



Prognostic Factors for Intravesical Recurrence in NMIBC: Evaluating the Role of Pyuria, Bacteriuria, and Comorbidities

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Abstract

Background: The discovery of risk factors that might predict the recurrence of non-muscle invasive bladder cancer (NMIBC) is essential.

Objectives: Therefore, this prospective cohort study aimed at examining the association between bacteriuria and pyuria before bacillus Calmette-Guérin (BCG) installation and the occurrence of intravesical recurrence (IVR) in patients diagnosed with NMIBC.

Methods: A total of 73 NMIBC patients undergoing transurethral resection of bladder tumor (TURBT) and BCG treatment were included. Pre-instillation urine samples were analyzed for pyuria and bacteriuria.

Results: The findings of this study indicated that preoperative pyuria was present in 31 (42.5%) of the studied patients. Furthermore, a statistically significant association was detected between preoperative pyuria and preoperative proteinuria ($P < 0.001$), preoperative hematuria ($P = 0.023$), preoperative bacteriuria ($P = 0.001$), and muscle invasion (MI) ($P = 0.028$). The results of the univariate analysis indicated substantial associations between the variables of smoking, diabetes, carcinoma in situ (CIS), age, and IVR. Subsequently, a multivariate analysis indicated that diabetes ($HR = 18.11$, $P = 0.004$) and CIS ($HR = 14.69$, $P = 0.039$) had a statistically significant link with IVR.

Conclusions: In conclusion, our study demonstrated that diabetes, CIS, and younger age were the sole independent prognostic factors for IVR. Furthermore, no statistically significant association was observed between pyuria, bacteriuria, and smoking with bladder tumor recurrence. The analyses revealed that pyuria emerged as a statistically significant predictive factor for IVR only among individuals without pre-instillation proteinuria.

Keywords: Bacteriuria, Bacillus Calmette Guerin Vaccine, Intravesical Instillations, Non-Muscle-Invasive Bladder Cancer, Pyuria, Recurrence

1. Background

Bladder cancer is among the most common cancers worldwide, with an estimated incidence of over 500,000 new cases and 200,000 deaths in 2019 (1-3). Non-muscle invasive bladder cancer (NMIBC) accounts for approximately 75% of bladder cancer cases and is known for its high recurrence (50 - 70% within 5 years) and progression rates (10 - 30%) (4). Management strategies, including transurethral resection of bladder

tumor (TURBT) and intravesical therapies aim at reducing recurrence and progression risks (3, 5). However, TURBT, with or without intravesical therapy, fails in about 50% of patients, increasing the likelihood of progression to muscle-invasive bladder cancer (MIBC) (6, 7). Factors such as lymphovascular invasion and high-grade tumors in re-TURB have been identified as predictors of response to bacillus Calmette-Guérin (BCG) treatment (8). Inflammation has been increasingly studied in cancer prognosis (9-11), with

conflicting evidence regarding the impact of pyuria on NMIBC recurrence and progression (12-14).

2. Objectives

Given the importance of predicting BCG treatment response, this study aimed at evaluating bacteriuria and pyuria as potential predictors of intravesical recurrence (IVR) in NMIBC patients before BCG therapy.

3. Methods

3.1. Study Subjects

This study was conducted as a prospective cohort, enrolling consecutive patients referred to our institution. The patients included in the study had a primary urothelial bladder tumor and underwent TURBT. Additionally, they were candidates for intravesical BCG treatment within 2 to 4 weeks after surgery. The pathology results confirmed that the patients had NMIBC. Patients with variant histology, those with symptomatic bacteriuria requiring treatment, and individuals for whom BCG instillation was contraindicated were excluded from enrollment.

3.2. Patient Grouping

The participants enrolled in the research were categorized into 2 groups, depending on whether they exhibited pyuria/bacteriuria or not. Tumor recurrence was assessed at 3-month intervals during 3 years of follow-up. Before the initial administration of the BCG, a urine specimen was collected from each patient for microscopic analysis and culture. All participants in the study provided written agreement, and the research protocol received approval from the institutional review board (IR.TUMS.VCR.REC.1398.738).

3.3. Data Collection

A questionnaire was utilized to gather demographic and clinical data from the patients. The examined variables encompassed presence of pyuria, bacteriuria, proteinuria, hematuria, concurrent presence of carcinoma in situ (CIS), tumor grade, and recurrence of disease during follow up (36 months).

3.4. Urine Analysis

A urine analysis was conducted on the sample provided, using a catheter and immediately before the initial BCG instillation. Pyuria was defined as the presence of > 5 white blood cells/HPF in centrifuged urine sediment. Bacteriuria was characterized

according to the widely accepted criteria described by Nicolle, (15) as the presence of $\geq 10^5$ CFU/ml of urine with a single organism, indicating significant bacteriuria.

