

Efficacy and safety of BCG and immune checkpoint inhibitors in non-muscle invasive bladder cancer: A meta-analysis with exploratory chemotherapy comparisons

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Abstract. Bladder cancer (BC) is a significant global health concern and includes non-muscle-invasive BC (NMIBC), which poses challenges due to recurrence and progression. Immunotherapy, such as immune checkpoint inhibitors (ICIs) and Bacillus Calmette-Guérin (BCG), shows promise particularly in cases of BCG failure or BCG-unresponsive NMIBC, with ICIs emerging as a potential treatment option for these challenging cases. To the best of our knowledge, the present study is the first to systematically compare the efficacy and safety of BCG with ICIs in NMIBC. The present meta-analysis identifies response predictors and treatment outcomes, which can help in recognizing potential biomarkers such as tumor characteristics, hemoglobin levels and baseline performance status, associated with therapy response. These insights may guide future research in developing personalized treatment strategies for BCG non-responsive NMIBC cases. Following the Preferred Reporting Standards for Systematic Reviews and Meta-Analyses guidelines, a systematic literature search identified relevant studies published between January 2015 and April 2024. Randomized controlled trials and clinical trials involving patients with BCG-refractory NMIBC were included in the primary analysis. Data extraction and analysis were conducted using Review Manager version 5.4, employing a random effects model. The risk of bias assessment followed

the Cochrane guidelines. The present study included 2,154 participants across 10 studies evaluating treatments for NMIBC. Primary comparisons focused on BCG vs. ICIs: Pembrolizumab significantly improved tumor control (OR, 4.67; 95% CI, 1.43-15.25; $P=0.01$), progression-free survival (PFS; OR, 4.85; CI, 1.58-14.85; $P=0.006$), and overall survival (OS; OR, 3.61; CI, 1.28-10.19; $P=0.02$). Atezolizumab similarly outperformed BCG in metastatic disease (OR, 0.19; CI, 0.06-0.59; $P=0.004$) and lymph node involvement (OR, 0.43; CI, 0.20-0.93; $P=0.03$). ICIs exhibited a favorable safety profile vs. BCG, with fewer incidents of anemia (OR, 2.87; $P=0.001$) and diarrhea (OR, 1.79; $P=0.03$), despite higher rates of asthenia (OR, 7.33; $P<0.00001$) and pyrexia (OR, 3.26; $P<0.00001$). Exploratory comparisons with chemotherapy revealed pembrolizumab's advantages in terms of PFS (OR, 1.36; $P=0.02$) and OS (OR, 1.31; $P=0.005$), while atezolizumab improved metastatic control (OR, 0.54; $P=0.0008$). Heterogeneity was low for BCG comparisons ($I^2=0\%$) but high for chemotherapy ($I^2=81-95\%$). In conclusion, ICIs, particularly pembrolizumab and atezolizumab, demonstrate superior efficacy and safety over BCG in BCG-refractory NMIBC, supporting their use as first-line alternatives. These findings advocate for a paradigm shift in managing BCG-unresponsive disease, emphasizing personalized immunotherapy.

Introduction

Bladder cancer (BC) is a significant global health burden, ranking as the ninth most common cancer worldwide, with nearly half a million new cases reported annually (1). BC encompasses two primary categories: Muscle-invasive BC (MIBC) and non-MIBC (NMIBC). Notably, NMIBC constitutes ~75% of BC cases and encompasses various pathological stages, including non-invasive bladder carcinoma confined to the epithelium or mucosa, tumor invading the subepithelial connective tissue and carcinoma *in situ* (2). Despite its generally favorable prognosis, NMIBC presents distinct challenges, particularly in high-risk subsets, such as those with high-grade tumors, large tumor size, multifocality and those with a history of prior recurrence (3). These subsets demonstrate significant

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rates of recurrence and progression. For example, patients with carcinoma *in situ* or those with a high number of early recurrences within the first year after initial treatment are considered at higher risk for progression to MIBC (4). BC has a multifactorial etiology, with smoking being the primary risk factor for its development. While the majority of BC tumors originate from urothelial cells, histological variations, such as squamous, neuroendocrine, micropapillary and sarcomatoid subtypes are less common. Notably, the classification of BC into NMIBC and MIBC guides therapeutic approaches (5,6). Moreover, the prognosis and treatment decisions for NMIBC are heavily influenced by tumor grading, depth of invasion and risk stratification systems, such as those developed by the European Organization for Research and Treatment of Cancer and the European Association of Urology (7,8).

The cornerstone of initial treatment for intermediate- and high-risk NMIBC involves transurethral resection of the bladder tumor followed by adjuvant therapy with intravesical Bacillus Calmette-Guérin (BCG) (9). This approach is considered the standard of care for these tumors. BCG therapy, pioneered by Morales (10), has demonstrated efficacy in reducing the risk of disease progression and recurrence. However, its use is limited by the associated adverse events and recent shortages. Despite its benefits, a subset of patients with high-risk factors, such as those with carcinoma *in situ*, multiple recurrent tumors or BCG failure, fail to achieve an adequate therapeutic response, necessitating alternative treatment approaches (11,12).

BC, particularly NMIBC, is predominantly treated with intravesical BCG therapy (13). However, resistance to BCG therapy remains a significant clinical challenge. This resistance is often associated with the expression of immunosuppressive molecules, such as programmed death ligands [programmed death ligand 1 (PD-L1) and programmed cell death 1 ligand 2], which can inhibit the immune response and hinder the effectiveness of treatment (14). Experimental studies have demonstrated that the upregulation of these ligands in the tumor microenvironment is linked to poor BCG response, as they interfere with T cell activation and tumor immunosurveillance (15,16).

Furthermore, the global shortage of BCG has created notable challenges in managing NMIBC. Production issues, increased demand and regulatory challenges have contributed to the scarcity of BCG, thereby impacting treatment protocols worldwide (17). These shortcomings necessitate alternative treatment strategies, including the use of intravesical chemotherapy or other immunotherapeutic agents, such as pembrolizumab (18). Mitomycin C, gemcitabine and docetaxel have been explored as substitutes. However, their efficacy and long-term outcomes compared with BCG are still under evaluation (19). Consequently, healthcare systems have had to adapt by prioritizing BCG allocation for high-risk patients and utilizing alternative treatment regimens for those with lower-risk profiles. Ongoing research and development efforts aim to address these shortcomings by improving the production processes and developing new immunotherapeutic options (13,20).

Food and Drug Administration-approved injectable immune checkpoint inhibitors (ICIs) for metastatic urothelial carcinoma represent a new era of treatment (21). These ICIs

show promise as second-line treatments for BCG-unresponsive NMIBC, either alone or in combination with other agents (22). However, systemic administration leads to more adverse events, prompting the exploration of alternative delivery routes. Notably, intravesical ICIs offer a strategy for enhancing the therapeutic index and reducing systemic toxicity (23). Preliminary studies, such as the combination of intravesical pembrolizumab with BCG induction therapy for patients with BCG-unresponsive NMIBC, showed encouraging outcomes, improving recurrence-free survival and progression-free survival (PFS) (24-26). Other ICIs, such as atezolizumab, avelumab and nivolumab, have also demonstrated potential in this setting, revolutionizing the treatment landscape for NMIBC, particularly in cases of BCG failure. Ongoing research continues to explore novel agents and combination approaches to further optimize outcomes and reduce adverse events (27,28).

The present study aimed to evaluate the efficacy and safety of immunotherapy in BCG-refractory NMIBC by comparing intravesical BCG with novel ICIs. Through a meta-analysis of clinical trials and randomized controlled trials (RCTs), the impact of ICIs on overall survival (OS) and progression-free survival (PFS), along with their safety profiles were assessed. Additionally, response predictors were identified and future directions for optimizing treatment and biomarker development were explored. The findings provide insights to guide clinicians in selecting the most effective therapy based on individual patient characteristics.

Materials and methods

Following the recommendations of the Preferred Reporting Standards for Systematic Reviews and Meta-Analyses 2020 guidelines (29) and the protocol registered in PROSPERO (<https://www.crd.york.ac.uk/prospero/>; no. CRD42024544722). The meta-analysis primarily compared BCG with ICIs (pembrolizumab/atezolizumab) in BCG-refractory NMIBC. Ethical approval was considered unnecessary as the study did not involve human or animal experiments.

Population, intervention, comparison, outcomes and study design (PICOS) question. The present study aimed to evaluate the efficacy and safety of immunotherapy in patients with BCG-refractory NMIBC by comparing ICIs (pembrolizumab, atezolizumab) with standard treatments. The study population included patients with BCG-refractory NMIBC, with ICIs as the intervention and BCG as the comparison. Primary outcomes assessed included OS, PFS and safety based on adverse events.

