CO181

Systematic Literature Review of Prognostic Factors and Treatment Effect Modifiers in Non-Muscle Invasive Bladder Cancer

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Key Takeaway

Several potential prognostic factors were identified, including age, tumor stage, tumor burden (size/number), presence of CIS, prior BCG therapy, and histological subtype, which should be considered when matching baseline characteristics to inform future indirect treatment comparisons of studies in patients with IR- or HR-NMIBC

Conclusions

Seven prognostic factors are consistently associated with clinical outcomes in IR- or HR-NMIBC and should be considered when matching baseline characteristics for indirect treatment comparisons

Tumor stage and CIS status emerged as potential treatment effect modifiers; however, treatment effect modifiers were reported in only 4 of 85 eligible RCTs and no variable was reported in ≥3 studies, precluding confirmation

Findings from this systematic literature review can inform future trial design and analytical approaches to reduce bias in comparative effectiveness research in localized bladder cancer

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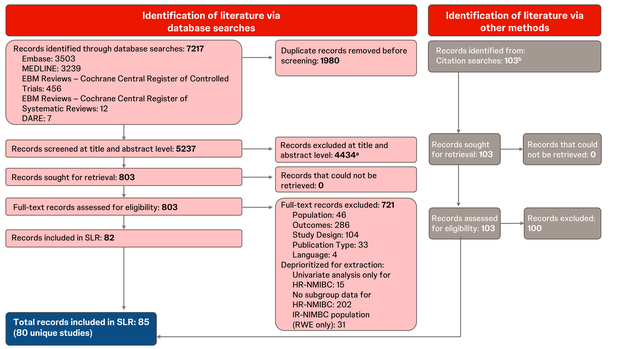
Disclosures
AMK is an Endowed Professor at the University of Texas MD Anderson Cancer Center; **RJ**, **SMH**, **SC**, and **JH** are full-time employees of Johnson & Johnson and hold stock in the company; **JY** and **BM** are employees of Cytel, Inc. The analysis was conducted by Cytel, Inc. and funded by Johnson & Johnson.

Introduction

- Bladder cancer (BC) is the ninth most common cancer globally, with 75% of newly diagnosed cases being non-muscle invasive BC (NMIBC)[1,2]
- High-risk (HR)-NMIBC constitutes 25% of diagnosed cases, while intermediate-risk (IR)-NMIBC accounts for 50–60% cases[3,4]
- Prognostic factors (PFs) and treatment effect modifiers (TEMs) are essential to improving risk stratification, guiding clinical decision-making, and informing indirect treatment comparisons (ITCs)[5]
- We conducted a systematic literature review (SLR) to identify PFs and TEMs in IR- and HR-NMIBC and to inform which baseline characteristics should be matched when conducting an ITC

Methods

Figure 1: PRISMA flow diagram for SLR



[a]In total, 775 studies were retroactively excluded based on prioritized population keyword searches conducted on the title and abstract. This pragmatic approach was implemented to ensure the review remained within its defined scope. [b]102 citation references from 14 SLRs and 1 citation reference from J&J.
DARE, Database of Abstracts of Reviews of Effects; EBM, Evidence-Based Medicine; IR, intermediate risk; NMIBC, non-muscle-invasive bladder cancer; SLR, systematic literature review

- Comprehensive searches of electronic databases were performed using the Ovid interface on 4 April 2025 to identify peer-reviewed publications of clinical and real-world evidence (RWE) studies specific to IR- and HR-NMIBC, inclusive of PFs and TEMs and specific for disease-related outcomes, published from 2014 to 2025 (**Figure 1**)
- Eligible studies enrolled patients with:
  - HR-NMIBC (carcinoma in situ [CIS]/Tis, CIS/Tis+ papillary, and papillary high-grade Ta or T1)
  - IR-NMIBC (low-grade Ta)
  - Bacillus Calmette-Guérin (BCG)-naïve, BCG-experienced, or BCG-unresponsive HR-NMIBC
- Clinical outcomes reviewed: complete response (CR), event-free survival (EFS), recurrence-free survival (RFS), cancer-specific survival (CSS), disease-free survival (DFS), overall survival (OS), progression-free survival (PFS), duration of response (DOR), time to radical cystectomy (RC), time to progression (TTP), time to recurrence (TTR), and RC rate
- Association between PFs and treatment outcome was considered significant at p≤0.05. TEMs with p≤0.1 were considered for potential interaction

Results

- The electronic database searches returned 5,237 records, of which 82 records (HR- or IR-NMIBC) were included for extraction (**Figure 1**)
  - Three additional records were included through supplementary searches, resulting in a total of 80 unique studies across 85 records
  - Of the included studies, 64 were retrospective studies or database analyses, and five studies were prospective observational studies
  - Ten additional records described results from randomized controlled trials (RCTs) and 1 study was a non-RCT