3.5. Data Analysis

A univariate analysis was conducted to examine the prognostic factors associated with IVR. Subsequently, multivariate analyses were conducted on the factors that exhibited a P-value below 0.2 in the univariate analysis. Finally, a subgroup univariable analysis was conducted on the variables under investigation. In our analysis, diabetes, CIS, and proteinuria were considered as potential confounders, and proteinuria was evaluated as an effect modifier in the association between pyuria and IVR. Moreover, there were no missing data for the analyzed variables. All patient records were complete, ensuring the integrity of our dataset.

4. Results

A total of 73 patients were included in the study. The mean (SD) age was 61.92 (12.27) years, and 15 (20.5%) patients were female. Pyuria was preoperatively observed in 31 (42.5%) patients. The relationship between pre-instillation pyuria and other clinicopathological variables is shown in Table 1. Pre-instillation pyuria was significantly associated with pre-instillation proteinuria ($P < 0.001$), pre-instillation hematuria ($P = 0.023$), pre-instillation bacteriuria ($P = 0.001$), and progression to MIBC ($P = 0.028$). Of the 73 patients, 24 (32.9%) developed IVR during a median follow-up of 36 months.

We examined the prognostic factors for postoperative bladder recurrence in all 73 patients. On univariable analysis, variables significantly associated with IVR were smoking, diabetes, concomitant CIS, and age (Table 2). A multivariable analysis revealed that diabetes ($HR = 18.11$, $P = 0.004$) and concomitant CIS ($HR = 14.69$, $P = 0.039$) were independent positive risk factors for IVR, while increasing age was an independent negative prognostic factor ($HR = 0.938$, $P = 0.022$).

Given the limited sample size of patients ($n = 73$), subgroup univariable analysis was performed to evaluate the correlation between pyuria and IVR across various subgroups (Figure 1). We observed that pyuria emerged as a significant predictor of IVR only within a subset of patients devoid of proteinuria [odds ratio (OR) = 8.67, 95% CI = 1.67 - 44.9, $P = 0.01$].

5. Discussion

In this study, we observed a 32.9% incidence of IVR among NMIBC patients undergoing BCG therapy. Our multivariate analysis identified younger age, diabetes,

Table 1. Demographics and Patient Characteristics^a

Variables	Total	Preoperative Pyuria		P-Value
		Yes	No	
Number of patients	73	31 (42.5)	42 (57.5)	
Age	61.92 ± 12.27	63.81 ± 9.94	60.52 ± 13.69	0.262
Gender				
Male	58 (79.5)	24	34	0.712
Female	15 (20.5)	7	8	
Smoke				0.247
Yes	39 (53.4)	19	20	
No	34 (46.6)	12	22	
Alcohol				0.058
Yes	10 (13.7)	7	3	
No	63 (86.3)	24	39	
Diabetes				0.763
Yes	8 (11)	3	5	
No	65 (89)	28	37	
Proteinuria				< 0.001 ^b
Yes	32 (43.8)	22	10	
No	41 (56.2)	9	32	
Hematuria				0.023 ^b
Yes	29 (39.7)	17	12	
No	44 (60.3)	14	30	
Bacteriuria				0.001 ^b
Yes	53 (72.6)	29	24	
No	20 (27.4)	2	18	
Primary tumor pathological grade				0.428
High	20 (27.4)	7	13	
Low	53 (72.6)	24	29	
CIS				0.637
Yes	6 (8.2)	2	4	
No	67 (91.8)	29	38	
MI IVR				0.028 ^b
Yes	6 (8.2)	0	6	
No	67 (91.8)	31	36	
LPI (during 3 years (36 months) follow up)				0.347
Yes	13 (17.8)	4	9	
No	60 (82.2)	27	33	
IVR				0.362
Yes	24 (32.9)	12	12	
No	49 (67.1)	19	30	

Abbreviations: CIS, carcinoma in situ; MI, muscle invasion; LPI, lamina propria invasion; IVR, intravesical recurrence.

^a Values are expressed as No. (%) or mean ± SD.

^b P < 0.05 was considered statistically significant.

and CIS as independent risk factors for recurrence, while no significant association was found between pyuria and IVR in the overall population. However, subgroup analysis revealed a significant relationship between pyuria and IVR among patients without proteinuria,

suggesting a potential interaction between inflammatory and metabolic factors in bladder cancer recurrence. These findings contribute to the ongoing efforts to refine risk stratification and optimize patient management in NMIBC.