Eligibility criteria. The inclusion criteria for the primary analysis in the present study were RCTs and clinical trials published between January 2015 and April 2024 that focused on patients diagnosed with BCG-refractory NMIBC. Studies evaluating ICIs, such as pembrolizumab or atezolizumab, and BCG therapy were included. Only trials assessing immunotherapy in BCG-refractory NMIBC patients, with or without prior platinum-based chemotherapy, were considered for analysis. The primary outcomes evaluated in these studies were OS, PFS and safety. Immunotherapy agents were considered 'similar' if they belonged to the same class

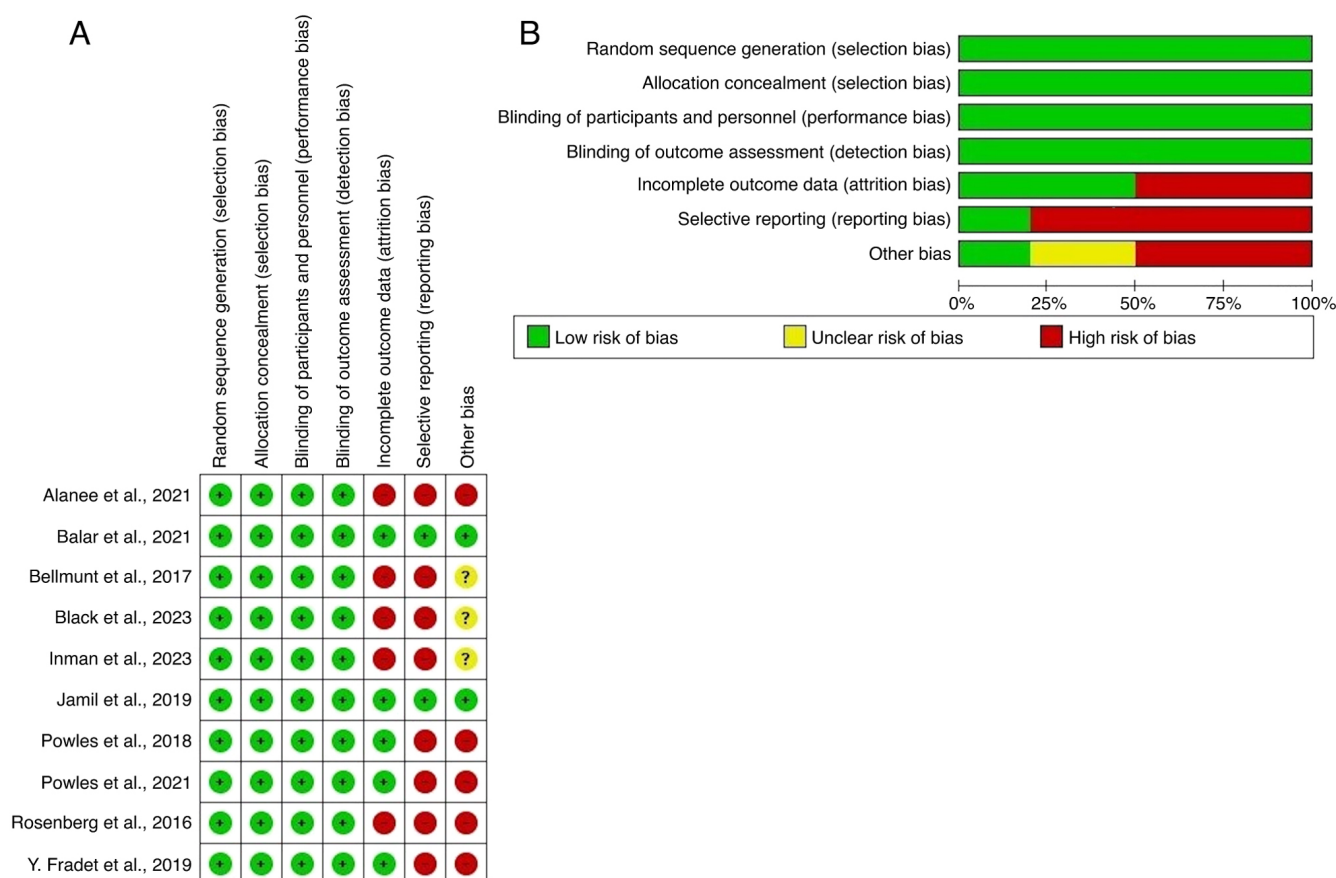


Figure 1. Risk of bias assessment of the selected studies. (A) Risk of bias summary for each study included in the meta-analysis, with individual judgments on domains such as selection bias, performance bias, detection bias, and reporting bias. (B) Risk of bias for each individual study, with assessments across multiple domains presented visually for comparison.

of ICIs targeting the programmed cell death protein 1/PD-L1 pathway. A risk of bias assessment was conducted following the Cochrane Collaboration's Risk of Bias 2.0 (RoB 2.0) guidelines (30), evaluating factors such as randomization methods, blinding and data reporting. The exclusion criteria were duplicate studies, case reports, retrospective analyses and non-English publications. For the primary analysis (BCG vs. ICIs), trials comparing ICIs with chemotherapy or those including non-NMIBC populations (such as locally advanced/metastatic urothelial carcinoma) were excluded. For the secondary analysis (ICIs vs. chemotherapy), trials involving BCG-refractory NMIBC, BCG-naïve NMIBC or platinum-refractory advanced/metastatic urothelial carcinoma were included. Studies focusing on non-urothelial cancer or non-refractory populations were excluded. Only prospective multicenter pharmaceutical trials with a single treatment arm were considered eligible, excluding studies involving animals, patients with diseases other than BC, reanalyzed RCTs, non-randomized allocation and publications in abstracts, reviews, editorials or letters.

Literature search approach. A comprehensive literature search was performed across PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Medline (<https://www.nlm.nih.gov/medline/>), Embase (<https://www.embase.com/search/>), Scopus (<https://www.scopus.com/search/>) and the Cochrane Research Register (<https://www.cochranelibrary.com/>) to identify relevant

studies for the present meta-analysis. The search strategy employed Boolean operators (AND, OR) in combination with key words such as 'non-muscle invasive bladder cancer', 'BCG therapy', 'immune checkpoint inhibitors', 'pembrolizumab', 'atezolizumab' and 'clinical trials.' Medical Subject Headings terms were used to refine the search and enhance specificity, including terms such as 'Bladder Neoplasms', 'Bacillus Calmette-Guerin' and 'Immunotherapy'. In addition, the reference lists of relevant systematic reviews and literature reviews were manually searched to ensure comprehensive coverage of the topic.

Study selection. In total, two independent reviewers rigorously screened each article based on its title and abstract, resolving discrepancies through discussion. Potentially eligible studies underwent full-text screening and additional trials were identified through a systematic review.

Data extraction. Data extraction involved meticulous collection of relevant information, including the study approach, participant characteristics, sample sizes, intervention specifics, control groups, duration of observation, survival measures and adverse events. These data were organized according to the PICOS structure and independently retrieved by two assessors, with discrepancies resolved through collaborative deliberation. Data extraction prioritized BCG vs. ICI outcomes (such as OS, PFS safety).

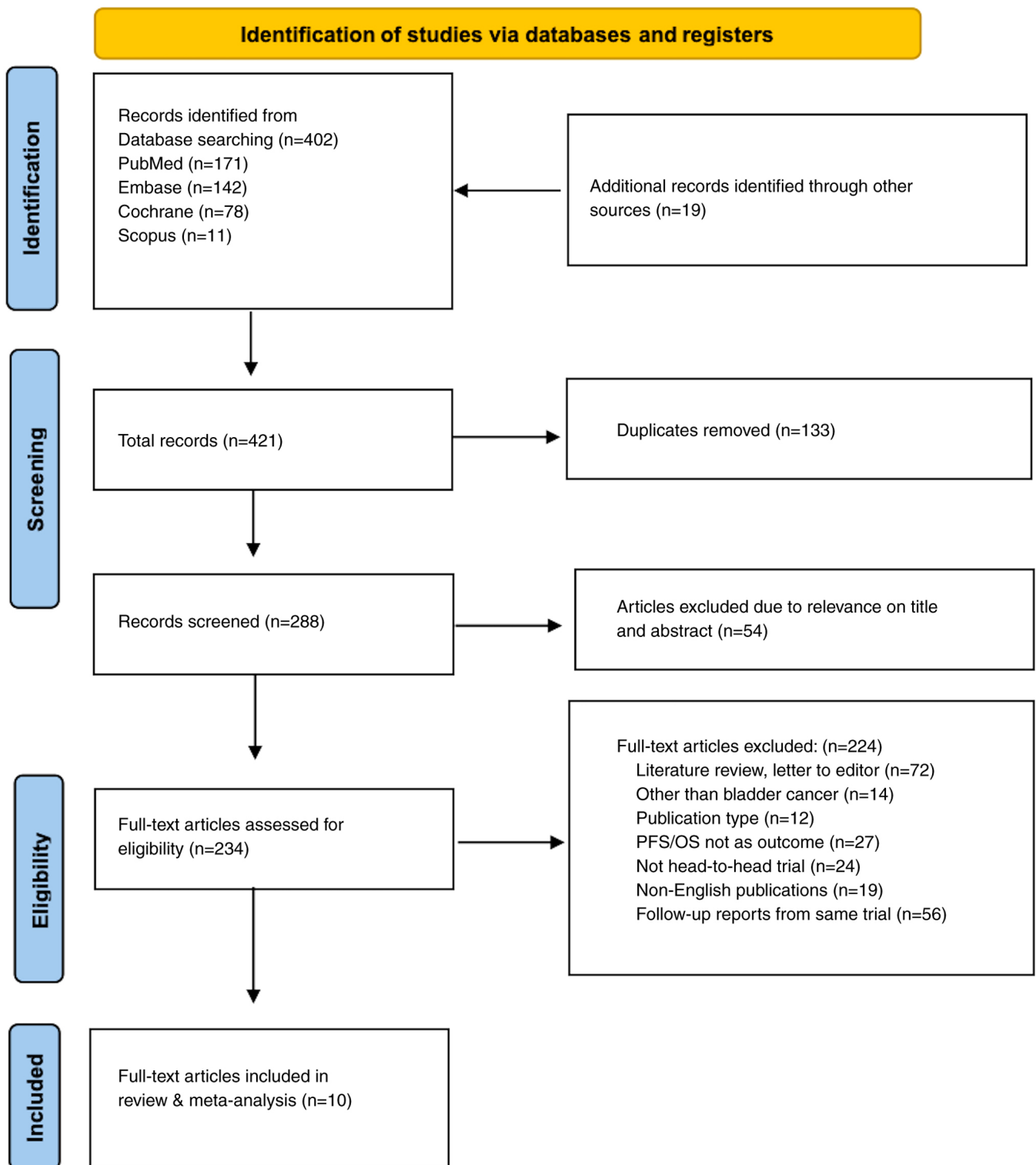


Figure 2. Flow chart for study selection. PFS, progression-free survival; OS, overall survival.

