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REVIEW

The efficacy of immune checkpoint inhibitors therapy versus chemotherapy in the treatment of advanced and metastatic urothelial carcinoma: a meta-analysis

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Abstract

Purpose The application of platinum-based chemotherapeutic agents is the traditional treatment paradigm for advanced and metastatic urothelial carcinoma, which has changed with the advent of immune checkpoint inhibitors (ICIs). This study aims to evaluate the efficacy of ICI therapy versus chemotherapy in the treatment of advanced and metastatic urothelial carcinoma.

Methods A systematic literature search of Web of Science, Embase, PubMed, and Cochrane Central Register of Controlled Trials was performed by two independent investigators. The primary endpoint was overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and adverse events (AEs).

Results The patients treated with ICI monotherapy had no significant difference in OS than those treated with chemotherapy monotherapy (HR: 0.965, 95% CI 0.865–1.076, $p=0.518$). However, the patients treated with ICI monotherapy had a higher ORR and lower incidence of high-grade (≥ grade 3) AEs than those treated with chemotherapy monotherapy (OR: 0.568, 95% CI 0.479–0.675, $p<0.001$; OR: 0.614, 95% CI 0.446–0.845, $p=0.003$). The patients treated with ICI in combination with chemotherapy had significantly better OS and PFS than those treated with chemotherapy alone (HR: 0.862, 95% CI 0.776–0.957, $p=0.006$; HR: 0.788, 95% CI 0.707–0.879, $p<0.001$). However, there was no significant difference in ORR or the incidence of grade 3 or higher AEs (OR: 0.951, 95% CI 0.582–1.554, $p=0.841$; OR: 0.942, 95% CI 0.836–1.062, $p=0.328$).

Conclusion ICI monotherapy did not show statistically significant difference in OS but demonstrated higher ORR and lower incidence of high-grade (≥ grade 3) AEs. And a statistically significant OS and PFS benefit was found in patients treated with first-line ICI in combination with chemotherapy compared to chemotherapy alone.

Keywords Urothelial carcinoma · Chemotherapy · Immune checkpoint inhibitors · Urology

Introduction

Urothelial carcinoma (UC) is one of the more common types of urological tumors, primarily arising from the bladder, as well as the urethra, ureter, and renal pelvis. The number of new diagnoses and deaths from bladder cancer alone reaches approximately 573,000 and 213,000 cases worldwide each year (Sung et al. 2021). The prognosis of advanced UC is extremely poor, with a 5-year survival rate of less than 5% for stage IV patients with metastases (Witjes et al. 2021). In recent years, with intensive research on immune checkpoint inhibitors (ICIs), such as antibodies to programmed cell death protein-1 inhibitor (PD-1) and its ligand programmed death ligand 1 (PD-L1), significant progress has been made in the treatment of tumors, including metastatic urothelial carcinoma (mUC) (Mollica et al. 2020). In addition, treatment guidelines published by organizations such as the European Association of Urology (EAU), the European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) have recognized the important role of ICI in the second-line treatment of advanced urothelial cancer, maintenance therapy after first-line platinum-based chemotherapy, and in patients who are not suitable for platinum-based chemotherapy (Witjes et al. 2021; Powles et al. 2022; Flaig et al. 2022). However, due

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to the limited sample size of the included studies, there is no clear conclusion on whether replacing platinum-based chemotherapeutic agents with ICI is effective in improving patient prognosis. Therefore, we performed a meta-analysis of all relevant clinical trials comparing the efficacy and safety of these two treatment regimens, using ICI alone or ICI in combination with chemotherapy as the experimental group and standard platinum-based chemotherapy regimens as the control group.

Materials and methods

Search strategies

To obtain eligible studies, multiple databases were searched for articles published until May 1, 2023. The databases searched included Web of Science, Embase, PubMed, and Cochrane Central Register of Controlled Trials. The following keywords were used for all the studies related to ICIs: immune checkpoint inhibitors, ICI, Atezolizumab, Avelumab, Durvalumab, Pembrolizumab, Nivolumab, Tislelizumab, Toripalimab, Urothelial carcinoma, bladder cancer, bladder tumor, bladder neoplasm.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the subjects included in the study should be patients with advanced or mUC, prospective phase III or IV clinical trials involving UC patients; (2) the intervention for the experimental group should be an first-line ICI alone or first-line ICI in combination with chemotherapy and for the control group, a platinum-based chemotherapeutic agent; (3) the format of the study should be a randomized controlled trial with at least one of the following indicators: overall survival (OS), progression-free survival (PFS), adverse events (AEs), or objective response rate (ORR).

