [IQR: 11.6-21.4]
Wan 2024 [20]	II	Pembrolizumab plus chemotherapy therapy	47	Unknown	Pembrolizumab plus chemotherapy therapy	Unknown
Zamarin 2025 [21]	I	Arm A/Arm B	19/17	56±9/43±9	Atezolizumab followed by CRT+ atezolizumab/CRT+ concurrent atezolizumab	Unknown
Li 2024 [22]	II	neoadjuvant chemo-immunotherapy	85	51 [IQR: 46-57]	neoadjuvant chemo-immunotherapy	11 [IQR: 6-14.5]
Monk BJ 2023 [23]	III	Durvalumab group/Placebo group	385/385	49 [IQR: 41-57]	Durvalumab/Placebo	18.5 [IQR: 13.2-21.5]
Lorusso 2024 [24]	III	Pembrolizumab group/Placebo group	529/531	Unknown	Pembrolizumab/Placebo	17.9 [IQR: 11.3.2-22.3]
Oaknin 2024 [25]	III	Atezolizumab group/Placebo group	410	Unknown	Atezolizumab/Placebo	Unknown
Monk- 2023 [26]	III	Pembrolizumab + Chemotherapy Versus Placebo + Chemotherapy	548/317	Unknown	Pembrolizumab + Chemotherapy Versus Placebo + Chemotherapy	39.1 (32.1-46.5)
Tewari 2024 [27]	III	Pembrolizumab group/Placebo group	308/309	51 (22-82)	Pembrolizumab/Placebo	Unknown
Nishio 2022 [28]	III	Pembrolizumab group/Placebo group	35/22	54±14/50±11.25	Pembrolizumab/Placebo	Unknown

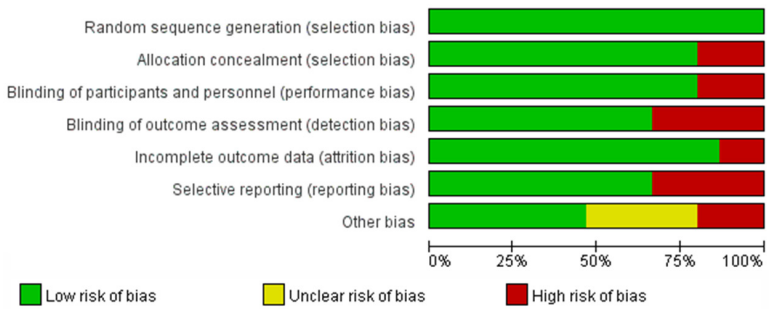

Figure 2. Risk of bias.

0.59-0.91), consistent with a shift away from disease stabilization toward deeper tumor regression. At the composite level, objective response rate (ORR) showed a nonsignificant trend in favor of the experimental strategy (RR 1.05, 95% CI 0.99-1.11), while disease control rate (DCR) was essentially comparable between groups (RR 1.03, 95% CI 0.97-1.09). Notably, heterogeneity was negligible across all pooled response outcomes (all I^2 = 0%), indicating a highly consistent direction of effect among studies (**Figure 6**).

Subgroup analysis of OS

A significant OS advantage was observed in both younger and older patients, including those aged <65 years (HR 0.69, 95% CI 0.56-0.80) and those aged ≥65 years (HR 0.66, 95% CI 0.42-0.98), indicating that age did not materially diminish treatment benefit. Likewise, improved OS was evident irrespective of baseline performance status, with favorable estimates in patients with ECOG PS 0 (HR 0.69, 95% CI 0.55-0.92) and ECOG PS 1 (HR 0.68, 95% CI 0.49-0.89). By race category, the benefit was maintained in White patients (HR 0.70, 95% CI 0.55-0.89) and in those categorized as Other (HR 0.66, 95% CI 0.50-0.85), whereas no estimate was available for Asian patients. According to chemotherapy backbone, carboplatin-based regimens appeared to derive a significant survival benefit (HR 0.55, 95% CI 0.39-0.93), while the cisplatin subgroup showed a numerically favorable but statistically nonsignificant trend (HR 0.74, 95% CI 0.55-1.09). When stratified by disease status, both metastatic (HR 0.63, 95% CI 0.54-0.88) and locally advanced disease (HR 0.77, 95% CI 0.65-0.90) favored the experimental strategy, with a greater magnitude of effect in the metastatic setting. A similar pattern was observed according to prior chemoradiotherapy exposure: patients with previous chemoradiotherapy appeared to experience a more pronounced OS benefit (HR 0.56, 95% CI 0.40-0.88), whereas those without prior chemoradiotherapy showed a weaker and statistically uncertain effect (HR 0.81, 95% CI 0.59-1.43) (**Figure 7**).