Data analysis and risk assessment. The analysis was conducted by using Review Manager version 5.4 (Cochrane Collaboration), employing a random-effects model to address expected variability. Primary analysis compared BCG vs. ICIs, while a secondary exploratory analysis included ICIs vs. chemotherapy. Categorical outcomes such as OS, PFS and adverse events were presented as odds ratios (ORs) with corresponding 95% confidence intervals

(CIs). Evaluation of statistical diversity was performed using Cochran's Q test (χ^2) and the I^2 index with significance set at $P < 0.05$. Publication bias was assessed using forest and funnel plots, with significance set at $P < 0.05$. Risk of bias assessment followed the Cochrane Collaboration tool, considering factors such as random sequence generation, allocation concealment, blinding and outcome data completeness (Fig. 1).

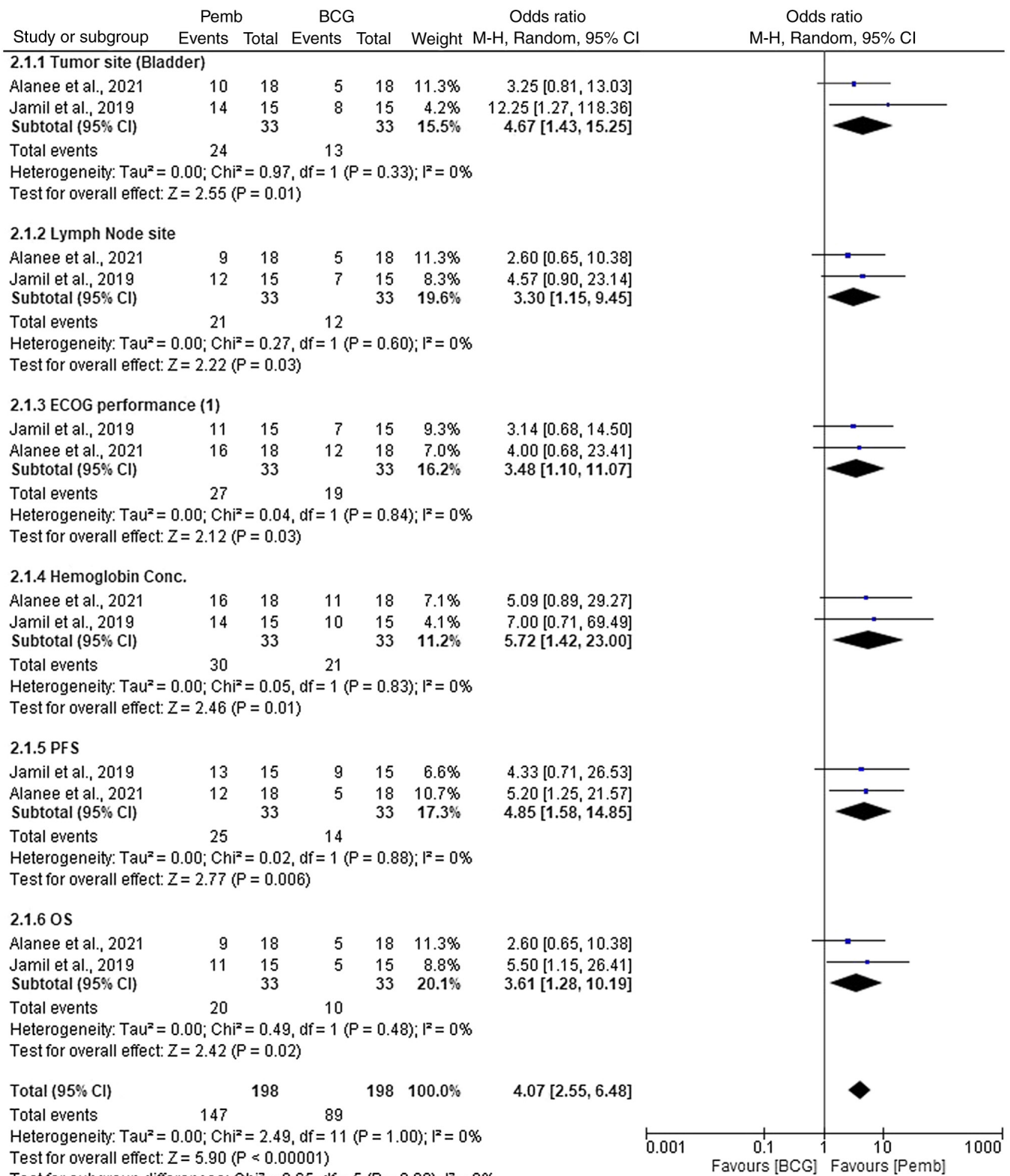


Figure 3. Forest plot showing the efficacy of Pemb vs. BCG in the treatment of non-muscle-invasive bladder cancer. Pemb, pembrolizumab; BCG, Bacillus Calmette-Guérin; CI, confidence interval; PFS, progression-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group performance status.

Results

Characteristics of the selected studies. In the systematic review and meta-analysis, 402 records were initially identified through database searching, with PubMed contributing 171,

Embase 142, Cochrane 78 and Scopus 11 records. Additionally, 19 records were identified from other sources. After removing duplicates ($n=133$), 288 records were screened, of which 54 were excluded as their titles and abstracts did not meet the inclusion criteria. Subsequently, 234 full-text articles were assessed for

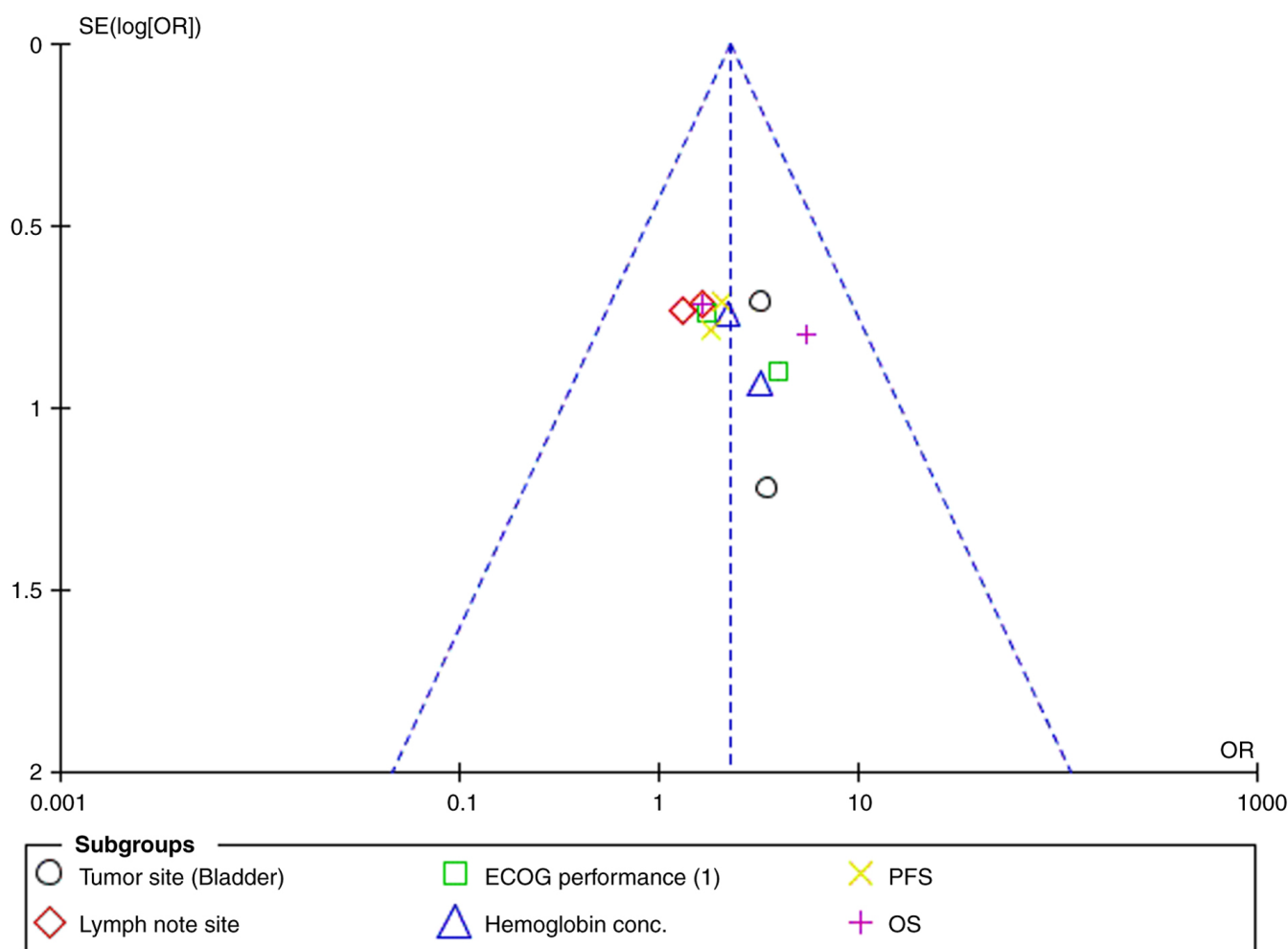


Figure 4. Funnel plot showing the heterogeneity of the efficacy of pembrolizumab vs. Bacillus Calmette-Guérin in the treatment of non-muscle-invasive bladder cancer. SE, standard error; OR, odds ratio; PFS, progression-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group performance status.

eligibility, resulting in the exclusion of 224 articles, primarily as they were literature reviews, letters to editors, unrelated to BC or did not meet other inclusion criteria. Finally, 10 full-text articles were included in the present review and meta-analysis (Fig. 2).

