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Meta-Analysis

Systemic Immune-Inflammation Index (SII) as Prognostic Indicator for BCG Therapy in Bladder Cancer: A Systematic Review and Meta-analysis

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Abstract

Background: Bacillus Calmette-Guérin (BCG) immunotherapy is a standard treatment for high-risk non-muscle invasive bladder cancer (NMIBC) after tumor resection. However, not all patients respond to BCG therapy. Reliable prognostic markers are needed to predict treatment outcomes.

Objectives: This study reviewed the prognostic value of systemic immune-inflammation index (SII) and related markers in BCG response.

Methods: A systematic literature search was conducted in PubMed, Web of Science, and Scopus databases from inception to October 2023 for studies on SII index, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) in bladder cancer patients receiving BCG therapy. Four retrospective studies involving 1124 patients met the inclusion criteria and were included in qualitative synthesis. Three studies were included in the meta-analysis of progression-free survival (PFS) and recurrence-free survival (RFS). Data on study characteristics and demographics, follow-up duration, cancer stage/grade, and pre-treatment marker levels were extracted. Hazard ratios (HRs) were pooled using a random effects model.

Results: Elevated pre-treatment SII was associated with significantly worse PFS (HR: 3.72, 95% CI: 1.74-7.98, $P<0.001$) and RFS (HR: 3.72, 95% CI: 1.42-9.77, $P=0.007$). However, significant heterogeneity was found among trials in the overall survival (OS) ($I^2=83.49$, $P=0.002$) and RFS ($I^2=89.69\%$, $P=0.002$). In multivariate analysis, SII>672.75 was an independent predictor of BCG failure (OR: 2.229, 95% CI: 1.172-4.238, $P=0.015$). NLR, PLR, and MLR also showed potential prognostic value with area under the curve (AUC) values ranging from 0.592 to 0.663 for predicting non-response to BCG therapy. Specifically, NLR>3.0435, PLR>123.4398, and MLR>0.1995 were significantly associated with non-response to BCG ($P<0.001$ for all). In univariate analysis, BCG non-response was associated with high pre-treatment levels of PLR, NLR, and MLR ($P<0.001$).

Conclusion: Pre-treatment SII and other inflammatory markers may predict poor outcomes after BCG immunotherapy in bladder cancer patients. SII holds promise as an accessible prognostic biomarker that can guide treatment decisions. Further large prospective studies are warranted to validate these preliminary findings.

Keywords: Bladder cancer, Bacillus Calmette-Guérin, Systemic inflammatory response index, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, and Monocyte-to-lymphocyte ratio

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Background

Bladder cancer is estimated to be one of the ten most prevalent cancers worldwide, ranking seventh among the most common cancers in men and seventeenth among women (1-4). Approximately 3% of all new cancer cases and 2.1% of all cancer-related deaths are attributed to bladder cancer. The survival rate for bladder cancer varies across different countries, depending on their diagnostic methods, risk factors, and treatment approaches (5,6). Genetic susceptibility, occupational risk, gender, and smoking are the most significant risk factors for bladder cancer (7). Additionally, mortality rates increase as the disease progresses to higher and more invasive grades (8). Moreover, the recurrence of bladder cancer can impose a significant financial burden on patients and the healthcare system. This burden should be addressed through

post-surgery management and the implementation of alternative treatments to help mitigate the costs (9). Bacillus Calmette-Guérin (BCG) instillation is believed to be the most effective treatment for non-muscle-invasive bladder cancer (NMIBC), particularly in the most aggressive cases (10,11). However, its instillation causes inflammation in the bladder mucosa. Direct and repeated use of this method is necessary to induce adequate immunity. The standard protocol for NMIBC now includes six weekly intravesical instillations of BCG after tumor resection, which has a success rate of over 50% (12-16). Unfortunately, we are currently experiencing a shortage of BCG due to recent manufacturing issues, particularly during the COVID-19 period (17). This shortage is primarily caused by the widespread use of BCG in clinical trials for COVID-19 treatment. As a result, we are prioritizing its use for patients who show the best response (18-20).