Subgroup analysis of PFS

A consistent reduction in the risk of progression or death was observed in both age groups, including patients aged <65 years (HR 0.72, 95% CI 0.66-0.80) and those aged ≥65 years (HR 0.66, 95% CI 0.45-0.88). Similarly, favorable effects were evident regardless of baseline performance status, with significant benefit in both ECOG 0 (HR 0.70, 95% CI 0.55-0.88) and ECOG 1 populations (HR 0.66, 95% CI 0.50-0.78). When stratified by race, prolonged PFS was observed among White patients (HR 0.71, 95% CI 0.51-0.85) and those categorized as Other (HR 0.65, 95% CI 0.46-0.80), whereas no clear benefit was demonstrated in Asian patients (HR 1.02, 95% CI 0.63-1.36). By chemotherapy backbone, both carboplatin-based (HR 0.65, 95% CI 0.49-0.88) and cisplatin-based regimens (HR 0.75, 95% CI 0.62-0.93) favored the experimental strategy. According to disease status, the treatment effect was present in both metastatic disease (HR 0.65, 95% CI 0.58-0.78) and locally advanced disease (HR 0.77, 95% CI 0.68-0.80), with a numerically greater benefit in the metastatic subgroup. Prior chemoradiotherapy also appeared to modify the magnitude, but not the direction, of benefit: patients with previous chemoradiotherapy derived a marked PFS advantage (HR 0.56, 95% CI 0.45-0.80), whereas those without prior chemoradiotherapy showed a directionally favorable but statistically nonsignificant effect (HR 0.79, 95% CI 0.58-1.23) (**Figure 8**).

Publication bias

In **Figure 9A**, the studies were distributed relatively closely around the pooled effect estimate and largely within the pseudo-95% confidence

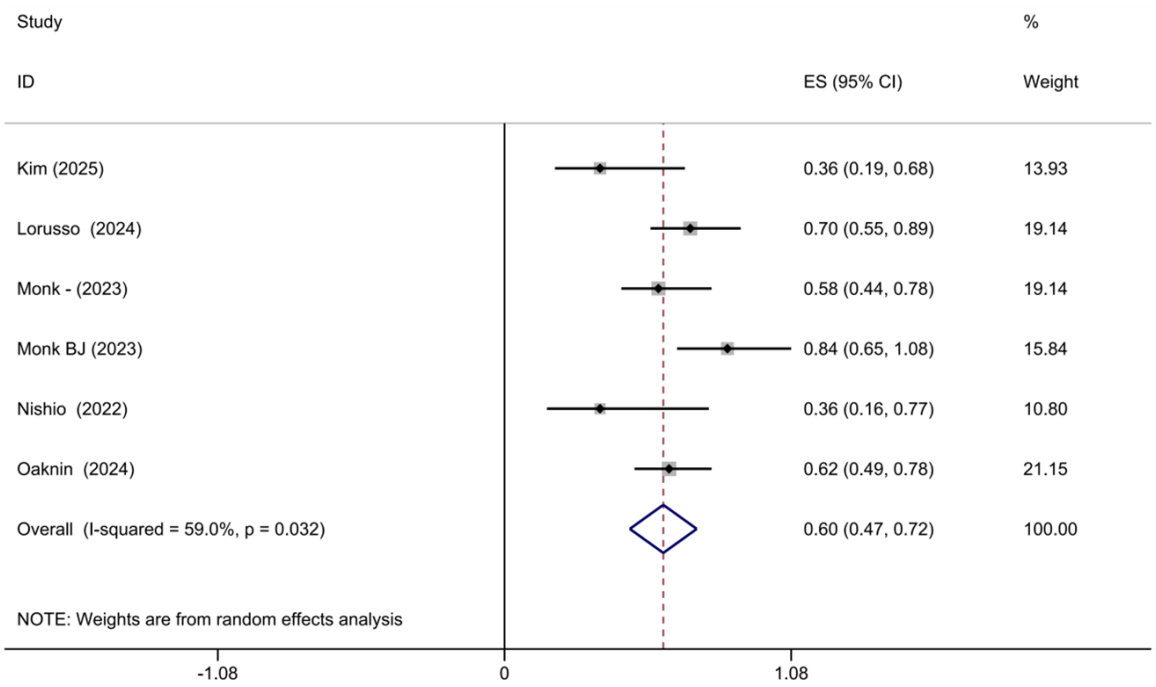

Figure 3. Forest plots of progression-free survival (PFS). Notes: PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; IV, inverse variance; df, degrees of freedom; I^2, inconsistency statistic; Z, standard normal deviate; Tau^2, between-study variance; Chi^2, Cochran's Q heterogeneity statistic.

