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Incidence, Risk Factors, and Clinical Outcomes of BCG-Related Complications

BCG ile İlgili Komplikasyonların Görülme Sıklığı, Risk Faktörleri ve Klinik Sonuçları

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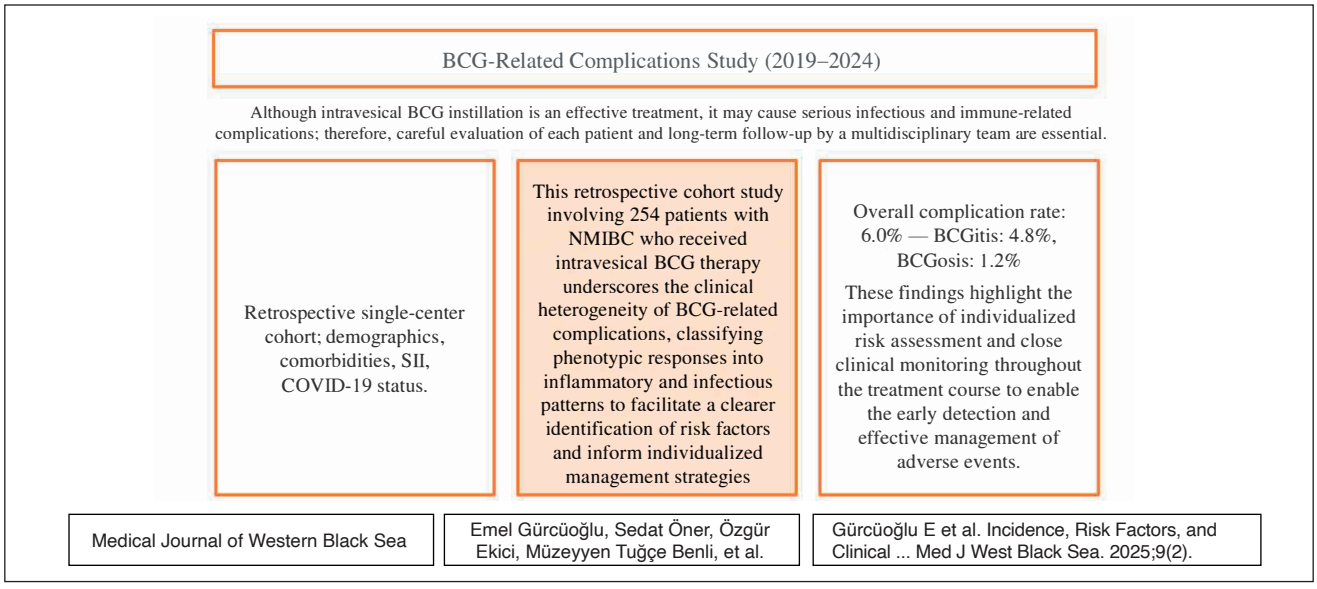
GRAPHICAL ABSTRACT



ABSTRACT

Aim: While intravesical Bacillus Calmette-Guérin (BCG) therapy provides successful outcomes in the treatment of non-muscle-invasive bladder cancer (NMIBC) due to its immunomodulatory effects, it can also lead to serious complications that may pose a life-threatening risk, albeit rarely. This study aimed to analyze the frequency, types, and clinical course of complications arising in patients who underwent intravesical BCG therapy in a tertiary healthcare center between 2019 and 2024. Additionally, findings that may contribute to the early recognition of these complications were examined. The obtained data are expected to aid in the effective management of BCG instillation-related complications and enhance patient safety.