Currently, prognostic markers are based on clinicopathological features, which have limitations. Therefore, we need new types of predictors (21-24). The immune system and inflammatory status of a patient have a significant impact on oncological outcomes (25). The systemic immune-inflammation index (SII) was initially utilized as a predictive indicator of hepatocellular carcinoma. Subsequently, it was also introduced as a prognostic marker for various malignant tumors (26, 27). SII, also known as systemic inflammation response index (SIRI), is calculated using the following formula: neutrophil count × monocyte count/lymphocyte count. Therefore, we can easily calculate this marker through blood sampling. Platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and monocyte-to-lymphocyte ratio (MLR) are additional ratios calculated from peripheral blood samples. According to previous studies, these ratios can help predict treatment outcomes in bladder cancer and other types of tumors. These ratios are also suitable for prognosis because they can be calculated using the absolute counts of monocytes, lymphocytes, and neutrophils in a blood sample (28-32). There have been some reports about SII or SIRI as potential prognostic factors for NMIBC. However, despite the need to evaluate the necessity of BCG therapy, the prognostic factors for this disease are limited. In conclusion, in the current study, we aimed to evaluate this factor by reviewing and analyzing previous studies and to investigate its value as a prognostic factor for the response to BCG therapy after surgery in patients. In addition, we made an attempt to assess other factors such as NLR, MLR, and PLR, which can serve as additional prognostic indicators.

Materials and Methods

This systematic review was conducted following pre-defined criteria and according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (33) (Figure 1).

Data Sources and Searches

A comprehensive search was conducted using a combination of MeSH terms and related keywords in title and abstract across PubMed, Web of Science, and Scopus databases from their inception until October 3, 2023, to identify studies which have investigated the efficacy of the indices SIR, SII, SIRI, NLR, PLR, and MLR in determining the outcomes after BCG therapy for bladder cancer. During the search, no restrictions were applied on the publication date or type of study. Additionally, the reference lists of the included articles were examined to identify any relevant studies that may have been missed during the initial search. The search terms used included "bladder cancer", "BCG", "SIR", "SII", "SIRI", "NLR", "PLR", and "MLR". To ensure that we did not miss any relevant articles, we avoided using specific words related to prognosis or its evaluation.

Inclusion and Exclusion Criteria

Studies were deemed eligible if they showcased the effects of BCG therapy on bladder cancer using at least one of the indices SIR, SII, SIRI, PLR, NLR, and MLR both pre- and post-therapy. We particularly focused on studies that provided indirect methods of adjustment for variables like age and gender. For our review, only studies published in English were eligible. No limitations were established regarding age, gender, comorbidities, study duration and location, and the method of reporting cancer diagnosis. However, articles that were not in English, did not provide sufficient data, had overlapping populations and time frames, lacked full text availability, or failed to clearly describe the methodology for index measurements were excluded. Authors, FS and AN, screened articles using predefined criteria and focused initially on the titles and abstracts. Eligible articles underwent a full-text review. The assessment prioritized both eligibility and quality. Studies not presenting patients with bladder cancer or those not providing the required indices with associated confidence intervals were subsequently excluded.

Data Extraction and Quality Assessment

From the identified studies, critical data were carefully collated using a structured format. The extraction encompassed details such as the primary and co-authors, publication year, study location and period, sample size, participants' gender, type of bladder cancer, BCG response status, and immune inflammation markers. Furthermore, relevant outcomes like follow-up duration, cancer stage and grade, survival type, and associated hazard ratios (HRs) were recorded. To validate the diagnosis of bladder cancer and the subsequent outcomes after BCG therapy, we strictly adhered to the criteria stipulated by each study. When ambiguities arose, we reached out to the original authors' study or relevant databases for clarity. To ensure the integrity of our review, we rigorously evaluated the methodological quality of each study using the Newcastle–Ottawa Scale (34) (Table 1).

Outcome Measures

The outcomes after BCG therapy in bladder cancer patients were evaluated using the indices SIR, SII, and SIRI. Furthermore, we meticulously assessed the results by incorporating NLR, PLR, and MLR. The precise way of computing these indices in each study is further elucidated in Table 2.

Progression-free survival (PFS) is defined as the length of time during and after treatment that the cancer does not grow or spread further. It measures the percentage of patients whose disease does not progress after treatment. Recurrence-free survival (RFS) refers to the length of time after primary treatment that the patient survives without any signs or symptoms of that cancer. It measures the percentage of patients who do not experience a recurrence within a specified period.