Study participants and baseline characteristics. This study included 2,154 participants from diverse clinical trials exploring treatments for BC. The age of the patients varied, with a median age of 63 years. A male predominance was observed in some trials. The participants had high-risk NMIBC including BCG-refractory NMIBC, defined as those with persistent or recurrent high-grade disease despite ≥ 2 prior courses of intravesical BCG therapy, or locally advanced or metastatic urothelial carcinoma, specifically after failure of first-line platinum-based chemotherapy. Patients with locally advanced or metastatic urothelial carcinoma were included in secondary analyses to assess broader efficacy, while the primary analysis focused on BCG-refractory NMIBC populations. Chemotherapy treatments varied across the trials, with most using cisplatin or carboplatin based regimens. However, some trials followed different protocols, including other platinum-based combinations. Trials spanned from Phase 1

to Phase 3, employing treatments such as pembrolizumab, atezolizumab, chemotherapy or intravesical BCG therapy. The follow-up durations ranged from 11.7 to 31.7 months. The mean PFS spanned 2.1 to 8.3 months and the mean OS ranged from 7.3 to 17.0 months. Adverse events, including fatigue, nausea, diarrhea, asthenia, pyrexia, anemia and treatment-related effects, were reported in all trials (Table SI).

Primary analysis: BCG vs. ICIs

Comparison of pembrolizumab vs. BCG in the treatment of NMIBC. In the comparison of pembrolizumab versus BCG for the treatment of NMIBC, pembrolizumab demonstrated superior efficacy across various parameters (Fig. 3). For tumor site (bladder), pembrolizumab showed a significantly high OR of 4.67 (95% CI, 1.43-15.25; $P=0.01$), indicating improved efficacy in tumor control compared with BCG. Similarly, for lymph node site, pembrolizumab again outperformed BCG with an OR of 3.30 (95% CI, 1.15-9.45; $P=0.03$). In terms of ECOG performance (1), pembrolizumab showed a strong advantage with an OR of 3.48 (95% CI, 1.10-11.07; $P=0.03$). Hemoglobin concentration was also in favor of pembrolizumab, with an OR of 5.72 (95% CI, 1.42-23.00; $P=0.01$). This result suggests that pembrolizumab was

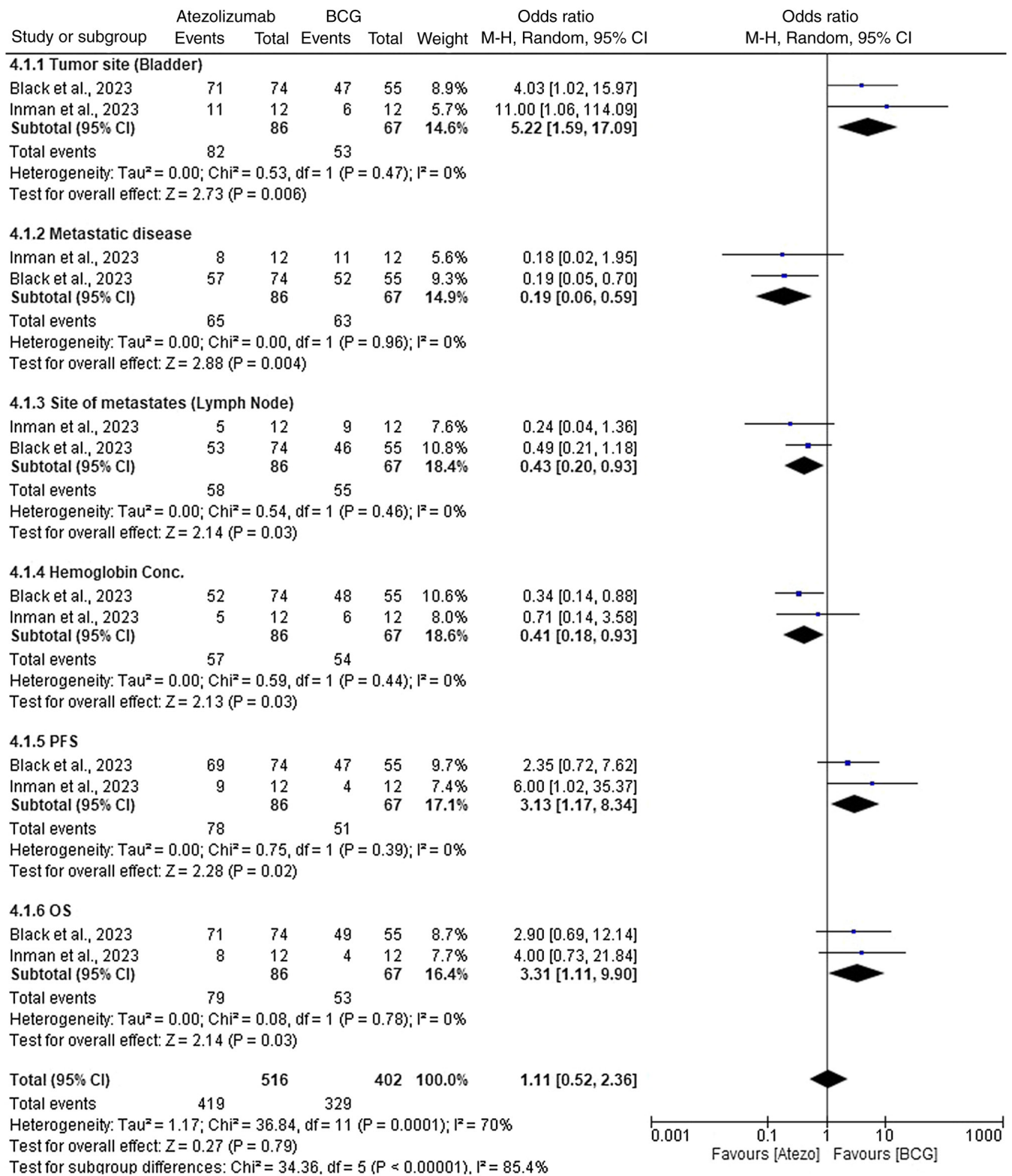


Figure 5. Forest plot showing the efficacy of atezolizumab vs. BCG in the treatment of non-muscle-invasive bladder cancer. BCG, Bacillus Calmette-Guérin; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

associated with a higher likelihood of improving hemoglobin concentration compared with BCG. Regarding PFS and OS, pembrolizumab demonstrated significant benefits, with ORs of 4.85 (95% CI, 1.58-14.85; P=0.006) and 3.61 (95% CI, 1.28-10.19; P=0.02), respectively. Across all parameters, pembrolizumab consistently showed higher ORs and

significant P-values, suggesting it may provide more effective outcomes compared with BCG. These findings highlight pembrolizumab's potential for improved treatment efficacy in NMIBC, possibly due to its targeted immune checkpoint inhibition mechanism compared with BCG's non-specific immune stimulation.

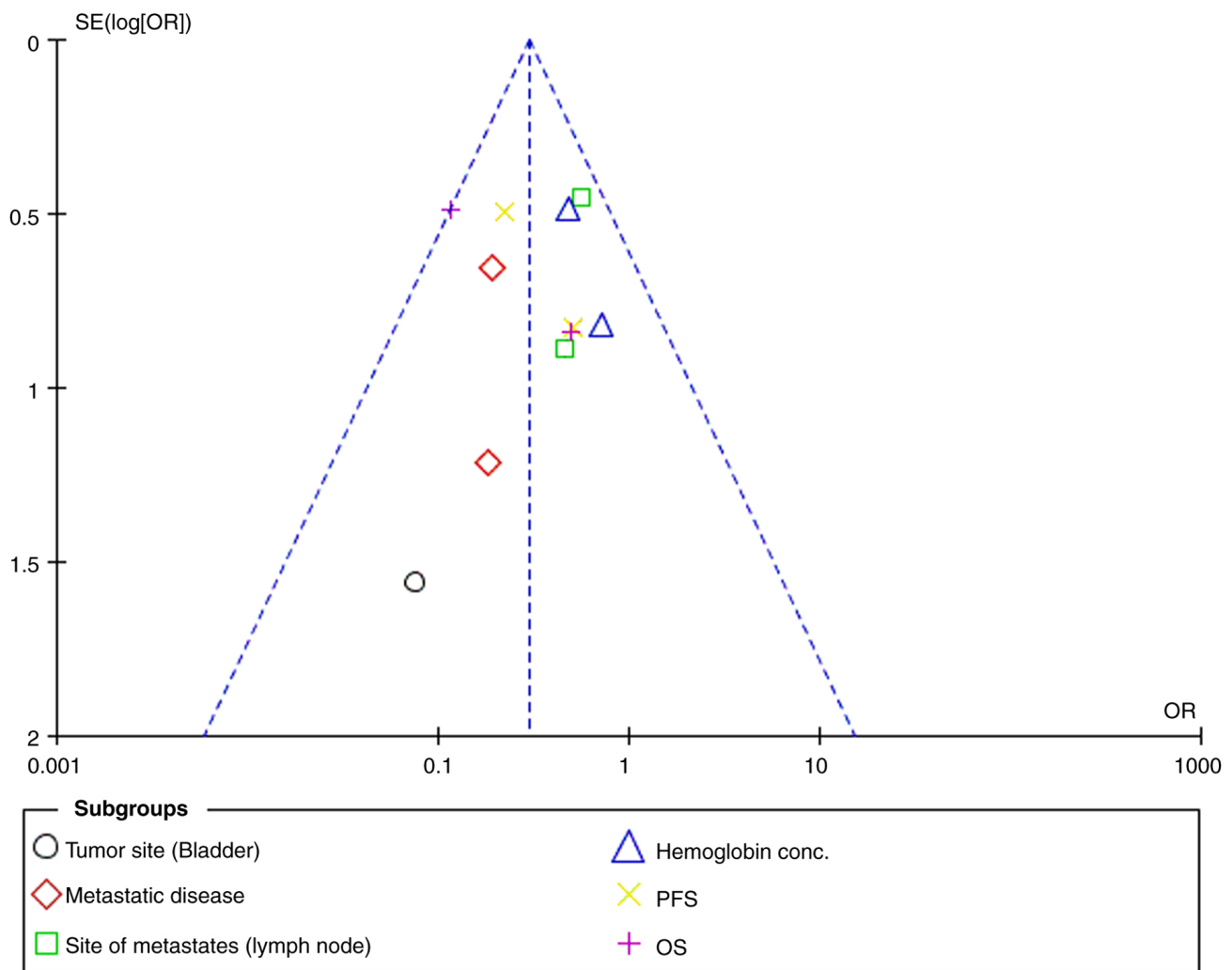


Figure 6. Funnel plot showing the heterogeneity of the efficacy of atezolizumab vs. BCG in the treatment of non-muscle-invasive bladder cancer. SE, standard error; OR, odds ratio; PFS, progression-free survival; OS, overall survival.