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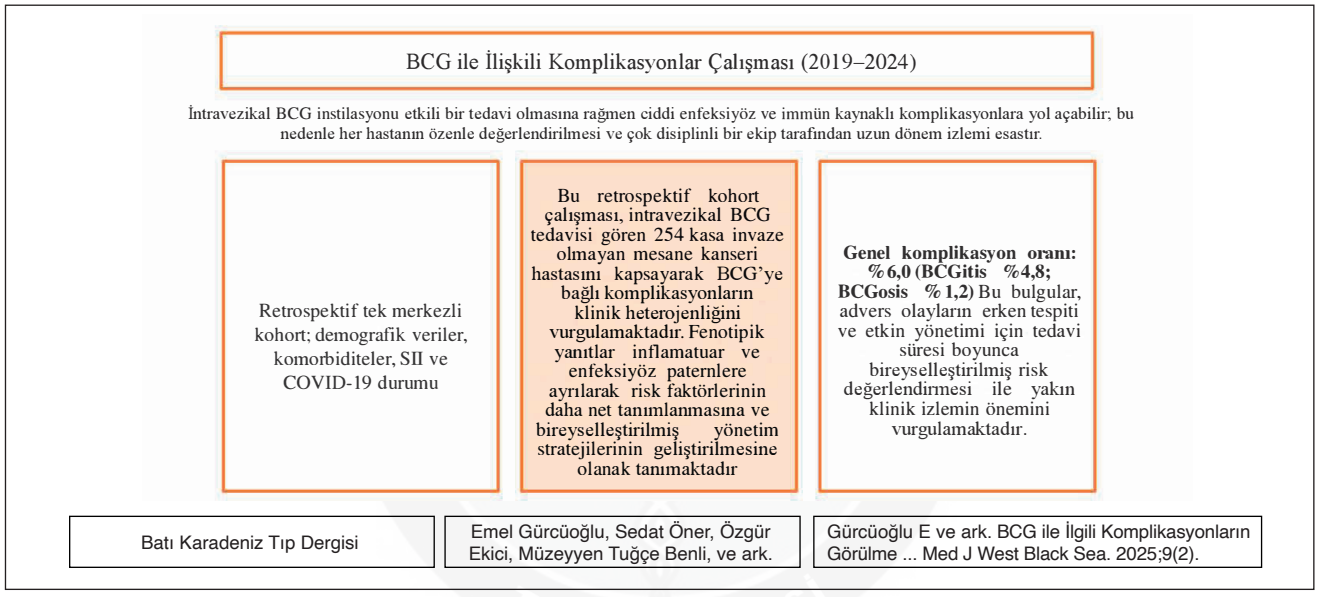
Material and Methods: A total of 400 patients who underwent intravesical BCG therapy were evaluated for complications using the hospital information management system. One hundred forty-six patients were excluded due to missing clinical/laboratory data or follow-ups conducted outside the center. The remaining 254 patients were assessed for demographic characteristics, comorbidities, smoking habits, Systemic Immune-Inflammation Index (SII), COVID-19 infection status, and complications related to BCG instillation.

Results: The mean age of the patients was 66.2±9.7 years, and 225 (90%) were male. BCG-related complications were observed in 15 patients (6.0%). Primary disease relapse occurred in 87 patients (34.8%), and 30 patients (12.0%) died. The incidence of BCG-related complications was significantly higher in patients under 65 years of age compared to those aged 65 and older (12.0% vs. 2.5%; p=0.002). Patients without any comorbidities (p=0.022) and those without diabetes (p=0.005) had a statistically significant higher risk of developing BCG-related complications.

Conclusion: This study highlights the challenges in managing complications associated with intravesical BCG therapy and underscores the importance of comprehensive patient monitoring to prevent adverse outcomes.

Keywords: Bacillus Calmette-Guérin, Bladder Neoplasms, Complications, Systemic Immune-Inflammation Index

GRAFİKSEL ÖZET



ÖZ

Amaç: Kasa invaze olmayan mesane kanseri (KİOMK) tedavisinde intravezikal BCG (Bacillus Calmette-Guérin) uygulaması immünmodülatör etkileri sayesinde başarılı sonuçlar sağlarken, nadir de olsa hasta hayatını tehlikeye atabilecek ciddi komplikasyonlara yol açabilmektedir. Bu çalışmada 2019-2024 yılları arasında üçüncü basamak bir sağlık kuruluşunda intravezikal BCG uygulanan hastalarda ortaya çıkan komplikasyonların sıklığı, türleri ve klinik seyirleri irdelenerek, komplikasyonların erken tanınmasına yararı olabilecek bulgular incelendi. Elde edilen verilerin, BCG instilasyonuna bağlı gelişen komplikasyonların etkin yönetimine ve hasta güvenliğinin artırılmasına katkı sağlaması amaçlandı.

Gereç ve Yöntemler: Hastane bilgi yönetim sisteminden, intravezikal BCG uygulanan toplam 400 hasta komplikasyonları açısından incelendi. Eksik klinik/laboratuvar verisi olan ya da takipleri merkez dışında sürdülen 146 hasta çalışma dışı bırakıldı. İkiyüzellidört hasta, demografik özellikler, yandaş hastalıklar, sigara alışkanlıkları, sistemik İmmün-İnflamatuvar İndeks (Systemic Immune-Inflammation Index, SII), COVID-19 enfeksiyon durumları ve BCG instilasyonu ile ilişkili gelişen komplikasyonlar incelendi.