Table 1. Quality Assessment of the Articles Included in the Study

First Author	Selection	Comparability	Outcome	Total *
Ye, 2022 (28)	*	**	**	5
Bi, 2020 (36)	*	**	***	6
Akan, 2020 (35)	**	**	***	7
Li, 2022 (37)	**	**	***	7

*poor, **fair, ***good

Data Synthesis

Using a structured format, we extracted demographic data, diagnosis specificities, treatment details, data collection methodologies, and emerging thematic insights from the selected studies. HR, as the effect size, with corresponding 95% confidence intervals was extracted for each trial. A random-effects model using the DerSimonian and Laird method was performed to estimate the pooled effect size. To assess the heterogeneity among the trials, I-square (I^2) statistic and Cochran's Q test were used. Forrest and funnel plots were drawn to demonstrate the findings and detect any existing publication bias, respectively. All analyses were done using STATA (Stata Corporation, College Station, TX)

Results

Characteristics of the Included Studies

Utilizing the PRISMA flowchart (Figure 1), we thoroughly searched three major databases and identified a total of 252 studies. With great care, we screened the articles

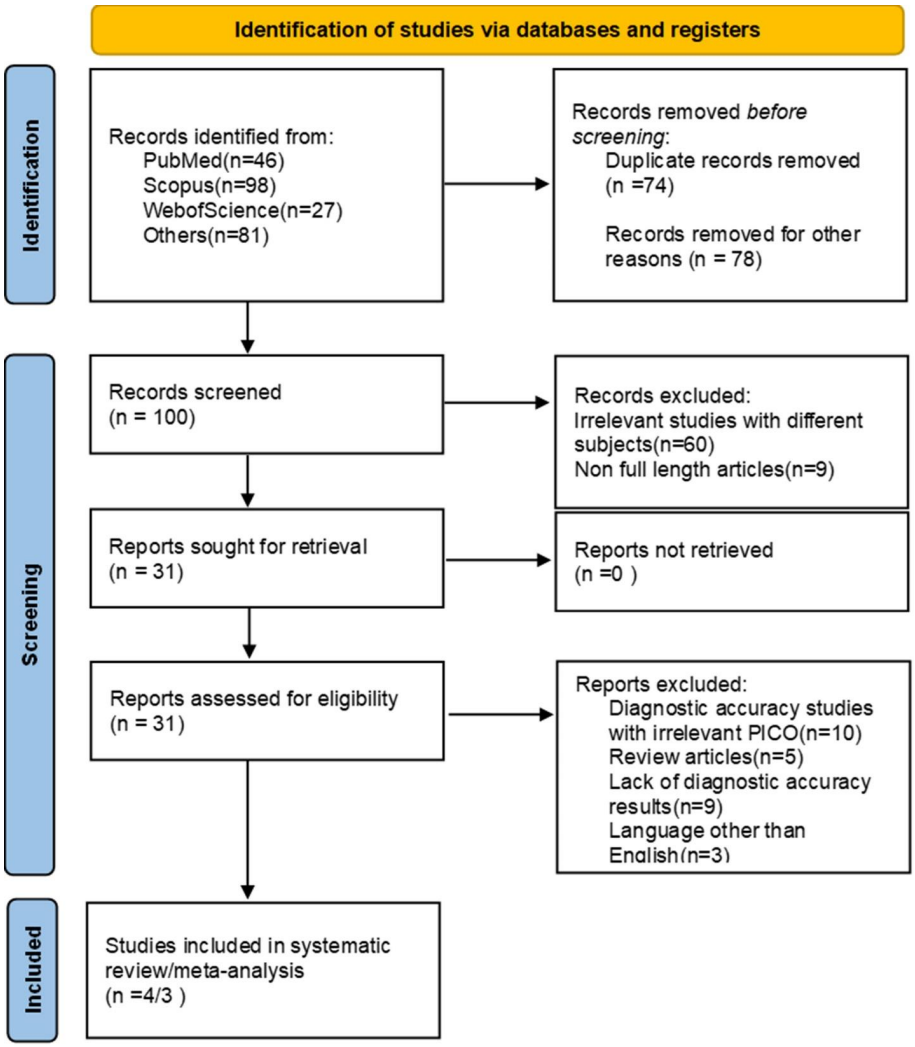

Figure 1. PRISMA Flowchart

Table 2. Characteristics of the Studies Included in Systematic Review

First Author, Year	Country	Sample (n)	Gender		BCG Responder	BCG failure	BCG Responder		BCG failure		Inflammation Marker	RFS (mon), median (IQR)		Follow-up (mon)	Stage (n)			Treatment		Grade	
			Male	Female			High Marker	Low Marker	High Marker	Low Marker		BCG Responder	BCG Failure		Ta	T1	Tis	BCG	TURBT	Low	High
Akan 2021 (35)	Turkey	96	86	10	59	37	2.04 (0.85)		2.67 (1.44)		NLR, median (IQR)	28 (27)	10 (10.5)								
							113.2 (48.9)		142.3 (58.3)		PLR, median (IQR)	30 (27)	12 (10.5)	34.635 ± 14.7	18	78		Yes	Yes	9	87
							450.5 (290.6)		779.3 (284.8)		SII, median (IQR)	32 (27)	14 (10.5)								
Ye 2022 (28)	China	540	340	200	395	145	188	207	121	24	SIRI (n)										
							188	207	121	24	SIRI (n)			60	251	289		Yes	Yes	279	261
							209	186	124	21	MLR (n)										
							110	285	74	71	NLR (n)										
Bi 2020 (36)	China	387	277	110										108	107	260	20	Yes	Yes	124	263
Li 2022 (37)	China	197	170	27										30.18 ± 15.69	40	157		Yes	Yes	55	142

Note. NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; RFS: recurrence-free survival; IQR: interquartile range

