Meta-analysis of efficacy comparisons between standard- and low-dose Bacillus Calmette-Guerin vaccines in managing non-muscular invasive bladder cancer

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Abstract. Intravesical Bacillus Calmette-Guerin (BCG) is the first-line therapy for non-muscle-invasive bladder cancer (NMIBC), yet its clinical use is limited by high adverse event rates and a global supply shortage. A comparison was conducted to explore the effectiveness of low- vs. standard-dose BCG vaccines in patients diagnosed with NMIBC). The search queries utilized for China National Knowledge Infrastructure and Wanfang databases included the key words 'dose', 'BCG vaccine' and 'bladder cancer/bladder tumour'. Embase, PubMed and Web of Science databases were searched using the key words 'dose', 'Bacillus Calmette-Guerin vaccine' and 'urinary bladder neoplasm' to identify randomized controlled trials published up to December 2024. The relevant data were collected from the included study articles and a meta-analysis was conducted utilizing the Review Manager 5.4 software to evaluate the therapeutic effects of low- and standard-dose BCG vaccines. In total, 13 studies were included in the present meta-analysis after literature search, selection process and quality assessment. The present meta-analysis findings suggested that the recurrence rate in patients receiving low-dose therapy was notably higher compared with that in patients receiving standard-dose therapy [odds ratio (OR)=1.38; 95% CI, 1.10-1.73; P=0.006]. However, the incidence of adverse events was lower compared with that in the standard-dose treatment group (OR=0.39; 95% CI, 0.29-0.52; P<0.00001) and no marked differences in tumour progression, tumour-specific or overall mortalities were detected between the two groups (all P>0.05). The funnel plot revealed no notable publication bias. In conclusion, the present meta-analysis confirmed the effectiveness of low-dose BCG treatment for patients with NMIBC and highlighted its potentially notable advantage in managing adverse events in patients with NMIBC in the future.

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Introduction

Superficial bladder cancer, also recognized as non-muscle-invasive bladder cancer (NMIBC), accounts for ~70% of bladder cancer diagnoses worldwide (1,2). Although NMIBC may not initially pose a threat to life, it is key to recognize that 50-70% of patients experience recurrence and 10-20% develop muscle invasion (1,2). A previous study has investigated strategies to lower the recurrence rate and progression of NMIBC and findings indicated that the intravesical Bacillus Calmette-Guérin (BCG) vaccine outperforms other chemotherapy agents including mitomycin C, gemcitabine and epirubicin, in efficacy (3). The standard management for high-risk tumours involves the use of intravesical BCG instillation after transurethral resection (4). Nonetheless, high-risk tumours frequently progress and produce adverse results. While the specific mechanisms are not fully understood, the immune response serves a key role in the function of BCG (5). Further understanding of its mechanisms can potentially enhance treatment efficacy and tolerability. However, the optimal strategy for BCG therapy remains controversial.

Adverse reactions to BCG are among the main reasons for treatment discontinuation. The predominant adverse effects typically involve symptoms associated with the lower urinary tract. It has been reported that ~63% of patients develop localized symptoms such as cystitis, urinary frequency and haematuria (6). Furthermore, ~31% of patients experience systemic manifestations such as malaise, rash, fever and sepsis (7). Numerous studies have investigated methodologies to reduce these adverse reactions, including the use of antibiotics, anticholinergic drugs, isoniazid or intravesical lidocaine (8,9). A potential method to minimize adverse reactions is to decrease the BCG dosage (8).

In 2016, Sanofi Pasteur in Lyon, France, discontinued the manufacture of the Connaught strain of BCG due to challenges in sustaining long-term production and ensuring a consistent supply. The time-consuming nature of quality testing, validation and packaging for BCG is attributed to the slow growth

of the microorganism, leading to a shortage of BCG (10,11). Following the initiation of BCG shortage, few meta-analyses assessing various outcomes of low-dose BCG, such as tumour prognosis and adverse reactions, have been conducted (12-14). Due to the BCG shortage, the present study performed a meta-analysis to evaluate the effectiveness of standard- and low-dose BCG therapy in patients with NMIBC, aiming to formulate clinical recommendations.

Numerous meta-analyses have probed the efficacy of low-dose BCG for the treatment of NMIBC (12-14); however, these studies were hampered by notable limitations: i) Small sample sizes with few studies that included RCTs; a focus on short-term endpoints such as tumour recurrence and progression while survival-related outcomes such as tumour-specific and all-cause mortality were disregarded; ii) limited data from Asian populations; and iii) a lack of in-depth safety stratification of low-dose regimens. By contrast, the present meta-analysis addresses these gaps with several key strengths: i) Inclusion of 13 RCTs (in total 1,768 patients) up to December 2024; ii) comprehensive evaluation of five core endpoints covering both efficacy (recurrence, progression and survival) and safety (adverse events); incorporation of Asian cohort data to fill regional evidence gaps; and iii) enhanced methodological rigor using sensitivity analyses alongside traditional I^2 heterogeneity tests to verify the stability of pooled effect sizes and increase the reliability of conclusions.