Table 2. Univariate and Multivariate Analysis in Total Patients

Variables	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	P-Value ^a	HR (95% CI)	P-Value ^b
Gender				
Female vs. male	0.44 (0.11 - 1.74)	0.242		
Smoking				
Yes vs. no	2.26 (0.82 - 6.25)	0.116	1.40 (0.43 - 4.61)	0.577
Alcohol				
Yes vs. no	0.86 (0.2 - 3.65)	0.835		
Diabetes				
Yes vs. no	7.83 (1.44 - 42.45)	0.017	18.11 (2.53 - 129.8)	0.004
Proteinuria				
Yes vs. no	1.45 (0.54 - 3.87)	0.74		
Hematuria				
Yes vs. no	1.13 (0.42 - 3.05)	0.813		
Pyuria				
Yes vs. no	1.58 (0.59 - 4.23)	0.363	1.85 (0.51 - 6.78)	0.352
Bacteriuria				
Yes vs. no	1.68 (0.53 - 5.33)	0.382		
Grade				
High vs. low	1.54 (0.53 - 4.49)	0.428		
CIS				
Yes vs. no	4.7 (0.80 - 27.76)	0.088	14.62 (1.14 - 187.4)	0.039
MI				
Yes vs. no	2.19 (0.41 - 11.77)	0.361		
LPI				
Yes vs. no	1.35 (0.39 - 4.67)	0.637		
Age (y)	0.97 (0.932 - 1.01)	0.146	0.938 (0.89 - 0.99)	0.022

Abbreviations: MI, muscle invasion; CIS, carcinoma in situ; OR, odds ratio.

^a P ≤ 0.01 was considered statistically significant.

^b P < 0.001 was considered statistically significant.

Various studies have explored the relationship between aging and its influence on bladder cancer recurrence, yielding conflicting results. While some suggest a positive correlation, others find a negative association or no significant relationship between age and tumor recurrence (16-20). Joudi et al. observed reduced response to intravesical immunotherapy among older patients, while another study reported higher 5-year recurrence-free survival (RFS) rates in older patients (20). Yuge et al., in a study involving 400 patients with NMIBC, concluded that advanced age does not impact disease recurrence in those undergoing BCG therapy; instead, tumor characteristics determine treatment outcomes (16). Elderly individuals often experience declines in immune function, which may affect responses to treatments like BCG immunotherapy (21). Contrary to expectations, our study found that younger age elevates the risk of IVR. Given the varied literature findings and the influence of tumor grade

and stage on bladder tumor recurrence, it is plausible that younger patients in our cohort had higher-grade tumors, potentially contributing to increased recurrence rates. Further research with larger datasets and molecular profiling is needed to clarify these discrepancies.

Our findings reinforce the strong association between diabetes and bladder cancer recurrence. Previous investigations have revealed a substantial correlation between diabetes and worse prognosis in several types of cancer, such as colon, breast, endometrial, liver, pancreatic, and bladder malignancies (21-25). However, the exact cause and method of this effect is not known. Potential mechanisms include chronic hyperglycemia, insulin resistance, and activation of insulin-like growth factor (IGF) pathways, all of which promote tumor proliferation and inhibit apoptosis. Moreover, diabetes-induced immune dysregulation could also impair the

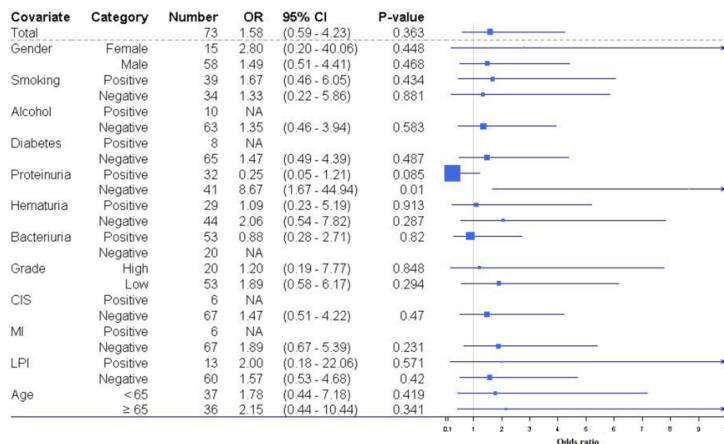


Figure 1. Subgroup univariable analysis of the association between intravesical recurrence (IVR) and pyuria among different patient subgroups. The figure depicts analyses examining the correlation between IVR and pyuria across distinct patient subsets. Odds ratios (ORs) less than 1 signify a negative prognostic factor.

effectiveness of BCG therapy, reducing its anti-tumor activity (26-29). Given these findings, our study underscores the need for strict glycemic control in diabetic patients undergoing BCG therapy as a potential strategy to reduce recurrence risk. Multiple previous investigations have documented a significantly elevated risk of recurrence of NMIBC in individuals with diabetes compared to those without diabetes, with recurrence rates ranging from 60% to 45% in the former group and 40% to 30% in the latter group (30-32). The findings from a meta-analysis of 21 cohort studies comprising 13 million individuals indicated a noteworthy correlation between diabetes and a heightened risk of bladder cancer or cancer-related mortality (33). Our study's results align with these observations.