The exclusion criteria were as follows: (1) duplicate publications; (2) reviews, conference papers, or preprints; and (3) studies that only dealt with the pharmacological effects of ICI without clinical trial data.

Data extraction and grouping

Shihao Li and Hong Xiong extracted the data from the identified publications independently. The following information was extracted from each publication: name of the first author, publication year, type of ICIs, number of cases in the experimental group, number of cases in the control group, survival outcome, and follow-up time. To further compare the differences between the treatment regimens, we grouped the patients according to the following rules: the observation index of Group A was the efficacy of ICI monotherapy versus chemotherapy monotherapy, and the efficacy of ICI in combination with chemotherapy versus chemotherapy alone was observed in Group B.

Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies Newcastle−Ottawa Score (NOS) quality assessment system (Stang 2010) was used to determine the quality of the enrolled studies. Enrolled studies were scored based on case definition, representation of cases, selection restrictions, definition of controls, comparability of cases and controls, determination of exposure, identical determination methods for cases and controls, and nonresponse rates. Studies with a score ≥ 6 were considered high quality.

Statistical analysis

The results were visualized using STATA 17SE software and Review Manager 5.3 software. The heterogeneity test was performed by I-squared (I^2) statistics. The data were analyzed using a fixed-effects model by default and a random-effects model if $I^2 > 50\%$. We judged that there was significant heterogeneity among the included studies when the p was < 0.05; otherwise, there was no significant heterogeneity. The potential publication bias was estimated using Begg's funnel plot. We judged that there was no publication bias if $p > 0.05$ for Begg's test.

Results

Results of the literature search

The initial search of the above databases retrieved a total of 3,98,799 articles, and after a hierarchical screening process, a total of 3 studies were finally included (Galsky et al. 2020; Powles et al. 2020, 2021). A flow chart of screening eligible articles for the meta-analysis is shown in Fig. 1.

Characteristics of the enrolled studies

The three included studies were published between 2019 and 2023 and involved three different ICIs, including atezolizumab, durvalumab, and pembrolizumab. The characteristics of the included studies are listed in Table 1. The NOS quality evaluation scale assessed the quality of the included studies. The methodological quality of the included literature was high (Fig. 2).