Materials and methods

Study selection. The 2020 Preferred Reporting Items for Systematic reviews and Meta-Analyses (15) and A Measurement Tool to Assess Systematic Reviews 2 guidelines (16) were followed in the present study. A systematic literature search was conducted on studies published until December 2024, in the China National Knowledge Infrastructure (CNKI, cnki.net), Embase (embase.com), Cochrane Library (cochranelibrary.com), Web of Science (webofscience.com), PubMed (pubmed.ncbi.nlm.nih.gov) and Wanfang databases (wanfangdata.com.cn). The Chinese search terms used were 'jiliang' (dose), 'kajiemiao' (BCG vaccine) and 'pangguangai/pangguangzhongliu' (bladder cancer/bladder tumour). The English search terms used were 'dose', 'Bacillus Calmette-Guerin Vaccine' and 'urinary bladder neoplasm'. Furthermore, all relevant article reference lists were scrutinized to identify additional relevant literature. Two assessors independently reviewed and chose articles based on eligibility criteria, with discrepancies resolved through consensus or a third senior investigator. Data associated with predefined endpoints were subsequently extracted.

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Patients diagnosed with NMIBC; ii) randomized controlled trials (RCTs) comparing low-dose BCG treatment regimens in the experimental group with standard-dose BCG treatment regimens in the control group; iii) the incorporation of key data for statistical analysis or comprehensive texts encompassing one of the specified clinical outcomes: Overall survival, tumour-specific survival, progression, recurrence risk and adverse events; and iv) two or more studies published by the same author or research centre, incorporating newly released, extensive or notably enhanced quality papers. Irrespective of whether two or more studies included entirely different patient cohorts from the same centre, the data from these studies were still examined. The exclusion criteria were as follows: i) Correspondence, review articles, animal experimental studies, commentaries, conference reports, case reports and clinical trial registries; and ii) articles without necessary data for statistical analysis.

Quality assessment. A pair of evaluators assessed the quality of RCT studies using the Cochrane risk of bias 2 tool (17). The Cochrane risk of bias tool involves criteria associated with incomplete outcome data, allocation concealment, blinding, random sequence generation, selective reporting and other forms of bias.

Statistical analysis. Utilizing the Review Manager software (version 5.4; The Cochrane Collaboration), the present study conducted a meta-analysis. By utilizing the inverse variance method, the combined hazard ratio with a 95% confidence interval (CI) for survival outcomes was calculated and the Mantel-Haenszel and DerSimonian-Laird methods (18,19) were applied to analyse the pooled odds ratio (OR) with a 95% CI for binary safety data. I^2 <25%, 25% ≤I^2 ≤50% and I^2 >50% were utilized to gauge heterogeneity, which indicated low, moderate and high heterogeneity, respectively. If the heterogeneity test yielded significant results (I^2>50% or P<0.05), a random-effects model was implemented. P<0.05 was considered to indicate a statistically significant difference.

In addition to using I^2 statistics to evaluate heterogeneity, sensitivity analysis and subgroup stratification analysis were conducted to ensure the robustness of the results. Sensitivity analysis was performed by removing a single included study one by one and recalculating the combined effect size of each outcome indicator. After any single study was removed, the combined OR of the recurren ce rate fluctuated between 1.32 and 1.45 (95% CI for all included intervals of 1.10-1.73) and the combined OR of the adverse event rate fluctuated between 0.38 and 0.46 (95% CI for all included intervals of 0.34-0.53), indicating that no extreme outlier study interfered with the overall results. Subgroup analysis was conducted according to BCG strains (Connaught vs. non-Connaught strain) and regions (Europe and America vs. Asia). The results revealed that the heterogeneity within each subgroup did not increase significantly (I^2<30%) and the recurrence risk of low-dose BCG in Asian populations (OR=1.29) was slightly lower compared with that in European and American populations (OR=1.47).

Results

Selected studies and quality assessment. Following the literature search, selection process (Fig. 1) and quality assessment (Fig. 2), 13 studies were included in the present meta-analysis. A summary of the general features of the included studies is presented in Table I (20-32). The included studies were published between 1992 and 2016, with the low-dose BCG regimens ranging from 27 to 80 mg and standard-dose regimens from 80 to 120 mg across different BCG strains (including the Connaught strain and Tokyo 172 strain), covering the most commonly used dosage ranges in clinical practice for NMIBC. In total, 1,768 patients were included, with 755 patients allocated to the control group receiving