Carcinoma in situ is known to be a biologically aggressive entity with a high propensity for recurrence and progression, even in patients receiving adequate BCG therapy. Our findings also unveiled that CIS was a positive risk factor for IVR. This outcome is in line with previous studies that have documented a correlation between CIS and adverse outcomes concerning RFS and disease prognosis in bladder cancer patients (34-36). This highlights the importance of early detection and intensive monitoring of CIS-positive patients, as well as exploring potential combination therapies to enhance treatment efficacy.

In the realm of cancer development, pyuria has been studied as a potential marker of chronic inflammation and a risk factor for bladder tumor recurrence (37). Malignant tumors frequently exhibit substantial

leukocyte infiltration, correlating with poorer prognoses (38-41). Notably, some studies have identified pyuria as a significant predictor for the ineffectiveness of BCG treatment (42). The simplicity and affordability of pyuria detection position it as an appealing option for biomarker analysis, providing economic advantages in cancer management (42). Multiple studies have associated pyuria with more aggressive forms of bladder cancer, characterized by deeper invasion and extensive mucosal lesions (12, 13, 43-45). Conversely, certain studies suggest that pyuria is not correlated with bladder cancer recurrence and survival (46). The variability in study outcomes may stem from various factors contributing to pyuria. For example, in a cohort study of individuals with NMIBC, negative urine cultures for bacteria alongside pyuria suggested localized inflammation associated with cancer (12).

While our overall analysis did not find a significant association between pyuria and IVR, a subgroup analysis was conducted to explore whether the association between pyuria and IVR varied across different clinical contexts. While this analysis was hypothesis-driven and based on known pathophysiological mechanisms, we acknowledge that subgroup analyses should be interpreted with caution due to the potential for overinterpretation and multiple comparisons. In our present study, pyuria was associated with IVR only in a subgroup of patients without proteinuria. This could be explained by the fact that proteinuria is linked to cancer-related inflammation and poorer prognosis; however, in the absence of proteinuria, pyuria may

correlate with the severity of cancer-associated inflammation and higher likelihood of cancer recurrence.

Proteinuria has been explored as a potential biomarker in NMIBC, with some studies suggesting that it may predict worse RFS, possibly due to its association with systemic inflammation and endothelial dysfunction (47). However, our study did not find a significant correlation between proteinuria and IVR, which may be due to variability in the etiology of proteinuria in different patient populations. Prior research has highlighted that elevated urinary fibronectin levels correlate with increased recurrence risk, as fibronectin may inhibit BCG binding to the bladder wall (48). Despite these findings, the role of proteinuria in bladder cancer prognosis remains elusive, and further studies with molecular characterization are needed.

While smoking is a well-established risk factor for bladder cancer, its role in post-treatment recurrence remains debated. A recent meta-analysis, incorporating 15 studies with a substantial sample size of 10 192 patients, suggests that both current and former smoking are linked to an increased risk of recurrence and death in individuals diagnosed with bladder cancer (49). Additionally, a more recent systematic review and meta-analysis, involving 28 studies with 7 885 patients diagnosed with NMIBC, revealed that individuals with a history of smoking experience a less favorable prognosis in terms of RFS compared to non-smokers (50). However, our study did not find a significant association between smoking and IVR, which may be due to a low prevalence of smokers in our study or a lack of detailed smoking history (current vs. former smokers). Given the strong biological rationale linking smoking to tumor recurrence via DNA damage and chronic inflammation, future studies should incorporate detailed smoking categorizations and larger sample sizes to assess its true impact.

Our study found no statistically significant association between bacteriuria and IVR, which contrasts with previous findings suggesting that bacteriuria might decrease recurrence likelihood in individuals with NMIBC (14). Divergent findings across studies may stem from variations in operational definitions of urinary tract infections, potentially influencing (51).

Alongside the strengths and positive findings of our study, like all research, it has its limitations. One of the key limitations is the small sample size. However, we performed thorough statistical analyses to mitigate the impact of this limitation and ensure the reliability of

our conclusions. Future studies with larger cohorts are needed to validate our findings further.

Although our findings demonstrated statistically significant associations, their clinical significance should also be considered. The association of diabetes and CIS with IVR aligns with previous studies and suggests that these factors may warrant closer monitoring in clinical practice. However, the lack of a significant association between pyuria and IVR in the overall population indicates that routine assessment of pyuria may not be a strong independent predictor of tumor recurrence in all patients. Further studies with larger sample sizes are needed to establish the clinical utility of these findings. In this regard, future research should focus on integrating clinical, metabolic, and molecular biomarkers to refine recurrence risk stratification in NMIBC. The observed interaction between pyuria and proteinuria in predicting IVR warrants further exploration, particularly through prospective multicenter trials and mechanistic studies examining inflammatory pathways. Moreover, incorporating liquid biopsy techniques and next-generation sequencing could provide deeper insights into tumor biology and treatment response.