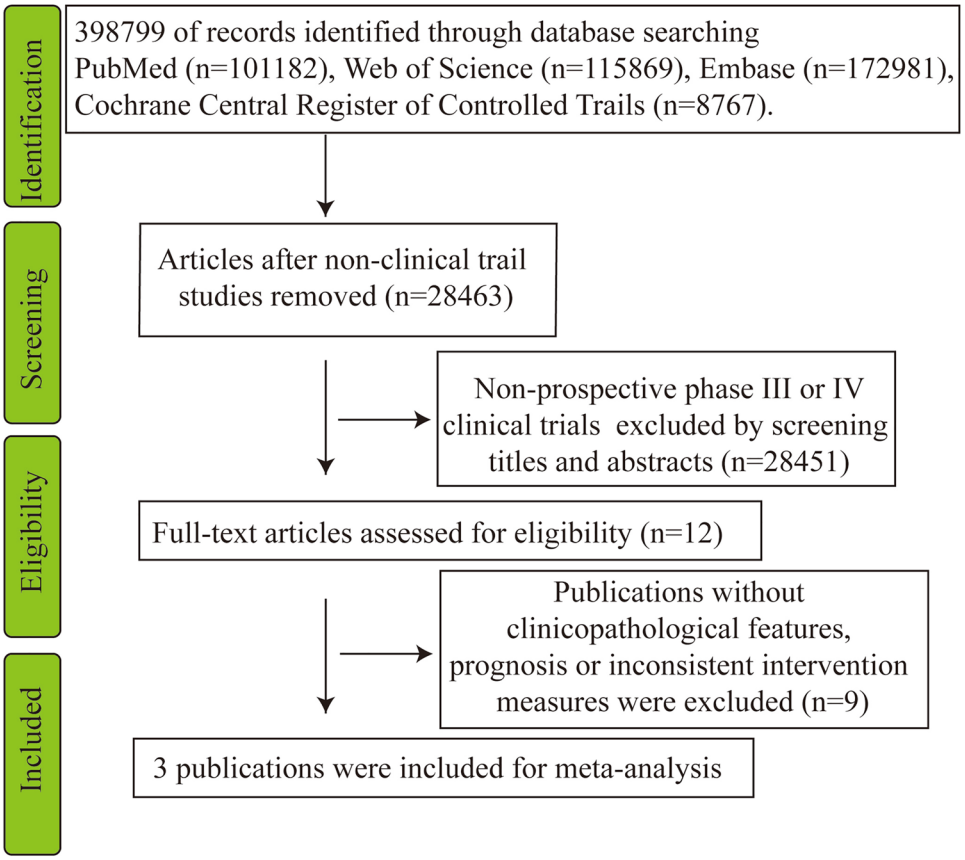

Fig. 1 Flowchart of literature screening

Table 1 Characteristics of the included studies

Name of the study	Author	Year	Drugs	Number of patients	Inclusion criteria	Follow-up time	NOS score
IMvigor130	Galsky (Powles et al. 2020)	2020	Atezolizumab	1213	OS, PFS, AEs, ORR	≥33	5
NCT02516241	Powles (Sivori et al. 2021)	2020	Durvalumab	1032	OS, AEs, ORR	≥51	8
KEYNOTE-361	Powles (Hasegawa et al. 2020)	2021	Pembrolizumab	1010	OS, PFS, AEs, ORR	≥42	8

Overall survival (*OS*), progression-free survival (*PFS*), adverse events (*AEs*), objective response rate (*ORR*)

Overall survival

In Group A, the OS data were from 3 randomized controlled trials (RCTs) with a total of 2068 randomized patients, without any selection for PD-L1 status (unselected) (Galsky et al. 2020; Powles et al. 2020, 2021). The results of the meta-analysis showed that ICI monotherapy had no better OS than platinum-based chemotherapy (HR: 0.965, 95% CI 0.865–1.076, $p = 0.518$; Fig. 3a).

In Group B, the OS data used to compare patients were from 3 RCTs with a total of 2240 randomized patients, without any selection for PD-L1 status (unselected) (Galsky et al. 2020; Powles et al. 2020, 2021). The results of the meta-analysis showed that ICI in combination with chemotherapy had a better OS than platinum-based chemotherapy (HR: 0.862, 95% CI 0.776–0.957, $p = 0.006$; Fig. 3b).

Progression-free survival

In Group B, the PFS data used for comparison were from 2 RCTs with a total of 1554 randomized patients (Galsky et al. 2020; Powles et al. 2021). The results of the meta-analysis showed that ICI in combination with chemotherapy had a better PFS than platinum-based chemotherapy (HR: 0.788, 95% CI 0.707–0.879, $p < 0.001$; Fig. 3c).