Heterogeneity across the subgroups was low, with I^2 values of 0% for tumor site (bladder), lymph node site, ECOG performance, hemoglobin concentration, PFS and OS, indicating minimal variability between studies. χ^2 tests also showed no significant heterogeneity ($P > 0.05$). The overall I^2 value was 0%, and the funnel plot (Fig. 4) did not indicate publication bias, suggesting consistent results across the trials analyzed.

Comparative efficacy of atezolizumab vs. BCG in NMIBC. In the comparison of atezolizumab versus BCG for the treatment of NMIBC, both treatments demonstrated varying levels of efficacy across different parameters (Fig. 5). For tumor site (bladder), atezolizumab showed improved efficacy with an OR of 5.22 (95% CI, 1.59-17.09; $P = 0.006$). Similarly, for metastatic disease, atezolizumab performed better with an OR of 0.19 (95% CI, 0.06-0.59; $P = 0.004$). Atezolizumab also showed superior outcomes in terms of site of metastases (lymph nodes) with an OR of 0.43 (95% CI, 0.20-0.93; $P = 0.03$), and hemoglobin concentration with an OR of 0.41 (95% CI, 0.18-0.93; $P = 0.03$). Atezolizumab again proved more effective in terms of PFS with an OR of 3.13 (95% CI, 1.17-8.34; $P = 0.02$), and OS with an OR of 3.31 (95% CI, 1.11-9.90; $P = 0.03$). The

overall effect for all parameters favored atezolizumab with an OR of 1.11 (95% CI, 0.52-2.36; $P = 0.79$); however, this was not statistically significant. These results highlight that atezolizumab generally provided more consistent and superior efficacy across multiple clinical outcomes, likely due to its immune-modulating properties compared with BCG's direct immunotherapy mechanism.

Throughout the results, low heterogeneity was observed for most individual parameters, with I^2 values of 0% for tumor site (bladder), metastatic disease, site of metastases (lymph node), hemoglobin concentration, PFS and OS. However, when examining the overall effect, moderate heterogeneity was observed, with $I^2 = 70\%$, and significant subgroup differences were noted ($P < 0.00001$) (Fig. 6).

Adverse events: ICIs vs. BCG therapy in NMIBC. In the comparison of adverse events between ICIs and BCG therapy for NMIBC, ICIs demonstrated a higher incidence of several adverse events (Fig. 7). Asthenia was significantly more common in the ICI group, with an OR of 7.33 (95% CI, 4.22-12.74; $P < 0.00001$), indicating a higher incidence compared with BCG therapy. Similarly, pyrexia (fever) was more frequently observed in the ICI group, with an OR of 3.26 (95% CI, 2.34-4.54; $P < 0.00001$), suggesting that fever

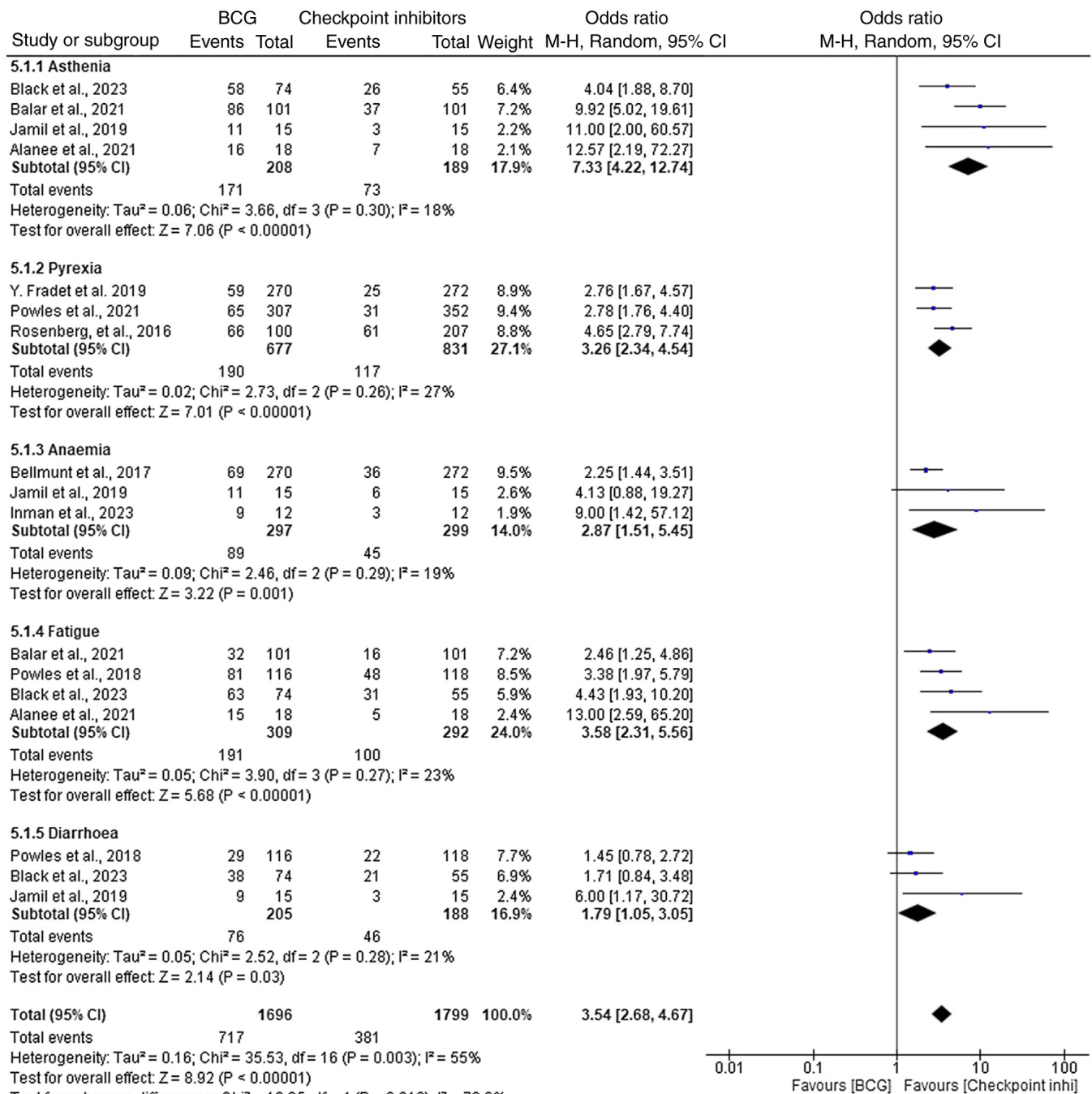


Figure 7. Forest plot showing the safety of using BCG vs. invasive checkpoint inhibitors for treating non-muscle-invasive bladder cancer. BCG, Bacillus Calmette-Guérin; CI, confidence interval.

management may be more challenging in patients receiving ICIs. Despite higher rates of certain adverse events, ICIs were associated with a lower incidence of anemia (OR, 2.87; 95% CI, 1.51-5.45; $P=0.001$), fatigue (OR, 3.58; 95% CI, 2.31-5.56; $P<0.00001$) and diarrhea (OR, 1.79; 95% CI, 1.05-3.05; $P=0.03$), suggesting improved tolerability and fewer serious complications compared with BCG therapy. Although the ORs are all >1 , indicating a higher likelihood of adverse events in the ICI group, the results show that ICIs demonstrate improved outcomes in terms of anemia management, fatigue and diarrhea, indicating a more favorable safety profile in these aspects.

Overall, low heterogeneity was observed throughout the results, with the I^2 values generally indicating minimal

variability across studies. The heterogeneity for asthenia, pyrexia, anemia, fatigue and diarrhea was 18, 27, 19, 23 and 21%, respectively. The overall I^2 value for all adverse events was 55%, indicating moderate heterogeneity. The funnel plot analysis further confirmed the absence of significant publication bias (Fig. 8). Statistical tests for heterogeneity showed acceptable values, with the $\chi^2=12.45$ ($P=0.09$) and $\tau^2=0.02$, indicating low to moderate variability in the data.

Exploratory analyses: ICIs vs. Chemotherapy
Comparative efficacy of pembrolizumab vs. chemotherapy in NMIBC. In the comparative analysis of pembrolizumab and chemotherapy (gemcitabine, docetaxel, everolimus or