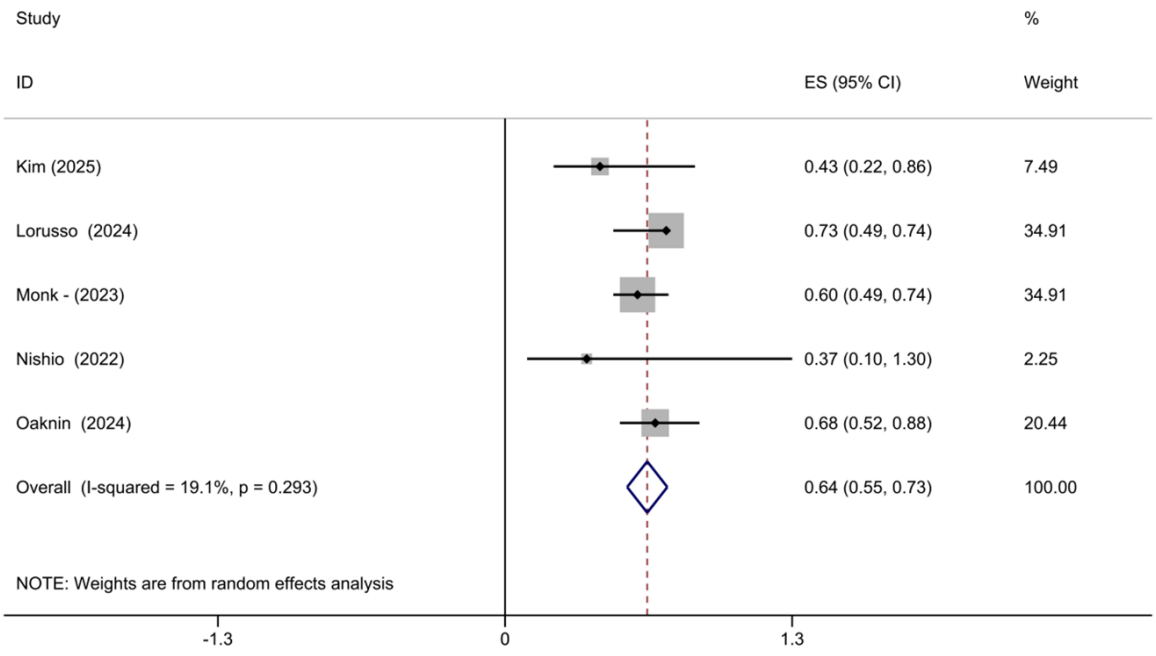

Figure 4. Forest plots of overall survival (OS). Notes: OS, overall survival; HR, hazard ratio; CI, confidence interval; IV, inverse variance; df, degrees of freedom; I^2, inconsistency statistic; Z, standard normal deviate; Tau^2, between-study variance; Chi^2, Cochran's Q heterogeneity statistic.

limits, indicating an overall acceptable symmetry for this endpoint. By contrast, panel B showed a somewhat less balanced distribution, with several smaller studies tending to cluster on the side of greater treatment effect and a relative sparsity of studies on the oppo-