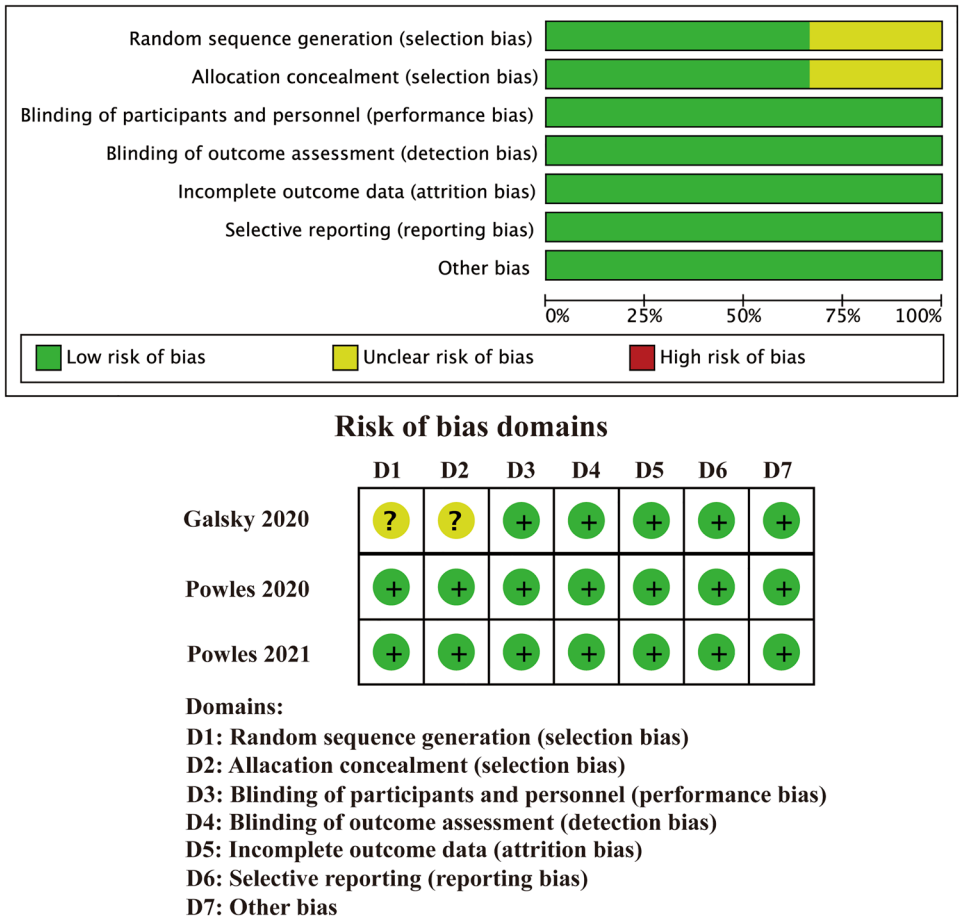

Fig. 2 Quality assessment of eligible studies

Objective response rate

In Group A, the data for ORR comparison were available from 3 RCTs, for a total of 2105 patients (Galsky et al. 2020; Powles et al. 2020, 2021). The results of the meta-analysis showed that ICI monotherapy had a higher ORR than platinum-based chemotherapy (OR: 0.568, 95% CI 0.479–0.675, $p < 0.001$; Fig. 4a).

In Group B, the ORR data used for comparison were from 2 RCTs with a total of 1389 patients (Powles et al. 2020, 2021). The results of the meta-analysis showed that there was no significant difference between the ICI in combination with chemotherapy groups and the platinum-based chemotherapy monotherapy groups (OR: 0.951 95% CI 0.582–1.554, $p = 0.841$; Fig. 4b).

Adverse events

In Group A, the data for comparison of AEs were available from 3 RCTs, for a total of 2259 any-grade AEs (Galsky et al. 2020; Powles et al. 2020, 2021). The results of the meta-analysis showed that the ICI monotherapy had a lower incidence of high-grade (≥ grade 3) AEs than the platinum-based chemotherapy (OR: 0.614, 95% CI 0.446–0.845, $p = 0.003$; Fig. 4c).

In Group B, the AEs data used for comparison were from 3 RCTs with a total of 2797 any-grade adverse events (Galsky et al. 2020; Powles et al. 2020, 2021). The results of the meta-analysis showed that there was no significant difference between the ICI in combination with chemotherapy groups and the platinum-based chemotherapy monotherapy groups (OR: 0.942, 95% CI 0.836–1.062, $p = 0.328$; Fig. 4d).

Publication bias

The potential publication bias was estimated using Begg's funnel plot. As shown in Fig. 5a, the Begg's funnel plot showed symmetry, $p = 1.000$, so we judged that there was no publication bias.

Sensitivity analysis

Sensitivity analysis was used to assess the robustness of the meta-analysis. The leave-one-out test showed that no single study influenced the results, indicating that the results of the meta-analysis were stable and reliable (Fig. 5b).