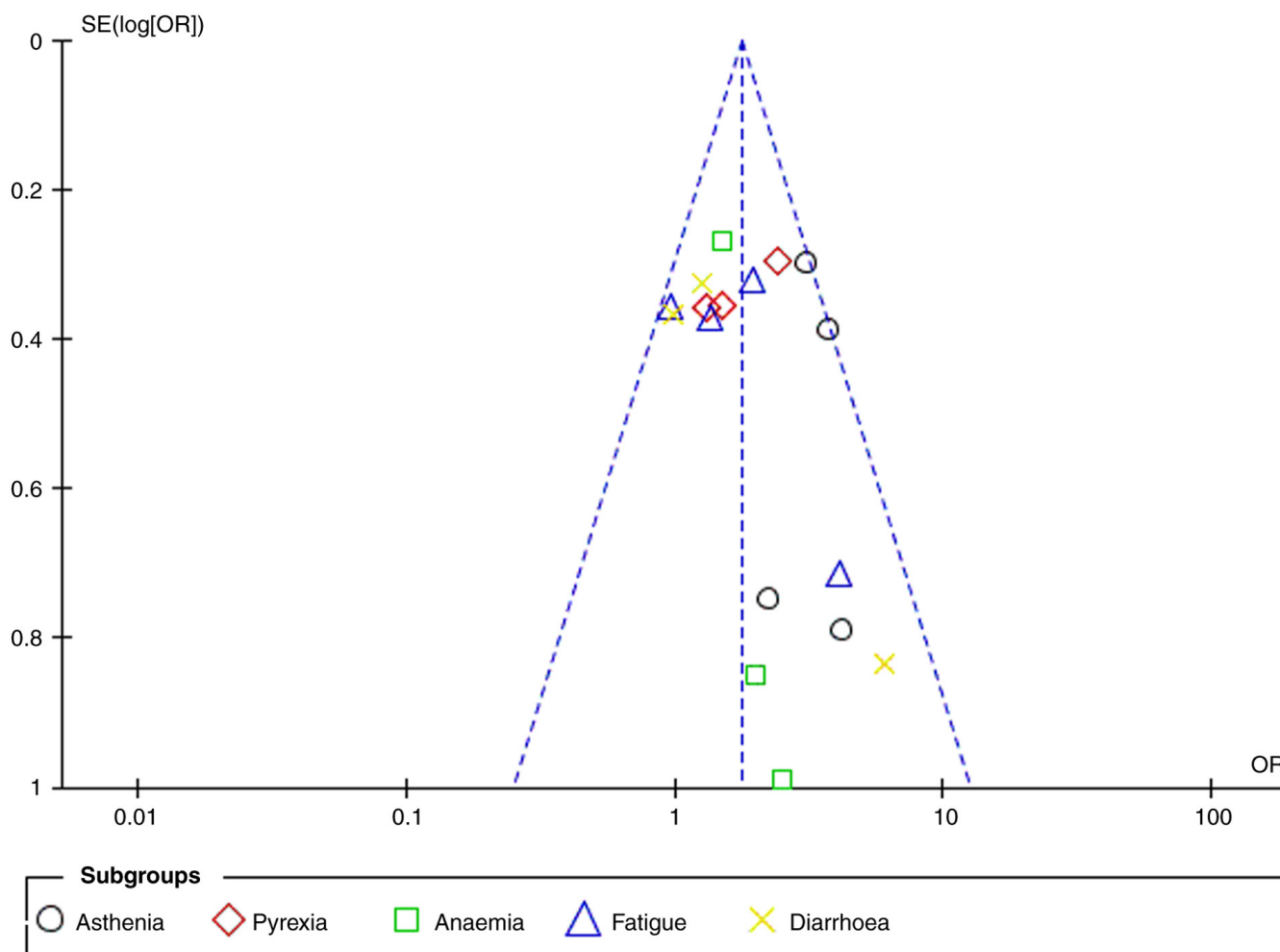


Figure 8. Funnel plot showing the heterogeneity of the safety of using Bacillus Calmette-Guérin vs. invasive checkpoint inhibitors for treating non-muscle-invasive bladder cancer. SE, standard error; OR, odds ratio.

valrubicin) for NMIBC, the treatment outcomes across various parameters were assessed (Fig. 9). For tumor site (bladder), pembrolizumab demonstrated a statistically significant advantage in terms of efficacy compared with chemotherapy, with an OR of 0.48 (95% CI, 0.39-0.58; $P < 0.00001$). This indicated that pembrolizumab had a higher probability of achieving tumor control compared with chemotherapy, regardless of the specific chemotherapy agent used. Similarly, pembrolizumab showed a significant benefit in lymph node involvement with an OR of 0.57 (95% CI, 0.46-0.72; $P < 0.00001$), suggesting that pembrolizumab may be more effective in managing lymph node metastasis. In terms of the Eastern Cooperative Oncology Group (ECOG) performance status (1), which measures a patient's level of functioning in terms of their ability to perform daily activities and their overall physical status, pembrolizumab showed superior efficacy with an OR of 0.62 (95% CI, 0.47-0.81; $P = 0.0005$), compared with chemotherapy. Hemoglobin concentration outcomes favored pembrolizumab with an OR of 0.65 (95% CI, 0.52-0.82; $P = 0.0002$), indicating a more favorable hematological profile. In terms of PFS, pembrolizumab also demonstrated a notable advantage with an OR of 1.36 (95% CI, 1.05-1.76; $P = 0.02$), suggesting prolonged disease control compared with chemotherapy. For OS, pembrolizumab had a statistically significant OR of 1.31

(95% CI, 1.08-1.59; $P = 0.005$) compared with chemotherapy. These findings indicate that pembrolizumab, by enhancing immune-mediated tumor clearance, offered superior efficacy in terms of survival and disease control, when compared with chemotherapy, which primarily exerts cytotoxic effects.

Heterogeneity across the results was assessed using I^2 and τ^2 values. Most subgroups, including tumor site (bladder), lymph node site, hemoglobin concentration and ECOG performance, showed low to moderate heterogeneity (I^2 values ranging from 0 to 43%). However, PFS and OS showed moderate heterogeneity ($I^2 = 42-43\%$). The overall heterogeneity was high ($I^2 = 81\%$), reflecting variability across the studies. The funnel plot indicated no substantial publication bias, suggesting the heterogeneity was due to true differences between the study populations (Fig. 10).

Comparative efficacy of atezolizumab vs. chemotherapy in NMIBC treatment. In the comparative analysis of atezolizumab versus chemotherapy for NMIBC treatment, multiple parameters were evaluated (Fig. 11). For tumor site (bladder), chemotherapy showed a slight advantage with an OR of 0.44 (95% CI, 0.23-0.84; $P = 0.01$). In metastatic disease, atezolizumab was more effective, with an OR of 0.54 (95% CI, 0.38-0.77; $P = 0.0008$), indicating improved control of the disease. Lymph node metastasis also favored atezolizumab with

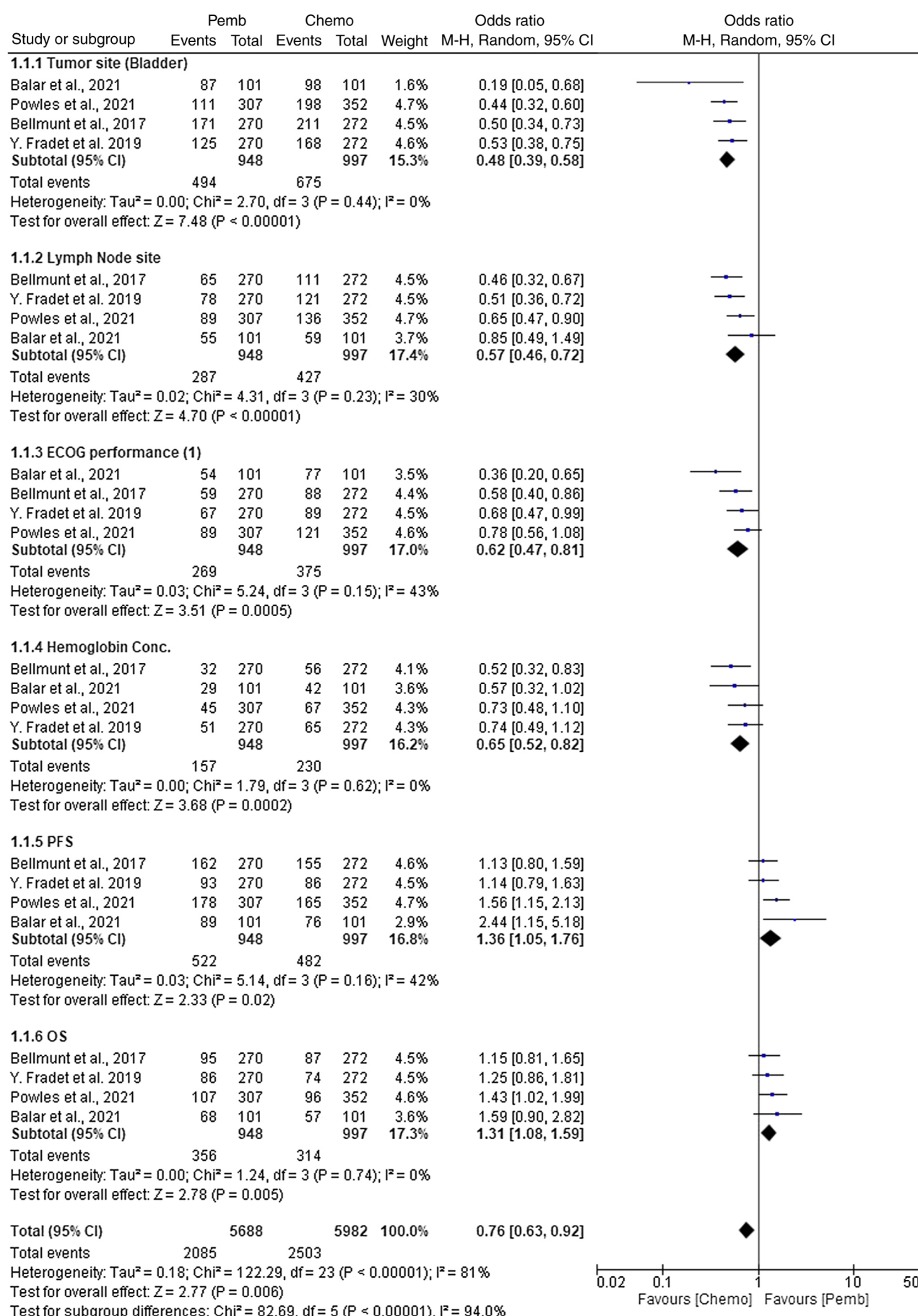


Figure 9. Forest plot showing the efficacy of Pemb vs. Chemo in combination with Pemb in the treatment of non-muscle-invasive bladder cancer. Chemo, chemotherapy; Pemb, pembrolizumab; CI, confidence interval; PFS, progression-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group performance status.