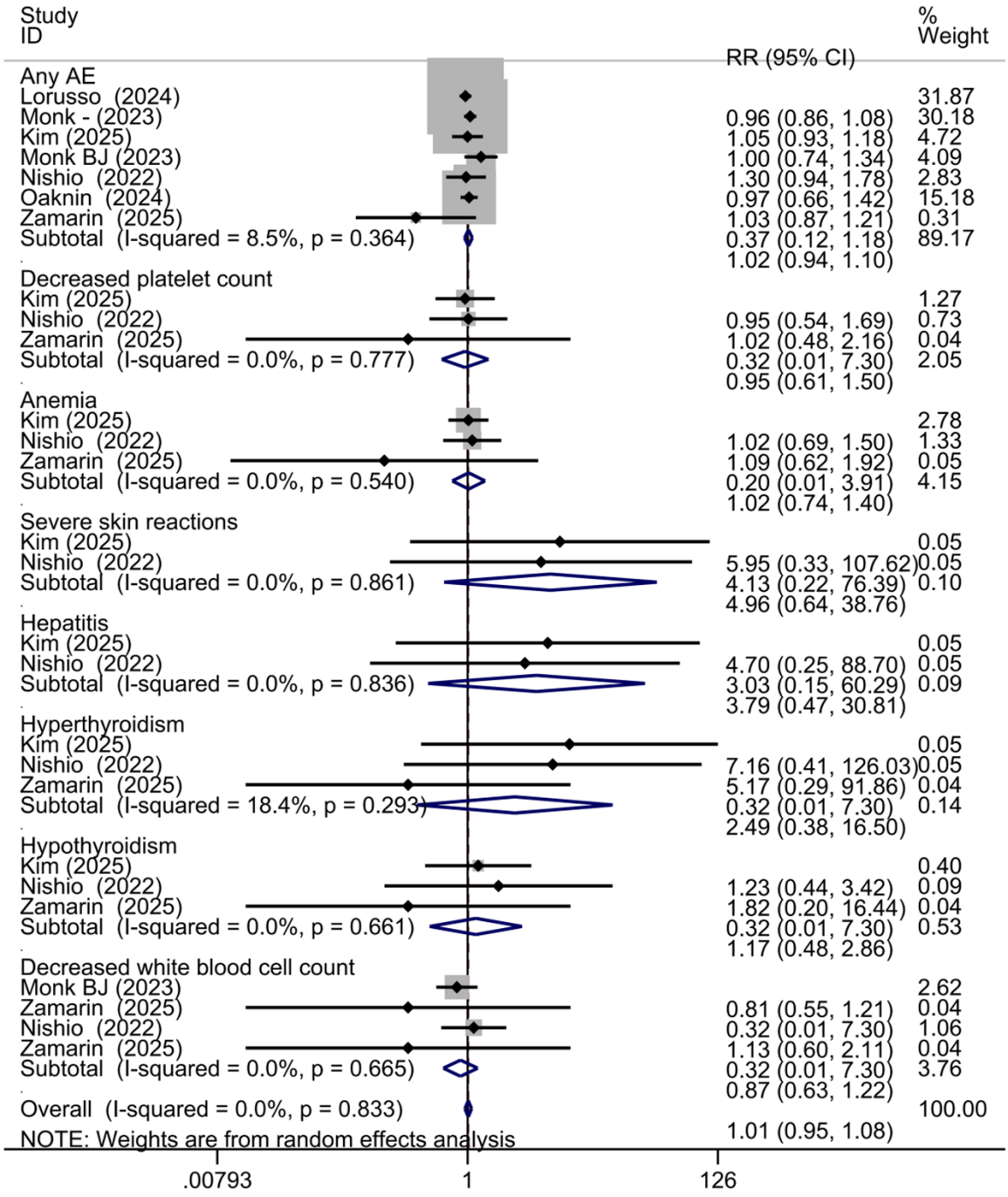

Figure 5. Forest plots of adverse event. Notes: AE, adverse event; irAE, immune-related adverse event; RR, risk ratio; CI, confidence interval; IV, inverse variance; df, degrees of freedom; I^2, inconsistency statistic; Z, standard normal deviate; Tau^2, between-study variance; Chi^2, Cochran's Q heterogeneity statistic; WBC, white blood cell.

site side, raising the possibility of small-study effects or selective reporting. Nevertheless, the number of included studies for each survival outcome was limited, and visual interpretation of funnel plots under such circumstances is inherently unstable and should be approached cautiously. Taken together, these findings do not suggest substantial publication bias at a gross visual level, but a moderate risk of reporting-related bias cannot be definitively excluded, particularly for the endpoint shown in **Figure 9B**.