Bulgular: Hastaların yaş ortalaması 66,2±9,7 idi ve 225'i (%90) erkekti. Hastaların 15'inde (%6,0) BCG işlemi ile ilişkili komplikasyon gelişmişti. Hastaların 87'sinde (%34,8) primer hastalık relapsı görülmüştü. Genel mortalite %12,0 olarak saptanırken, KİOMK veya BCG ilişkili komplikasyonlara bağlı mortalite yalnızca bir hastada (%0,4) görülmüştür. 65 yaş altındaki hastalarda BCG işlemi ile ilişkili komplikasyon gelişme oranı 65 yaş ve üzeri olanlara göre anlamlı yüksek bulundu (%12,0 vs. %2,5; p=0,002). Herhangi bir komorbiditesi olmayanlarda (p=0,022), diyabeti olmayanlarda (p=0,005) BCG işlemi ile ilişkili komplikasyon gelişme riski istatistiksel olarak anlamlı yüksekti.

Sonuç: Bu çalışma, intravesikal BCG tedavisiyle ilişkili komplikasyonların yönetimindeki zorlukları vurgulamakta ve olumsuz sonuçların önlenmesi için kapsamlı hasta takibinin önemine dikkat çekmektedir.

Anahtar Sözcükler: Bacillus Calmette-Guérin (BCG), Mesane Neoplazileri, KİOMK, Komplikasyonlar, Sistemik İmmün-İnflamasyon İndeksi

INTRODUCTION

Non-muscle-invasive bladder cancer (NMIBC) ranks among the most prevalent urothelial malignancies worldwide. Although carcinoma in situ (CIS) is classified within this category because it spares the detrusor muscle, it frequently displays a more aggressive biological course than other papillary tumours. In patients with intermediate- and high-risk NMIBC, intravesical Bacillus Calmette-Guérin (BCG) therapy administered after transurethral resection of the bladder tumour (TUR-B) affords superior protection against tumour recurrence compared with TUR-B alone or intravesical chemotherapy. The standard BCG regimen comprises a six-week induction phase, followed by a maintenance schedule of three weekly instillations delivered at months 3, 6, 12, 18, 24, 30 and 36 (1,2).

Following BCG instillation, the attenuated bacillus directly interacts with tumor cells in the affected tissue, triggering apoptosis, necrosis, cytotoxicity, and oxidative stress mechanisms. This process leads to immune system activation, initiating an inflammatory response and activating various inflammatory pathways. The activation of these pathways can result in a broad spectrum of complications, ranging from mild local reactions to severe systemic infections. Understanding the risk factors for potential complications is crucial for improving clinical outcomes (3,4).

Accordingly, this retrospective study of a large cohort treated with intravesical BCG instillation between 2019 and 2024 aims to characterise the incidence, phenotypic distribution, risk determinants and clinical outcomes of BCG-related complications; to quantify the potential predictive value of the systemic immune-inflammation index (SII); and to examine the impact of the COVID-19 pandemic on patient follow-up and complication rates. Derived from real-world data in a tuberculosis-endemic tertiary centre and spanning the pandemic period, the present analysis offers a modest yet pertinent contribution to the evidence base that guides risk-adapted surveillance after BCG therapy.

MATERIALS and METHODS

Study Design and Population

This retrospective cohort study was conducted at Bursa City Hospital, a tertiary healthcare institution with a 1,500-bed capacity. The study included patients diagnosed with non-muscle-invasive bladder cancer (NMIBC) who underwent intravesical BCG therapy between 2019 and 2024.

A total of 400 patients were initially assessed. However, cases with secondary bacterial septicemia, severe organ infections, incomplete clinical or laboratory data, or patients whose follow-ups were conducted outside our institution were excluded from the study. Ultimately, 254 patients were included in the final analysis.

Data retrieved from medical records included age, sex, smoking habits, comorbidities, immune status (chronic corticosteroid use or immunosuppressive therapy), and systemic immune-inflammation index (SII) values calculated before the first and after the final instillation. All patients received commercially available BCG products in full doses, with no modified dose applications. Given the overlap with the COVID-19 pandemic, patients' history of COVID-19 infection and its potential association with complications were also evaluated.

Management of BCG-Related Complications

In cases of complications following BCG instillation, diagnostic and therapeutic protocols were implemented in accordance with urology guidelines (5). Management strategies varied depending on the timing and severity of complications, ranging from supportive agents such as non-steroidal anti-inflammatory drugs (NSAIDs) to antibiotic therapy. For patients requiring empirical antibiotic treatment due to severe complications, subsequent BCG instillations were postponed.

A retrospective evaluation of these cases revealed that patients exhibited distinct clinical characteristics and clustered into different phenotypic profiles. Therefore, to perform a more detailed analysis of risk factors and clinical monitoring of patients who developed infection or inflammation, cases were categorized based on the severity of clinical symptoms into mild/moderate and severe inflammatory responses (BCG-itis) or systemic and organ-involved BCG-related infections (BCG-osis).