Prognostic factors

- Of the 85 eligible records in this SLR, 82 records (97.6%) reported PFs in patients with HR-NMIBC
- Details on PFs reported are summarized in **Table 1**
- The most commonly studied clinical outcomes across various studies was RFS, followed by PFS and OS
  - CSS and DFS were less frequently studied
- Seven PFs including age, tumor stage, tumor burden (size/number), CIS, BCG therapy, histological subtype, and tumor grade were moderately or highly associated with one or more clinical outcomes (>50% to ≤70% or >75% of studies with p≤0.05)
- Age was the most consistently reported PF, indicating high association with OS (20 of 21 studies) and CSS (12 of 14 studies)

Table 1: Number of publications reporting each variable per outcome

Variables	≥3 Publications reporting variable per outcome									
	OS	PFS	RFS	CSS	DFS	TTR	TTP	EFS	MFS	CR
Age	21	24	28	14	3	1	1		2	1
Sex	7	18	21	9	2	1				1
Race			1							
Ethnicity	1			1						
Smoking status/ nicotine use	1	5	8	1	1			1		
Payer type										
ECOG PS	1		1							
Comorbidities	2		1							
Prior malignancies										
Tumor grade	6	16	18	7	1	1				1
Tumor stage	6	21	19	8	2	1			1	1
CIS	6	18	18	7	2	1	2			1
Histology		6	4	2	2					
Tumor size	8	17	22	10	1	2	2			1
Tumor number	7	19	16	8	2	2	1			1
Hemoglobin	2			1						
Prior treatments		1	5							
Total doses of prior BCG										
BCG therapy	5	12	17	1	1	2	1			

Very low association: ≤25% of studies; Low association: >25% to ≤50% of studies; Moderate association: >50% to ≤75% of studies; High association: >75% of studies; No association

No data were reported for the outcomes of DOR or RC rate.
BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; CR, complete response; CSS, cancer-specific survival; DFS, disease-free survival; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; MFS, metastasis-free survival; OS, overall survival; PFS, progression-free survival; PS, performance status; RC, radical cystectomy; RFS, recurrence-free survival; TTP, time to progression; TTR, time to recurrence.

Treatment effect modifiers

- TEMs were reported in only 4 RCTs from the 85 eligible records, of which 2 studies reported TTR, 1 study reported OS, DFS, cancer-specific mortality, TTR, TTP/time to metastasis, and RFS, and 1 study reported EFS
- No variable was reported in ≥3 studies to confirm treatment effect modification (**Table 2**)
- Most clinical variables, including age, histological grade, prior treatment, and disease risk status, did not significantly modify treatment efficacy
  - Age was the only variable investigated as a TEM for OS
  - Tumor stage and CIS status showed potential as TEMs in specific therapeutic contexts, particularly with celecoxib and radiofrequency-induced thermo-chemotherapy effect therapy[6,7]

Table 2: Overview of publications by treatment effect modifiers of interest

Variable	OS	DFS	CSM	TTR	TTP/TTM	RFR	PFS	EFS	MFS	CR	DOR	TTRC	RC rate
Age	1		1	1	1			1					
Sex	–		–	–	–			1					
Race	–		–	–	–			1					
Ethnicity	–		–	–	–			1					
Tumor grade				1									
Tumor stage				1				1					
Histology		1		–				1					
Prior treatments				1									
Prior BCG therapy		1											
CIS		1		–				1					
Risk status				1		1							

–, not available; BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; CR, complete response; CSM, cancer-specific mortality; DFS, disease-free survival; DOR, duration of response; EFS, event-free survival; MFS, metastasis-free survival; OS, overall survival; PFS, progression-free survival; RC, radical cystectomy; RFR, recurrence-free rate; RFS, recurrence-free survival; TTM, time to metastasis; TTP, time to progression; TTR, time to recurrence; TTRC, time to radical cystectomy.

Limitations

- Although this SLR followed a methodologically robust approach to ensure validity of the findings, the following limitations need to be considered while interpreting the evidence:
  - No extraction of PFs if assessed as part of a univariate analysis
  - Prioritization of studies with data available for patients with HR-NMIBC
  - RWE studies in IR-NMIBC were excluded, as were studies without a subgroup analysis for high risk or those with mixed groups of patients with IR-/HR-NMIBC
  - Owing to incomplete information, there are likely additional prognostic factors that were not identified due to incomplete information
  - TEM analyses were sparse and inconsistently reported (only 4 RCTs provided TEM data; no variable reported in ≥3 studies)
  - Heterogeneity of the included studies
  - Confounding factors within the multivariate analyses of included studies
  - Recent trials that read out after April 2025, such as POTOMAC and CREST, were not included

References

1. Bray F, et al. *CA Cancer J Clin* 2024;74(3):229-263. **2.** Babjuk M, et al. *Eur Urol* 2022;81(1):75-94. **3.** Ravvaz K, et al. *J Urol* 2017;198(4):824-831. **4.** Li R, et al. *Eur Urol Oncol* 2025;8(6):1685-1695. **5.** Phillippo DM, et al. *Med Decis Making* 2018;38(2):200-211. **6.** Kelly JD, et al. *Eur Urol* 2019;75(4):593-601. **7.** Tan WS, et al. *Eur Urol* 2019;75(1):63-71.

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