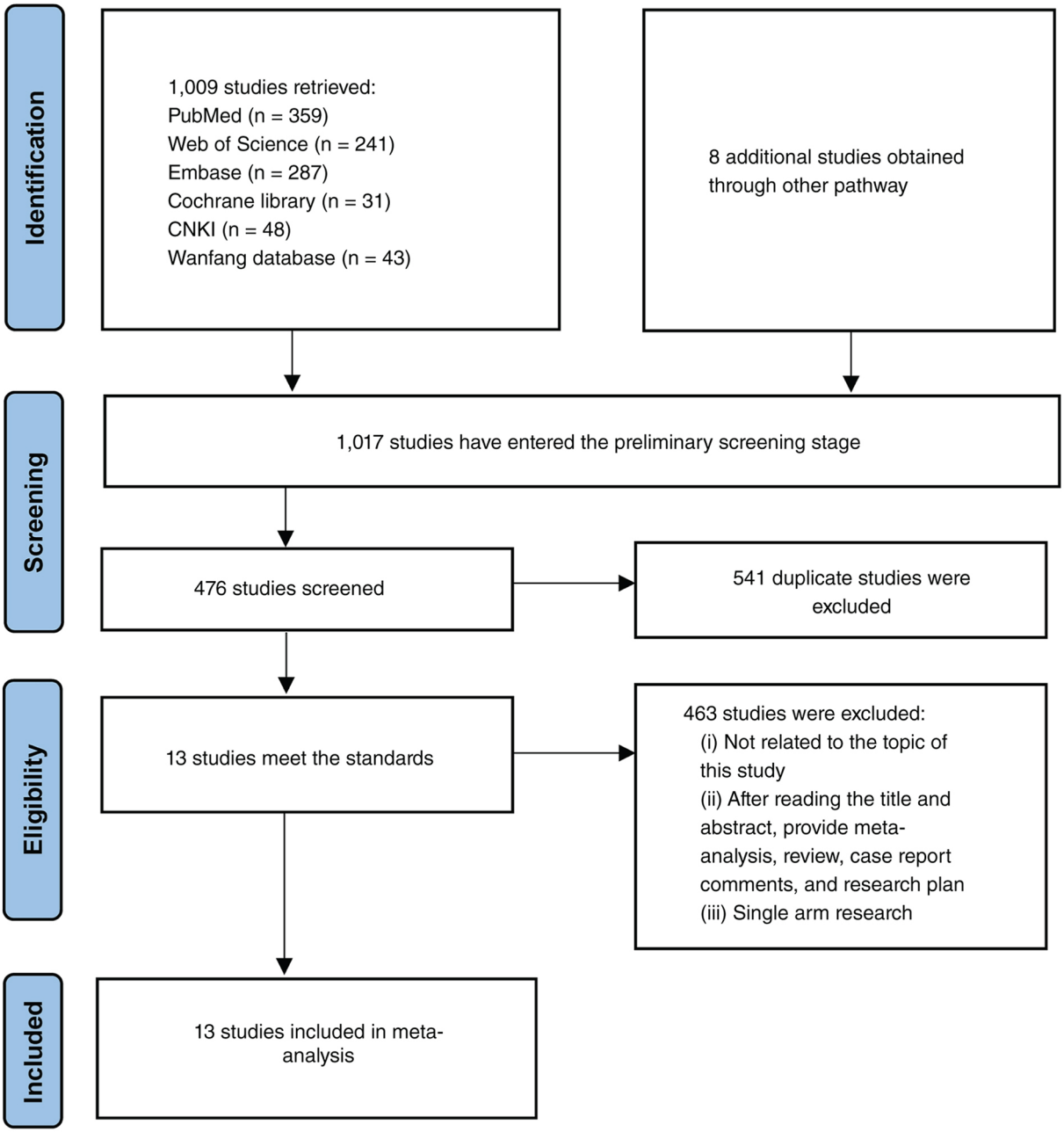

Figure 1. Flowchart of study selection. CNKI, China National Knowledge Infrastructure.

standard-dose BCG treatment and 1,013 patients allocated to the observation group receiving low-dose BCG treatment.

All 13 studies provided data on tumour recurrence following BCG treatment, with findings that indicated a significantly higher recurrence rate in the low-dose group compared with that in the standard-dose group (OR=1.38; 95% CI, 1.10-1.73; Fig. 3).

In terms of tumour progression, the present meta-analysis of eight studies revealed no marked differences between the groups (OR=1.11; 95% CI, 0.76-1.62; Fig. 4).

Furthermore, four studies reported tumour-specific survival and the present meta-analysis revealed no notable differences between the groups (OR=1.02; 95% CI, 0.60-1.75; Fig. 5).

Additionally, four studies reported mortality outcomes and the studies demonstrated low heterogeneity (I^2=0%). A random-effects model revealed no notable discrepancies between the groups (OR=1.09; 95% CI, 0.76-1.56; Fig. 6).