5.1. Conclusions

Our study revealed that diabetes, CIS, and younger age were the only independent prognostic factors for IVR. Moreover, our study found no statistically significant association between pyuria, bacteriuria, and smoking with bladder tumor recurrence. However, our analyses demonstrated that pyuria emerged as a statistically significant predictive factor for IVR only among individuals without pre-instillation proteinuria.

Footnotes

Authors' Contribution: Conception and design of the study: S. O. M.; Collecting and analyzing and interpretation of the data, drafting and critical revision: S. O. M., I. M. O., E. A., M. H., M. R. N., A. K., and S. A. M.; All authors have approved the final manuscript.

Conflict of Interests Statement: The authors declare no conflict of interests.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: All procedures performed in this study were in accordance and the work was accepted by

the Tehran University of Medical Sciences Ethics Committee ([IR.TUMS.VCR.REC.1398.738](https://doi.org/10.1001/jama.2020.17598))

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References

1. Lenis AT, Lec PM, Chamie K, Mshs MD. Bladder Cancer. *Jama*. 2020;**324**(19). <https://doi.org/10.1001/jama.2020.17598>.
2. Richters A, Aben KKH, Kiemeny L. The global burden of urinary bladder cancer: an update. *World J Urol*. 2020;**38**(8):1895-904. [PubMed ID: 31676912]. [PubMed Central ID: PMC7363726]. <https://doi.org/10.1007/s00345-019-02984-4>.
3. Zi H, He SH, Leng XY, Xu XF, Huang Q, Weng H, et al. Global, regional, and national burden of kidney, bladder, and prostate cancers and their attributable risk factors, 1990-2019. *Mil Med Res*. 2021;**8**(1):60. [PubMed ID: 34819142]. [PubMed Central ID: PMC8611255]. <https://doi.org/10.1186/s40779-021-00354-z>.
4. Kamat AM, Hahn NM, Efstathiou JA, Lerner SP, Malmstrom PU, Choi W, et al. Bladder cancer. *Lancet*. 2016;**388**(10061):2796-810. [PubMed ID: 27345655]. [https://doi.org/10.1016/S0140-6736\(16\)30512-8](https://doi.org/10.1016/S0140-6736(16)30512-8).
5. Taylor J, Becher E, Steinberg GD. Update on the guideline of guidelines: non-muscle-invasive bladder cancer. *BJU Int*. 2020;**125**(2):197-205. [PubMed ID: 31597003]. <https://doi.org/10.1111/bju.14915>.
6. Packiam VT, Johnson SC, Steinberg GD. Non-muscle-invasive bladder cancer: Intravesical treatments beyond Bacille Calmette-Guerin. *Cancer*. 2017;**123**(3):390-400. [PubMed ID: 28112819]. <https://doi.org/10.1002/cncr.30392>.
7. Kamat AM, Colombel M, Sundi D, Lamm D, Boehle A, Brausi M, et al. BCG-unresponsive non-muscle-invasive bladder cancer: recommendations from the IBCG. *Nat Rev Urol*. 2017;**14**(4):244-55. [PubMed ID: 28248951]. <https://doi.org/10.1038/nrurol.2017.16>.
8. Ferro M, Barone B, Crocetto F, Lucarelli G, Busetto GM, Del Giudice F, et al. Predictive clinico-pathological factors to identify BCG, unresponsive patients, after re-resection for T1 high grade non-muscle invasive bladder cancer. *Urol Oncol*. 2022;**40**(11):490 e13-20. [PubMed ID: 35676172]. <https://doi.org/10.1016/j.urolonc.2022.05.016>.
9. Gakis G. The role of inflammation in bladder cancer. *Adv Exp Med Biol*. 2014;**816**:183-96. [PubMed ID: 24818724]. https://doi.org/10.1007/978-3-0348-0837-8_8.
10. Redelman-Sidi G, Glickman MS, Bochner BH. The mechanism of action of BCG therapy for bladder cancer—a current perspective. *Nat Rev Urol*. 2014;**11**(3):153-62. [PubMed ID: 24492433]. <https://doi.org/10.1038/nrurol.2014.15>.
11. Fukushima H, Kobayashi M, Kawano K, Morimoto S. Effect of Preoperative Bacteriuria and Pyuria on Intravesical Recurrence in Patients with Upper Tract Urothelial Carcinoma Undergoing Radical Nephroureterectomy. *In Vivo*. 2017;**31**(6). <https://doi.org/10.21873/invivo.11193>.