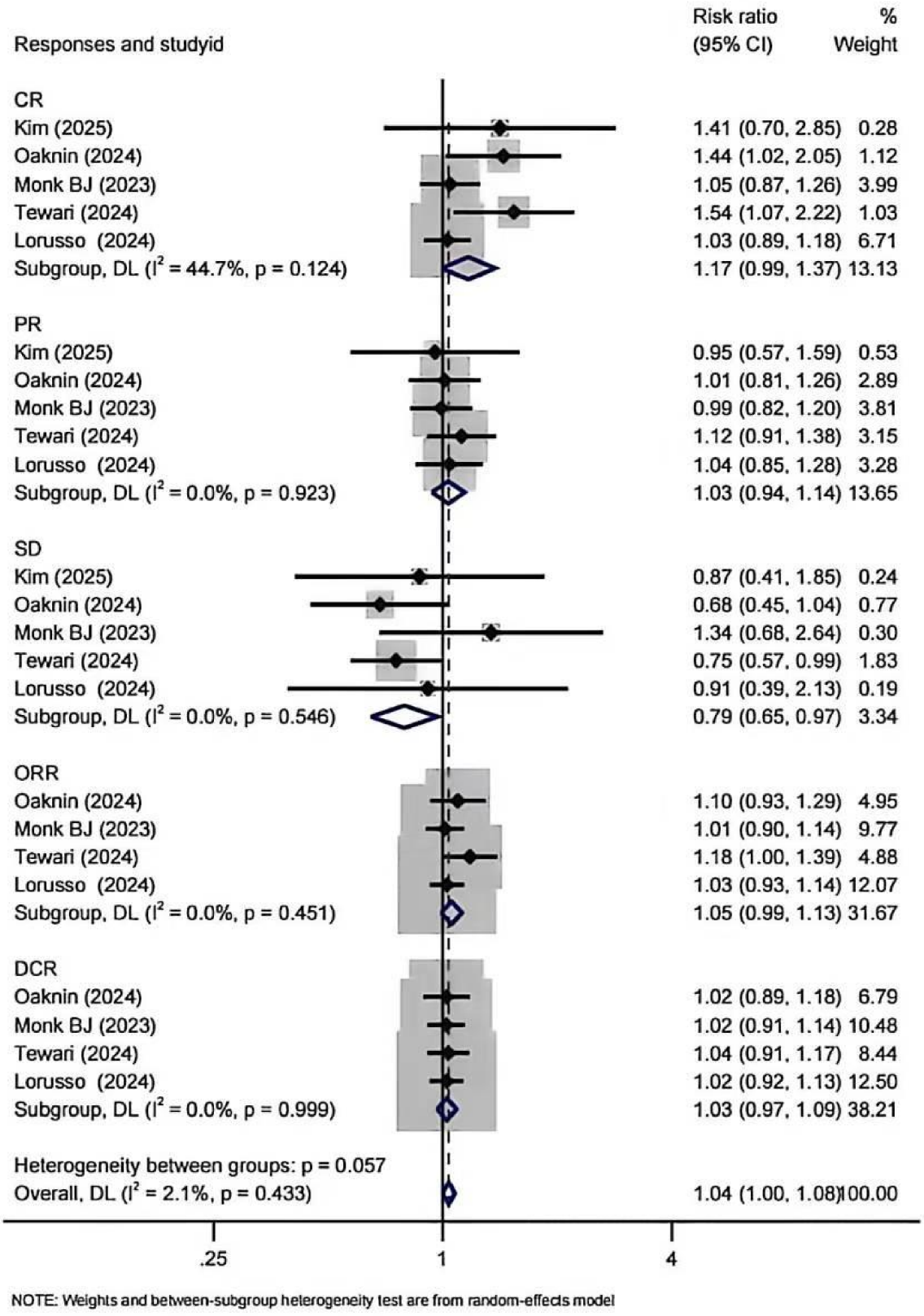

Figure 6. Forest plots of responses. Notes: CR, complete response; PR, partial response; SD, stable disease; ORR, objective response rate; DCR, disease control rate; RR, risk ratio; CI, confidence interval; IV, inverse variance; df, degrees of freedom; I^2, inconsistency statistic; Z, standard normal deviate; Tau^2, between-study variance; Chi^2, Cochran's Q heterogeneity statistic.

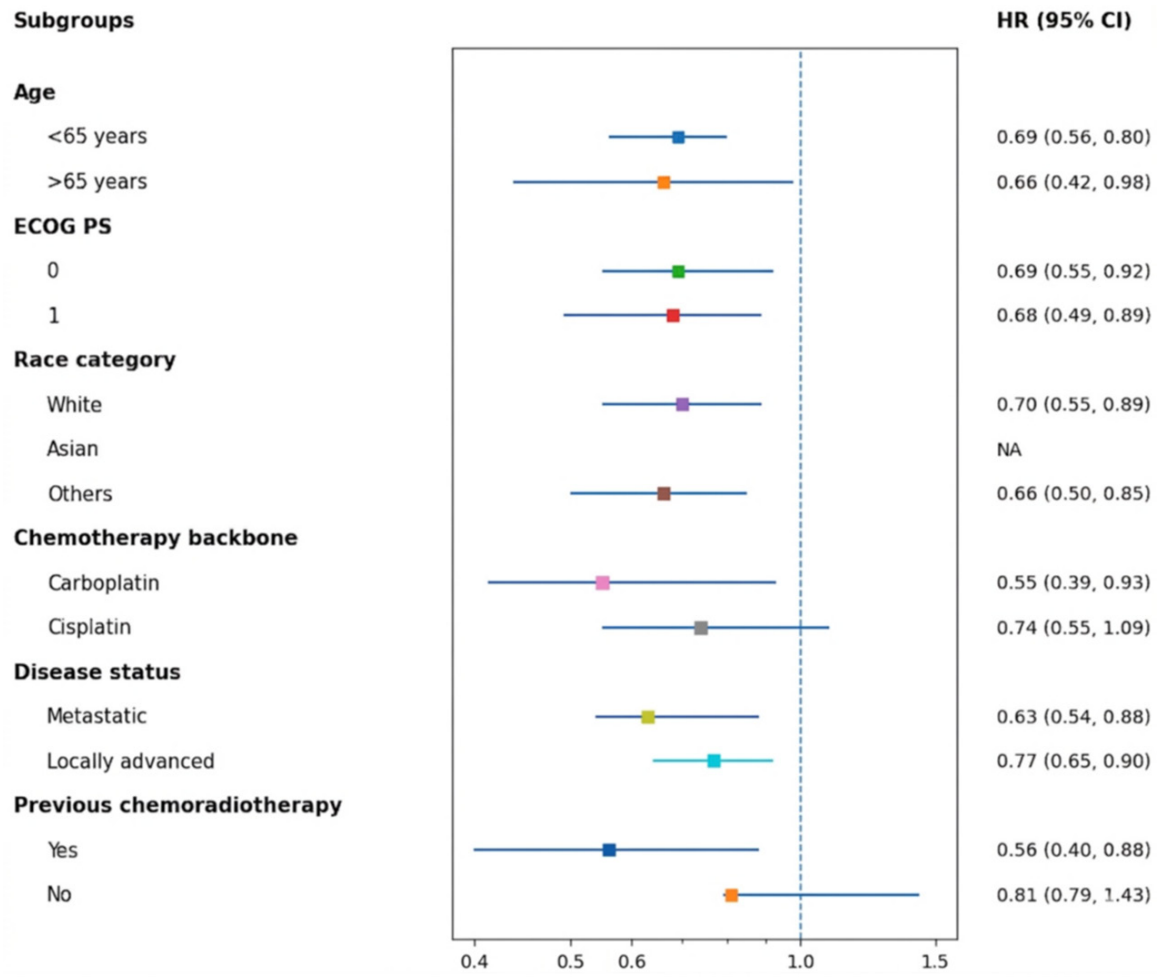

Figure 7. Subgroup analysis of overall survival (OS). Notes: OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IV, inverse variance; df, degrees of freedom; I^2, inconsistency statistic; Z, standard normal deviate; Tau^2, between-study variance; Chi^2, Cochran's Q heterogeneity statistic.