In total, 11 studies reported the occurrence of adverse events in patients after BCG treatment. There was a significantly lower incidence of adverse events in the low-dose group compared with that in the standard-dose group (OR=0.39; 95% CI, 0.29-0.52; Fig. 7).

Publication bias assessment. Assessment using a funnel plot revealed no significant presence of publication bias (Fig. 8).

Discussion

The present meta-analysis revealed that the recurrence rate was significantly higher in the low-dose BCG group compared with

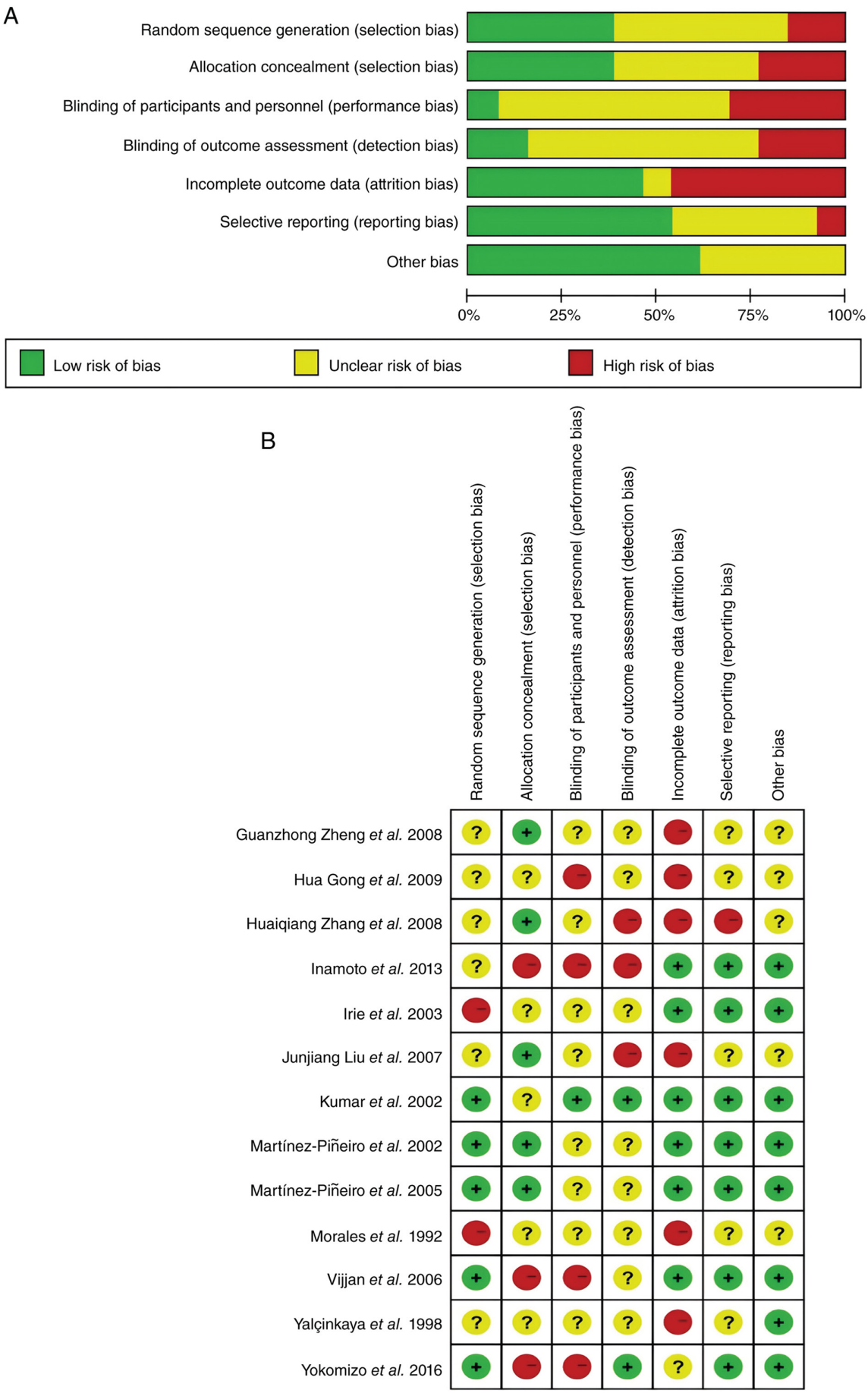

Figure 2. Quality evaluation of included randomized controlled trials. The 13 included studies were evaluated using the Cochrane Risk of Bias tool (A) Risk of bias graph. (B) Risk of bias summary). Green, low risk of bias; yellow dots indicate unclear risk of bias; Red dots indicate high risk of bias.

Table I. General characteristics of studies included in the present meta-analysis.