Ethical Considerations

This study was conducted with approval from the institutional ethics committee, and patient confidentiality was strictly maintained.

Statistical Analysis

Sample size calculation was performed using G-Power software (version 3.1.9.6, Franz Faul, Universität Kiel, Germany). With an effect size of 0.3, a Type I error rate of 0.05, and a power of 0.95, the minimum required sample size was determined to be 220.

All statistical analyses were performed using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data were presented as mean ± standard deviation for numerical variables and as frequency (n) and percentage (%) for categorical variables. Comparisons between categorical variables were conducted using the Chi-Square test. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Differences between groups for non-normally distributed continuous variables were analyzed using the Mann-Whitney U test for two groups. Correlations between continuous variables were evaluated using

Pearson correlation analysis, while Spearman correlation analysis was used for ordinal variables. Results were assessed at a 95% confidence interval, and **p<0.05** was considered statistically significant. Bonferroni correction was applied where necessary.

RESULTS

Baseline demographic characteristics are summarised in Table 1. The patient population consisted of 254 individuals (mean age 66.2 ± 9.7 years), 225 of whom (90%) were male; 63.2% were aged ≥ 65 years. Nearly half of the patients (48.4%) commenced intravesical BCG therapy after the peak of the COVID-19 pandemic. At least one chronic comorbidity was documented in 82% of participants, the most common being coronary artery disease (50.0%) and diabetes mellitus (41.6%). BCG-related adverse events—hereafter referred to collectively as BCG-itis/osis—were documented in 15 patients (6.0%): 12 (4.8%) developed mild-to-severe BCG-itis and three (1.2%) disseminated infection (BCG-osis). Tumour recurrence occurred in 87 patients (34.8%), overall (all-cause) mortality was 12.0% (30/254), whereas disease-specific mortality attributable to NMIBC or BCG-related complications occurred in only one patient (0.4%). Median baseline and post-treatment systemic immune-inflammation index (SII) values were 864.8 ± 673.2 and 976.4 ± 1282.6, respectively. Complications were significantly more frequent in patients < 65 years than in those ≥ 65 years (12.0% vs 2.5%; p = 0.002), in individuals without comorbidity (p = 0.022) or without diabetes (p = 0.005), and in those treated after rather than during the pandemic (10.1% vs 2.4%; p = 0.011). No significant association was found between complication risk and sex, tumour recurrence, immunosuppression, a documented history of COVID-19, or overall survival (Table 3).

Neither the baseline nor the post-treatment SII proved to be a reliable early-warning biomarker for BCG-itis/osis (Table 4); however, the second SII value correlated weakly but significantly with the total number of complications (r = 0.184; p = 0.009).

To illustrate the clinical heterogeneity of BCG-related complications, five representative cases are summarised below:

1-Fulminant BCG-osis A 71-year-old man with hypertension and coronary artery disease developed sepsis ≈ 2 weeks after the third instillation; *Mycobacterium tuberculosis* complex grew from a tracheal aspirate. Despite broad-spectrum antibiotics and quadruple anti-TB therapy, multiorgan failure ensued and the patient died on day 20-25.

2-Severe serositis (BCG-itis) A 68-year-old man without comorbidity presented 6 weeks after his last instillation with pleuro-pericardial effusion and markedly elevated inflammatory markers; all cultures were negative. Prednisolone 1 mg kg^{-1} (plus supportive NSAID/quinolone) achieved full clinical and laboratory remission by month fifth.

Table 1: Distribution of the patients in terms of some variables.

	n	%
Total	250	(100)
Gender		
Male	225	(90.0)
Female	25	(10.0)
Age		
<65	92	(36.8)
65+	158	(63.2)
Pandemics period		
Before & during pandemics	127	(51.6)
After pandemics	119	(48.4)
Comorbidity	205	(82.0)
Coronary artery disease	125	(50.0)
Diabetes mellitus	104	(41.6)
Chronic obstructive pulmonary disease	47	(18.8)
Immunological suppression	39	(15.6)
Neurological disease	18	(7.2)
Chronic kidney failure	18	(7.2)
Secondary malign disease	11	(4.4)
Alzheimer	1	(0.4)
COVID-19	33	(13.2)
Smoking	97	(74.6)
Complication (BCG)	15	(6.0)
BCGitis total	12	(4.8)
BCGitis mild	3	(1.2)
BCGitis moderate	5	(2.0)
BCGitis severe	4	(1.6)
BCGosis	3	(1.2)
Complete urinary test		
<100	145	(58.0)
>100	105	(42.0)
Relapses		
0	163	(65.2)
1	72	(28.8)
2	15	(6.0)
All-cause mortality (Exitus)	30	(12.0)
NMIBC/BCG-related mortality	1	(0.4)

BCG: Bacillus Calmette-Guérin, **BCGitis:** Inflammatory reaction due to BCG instillation, **BCGosis:** Disseminated infection due to BCG instillation, **COVID-19:** Coronavirus Disease 2019, **COPD:** Chronic obstructive pulmonary disease, **NMIBC:** Non-muscle-invasive bladder cancer

Table 2: The mean values of some continuous variables.