and removed any duplicates or irrelevant ones, ultimately identifying 4 articles for systematic review and 3 articles for meta-analysis. Regrettably, one study did not provide sufficient information about survival and HR, which disqualified it from being included in the meta-analysis. All of the studies included in our analysis were conducted retrospectively on patients with bladder cancer who had undergone TURBT and BCG instillation.

Moreover, three of the studies we reviewed evaluated other inflammation markers, all of which were assessed via blood sampling. Table 2 contains further information about each study, including follow-up duration, disease stage and grade, demographic data, and marker levels.

Systematic Review

Based on the characteristics of the studies included in Table 2, one study lacked survival information and was excluded from the meta-analysis. Meanwhile, two studies had complete information on PFS and RFS, as well as their HR with upper and lower limits. The other studies had partial information, including PFS and RFS but not HR.

A study carried out by Ye et al analyzed 540 patients with NMIBC after surgery to identify potential factors that could predict their response to BCG treatment. They found that the area under the curve (AUC) values for PLR, NLR, and MLR were 0.592 (with a sensitivity of 75.9% and a specificity of 42.5%), 0.616 (with a sensitivity of 51% and a specificity of 72.2%), and 0.663 (with a sensitivity of 85.5% and a specificity of 47.1%), respectively. Furthermore, their univariate analysis revealed that non-response to BCG was associated with PLR>123.4398 (P<0.001), NLR>3.0435 (P<0.001), and MLR>0.1995 (P<0.001). Through forward stepwise multivariate analysis, the researchers also identified independent predictors of BCG non-response, including MLR>0.1995 (P=0.015; OR: 2.229, 95%, CI: 1.172–4.238). However, due to the lack of sufficient studies on the other markers beyond SIRI, we were unable to perform a meta-analysis on these factors. The emphasis of the study on SIRI will be discussed later.

Akan et al conducted a retrospective investigation on 96 patients, dividing them into two groups: one with a response to BCG (59) and the other with BCG failure (37). Group two exhibited significantly higher NLR, PLR, and SII (P=0.007, P=0.005, and P=0.000). The area under the ROC curve of SII, as a predictor for BCG failure, was 0.761 with a standard error of 0.05, significantly higher than 0.5 (P=0.001). A cut-off of 672.75 for SII was used, which had 67.6% sensitivity, 79.7% specificity, and 75% accuracy. This study reported that SII and RFS had a significant inverse correlation (P=0.003), while SII and PFS were not correlated (P>0.05).