First author, year	Country	Dose, mg		Sample size, n		Age, years		Sex (F/M), n		(Refs.)
		Low-dose group	Standard-dose group	Low-dose group	Standard-dose group	Low-dose group	Standard-dose group	Low-dose group	Standard-dose group	
Morales *et al*, 1992	Canada	60	120	49	48	NA	NA	NA	NA	(20)
Yalçinkaya *et al*, 1998	Turkey	54	81	25	25	56.28 (37.00-70.00)	55.27 (32.00-68.00)	4/21	3/22	(21)
Kumar *et al*, 2002	India	40	120	13	13	55.90±10.83	56.70±12.80	2/11	1/12	(22)
Martínez-Piñeiro *et al*, 2002	Spain	27	81	248	252	62.90±11.60	64.10±10.30	22/226	27/225	(23)
Irie *et al*, 2003	Japan	40	80	41	39	62.20±11.20	61.60±15.70	8/33	4/35	(24)
Martínez-Piñeiro *et al*, 2005	Spain	27	81	73	82	68.30±8.80	65.80±11.10	7/66	5/77	(25)
Vijjan *et al*, 2006	India	80	120	65	41	54.00±11.80	59.00±10.20	4/33	5/36	(26)
		40				54.00±12.40		6/22		
Liu *et al*, 2007	China	60	120	31	32	52.40	49.80	3/28	5/27	(27)
Zhang *et al*, 2008	China	60	120	100	50	59.00 (32.00-74.00)	56.00 (36.00-75.00)	9/41	11/39	(28)
		40				55.00 (31.00-75.00)		8/42		
Zheng *et al*, 2008	China	60	120	205	36	61.40±22.60	57.2±14.5	31/132	9/27	(29)
		30				59.60±18.30		8/34		
Gong *et al*, 2009	China	60	120	64	32	36.00-77.00	38.00-78.00	7/25	8/24	(30)
		30				39.00-77.00		6/26		
Inamoto *et al*, 2013	Japan	40	81	18	20	71.00±10.80	72.70±10.50	4/14	3/17	(31)
Yokomizo *et al*, 2016	Japan	40	80	81	85	NA	NA	NA	NA	(32)

NA, not available; F, female; M, male.

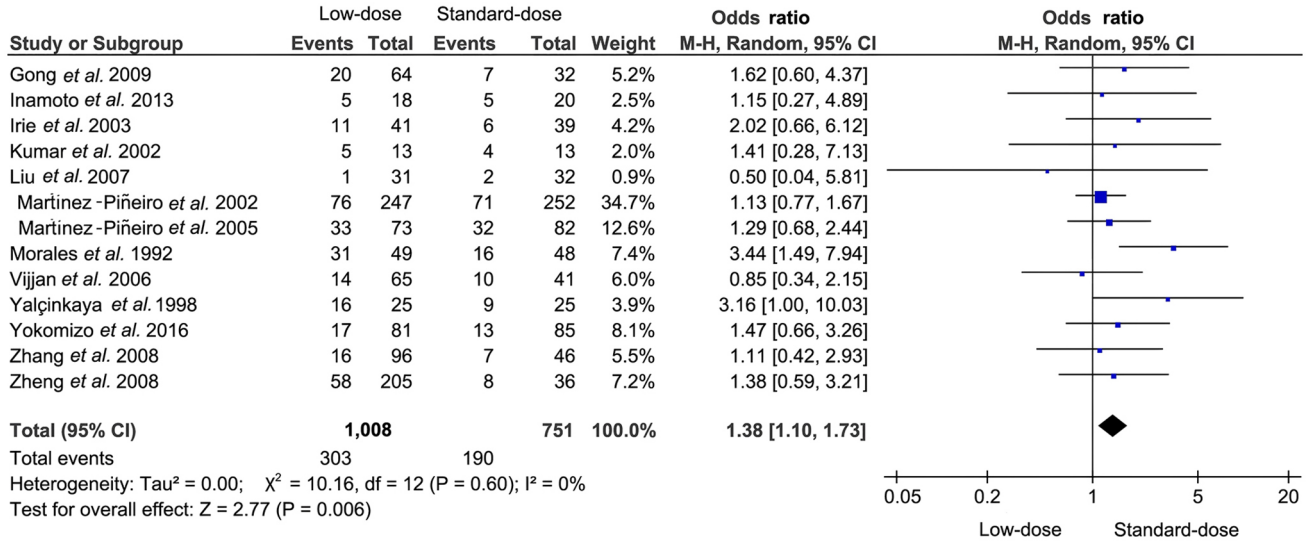

Figure 3. Forest plot of tumour recurrence. Dots represent the individual effect size (OR) of each included study.