Sensitivity analysis

We conducted sensitivity analyses by sequentially omitting each study and re-estimating the pooled effect sizes for progression-free survival (PFS) and overall survival (OS). Despite the inclusion of randomized controlled trials, single-arm trials, and retrospective studies, the direction and magnitude of the pooled hazard ratios remained largely consistent, with no individual study substantially altering the overall results. Specifically, exclusion of any single study resulted in pooled HRs for PFS ranging from 0.61 to 0.65 and for OS ranging from 0.62 to 0.65, indicating that the main findings are robust to the variability in study design. These analyses support the reliability of our meta-analysis conclusions, while acknowledging that residual heterogeneity, due to differences in trial phase, sample size, treatment regimens, and follow-up duration, remains a limitation. The results reinforce that the beneficial effects of neoadjuvant immune checkpoint inhibitors combined with chemotherapy are generally consistent across the diverse study designs included in this review.

Discussion

The meta-analysis provides a timely synthesis of comparative data on neoadjuvant immune checkpoint inhibitors with chemotherapy versus the chemotherapy-based controls for cervical cancer, and indicates a consistent pattern of clinical benefit in a variety of dimensions of efficacy. The most notable was the addition of immunotherapy which was coupled with a significant increase in progression-free survival

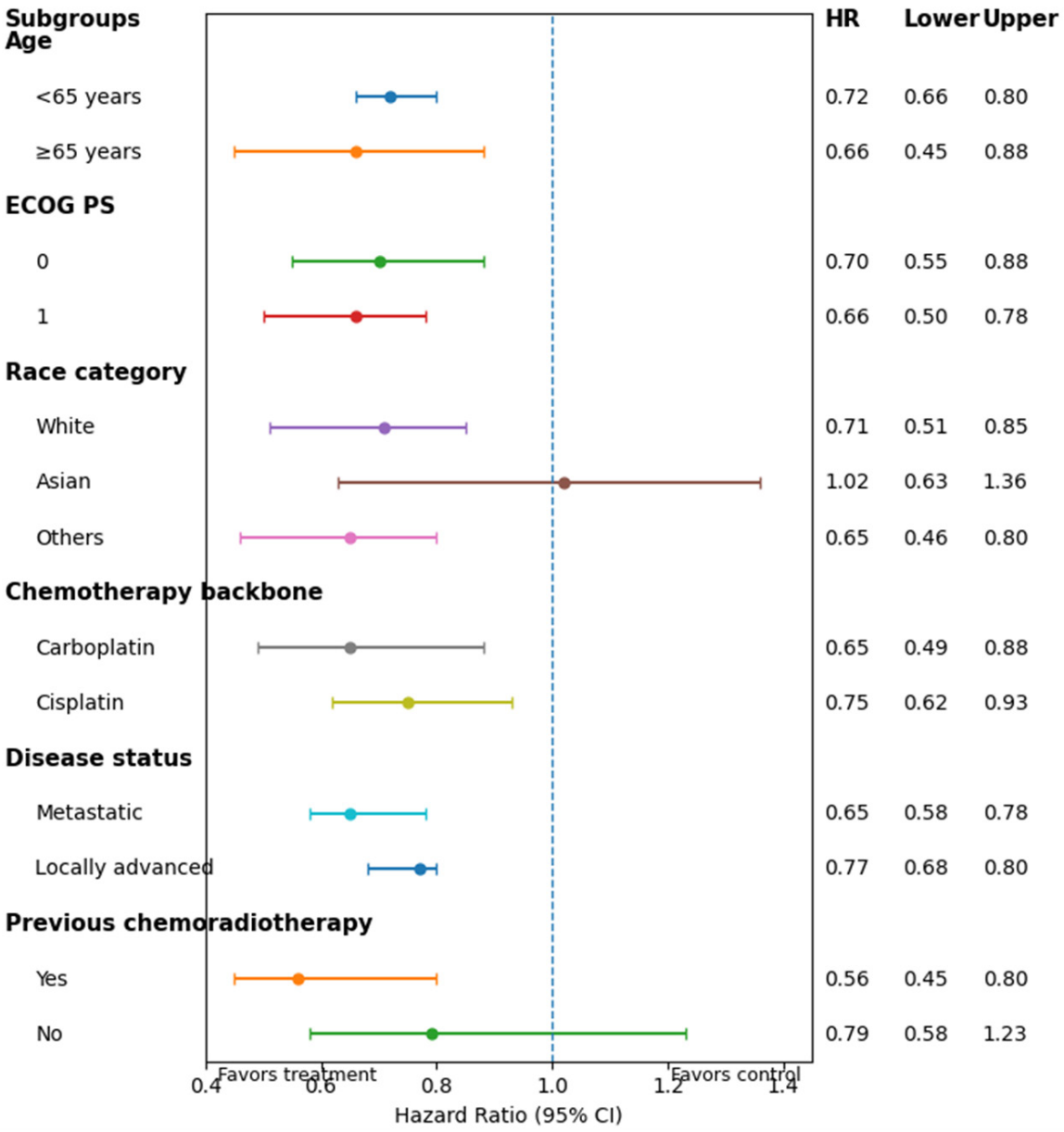

Figure 8. Subgroup analysis of progression-free survival (PFS). Notes: PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

and overall survival, with a largely similar safety profile and with indications of deeper antitumor activity, especially a decrease in stable disease. Beyond the pooled benefit of survival, the current research incorporates the extra information of response outcomes, adverse events, subgroup effects of treatment and assessment of publication bias in one analysis, thus providing a more holistic review of the developing role that neoadjuvant or peri-neoadjuvant immunochemotherapy may play in this disease context.