Progression-free Survival

A total of 1124 participants from 3 trials were included in the analysis (Table 3). The model revealed that high expression of SIRI was significantly associated with a 3.72 times higher risk of mortality, compared to low expression

(HR=3.72, 95% CI=1.74, 7.98, *P*<0.001). However, significant heterogeneity was found among the trials (I^2=83.49, *P*=0.002) (Figure 2). Furthermore, no severe asymmetry was seen in the funnel plot, indicating no potential publication bias (Figure 3).

Recurrence-free Survival

A total of 737 participants from 2 trials were included in the analysis (Table 3). The model revealed that high expression of SIRI was associated with a 3.72 times higher risk of mortality, compared to low expression (HR=3.72, 95% CI=1.42-9.77, *P*=0.007). However, significant heterogeneity was found among the trials (I^2=89.69, *P*=0.002) (Figure 4). Furthermore, no severe asymmetry was seen in the funnel plot, indicating no potential publication bias (Figure 5).

Discussion

In our systematic review and meta-analysis, data from 1124 patients across four studies were examined to assess the prognostic significance of the SII or SIRI and its related markers, including NLR, PLR, and MLR, in predicting the response to BCG therapy in bladder cancer patients. Elevated SIRI expression was associated with a nearly four-fold increase in mortality risk (HR: 3.72, 95% CI: 1.74-7.98) and a reduction in RFS. Furthermore, markers such as NLR, PLR, and MLR were shown to be potential predictive indicators, underlining the potential of SIRI as a crucial prognostic biomarker for BCG therapy outcomes after tumor resection. The prognostic significance of inflammation-related markers such as NLR, PLR, and MLR in oncology has been a recurrent theme in prior studies. Previous studies on gastric cancer have linked elevated levels of NLR and PLR, alongside a concomitant decrease in MLR, with an escalated risk of postoperative complications like recurrence and metastasis (38,39). This trend is mirrored in colorectal cancer, where these markers have been associated with the duration of survival following radical resection (40). Notably, similar conclusions regarding the prognostic implications of these markers have been delineated in the context of hepatocellular carcinoma (41). Moreover, their relevance extends to lung cancer as well, with evidence provided by Wang et al suggesting that diminished levels might correlate with improved postoperative survival outcomes (42).

The urinary tract system plays an integral role in the inflammatory processes underlying various cancers, especially bladder cancer. As one of the most prevalent malignancies, bladder cancer arises in the lower urinary tract and can present as non-muscle-invasive, muscle-invasive, or metastatic disease. NMIBC accounts for approximately 80% of new diagnoses (43-46). Treatment options include observation, immunotherapy with BCG, chemotherapy, radiation therapy, cystectomy, and transurethral resection. The optimal approach depends on considerations of efficacy, recurrence risk, side effects, mortality, cost, and quality of life (44,47,48). To determine the ideal therapy for each patient, convenient and accessible prognostic factors should be identified and measured. Recent advances in bladder cancer prognosis have underscored the significance of systemic immune markers. Among these markers, the SIRI, as highlighted by Ni et al, stands prominently for its association with survival outcomes of post-radical cystectomy (49). Chen et al further elucidated the predictive potential of certain markers like NLR, PLR, and MLR, emphasizing their combined efficiency in anticipating the grade and recurrence of NMIBC (50). Complementing these findings, other studies pivot towards the SII (51). Such markers, in some contexts, have even demonstrated predictive efficacy surpassing traditional TNM classifications (52). While the existing literature provides a thorough overview of prognostic markers in bladder cancer, our research takes a unique approach, focusing specifically on the therapeutic potential of BCG in bladder

Table 3. Survival Measures in the Meta-analysis of Systemic Immune-inflammation Index

First Author, Year	High Level (n)	Low Level (n)	Survival Measure	HR (CI)
Bi 2020 (36)	145	242	PFS	2.11 (1.39-3.20)
Li 2022 (37)	78	119	RFS	2.278 (1.48-3.50)
	78	119	PFS	3.191 (1.84-5.52)
Ye 2022 (28)	309	231	RFS	6.098 (3.90-9.52)
			PFS	8.514 (4.37-16.56)

Note. PFS: progression-free survival; RFS: recurrence-free survival; HR: hazard ratio; CI: confidence interval.