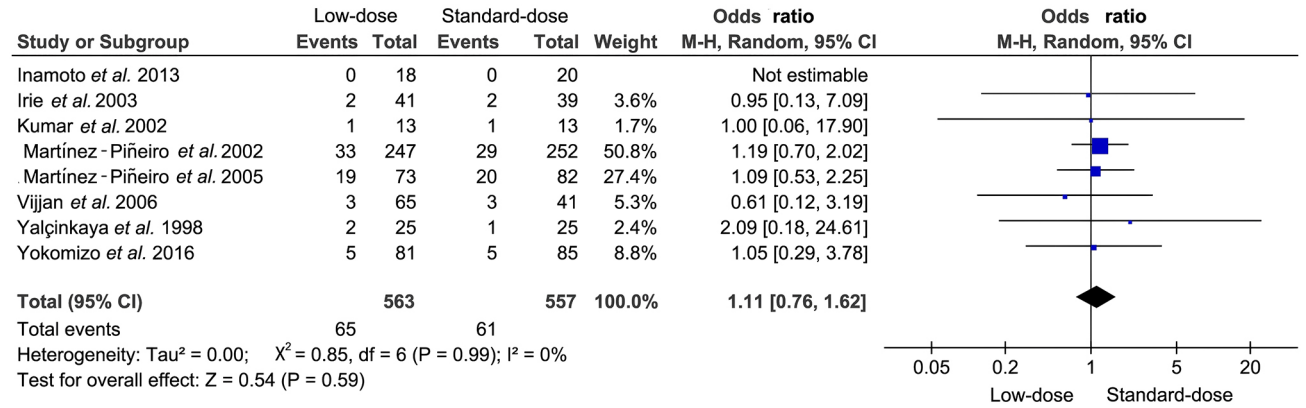

Figure 4. Forest plot of the meta-analysis for tumour progression. Colored data points in the plot represent the individual effect size (OR) of each included study.

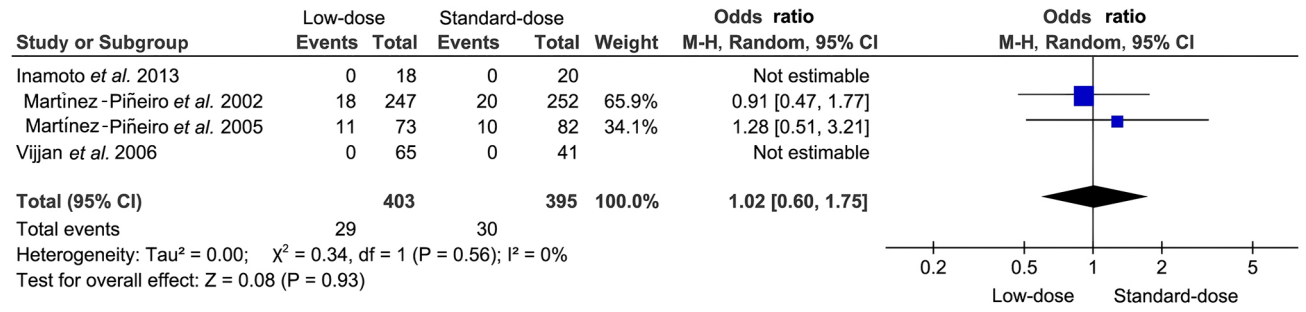

Figure 5. Forest plot of the meta-analysis for tumour-specific survival. Colored data points in the plot represent the individual effect size (OR) of each included study.

that in the standard-dose group (OR=1.38; 95% CI, 1.10-1.73; P=0.006), while no significant differences in tumour progression (OR=1.11; 95% CI, 0.76-1.62; P=0.59), tumour-specific (OR=1.02; 95% CI, 0.60-1.75; P=0.930) or all-cause mortality (OR=1.09; 95% CI, 0.76-1.56; P=0.650) were detected between the two groups. Furthermore, the incidence of adverse events in the low-dose group was markedly lower than the standard-dose group (OR=0.39; 95% CI, 0.29-0.52; P<0.001).

The OR value of 1.38 for tumour recurrence indicated that the risk of recurrence in the low-dose BCG group was 38% higher compared with that in the standard-dose group, with a statistically significant difference (P=0.006). These results confirmed a quantitative association between reduced BCG dosage and elevated recurrence risk, which is consistent with the dose-response relationship implied in early BCG therapy studies. However, it is key to distinguish statistical significance

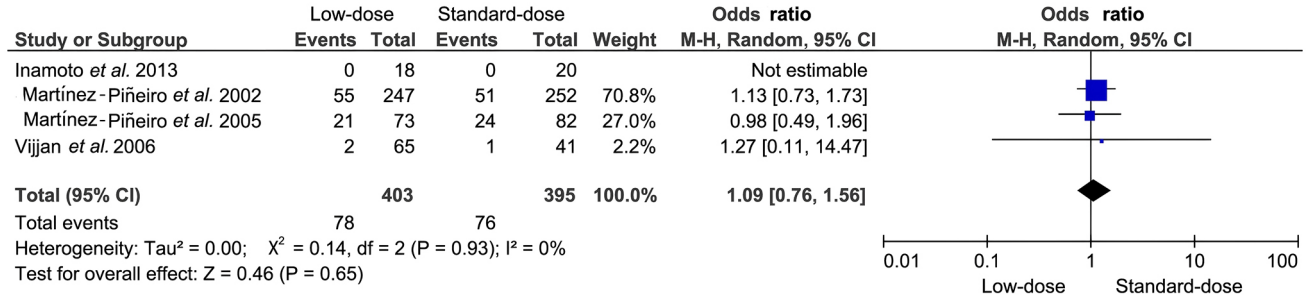

Figure 6. Forest plot of the meta-analysis for overall mortality. Colored data points in the plot represent the individual effect size (OR) of each included study.