	Mean	SD	Minimum	Maximum
Age (years)	66.2	9.7	33	92
Number of BCG complication	0.3	1.3	0	11
Number of BCG applied	5.3	3.3	1	16
Years passed after operation	3.1	1.7	1	8
Years passed after BCG	2.9	1.8	1	6
PNL first (/μL)	5821.9	2644.4	2210	20800
Plathelet (/μL)	250.0	75.8	111	644
Lymphocyte (/μL)	1998.9	822.6	320	5950
SII first	864.8	673.2	139.3	5519.5
Neutrophil (/μL)	5461.9	2741.5	2100	19630
Plathelet (/μL)	261.5	83.8	23	587
Lymphocyte (/μL)	1979.3	824.5	132	4700
SII second	976.4	1282.6	106.0	11903.8
Relapse	0.4	0.6	0	2

SD: Standard deviation, **PNL:** Polymorphonuclear leukocyte, **BCG:** Bacillus Calmette-Guérin, **SII:** Systemic immune-inflammation index.

Table 3: Comparison of the rates of patients with BCG complications according to some variables.

		Complication (BCG)				Total	p
		None		Present			
		n	%	n	%	n	
Gender	Male	211	(93.8)	14	(6.2)	225	0.657
	Female	24	(96.0)	1	(4)	25	
Age (years)	<65	81	(88.0)	11	(12)	92	**0.002**
	65+	154	(97.5)	4	(2.5)	158	
Comorbidity	None	39	(86.7)	6	(13.3)	45	**0.022**
	Present	196	(95.6)	9	(4.4)	205	
Diabetes mellitus	None	132	(90.4)	14	(9.6)	146	**0.005**
	Present	103	(99.0)	1	(1)	104	
Coronary artery disease	None	117	(93.6)	8	(6.4)	125	0.79
	Present	118	(94.4)	7	(5.6)	125	
COPD	None	189	(93.1)	14	(6.9)	203	0.215
	Present	46	(97.9)	1	(2.1)	47	
COVID-19	None	204	(94.0)	13	(6)	217	0.987
	Present	31	(93.9)	2	(6.1)	33	
Pandemics period	Before & during pandemics (2019-2022)	124	(97.6)	3	(2.4)	127	**0.011**
	After pandemics (2023-2024)	107	(89.9)	12	(10.1)	119	
Smoking	None	30	(90.9)	3	(9.1)	33	0.57
	Present	91	(93.8)	6	(6.2)	97	
Complete urinary test	<100	138	(95.2)	7	(4.8)	145	0.359
	>100	97	(92.4)	8	(7.6)	105	
Relapse	0	150	(92.0)	13	(8)	163	0.146
	1	71	(98.6)	1	(1.4)	72	
	2	14	(93.3)	1	(6.7)	15	
Exitus	None	207	(94.1)	13	(5.9)	220	0.87
	Present	28	(93.3)	2	(6.7)	30	

Chi-Square test is used. **BCG:** Bacillus Calmette-Guérin, **COVID-19:** Coronavirus Disease 2019, **COPD:** Chronic obstructive pulmonary disease.

Table 4. Comparison of mean values of some variables according to groups with and without BCG complications.

	Complication of BCG										
	None					Present					p
	Mean	SD	Med.	Q1	Q3	Mean	SD	Med.	Q1	Q3	
Age (years)	66.4	9.6	68.0	60	73	62.1	11.0	63.0	59	67	0.090
Number of BCG applied	5.2	3.3	5.0	2	7	5.6	2.6	5.0	3.5	7	0.500
Years passed after operation	3.2	1.7	3.0	2	5	2.4	1.5	2.0	1	3	0.073
Years passed after BCG	**3.0**	**1.7**	3.0	1	4.5	2.1	1.9	1.0	1	2	**0.038**
Relapse	0.4	0.6	0.0	0	1	0.2	0.6	0.0	0	0	0.099
Lab findings											
Neutrophil first (/μL)	5733.1	2578.2	5020.0	4140	6877.5	7172.0	3319.3	6650.0	5350	7905	**0.032**
Neutrophil second (/μL)	5343.8	2617.7	4690.0	3800	5930	7490.9	3993.0	7340.0	4455	10855	0.105
p (between 1st & 2nd values)	.105					.859					
Plathelet first (/μL)	**250.8**	76.9	238.5	199	289.8	239.1	59.1	223.0	195.5	260	0.572
Plathelet second (/μL)	263.2	83.4	255.0	215	309	231.8	89.2	257.0	212.5	266.5	0.489
p (between 1st & 2nd values)	**.008**					0.374					
Lymphocyte first (/μL)	1991.7	831.6	1870.0	1400	2460	2109.3	685.1	2130.0	1725	2535	0.409
Lymphocyte second (/μL)	2008.1	811.3	1960.0	1430	2540	1484.7	932.3	1630.0	590	2340	0.121
p (between 1st & 2nd values)	.767					.091					
SII first	862.1	679.8	670.3	469.1	1057.3	906.5	582.1	723.3	550	1152.7	0.542
SII second	894.3	1000.6	596.5	425.9	938.8	2380.4	3398.7	1241.0	439.7	2280.2	0.100
p (between 1st & 2nd values)	.731					.374					