A statistically significant survival benefit was linked to the use of immune checkpoint blockade. This finding aligns with the trend in modern cervical cancer therapy, whereby PD-1/PD-L1-specific types of therapies have been shown to be effective in recurrent, metastatic and high-risk locally advanced disease [29], such that immunotherapy has increasingly become a primer of care treatment. In the neoadjuvant system, our meta-analyses indicate that such an advantage is not simply incidental, or only present in single trials, but actually is

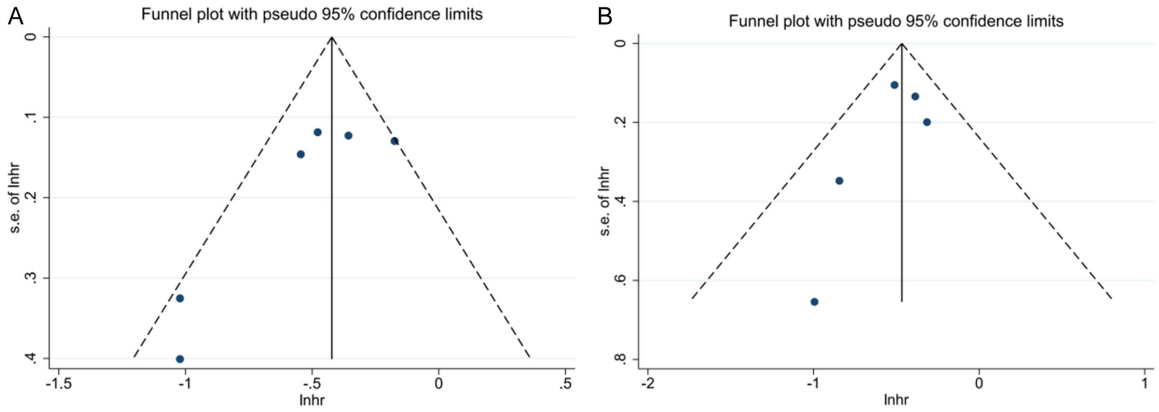

Figure 9. Funnel plots of survival (A), subgroup analysis of PFS, (B) subgroup analysis of OS. Notes: PFS, progression-free survival; OS, overall survival; HR, hazard ratio; SE, standard error.

seen to have some degree of regularity across trials. This effect, biologically possible, is mechanistically interesting since cervical cancer is a virally-induced cancer that is marked by stabilized HPV-related antigenicity, immune escape, and consistent stimulation of the checkpoint pathways, making the tumor especially amenable to immune reinvigoration [30-32]. The pragmatic implication is that survival, not response in isolation, eventually may be the most convincing end outcome to justify previous immunotherapy integration; though, it is also a warning that long-term validation in fully-grown prospective data sets is still necessary before this may be adopted routinely on a universal basis.

The survival advantage seems to be coupled with the change in tumor-response relationships and not the radical rise in conventional composite response rates. We have found a marginal increase in complete response and no apparent increase in partial response, and a considerable decrease in stable disease, with no significant changes in ORR and DCR. The interesting aspect of this trend is that it contrasts with the simplistic assumption that effective immunotherapy should be associated with significant improvements in overall radiographic response. History of immuno-oncology trials in solid tumors has indicated that immune based therapies can change the depth, dynamics and quality of tumor regression that standard dichotomized response endpoints do not reflect well [33, 34]. A likely reason is that immunochemotherapy could be able to cause deeper tumor elimination in an assortment of patients in spite of keeping overall response rates comparatively consistent. This has significant ramifications on interpretation of trial results: use of ORR can be overly optimistic in estimating clinically relevant benefit and future research ought to use pathologic response, molecular residual disease and durable remission to more effectively quantify therapeutic worth.

The introduction of immune checkpoint inhibitors did not seem to have a significant effect on the prevalence of the overall incidence of adverse events in the evidence base available. This finding is in line with the ever-increasing appreciation that, in most cases, immunotherapy can be safely overlaid on established treatment backbones without a toxicity penalty. Tolerability is critical in cervical cancer, where patients may already face significant treatment burden due to platinum-based treatment using chemotherapy, radiotherapy or combined-modality approaches, preserving tolerability is of particular importance [35, 36]. One possible reason is that the adverse reactions reported in the pooled analyses were predominated by the common treatment-related toxicities but not immune-specific toxicities that could be less common but have a clinical distinctive characteristic. By this means, the reassuring over-all safety signal should not be construed to mean that toxicity is inconsequential, but it indicates that immunochemotherapy might be practicable at the population level, but that careful prospective reporting of grade-specific, organ-specific and immune-mediated toxicities that might not be fairly reflected in aggregate event counts is necessary.