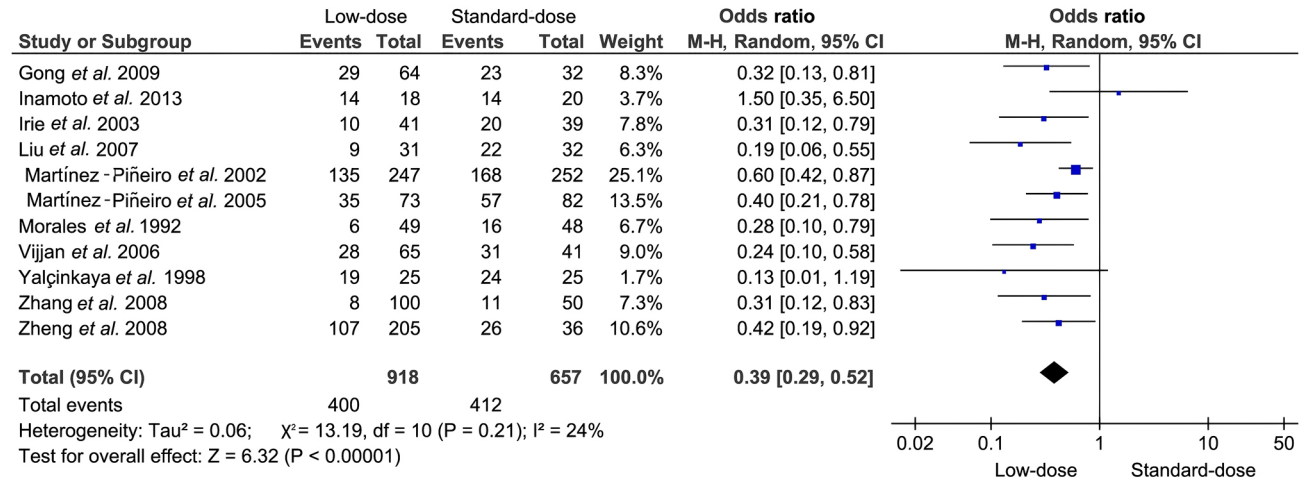

Figure 7. Forest plot of the meta-analysis for adverse events. Colored data points in the plot represent the individual effect size (OR) of each included study.

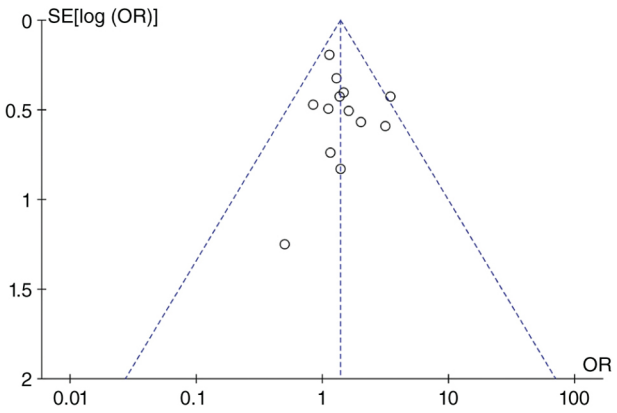

Figure 8. Publication bias. OR, odds ratio.

from clinical significance when interpreting these findings. First, NMIBC recurrence is mostly non-muscle-invasive and can be effectively managed with secondary transurethral resection or reinitiation of intravesical perfusion therapy (33,34). The absence of significant differences in tumour progression and survival outcomes between the two groups suggested that the increased recurrence risk in the low-dose group does not translate to a higher likelihood of malignant transformation or shortened patient survival, which is the core concern in clinical oncology practice. Second, from the perspective of treatment tolerability, the marked reduction in adverse events in the low-dose group directly decreased the rate of treatment discontinuation (a common challenge in standard-dose BCG therapy due to severe lower urinary tract symptoms or systemic reactions) (35,36). For certain populations such as elderly patients with comorbid urinary system diseases or immunocompromised patients, the improved tolerability of low-dose BCG yields a more favourable benefit-risk ratio, even with a moderately increased recurrence risk. Third, against the backdrop of the global BCG supply shortage, low-dose BCG serves as a valuable alternative treatment option. The manageable recurrence risk can be mitigated by adjuvant strategies, such as prolonged maintenance perfusion or combination with local immune modulators, ensuring that patients still receive effective antitumour prophylaxis without interruption of treatment due to drug scarcity (37,38).