12. Azuma T, Nagase Y, Oshi M. Pyuria predicts poor prognosis in patients with non-muscle-invasive bladder cancer. *Clin Genitourin Cancer*. 2013;**11**(3):331-6. [PubMed ID: 23664207]. <https://doi.org/10.1016/j.clgc.2013.04.002>.
13. Satake N, Ohno Y, Nakashima J, Ohori M, Tachibana M. Prognostic value of preoperative pyuria in patients with non-muscle-invasive bladder cancer. *Int J Urol*. 2015;**22**(7):645-9. [PubMed ID: 25912166]. <https://doi.org/10.1111/iju.12788>.
14. Herr H, Donat SM. Commentary: Does Asymptomatic Bacteriuria Reduce the Risk of Recurrence of Non-muscle-invasive Bladder Tumors? *Urology*. 2016;**98**:1-3. [PubMed ID: 27496297]. <https://doi.org/10.1016/j.urology.2016.07.033>.
15. Nicolle LE. Asymptomatic bacteriuria in the elderly. *Infect Dis Clin North Am*. 1997;**11**(3):647-62. [PubMed ID: 9378928]. [https://doi.org/10.1016/S0891-5520\(05\)70378-0](https://doi.org/10.1016/S0891-5520(05)70378-0).
16. Yuge K, Kikuchi E, Matsumoto K, Takeda T, Miyajima A, Oya M. Could patient age influence tumor recurrence rate in non-muscle-invasive bladder cancer patients treated with BCG immunotherapy? *Jpn J Clin Oncol*. 2011;**41**(4):565-70. [PubMed ID: 21233106]. <https://doi.org/10.1093/jcco/hyq241>.
17. Goodwin JS, Samet JM, Key CR, Humble C, Kutvirt D, Hunt C. Stage at diagnosis of cancer varies with the age of the patient. *J Am Geriatr Soc*. 1986;**34**(1):20-6. [PubMed ID: 3941240]. <https://doi.org/10.1111/j.1532-5415.1986.tb06335.x>.
18. Herr HW. Age and outcome of superficial bladder cancer treated with bacille Calmette-Guerin therapy. *Urology*. 2007;**70**(1):65-8. [PubMed ID: 17656210]. <https://doi.org/10.1016/j.urology.2007.03.024>.
19. Inoue T, Miyake M, Nishimura N, Onozawa M, Kashima S, Numakura K, et al. Association of Increased Age With Decreased Response to Intravesical Instillation of Bacille Calmette-Guerin in Patients With High-Risk Non-Muscle Invasive Bladder Cancer: Retrospective Multi-Institute Results From the Japanese Urological Oncology Research Group JUOG-UC-1901-BCG. *Urology*. 2022;**167**:158-64. [PubMed ID: 35700751]. <https://doi.org/10.1016/j.urology.2022.05.034>.
20. Joudi FN, Smith BJ, O'Donnell MA, Konety BR. The impact of age on the response of patients with superficial bladder cancer to intravesical immunotherapy. *J Urol*. 2006;**175**(5):1634-9. discussion 1639-40. [PubMed ID: 16600718]. [https://doi.org/10.1016/S0022-5347\(05\)00973-0](https://doi.org/10.1016/S0022-5347(05)00973-0).
21. Tseng CH, Chong CK, Tseng CP, Chan TT. Age-related risk of mortality from bladder cancer in diabetic patients: a 12-year follow-up of a national cohort in Taiwan. *Ann Med*. 2009;**41**(5):371-9. [PubMed ID: 19191082]. <https://doi.org/10.1080/07853890902729778>.
22. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. *Am J Epidemiol*. 2004;**159**(12):1160-7. [PubMed ID: 15191933]. <https://doi.org/10.1093/aje/kwh161>.
23. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. *Diabetes Care*. 2010;**33**(7):1674-85. [PubMed ID: 20587728]. [PubMed Central ID: PMC2890380]. <https://doi.org/10.2337/dc10-0666>.
24. Larsson SC, Orsini N, Brisman K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia*. 2006;**49**(12):2819-23. [PubMed ID: 17021919]. <https://doi.org/10.1007/s00125-006-0468-0>.
25. Chen Y, Wu F, Saito E, Lin Y, Song M, Luu HN, et al. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia Cohort Consortium. *Diabetologia*. 2017;**60**(6):1022-32. [PubMed ID: 28265721]. [PubMed Central ID: PMC5632944]. <https://doi.org/10.1007/s00125-017-4229-z>.
26. Cresswell J. Diabetes mellitus and non-muscle-invasive bladder cancer: not just a coincidence? *BJU Int*. 2013;**112**(8):1055-6. [PubMed ID: 24283997]. <https://doi.org/10.1111/bju.12491>.
27. Ryu TY, Park J, Scherer PE. Hyperglycemia as a risk factor for cancer progression. *Diabetes Metab J*. 2014;**38**(5):330-6. [PubMed ID: 25349819]. [PubMed Central ID: PMC4209346]. <https://doi.org/10.4093/dmj.2014.38.5.330>.