Mann-Whitney U test is used. **SD:** Standard deviation, **Med.:** Median, **Q1:** First quartile (25th percentile), **Q3:** Third quartile (75th percentile), **BCG:** Bacillus Calmette-Guérin, **SII:** Systemic immune-inflammation index.

Table 5: Correlation analyses.

		Age (years)	Number of BCG complication	Years passed after operation	Years passed after BCG	Complete urinary test	SII first (/μL)	SII second
Age (years)	**r**					0.184	0.159	0.061
	p					**0.003**	**0.013**	0.392
Number of BCG complication	**r**	-0.081				0.065	0.030	0.184
	p	0.204				0.307	0.638	**0.009**
Years passed after operation	**r**	0.018	-0.060			-0.050	-0.159	-0.131
	p	0.791	0.372			0.465	**0.019**	0.086
Years passed after BCG	**r**	0.090	-0.103	0.890		-0.101	-0.071	-0.043
	p	0.160	0.108	**<0.001**		0.113	0.276	0.547
Relapse	**r**	0.025	-0.077	0.450	0.299	-0.025	-0.002	0.013
	p	0.700	0.223	**<0.001**	**<0.001**	0.696	0.978	0.851

BCG: Bacillus Calmette-Guérin, **SII:** Systemic immune-inflammation index.

3-Early delayed-type hypersensitivity In a healthy 59-year-old man, high fever, hypotension and dyspnoea emerged within hours of the first instillation. Cultures remained sterile; high-dose intravenous methylprednisolone followed by a tapering course led to complete recovery, with no sequelae at 7-month follow-up.

4,5-Cases 4 and 5 - Late Vertebral BCG-osis (Pott Disease):Two men aged 74 and 76 years, each with COPD and coronary artery disease, developed thoracic or lumbar vertebral destruction 9 and 20 months after their final maintenance instillation. Biopsy confirmed *M. tuberculosis complex* by PCR. Surgical debridement/stabilisation combined with a 12-month HRZE regimen prevented neurological deficit in both cases.

Table 6. Comparison of the rates of patients with BCGitis according to some variables.

		BCGitis				Total	p
		None		Present			
		n	%	n	%	n	
Gender	Male	214	(95.1)	11	(4.9)	225	.844
	Female	24	(96.0)	1	(4.0)	25	
Age (years)	<65	84	(91.3)	8	(8.7)	92	**.028**
	65+	154	(97.5)	4	(2.5)	158	
Comorbidity	None	40	(88.9)	5	(11.1)	45	**.029**
	Present	198	(96.6)	7	(3.4)	205	
Diabetes mellitus	None	135	(92.5)	11	(7.5)	146	**.017**
	Present	103	(99.0)	1	(1.0)	104	
Coronary artery disease	None	118	(94.4)	7	(5.6)	125	.554
	Present	120	(96.0)	5	(4.0)	125	
COPD	None	192	(94.6)	11	(5.4)	203	.342
	Present	46	(97.9)	1	(2.1)	47	
COVID-19	None	207	(95.4)	10	(4.6)	217	.716
	Present	31	(93.9)	2	(6.1)	33	
Pandemics period	Before & during pandemics (2019-2022)	124	(97.6)	3	(2.4)	127	.058
	After pandemics (2023-2024)	110	(92.4)	9	(7.6)	119	
Smoking	None	31	(93.9)	2	(6.1)	33	.643
	Present	93	(95.9)	4	(4.1)	97	
Complete urinary test	<100	139	(95.9)	6	(4.1)	145	.565
	>100	99	(94.3)	6	(5.7)	105	
Relapse	0	153	(93.9)	10	(6.1)	163	.275
	1	71	(98.6)	1	(1.4)	72	
	2	14	(93.3)	1	(6.7)	15	
Exitus	None	209	(95.0)	11	(5.0)	220	.689
	Present	29	(96.7)	1	(3.3)	30	

Mann-Whitney U test is used. **BCG:** Bacillus Calmette-Guérin, **BCGitis:** Inflammatory reaction due to BCG instillation, **COVID-19:** Coronavirus Disease 2019, **COPD:** Chronic obstructive pulmonary disease.