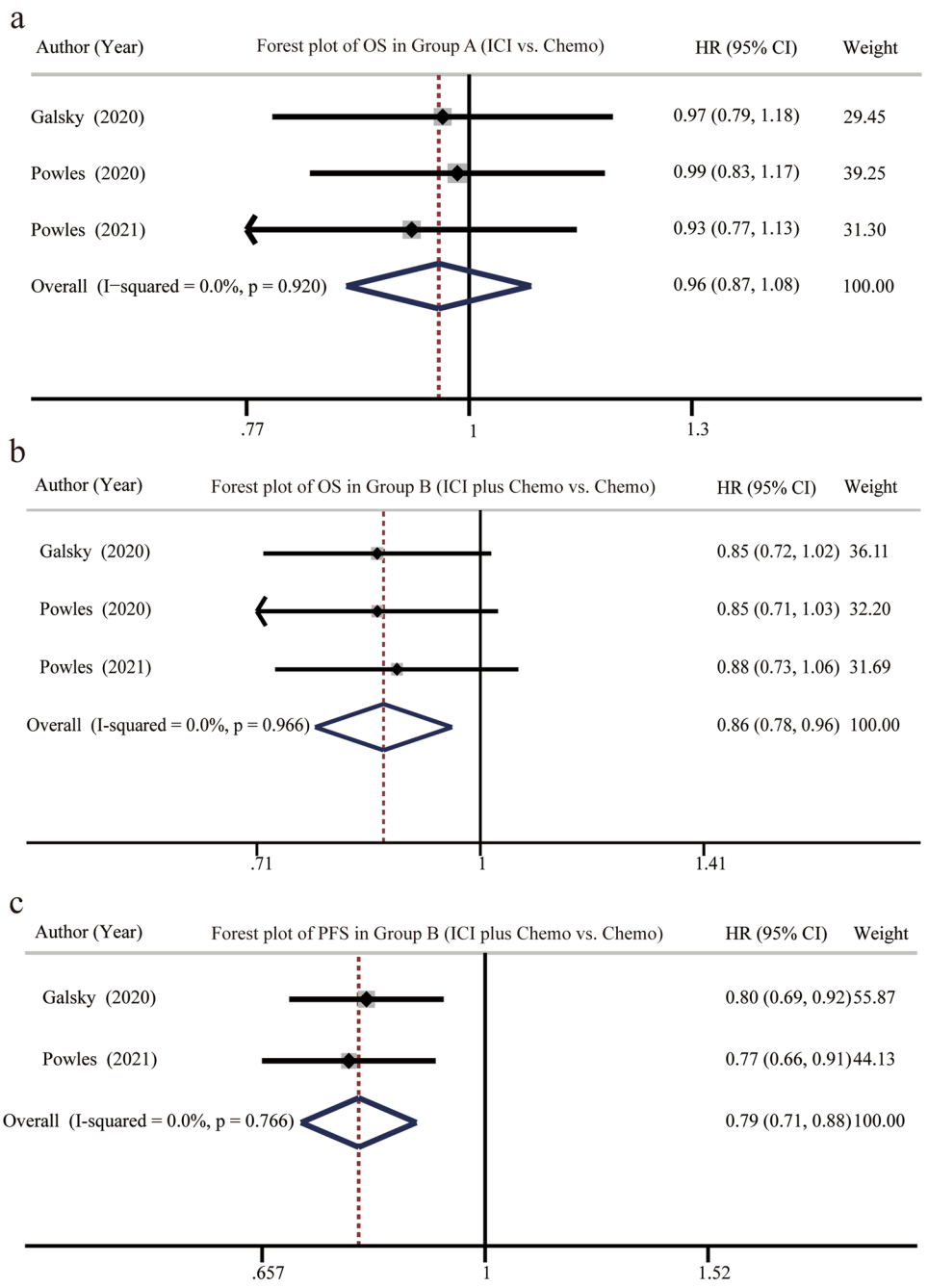

Fig. 3 Forest plot of OS and PFS in each treatment group. **a** Forest plot of OS in Group A, **b** Forest plot of OS in Group B, **c** Forest plot of PFS in Group B

Discussion

The immune checkpoint (IC) represents the inhibitory receptor whose main physiological function is to ensure peripheral immune tolerance by controlling the function of effector cells (Sivori et al. 2021). PD-1, one of the immune checkpoint receptors, is mainly expressed in T cells, monocytes, and natural killer (NK) cells, and its main ligand PD-L1 is mainly found on the surface of dendritic cells and macrophages, while this ligand can also be found on the surface of tumor cells (Hasegawa et al. 2020). The expression of this tumor-directed receptor on tumor-responsive effector cells and their ligands on tumor cells leads to a major mechanism of evasion of antitumor immunity. In contrast, ICIs work precisely by blocking the PD-1/PD-L1 pathway to enhance antitumor T-cell responsiveness and promote immune control of cancer cells. In fact, the first precedent for the use of immunotherapy for cancer treatment dates back to the late nineteenth century, when William B. Coley injected an inoperable cancer patient with streptococcal organisms in 1891, hoping that the bacterial infection would have the side effect of shrinking the malignant tumor (McCarthy 2006), and