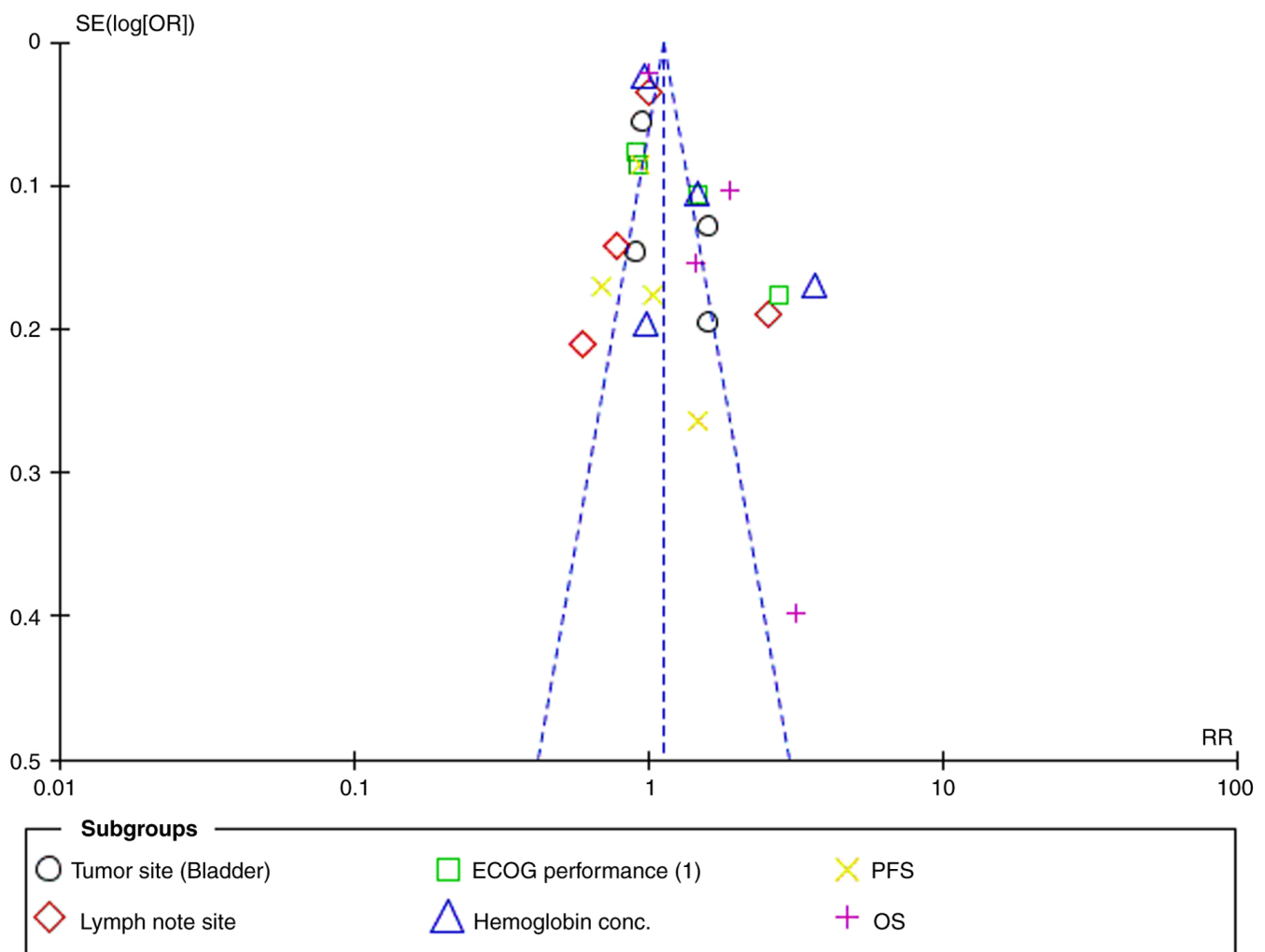


Figure 10. Funnel plot showing the heterogeneity of the efficacy of pembrolizumab vs. chemotherapy in combination with pembrolizumab in the treatment of non-muscle-invasive bladder cancer. SE, standard error; OR, odds ratio; PFS, progression-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group performance status.

an OR of 0.49 (95% CI, 0.34-0.70; $P < 0.0001$), demonstrating its superior efficacy in managing lymph node involvement. For hemoglobin concentration, chemotherapy was more effective, showing an OR of 0.43 (95% CI, 0.30-0.62; $P < 0.00001$). In terms of PFS, atezolizumab showed a clear benefit (OR, 10.67; 95% CI, 6.91-16.49; $P < 0.00001$), while for OS, chemotherapy demonstrated improved outcomes with an OR of 2.87 (95% CI, 1.87-4.39; $P < 0.00001$). Despite the high heterogeneity observed across the studies, the subgroup analyses revealed that atezolizumab had a superior response in metastatic and lymph node metastasis, while chemotherapy performed better in bladder tumor control and hemoglobin concentration. The overall effect, however, showed no significant difference between the two treatments (OR, 1.07; 95% CI, 0.54-2.13; $P = 0.85$). These findings suggest that while chemotherapy may be more effective in specific areas, atezolizumab offers a better option for metastatic disease and PFS, thus supporting its use in these subgroups.

Overall, low heterogeneity was observed across individual subgroups, with I^2 values consistently $< 50\%$, indicating minimal variation between the studies. The χ^2 tests further supported the absence of significant heterogeneity, with $P > 0.05$

in all comparisons. The funnel plot showed no significant asymmetry (Fig. 12), reinforcing that the low heterogeneity was not due to publication bias. The overall heterogeneity across all studies was $I^2 = 95\%$, indicating high variability when combining all parameters.

Assessment of publication bias and risk of bias. In the present meta-analysis, publication bias was assessed using the Cochrane Risk of Bias 2 tool. Specifically, the risk of bias was evaluated across several domains: Randomization, where most studies demonstrated adequate methods (31); deviation from intended interventions, with some trials showing discrepancies in adherence to treatment protocols (32); missing outcome data, where only a small number of studies had incomplete data, which did not significantly affect the results (33); measurement of outcomes, with most trials adequately blinding outcome assessors; and selection of the reported result (34), which was generally well-reported across studies (Fig. 1). Despite the low to moderate heterogeneity, the robustness of the findings suggests that the results are reliable, with minimal risk of publication bias affecting the conclusions of the present meta-analysis.

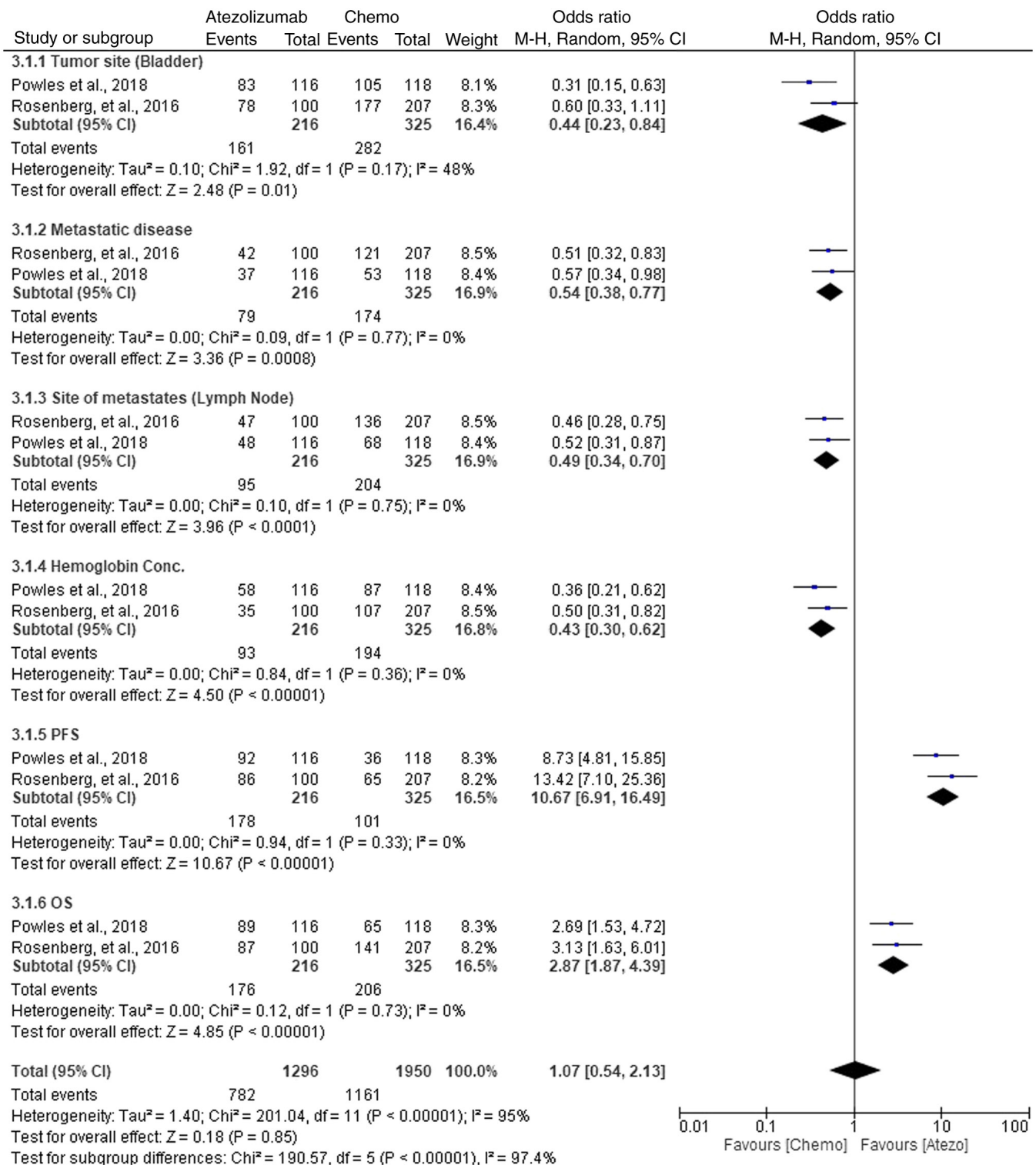


Figure 11. Forest plot showing the efficacy of atezolizumab vs. Chemo in combination with atezolizumab in the treatment of non-muscle-invasive bladder cancer. Chemo, chemotherapy; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