In the sub-analysis restricted to the 12 BCG-itis patients, complication rates remained significantly higher in those < 65 years (p = 0.028), without comorbidities (p = 0.029) and without diabetes (p = 0.017). Pandemic period, sex, tumour recurrence and overall survival did not influence BCG-itis incidence (all p > 0.05) (Table 6).

DISCUSSION

Intravesical administration of Bacillus Calmette-Guérin (BCG) serves as an adjuvant immunotherapeutic strategy following surgical resection for non-muscle-invasive bladder cancer (NMIBC); by inducing a Th1-mediated cellular immune response within the bladder wall, it aims to prevent tumor recurrence and progression, yet it may also precipitate serious infectious and immune-mediated complications (1,5).

Within hours to days of instillation, patients can develop systemic inflammation—manifested as high fever, chills, and malaise—which in more severe cases, particularly after traumatic catheterization, may progress to granulomatous pneumonia or hepatitis (6) Mechanistically, BCG invasion of the urothelium triggers pro-inflammatory cytokine cascades that polarize $CD4^+$ T cells toward a Th1 phenotype and amplify IFN-γ production, thereby enhancing the antitumor functions of macrophages and $CD8^+$ T cells. Under physiological regulation, this response remains localized; however, dysregulated activation of the NF-κB pathway can convert it into a systemic, cytokine-storm-like syndrome (7).

Although two patients presented with similar baseline parameters, their clinical courses diverged markedly. In a patient over 65 years old with hypertension and coronary artery disease, fulminant BCG-sepsis developed approxi-

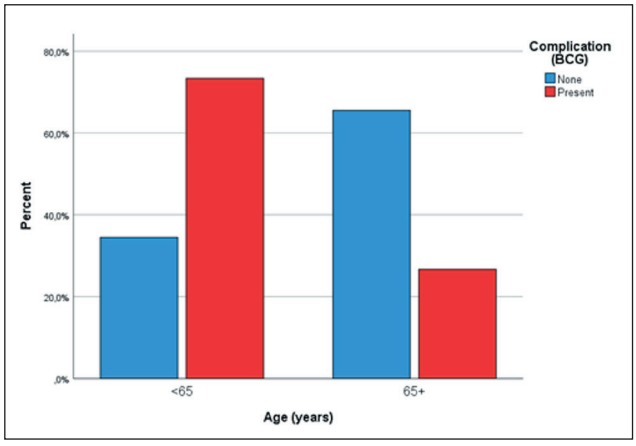


Figure 1: Comparison of the complication rates in terms of age groups.

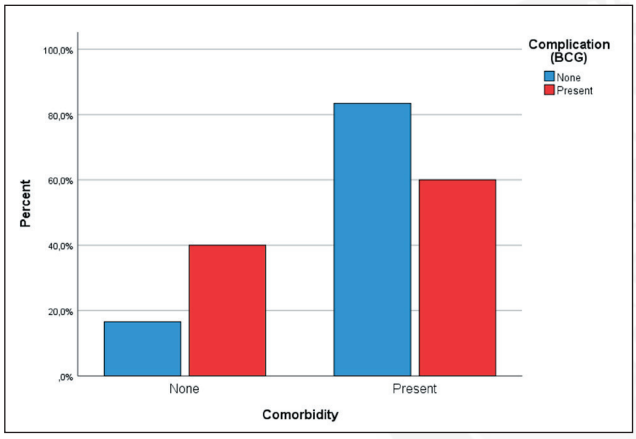


Figure 2: Comparison of the complication rates in terms of presence or absence of comorbidity.