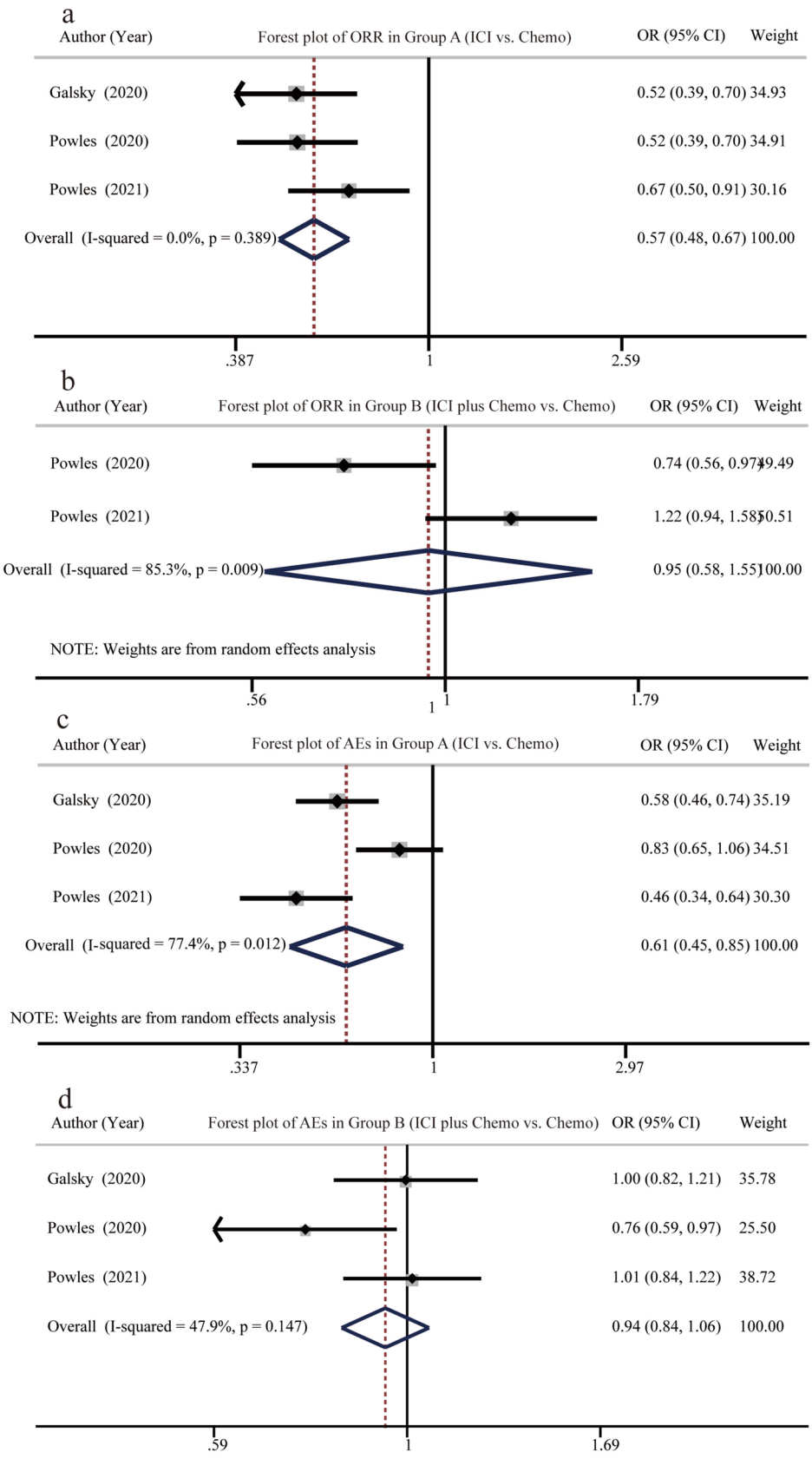

Fig. 4 Forest plot of ORR and AEs in group A (**a** and **c**) and group B (**b** and **d**)