28. Li W, Zhang X, Sang H, Zhou Y, Shang C, Wang Y, et al. Effects of hyperglycemia on the progression of tumor diseases. *J Exp Clin Cancer Res.* 2019;**38**(1):327. [PubMed ID: 31337431]. [PubMed Central ID: PMC6651927]. <https://doi.org/10.1186/s13046-019-1309-6>.
29. Lu CC, Chu PY, Hsia SM, Wu CH, Tung YT, Yen GC. Insulin induction instigates cell proliferation and metastasis in human colorectal cancer cells. *Int J Oncol.* 2017;**50**(2):736-44. [PubMed ID: 28101572]. <https://doi.org/10.3892/ijo.2017.3844>.
30. Ahn JH, Jung SI, Yim SU, Kim SW, Hwang EC, Kwon DD. Impact of Glycemic Control and Metformin Use on the Recurrence and Progression of Non-Muscle Invasive Bladder Cancer in Patients with Diabetes Mellitus. *J Korean Med Sci.* 2016;**31**(9):1464-71. [PubMed ID: 27510392]. [PubMed Central ID: PMC4974190]. <https://doi.org/10.3346/jkms.2016.31.9.1464>.
31. Hwang EC, Kim YJ, Hwang IS, Hwang JE, Jung SI, Kwon DD, et al. Impact of diabetes mellitus on recurrence and progression in patients with non-muscle invasive bladder carcinoma: a retrospective cohort study. *Int J Urol.* 2011;**18**(11):769-76. [PubMed ID: 21914000]. <https://doi.org/10.1111/j.1442-2042.2011.02845.x>.
32. Rieken M, Xylinas E, Kluth L, Crivelli JJ, Chrystal J, Faison T, et al. Association of diabetes mellitus and metformin use with oncological outcomes of patients with non-muscle-invasive bladder cancer. *BJU Int.* 2013;**112**(8):1105-12. [PubMed ID: 24053906]. <https://doi.org/10.1111/bju.12448>.
33. Xu Y, Huo R, Chen X, Yu X. Diabetes mellitus and the risk of bladder cancer: A PRISMA-compliant meta-analysis of cohort studies. *Medicine (Baltimore).* 2017;**96**(46): e8588. [PubMed ID: 29145273]. [PubMed Central ID: PMC5704818]. <https://doi.org/10.1097/MD.00000000000008588>.
34. Mirabal JR, Taylor JA, Lerner SP. CIS of the Bladder: Significance and Implications for Therapy. *Bladder Cancer.* 2019;**5**(3):193-204. <https://doi.org/10.3233/blc-190236>.
35. Drejer D, Beji S, Oezeki R, Nielsen AM, Hoyer S, Bjerklund Johansen TE, et al. Comparison of White Light, Photodynamic Diagnosis, and Narrow-band Imaging in Detection of Carcinoma In Situ or Flat Dysplasia at Transurethral Resection of the Bladder: the DaBlaCa-8 Study. *Urology.* 2017;**102**:38-42. [PubMed ID: 27894979]. <https://doi.org/10.1016/j.urology.2016.11.032>.
36. Shariat SF, Palapattu GS, Karakiewicz PI, Rogers CG, Vazina A, Bastian PJ, et al. Concomitant carcinoma in situ is a feature of aggressive disease in patients with organ-confined TCC at radical cystectomy. *Eur Urol.* 2007;**51**(1):52-60. [PubMed ID: 17011114]. <https://doi.org/10.1016/j.eururo.2006.08.037>.
37. Sazuka T, Sakamoto S, Imamura Y, Nakamura K, Yamamoto S, Arai T, et al. Relationship between post-void residual urine volume, preoperative pyuria and intravesical recurrence after transurethral resection of bladder carcinoma. *Int J Urol.* 2020;**27**(11):1024-30. [PubMed ID: 32875619]. <https://doi.org/10.1111/iju.14352>.
38. Jimenez DG, Sobti A, Askmyr D, Sakellariou C, Santos SC, Swoboda S, et al. Tonsillar Cancer with High CD8(+) T-Cell Infiltration Features Increased Levels of Dendritic Cells and Transcriptional Regulation Associated with an Inflamed Tumor Microenvironment. *Cancers (Basel).* 2021;**13**(21). [PubMed ID: 34771506]. [PubMed Central ID: PMC8582523]. <https://doi.org/10.3390/cancers13215341>.
39. Zhang XW, Wald A, Salzmann M, Halama N, Hassel JC. Cytokine alterations during paraneoplastic neutrophilia and leukemoid reaction in patients with advanced melanoma. *Cancer Immunol Immunother.* 2023;**72**(2):509-13. [PubMed ID: 35841421]. [PubMed Central ID: PMC9870824]. <https://doi.org/10.1007/s00262-022-03249-7>.