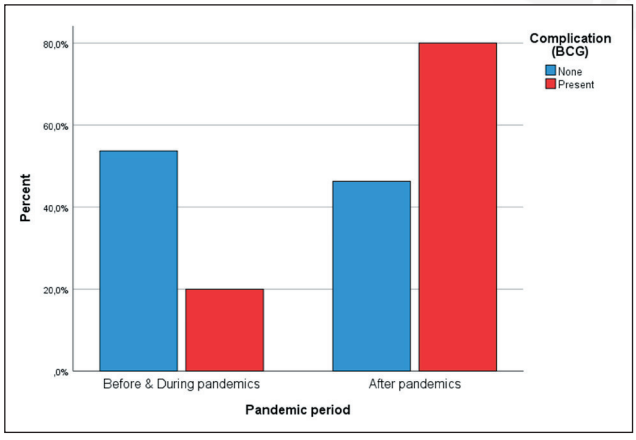


Figure 3: Comparison of the complication rates in terms of pandemic-related periods.

mately two weeks after the third instillation and rapidly progressed to multiorgan failure. Conversely, a patient under 65 without any systemic comorbidity experienced a severe hypersensitivity reaction within hours of the first instillation, which resolved without sequelae following high-dose corticosteroid therapy. Furthermore, two older patients with comorbidities subsequently developed vertebral involvement (Pott's disease), underscoring how distinct host immune-response mechanisms dictate the trajectory of BCG-related complications.

Genetic predisposition, insufficient immunoregulation, and exaggerated pro-inflammatory cytokine release elevate the risk of inflammatory complications in young, otherwise healthy patients; we postulate that a robust host immune response in this subgroup drives cytokine production to pathological levels, thereby accentuating inflammatory sequelae. By contrast, advanced age and comorbidities—particularly diabetes-associated chronic hyperglycemia—have been shown to impair macrophage phagocytic function, suppress IL-1β and IL-6 production, skew the immune response toward IL-10 dominance, and attenuate mast cell activation (4,8). This immunological shift appears to mitigate the incidence of complications driven by excessive immune reactivity. However, this altered immune profile—while dampening Th1-mediated cytokine responses—may facilitate BCG persistence within the bladder mucosa and predispose to late disseminated BCG-osis (8).

Such duality complicates differentiation between cytokine storm and true sepsis, highlighting the pressing need for reliable early biomarkers of BCG-induced complications. In our evaluation of the Systemic Immune-Inflammation Index (SII), neither baseline nor induction-phase values served as effective early indicators; nevertheless, modest post-treatment elevations correlated with complication frequency. Defining validated post-treatment SII thresholds and embedding them into a risk-adapted surveillance protocol—where exceeding the established cutoff prompts intensified clinical and imaging follow-up—could enable SII to function as a robust early-warning system for impending BCG-related complications.(9,10).

During the COVID-19 pandemic, we found no discernible correlation between SII-measured cytokine release and complication rates. This likely reflects both the relatively small number of pandemic-era complication cases and healthcare system constraints that hindered early detection. Consequently, identifying biomarkers capable of forecasting the transition from localized inflammation to systemic cytokine storm at an early stage is of paramount importance. Although ferritin, IL-6, and tryptase possess recognized diagnostic potential in early sepsis and in distinguishing hypersensitivity reactions their validity for early and differential diagnosis of BCG-related complications remains unestablished (3,11).

Therefore, prospective studies are needed to evaluate these biomarkers—alongside primary immunomodulation strategies such as low-dose corticosteroid administration—to elucidate their clinical effects within the context of BCG therapy.

Our study's retrospective design, limited sample size, and pandemic-specific follow-up challenges constitute its primary limitations; nevertheless, the data provide valuable insights into the heterogeneous clinical spectrum of BCG-related complications. Future research should focus on establishing risk-adapted surveillance protocols and translating defined biomarkers into clinical practice to strengthen the management of infectious and inflammatory sequelae. Multicenter prospective trials will be essential for standardizing treatment algorithms, thereby improving patient safety and clinical outcomes through timely recognition, appropriate intervention, and avoidance of unnecessary therapies

Conclusion

Intravesical BCG instillation remains an effective immunotherapeutic modality for non-muscle-invasive bladder cancer; however, it is associated with significant infectious and immune-mediated adverse events. To reduce morbidity and mortality, the integration of close surveillance with advanced diagnostic techniques is essential. Findings from case series offer valuable insights into pathogenesis, prognostic biomarkers, and management strategies, and may also guide the development of monitoring frameworks and biomarkers capable of predicting the trajectory and outcomes of immune-related reactions in other immunotherapy settings. Therefore, prospective, multicenter trials are warranted to comprehensively address these critical issues.

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Author Contributions

Emel Gürcüoğlu: Conceptualization, study design, data analysis, manuscript writing. **Sedat Öner & Özgür Ekici:** Patient recruitment, clinical data collection, urological perspectives. **Müzeyyen Tuğçe Benli:** Data interpretation. **Tülay Bulut:** Tuberculosis-related insights

Conflicts of Interest

The authors declare that there is no conflict of interest.

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Ethical Approval

Ethical approval for this study was obtained from the Ethics Committee of Bursa City Hospital (Approval No: 2025-2/2, Date: January 22, 2025).

Review Process

Extremely and externally peer-reviewed.

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