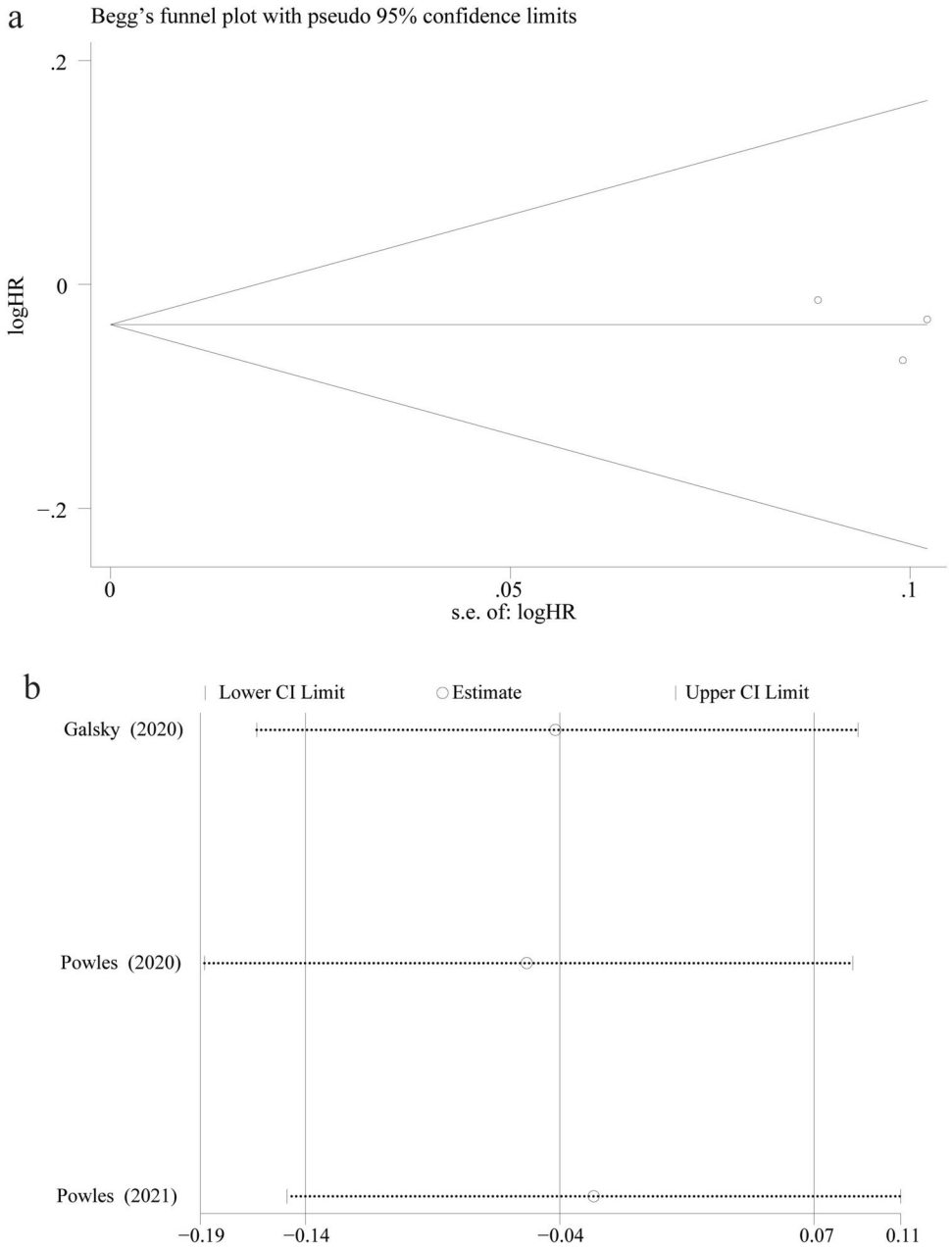

Fig. 5 OS analysis. **a** Duval and Tweedie nonparametric trim and fill method for group A, **b** sensitivity analysis of group A using the leave-one-out test

these bacterial products were collectively known as Coley's Toxins. Calmette–Guérin (BCG) has been shown to have the ability to induce inflammation and has been used for over 30 years for the treatment and secondary prevention of non-muscle invasive bladder cancer (Redelman-Sidi et al. 2014).

Since the approval of ipilimumab (human IgG1 k anti-CTLA-4 monoclonal antibody) by the US Food and Drug Administration (FDA) in 2011, six additional ICIs have been approved for cancer treatment. These include the PD-1 inhibitors nivolumab, pembrolizumab, and cemiplimab and the PD-L1 inhibitors atezolizumab, avelumab, and durvalumab. Nivolumab is the first human IgG4 monoclonal antibody against PD-1 and was initially approved for the treatment of progressive, advanced, unresectable, metastatic melanoma, with results showing significant improvement in patient OS (Hodi et al. 2010). As clinical studies progressed, nivolumab was shown to be useful in the treatment of small cell lung cancer, non-small cell lung cancer, and other malignancies, all resulting in patients with clinical benefit (Wu et al. 2019; Ready et al. 2019) and prolonged disease-free survival in patients with mUC (Bajorin et al. 2021). Pembrolizumab is another PD-1 inhibitor that was approved for clinical trials in 2014. In a recent clinical trial (KEYNOTE-361), pembrolizumab did not appear to show satisfactory efficacy in the treatment of advanced UC, and overall patient survival was not significantly improved (Powles et al. 2021).

Avelumab is a PD-L1 blocking antibody approved for use in clinical trials in 2015. Avelumab demonstrated antitumor activity in the treatment of patients with platinum-resistant mUC, and a manageable safety profile was reported in all patients treated with avelumab. These data provided the rationale for the therapeutic use of avelumab in mUC, and on this basis, accelerated approval was granted by the FDA (Patel et al. 2018). In February 2016, the FDA granted the designation of the anti-PD-L1 monoclonal antibody durvalumab as a second-line or subsequent monotherapy for patients with locally advanced or metastatic urothelial malignancies, with accelerated approval. Based on data from late-stage phase I/II clinical trials, durvalumab demonstrated promising clinical activity and an encouraging and manageable safety profile in patients with locally advanced, metastatic UC (Powles et al. 2017). In May of 2016, atezolizumab was also approved for the treatment of locally advanced or metastatic urothelial malignancies and was the first PD-1/PD-L1 inhibitor approved in cisplatin chemotherapy for advanced or metastatic bladder cancer, which was later approved as a first-line agent (Rosenberg et al. 2016). In addition to these FDA-approved antibodies against PD-1, the National Medical Product Administration (NMPA) approved tislelizumab for marketing in 2019 for patients with relapsed or refractory classical Hodgkin's lymphoma (r/r cHL) after at least second-line chemotherapy (Lee and Keam 2020). Tislelizumab has been shown in clinical trials to extend overall survival in patients with advanced uroepithelial cancer with a manageable safety profile (Ye et al. 2021). It was approved in 2020 for the treatment of patients with high PD-L1 expression after platinum-based chemotherapy (Administration NMPA 2021). In this study, we focused on the differences in the efficacy and prognosis of ICI versus chemotherapy in the treatment of advanced and mUC to ensure maximum patient benefit in clinical treatment. In summary, the application of ICI to the clinical treatment of malignancies of urothelial origin should be effective.