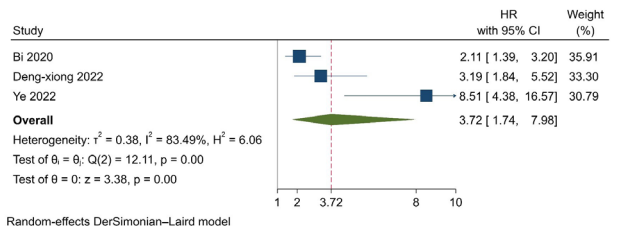

Figure 2. Forrest Plot Presenting Results of the Random-Effects Model and the Estimated Pooled Hazard Ratio for Progression-Free Survival

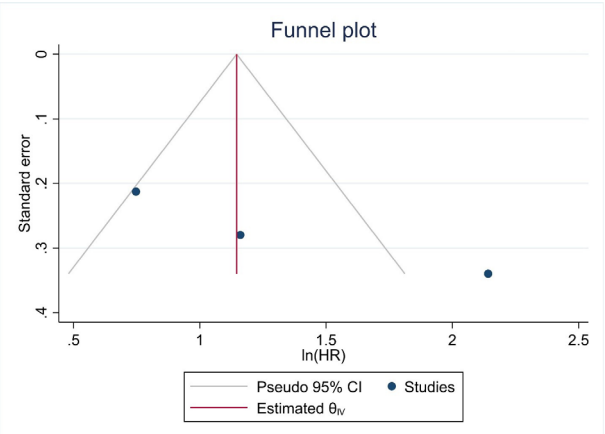

Figure 3. Funnel Plot for the Assessment of Publication Bias

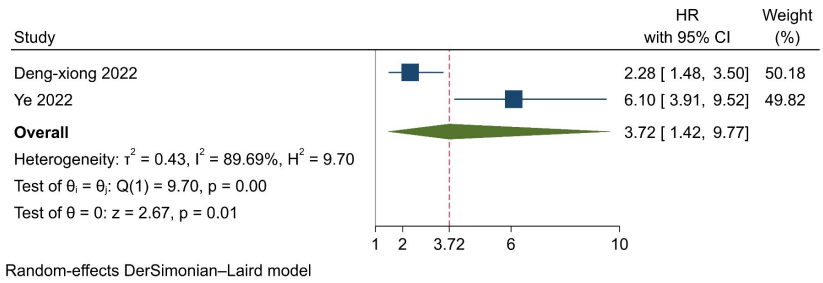

Figure 4. Forrest Plot Presenting Results of the Random-Effects Model and the Estimated Pooled Hazard Ratio for Recurrence-Free Survival

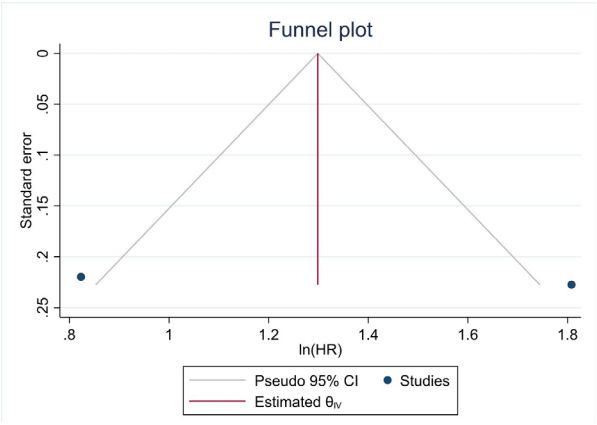

Figure 5. Funnel Plot for the Assessment of Publication Bias

cancer treatment. We combined the insights from SIRI, NLR, PLR, and additional markers into a comprehensive meta-analysis, using a pioneering approach which has not been previously explored based on our knowledge.