A notable study by Morales *et al* (39) used an approach involving adjuvant BCG bladder instillation in NMIBC, which has now become an established standard of care (39). Furthermore, accumulated data consistently support the advantage of maintenance BCG therapy over standard induction therapy in preventing recurrence, leading to the recommendation of maintenance therapy in current guidelines including the European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer, the American Urological Association Guidelines on Bladder Cancer and the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Bladder Cancer (6,39,40). Despite increasing demand for BCG, supply shortages persist, necessitating

additional therapeutic interventions such as low-dose BCG regimens, BCG-chemotherapy combinations and optimized maintenance perfusion protocols (10,41). The present meta-regression analysis reported that although the low-dose BCG treatment group had a higher recurrence rate, no notable variance was detected in terms of tumour-specific survival, tumour progression or mortality. This finding illustrated that desirable treatment effects can be attained even when low-dose therapy is employed. By contrast, adverse events associated with BCG treatment are linked to the dosage, which has a noticeable effect on quality of life of patients. The era of personalized medicine underscores the quest for an enhanced quality of life of patients, prompting renewed research interest in low-dose BCG treatment. The present study was motivated not only by supply shortages but also by the goal of optimizing the quality of life of patients.

Numerous studies have explored approaches to improve the effectiveness of BCG instillation. First, combining immune checkpoint inhibitors, a well-established cancer treatment, with BCG has potential. According to Wang *et al* (41), the application of BCG results in increased expression of programmed death-ligand 1 (PD-L1) on the surface of bladder cancer cells. In a murine model of breast cancer, the concomitant administration of BCG and anti-PD-L1 antibodies resulted in notable oncolytic effects through immunogenic mechanisms (42). Furthermore, one attempt has been made to prolong the presence of BCG within the bladder (43). Drug exposure duration can be extended through intravesical drug delivery systems. Hydrogels that allow sustained release of the drug may prolong the duration and efficacy of treatment, preventing washout during urination (43). Third, transgenic BCG can enhance the immune response to BCG. Recombinant BCG can evade host innate immune responses and increase the levels of antitumour cytokines (44). Furthermore, a previous study attempted to increase the invasiveness of BCG. Implementing drug delivery systems such as liposomes can facilitate the phagocytic activity and antitumour effects of BCG (45). These improved tools enable the use of low-dose BCG to minimize adverse reactions. For almost 50 years, BCG has been the principal therapy for intermediate-to high-risk NMIBC; nevertheless, the standard dosage has generally been determined based on empirical practice. Due to the scarcity of BCG, certain patients may not be able to adhere to standard protocols. The use of low-dose BCG may serve as an alternative approach for an extensive range of patients, as it provides similar progression, tumour-specific survival and overall survival outcomes to those of standard-dose treatment, while also leading to reduced adverse events and discontinuation. High-quality RCTs should determine the optimal BCG dosage in patients with NMIBC in the future.

The present study had certain limitations. First, the BCG strains utilized across the studies varied. Furthermore, differences in the frequency of BCG instillations were observed and varying frequencies may have affected the findings. Although the low-dose group displayed an elevated recurrence rate, the similar tumour progression, tumour-specific survival and mortality in both the low and standard-dose groups may explain the therapeutic effectiveness of BCG obtained despite the use of lower doses. During the BCG shortage, the technology-driven nature of low-dose BCG treatment and its potential as a substitute offer notable advantages, such as improved patient tolerability, decreased adverse events, comparable tumour progression and survival outcomes, and more efficient use of scarce BCG supplies (7,31). Nevertheless, these findings should be supported by comprehensive and carefully designed RCTs in the future to validate clinical results.

In conclusion, the present meta-analysis confirmed the effectiveness of low-dose BCG treatment for patients with NMIBC and highlighted its notable advantage in managing adverse events in patients. Although the low-dose group had a significantly greater recurrence risk (OR=1.38), it did not affect long-term survival or disease progression. In clinical practice, the balance between efficacy and tolerability should be considered and low-dose BCG can be used as an alternative scheme in the context of BCG shortage. Future large-scale and multi-centre RCTs are warranted to confirm the optimal dosage and applicable population of patients receiving low-dose BCG and to explore the synergistic effect of combined therapy to further improve the treatment outcomes of patients with NMIBC.

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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

XL conducted the literature search, performed the data extraction and statistical analysis and drafted the manuscript. YB conceptualized and designed the present study, supervised the meta-analysis process, interpreted the results and critically revised the manuscript. Both authors read and approved the final manuscript. XL and YB confirm the authenticity of all the raw data

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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