The most common AEs during ICI treatment are primarily cutaneous, intestinal, endocrine, pulmonary, and musculoskeletal damage. Approximately 23–33% of patients treated with ipilimumab monotherapy, 8–19% of patients treated with anti-PD-1 antibodies, and 44% of patients treated with the combination of ipilimumab and nivolumab experienced varying degrees of diarrhea (Spain et al. 2016). The incidence of grade 3 and 4 AEs reached 9% in patients treated with the combination (Spain et al. 2016). Compared with AEs from chemotherapy, immune-related adverse reactions (irAEs) associated with immunotherapy are usually longer in onset and longer in duration, and effective management depends on early identification and timely intervention of immunosuppressive and/or immunomodulatory strategies (Puzanov et al. 2017). In general, biomarkers from affected organs or the tumor microenvironment require tissue biopsy, which helps to predict biological behavior, especially for highly heterogeneous tumor tissues (Shioga et al. 2020). In addition, histopathology and immunohistochemistry are well-established clinical routines. It has been noted that monotherapy with ICI in patients with high PD-L1 expression may not improve prognosis (Guo et al. 2021). However, the study by Rizzo et al. noted that ICIs were associated with higher OS in PD-L1-positive patients (HR: 0.86, 95% CI 0.78–0.96); conversely, no differences were observed in PD-L1-negative patients (HR: 1.03, 95% CI 0.89–1.19) (Rizzo et al. 2022). Moreover, gut microbiota is also an important biomarker. The study by Hopkins et al. noted that the use of antibiotics in patients with UC treated with ICI resulted in decreased survival in cancer patients, whereas in patients receiving chemotherapy, no association between antibiotics and decreased survival was observed, suggesting that antibiotics may reduce the effectiveness of ICI therapy (Hopkins et al. 2020a). Proton pump inhibitors (PPIs) were negatively associated with patients with advanced UC treated with ICIs, independent of chemotherapy (Hopkins et al. 2020b). From some similar types of studies, it appears that antibiotics and PPIs may affect the efficacy of ICI by influencing the intestinal microecological balance, thus affecting the survival of patients with advanced UC (Gopalakrishnan et al. 2018; Maier et al. 2018).

Of course, there are still some limitations of our meta-analysis. The first is the study on baseline and prognosis, where it was noted that the patient population aged 80 years and older had better tolerability of ICI (Nebhan et al. 2021). Although patients in this age group represent a large proportion of those diagnosed with UC, there may be an underrepresentation in clinical trials. Then there is the question of whether the combination regimen of ICI and platinum-based chemotherapeutic agents can increase the clinical benefit for patients. Although we searched the literature in several databases, we did not find more studies of this type in existence, and we still need more data from studies of the same type for further analysis. From the data derived from the Begg's funnel plot, there was no potential publication bias in the included literature regarding the combination regimen of ICI and platinum-based chemotherapeutic agents; thus, our study is credible.

Conclusion

ICI monotherapy did not show statistically significant difference in OS but demonstrated higher ORR and lower incidence of high-grade (≥ grade 3) AEs. And a statistically significant OS and PFS benefit was found in patients treated with first-line ICI in combination with chemotherapy compared to chemotherapy alone. In a word, ICIs are effective in providing clinical benefit to patients with

advanced and metastatic UC compared to platinum-based chemotherapy monotherapy.

Author contributions GZH took the whole responsibility of literature search, study design, and manuscript drafting. SHL and HX contributed to data extraction, concept formation, statistical revision, and major revision of the manuscript. YZ contributed to study design, concept formation, and major revision of the manuscript. HWL took the responsibility of collection of all information from the other authors, major revision of the manuscript, and full access to the data. All authors read and approved the final version of the manuscript.

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Ddata availability The data analyzed in this study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest No potential conflicts of interest was disclosed.

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