40. Markowski AR, Markowska AJ, Ustymowicz W, Pryczynicz A, Guzinska-Ustymowicz K. Simultaneous analysis of tumor-infiltrating immune cells density, tumor budding status, and presence of lymphoid follicles in CRC tissue. *Sci Rep.* 2022;**12**(1):21732. [PubMed ID: 36526699]. [PubMed Central ID: PMC9758132]. <https://doi.org/10.1038/s41598-022-26225-8>.
41. Devi-Marulkar P, Fastenackels S, Karapentiantz P, Goc J, Germain C, Kaplon H, et al. Regulatory T cells infiltrate the tumor-induced tertiary lymphoid structures and are associated with poor clinical outcome in NSCLC. *Commun Biol.* 2022;**5**(1):1416. [PubMed ID: 36566320]. [PubMed Central ID: PMC9789959]. <https://doi.org/10.1038/s42003-022-04356-y>.
42. Tsukamoto R, Sazuka T, Hattori Y, Sato H, Arai T, Goto Y, et al. Relationship between Preoperative Pyuria and Bacille Calmette-Guerin Treatment in Intravesical Recurrence after Transurethral Resection of High-Risk, Non-Muscle Invasive, Bladder Carcinoma: A Retrospective Study of Human Data. *Cancers (Basel).* 2023;**15**(6). [PubMed ID: 36980524]. [PubMed Central ID: PMC10046501]. <https://doi.org/10.3390/cancers15061638>.
43. Poletajew S, Gajewska D, Kaczmarek K, Krajewski W, Lykowski M, Sondka-Migdalska J, et al. Preoperative pyuria predicts the presence of high-grade bladder carcinoma in patients with bladder tumors. *Cent European J Urol.* 2020;**73**(4):423-36. [PubMed ID: 33552566]. [PubMed Central ID: PMC7848834]. <https://doi.org/10.5173/cej.2020.0289>.
44. Babjuk M, Burger M, Capoun O, Cohen D, Comperat EM, Dominguez Escrig JL, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ). *Eur Urol.* 2022;**81**(1):75-94. [PubMed ID: 34511303]. <https://doi.org/10.1016/j.eururo.2021.08.010>.
45. Suh J, Yuk HD, Jeong CW, Kwak C, Kim HH, Ku JH. Pyuria as a Predictive Marker of Bacillus Calmette-Guerin Unresponsiveness in Non-Muscle Invasive Bladder Cancer. *J Clin Med.* 2021;**10**(17). [PubMed ID: 34501211]. [PubMed Central ID: PMC8432248]. <https://doi.org/10.3390/jcm10173764>.
46. Milojevic B, Dzamic Z, Bojanic N, Durutovic O, Janicic A, Kajmakovic B, et al. Urothelial carcinoma of the upper urinary tract: preoperative pyuria is not correlated with bladder cancer recurrence and survival. *Int Urol Nephrol.* 2019;**51**(5):831-8. [PubMed ID: 30937606]. <https://doi.org/10.1007/s11255-019-02133-1>.
47. Satoh A, Hanawa Y, Nakamura S. Clinical study of bladder cancer: Proteinuria as a predictor of recurrence and efficacy of intravesical bacille Calmette-Guerin therapy. *Int J Urol.* 2004;**11**(7):476-82. [PubMed ID: 15242355]. <https://doi.org/10.1111/j.1442-2042.2004.00847.x>.
48. Malmstrom PU, Larsson A, Johansson S. Urinary fibronectin in diagnosis and follow-up of patients with urinary bladder cancer. *Br J Urol.* 1993;**72**(3):307-10. [PubMed ID: 8220992]. <https://doi.org/10.1111/j.1464-410x.1993.tb00723.x>.
49. Hou L, Hong X, Dai M, Chen P, Zhao H, Wei Q, et al. Association of smoking status with prognosis in bladder cancer: A meta-analysis. *Oncotarget.* 2017;**8**(1):1278-89. [PubMed ID: 27902481]. [PubMed Central ID: PMC5352054]. <https://doi.org/10.18632/oncotarget.13606>.
50. Slusarczyk A, Zapala P, Zapala L, Radziszewski P. The impact of smoking on recurrence and progression of non-muscle invasive bladder cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol.* 2023;**149**(6):2673-91. [PubMed ID: 36404390]. [PubMed Central ID: PMC10129946]. <https://doi.org/10.1007/s00432-022-04464-6>.
51. Tzimenatos L, Mahajan P, Dayan PS, Vitale M, Linakis JG, Blumberg S, et al. Accuracy of the Urinalysis for Urinary Tract Infections in Febrile Infants 60 Days and Younger. *Pediatrics.* 2018;**141**(2). [PubMed ID: 29339564]. [PubMed Central ID: PMC5810602]. <https://doi.org/10.1542/peds.2017-3068>.