In both OS and PFS, positive estimates were observed in both age groups, and both ECOGs performance-status groups, suggesting that there is no clear limitation to benefit to a strictly defined population group of ideals. This overall consistency can be clinically relevant since it is an indication of some strength of treatment effect despite the heterogeneity of the studies incorporated. Such consistency may be biologically indicated by the fact that HPV-induced immune susceptibility is a characteristic feature of the disease core that cannot entirely lie in age or an established status of health performance. Meanwhile, subgroup results are to be viewed with caution. The unresponsiveness to benefit of certain subgroups, including the Asian subgroup of PFS, may be due to small sample sizes, lack of representation, or trial imbalances rather than true biological resistance. Those findings thus confirm general clinical applicability, but likewise caution of the potential to overinterpret the seemingly subgroup differences when it has not been corroborated at the patient level.

The current results also extend to the current development of neoadjuvant treatment models in cervical cancer. Classically, the application of neoadjuvant chemotherapy is selective to downstage tumor, enhance resectability, and deal with occult systemic disease, although its effect on cancer treatment has been erratic. We believe that our findings indicate that immunologic intensification is one of the directions to address the shortcomings of chemotherapy. A biologic rationale underpinning this idea is that chemotherapy causes immunogenic cell death, exposes neoantigens, and reorganizes the tumor microenvironment, which enhances the effect of checkpoint blockade; immunotherapy can also rejuvenate exhausted T-cell responses and stabilize antitumor immunity, in advance of local therapy. Should this be verified in prospective studies that follow, this approach has the potential to transform preoperative management into an area that is no longer cytotoxic downstaging, but instead one based on biological addition of disease control. Nevertheless, this promise should be counterweighed by the necessity to identify which patients are most likely to benefit, the regimens that are the most effective, and the endpoints that can best reflect meaningful neoadjuvant success.

Based on the pooled evidence, certain trends can be observed that may inform clinical decision-making for neoadjuvant immunotherapy combined with chemotherapy in cervical cancer. Patients with locally advanced or high-risk disease appear to derive the most pronounced survival benefit, suggesting that this population may represent an optimal target for therapy. Regarding chemotherapy backbone, regimens based on carboplatin consistently showed favorable outcomes, whereas cisplatin-based regimens demonstrated numerically positive but less consistent effects, indicating that carboplatin may be preferred in combination with immune checkpoint inhibitors. Furthermore, the timing of neoadjuvant administration prior to surgery appears generally favorable, although the optimal treatment duration remains to be fully defined. These observations should be interpreted as evidence-supported guidance rather than definitive rules, as variations in trial design, patient characteristics, and follow-up duration may influence outcomes. Prospective studies are warranted to refine patient selection criteria, optimize chemotherapy backbones, establish ideal treatment duration, and determine the best timing of surgery to maximize clinical benefit.

Several limitations of this meta-analysis should be acknowledged. First, the included articles were very diverse in terms of phase, design, treatment backbone, comparator strategy, follow-up time and timing of exposure to immunotherapy and this of course restrains simple comparability. Second, it involved a relatively small number of studies that were contributing to a certain pooled endpoint, especially survival and subgroup analyses, which diminished statistical power and precision. Third, some of the subgroup results were made based on trial-level, instead of individual-patient, data and should, thus, be regarded as exploratory. Fourth, even though the overall risk-of-bias profile was satisfactory, there were still issues in the areas pertaining to the blinding, selective reporting, and other nonstandard biases, which could have affected the pooled estimates. Lastly, the funnel plots had no gross publication bias, however, the small number of studies prevents the reliability of assessing visual asymmetry. Combined, the above restrictions demand that the existing evidence is positive but not conclusive.

In conclusion, this meta-analysis indicates that neoadjuvant immune checkpoint inhibitors in combination with chemotherapy provide significant survival benefit in cervical cancer with no apparent overall escalation of the frequency of common adverse events, and with evidence of greater depth of response. The effect was found to be widely applicable in large clinical subgroups suggesting the possibility of generalizability of this approach, but the effect size could differ depending on the context of the treatment and pre-exposure. These findings support earlier integration of immunotherapy into cervical cancer treatment and validate additional biomarker-driven, sufficiently powered prospective studies to improve patient selection, regimen design, and determine the ultimate role of neoadjuvant immunochemotherapy into clinical practice.

Disclosure of conflict of interest

None.

Address correspondence to: Jing Wang, Department of Gynecology, Xianju People's Hospital, Zhejiang Southeast Campus of Zhejiang Provincial People's Hospital, Affiliated Xianju's Hospital, Hangzhou Medical College, No. 53 Chengbei East Road, Xianju County, Taizhou, Zhejiang, China. Tel: +86-159-58326824; E-mail: m15958326824@163.com

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