Prolonged investigations into tumor recurrence and prognosis have suggested that host inflammatory factors significantly contribute to tumor development. Neutrophils, which the body rapidly deploys as a primary immune defense during infections, can paradoxically aid tumor progression in cancer scenarios. In cancer settings, these neutrophils can foster tumor growth by enhancing neovascularization and facilitating metastasis, primarily due to the secretion of specific cytokines such as OSM, TGF-β, HGF, and CXCL8 (53). Moreover, platelets, which are well-recognized for their role in hypercoagulability in cancer patients, also play a role in tumor evolution. They not only release various chemokines and cytokines that promote tumor growth but also shield the tumor cells against immune mechanisms, such as tumor necrosis factor α and natural killer cells, utilizing specific pathways like the GP receptor and tumor cell integrin α vβ (54). Lymphocytes, conversely, bolster the immune response of the body against malignancies, as emphasized by Hanahan and Weinberg (55). They play a pivotal role in stimulating the host's immune defense, mediating cancer immunosurveillance, and facilitating immune clearance (56).

Having a clear understanding of the connection between increased systemic inflammation and the failure of BCG therapy is crucial. BCG elicits a localized Th1 immune reaction, prompting cytotoxic T cells to target tumor cells (57,58). Nevertheless, prevailing literature indicates that systemic inflammation may obstruct tumor-specific T-cell responses while amplifying immunosuppressive pathways (59,60). In this context, SIRI and similar inflammatory indicators might represent the underlying conditions that counteract therapeutic effects of BCG. Further investigation into the mechanisms by which systemic inflammation modulates anti-tumor immune responses may elucidate the pathways involved, enable improved prognostication of BCG therapy outcomes, and uncover potential therapeutic targets to enhance the efficacy of BCG immunotherapy. The clinical relevance of inflammatory indicators such as NLR, PLR, and MLR is underscored by their accessible and economical profiling. Evaluating these markers in tandem, as opposed to singular analyses, provides a more comprehensive understanding of the patient risk, thereby facilitating personalized post-operative interventions and enhancing therapeutic outcomes. This consideration gains paramount significance in light of recent BCG supply disruptions, underscoring the need for therapeutic optimization (61,62). Patients presenting with elevated pre-treatment SIRI levels may warrant intensified surveillance or alternative therapeutic modalities due to the 4-fold risk of BCG therapy failure based on our study, including checkpoint inhibitors, mitomycin C, and thermotherapy, to counteract the heightened risk of suboptimal efficacy of BCG.

Limitations

While our results are promising, they are constrained by the heterogeneity and retrospective nature of the included studies. The significant heterogeneity (I^2>80%) suggests that the pooled effect estimates should be interpreted with caution. We could not account for potential confounders, such as differences in BCG strains, treatment protocols, patient characteristics, and comorbid conditions across studies. We attempted to use a wide range of search criteria, but we still found a low number of studies to include, despite the significance of the topic in reducing the failure of bladder cancer treatment. Therefore, an updated meta-analysis study with a large number of included studies is necessary to validate our results in the future. To address this issue and identify better and new treatment targets, we require more cross-sectional or cohort studies with larger populations and higher quality, using standard methods.

Conclusion

In light of the present systematic review and meta-analysis, it is evident that elevated levels of SIRI, alongside markers including NLR, PLR, and MLR, hold considerable prognostic significance in predicting responses to BCG therapy among bladder cancer patients. Patients demonstrating heightened SIRI levels prior to treatment might require a tailored approach, with intensified monitoring or alternative therapeutic modalities to offset the potential reduced efficacy of BCG therapy. These findings emphasize the clinical importance of systemic inflammatory indicators, not just as standalone markers but more potently when evaluated collectively, enhancing our understanding of the patient risk and facilitating the tailoring of post-operative interventions. Given the recent disruptions in BCG supply, this information becomes even more critical for therapeutic optimization. Nonetheless, the inherent heterogeneity and retrospective nature of the assessed studies call for prudence in interpreting these results. To solidify these insights and account for potential confounders, future research endeavors should prioritize large-scale multicenter prospective studies and randomized trials.

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Authors' Contribution

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Visualization: Farima Safari, Seyed Ali Nabavizadeh.
Writing-original draft: Farima Safari, Seyed Ali Nabavizadeh.
Writing-review & editing: Atefeh Seghatoleslam, Erfan Sadeghi, Hadi Ghasemi.

Competing Interests

The authors declare that they have no conflicts of interests.

Ethical Approval

Not applicable.

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