Discussion

The present systematic review and meta-analysis aimed to evaluate the efficacy and safety of ICIs compared with BCG therapy for BCG-refractory NMIBC, alongside exploratory comparisons with chemotherapy. The findings revealed that pembrolizumab and atezolizumab, two commonly used ICIs, demonstrated superior efficacy over chemotherapy and BCG

across multiple clinical parameters, including tumor control, PFS and OS. Specifically, pembrolizumab showed significant benefits in managing tumor site, lymph node involvement, ECOG performance status and hematological outcomes, consistently outperforming BCG in tumor control, survival, and lymph node involvement. An increase in hemoglobin levels can be indicative of improved overall health and better systemic response to treatment (35), suggesting that pembrolizumab

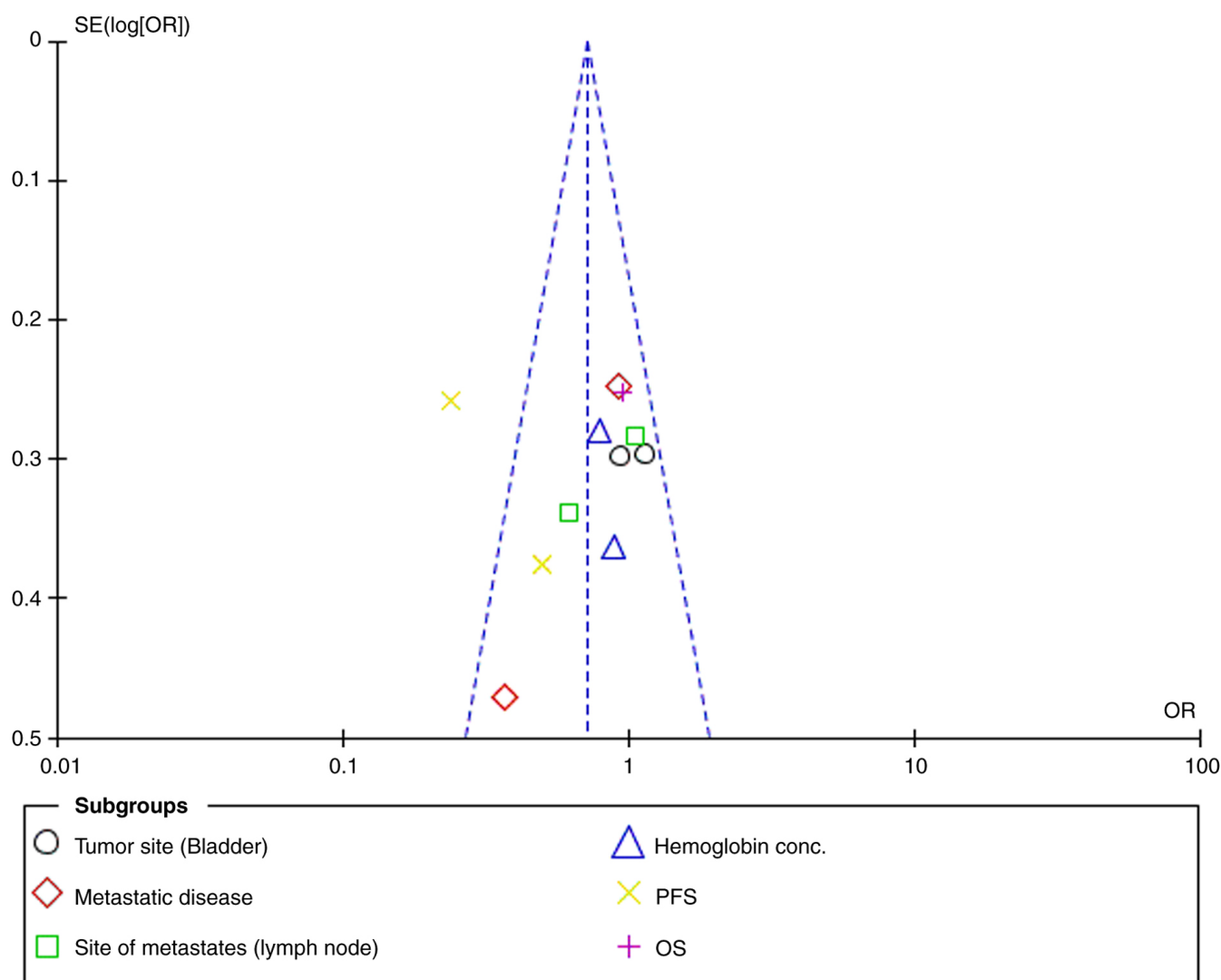


Figure 12. Funnel plot showing the heterogeneity of the efficacy of atezolizumab vs. chemotherapy in combination with atezolizumab in the treatment of non-muscle-invasive bladder cancer. SE, standard error; OR, odds ratio; PFS, progression-free survival; OS, overall survival.

may contribute to enhanced treatment outcomes beyond tumor control, possibly through its immune-modulating effects. Despite higher incidences of certain adverse events, such as asthenia and pyrexia, ICIs were associated with a more favorable safety profile in managing anemia, fatigue and diarrhea. The overall heterogeneity in the analysis was moderate ($I^2=55\%$), with minimal variation across most subgroups, indicating consistent findings. These results suggest that ICIs, particularly pembrolizumab and atezolizumab, offer superior efficacy and a potentially more favorable safety profile compared with chemotherapy and BCG, marking them as promising treatment options for advanced NMIBC.

Pembrolizumab and atezolizumab have been extensively studied in patients with advanced urothelial carcinoma, with notable improvements in OS and durable responses observed in previous trials (36,37). For instance, a randomized phase 3 trial comparing pembrolizumab with standard chemotherapy regimens demonstrated a superior OS outcome with pembrolizumab, alongside favorable safety profiles (38). These findings align closely with the outcomes of the present meta-analysis, which also revealed significant improvements in OS with

pembrolizumab and atezolizumab compared with chemotherapy in patients with advanced urothelial carcinoma.

Chemotherapy remains a cornerstone of BC treatment, albeit with varying efficacy and tolerability profiles among different agents (39,40). The present meta-analysis identified modest clinical benefits associated with various chemotherapy regimens, such as vinflunine, gemcitabine and taxanes, while highlighting significant toxicity concerns (41). Notably, while the present meta-analysis did not specifically analyze chemotherapy type and patient selection, the findings align with existing research emphasizing the role of these factors in optimizing treatment outcomes, as observed in a comparative study evaluating different chemotherapy regimens (42).

BCG therapy has long been established as the mainstay in the management of NMIBC, although its efficacy may be limited in patients who are unresponsive or intolerant to treatment (43). Emerging evidence suggests that combination therapies, such as pembrolizumab + BCG or atezolizumab + BCG, hold promise in improving treatment outcomes in these patients (44). The present meta-analysis contributes to this growing body of evidence by demonstrating the safety and

potential efficacy of immunotherapy in advanced BC, particularly in the BCG-unresponsive NMIBC setting. While effective, intravesical BCG therapy is associated with several adverse events. Common side effects include cystitis, hematuria and flu-like symptoms, with severe complications such as sepsis being rare but notably concerning (45). In comparison, intravesical chemotherapy agents such as gemcitabine and docetaxel generally exhibit severe adverse events. For instance, gemcitabine has been associated with local side effects, such as irritative voiding symptoms and chemical cystitis, but systemic side effects are minimal (46,47). Moreover, the toxicity profile of docetaxel is also manageable, with less severe local toxicity compared with BCG (47). Pembrolizumab, an ICI, represents a novel approach for treating NMIBC, particularly in BCG-unresponsive cases (48). However, its side effects include immune-related adverse events, such as colitis, hepatitis and pneumonitis, which can be serious but are typically manageable with appropriate interventions (49). Although, pembrolizumab has a different side effect profile, its use in combination with BCG has been investigated to enhance therapeutic outcomes while effectively managing adverse effects (49,50). Furthermore, the findings of the present study resonate with those of comparative studies exploring similar combination therapies and treatment modalities. For instance, studies comparing pembrolizumab + BCG or atezolizumab + BCG with standard BCG therapy alone have consistently shown improved outcomes in terms of response rates and adverse event profiles (51,52). Hence, the comparative analyses in the present study provide additional support for the efficacy and safety of combination immunotherapy in BC management, reinforcing the relevance of the findings of the meta-analysis in the context of existing literature (53).

The strength of the present meta-analysis lies in the comprehensive inclusion of relevant studies evaluating the efficacy and safety of ICIs, BCG therapy and chemotherapy in BC treatment. By synthesizing data from multiple trials, a robust overview of the current evidence landscape has been provided, offering valuable insights into the comparative effectiveness of these therapeutic modalities. The combination of ICIs with BCG therapy was not explored in the present study as the analysis specifically aimed to compare the effectiveness of ICIs against standard therapies in patients with BCG-refractory NMIBC. The present study provides critical evidence to guide treatment decisions, particularly for BCG-unresponsive patients. Consequently, the findings suggest that ICIs, such as pembrolizumab and atezolizumab, offer improved efficacy and safety profiles compared with BCG, marking a promising therapeutic option for high-risk cases. These insights could influence clinical guidelines, promote personalized treatment strategies and improve patient outcomes. Nevertheless, further clinical trials are needed to optimize these combinations and establish the best treatment protocols. However, the findings of the present study suggest a promising shift toward more personalized and potent therapies in managing BCG-refractory NMIBC.

The limitations of the present study include potential publication bias, heterogeneity among the included studies, variations in study design and methodology and the inability to access individual patient data for more detailed analyses.

Therefore, these factors may have influenced the overall interpretation of the results and should be considered when interpreting the findings of the present meta-analysis.

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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

MMA, XM and KMA conceptualized the study and contributed to the original draft, including the literature search, data collection and analysis. LD, GL and XM were responsible for data acquisition and analysis. KMA, LD and MMA interpreted the results. MA and GL confirm the authenticity of all the raw data. GL and XM revised and edited the manuscript, while MMA, GL and KMA provided critical analysis and thorough revisions of the results. GL supervised the study. 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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