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ORIGINAL RESEARCH

Healthcare Resource Utilization and Cost Burden of BCG-Treated Non-Muscle Invasive Bladder Cancer Patients in Germany: A Retrospective Claims Analysis

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Background: Intermediate and high-risk non-muscle-invasive bladder cancer (NMIBC) is typically managed with transurethral resection of the bladder tumour (TURBT) followed by intravesical Bacillus Calmette–Guérin (BCG) immunotherapy; however, NMIBC patients can become refractory or unresponsive to BCG treatment, and/or progress to muscle-invasive bladder cancer (MIBC). Healthcare resource utilization (HCRU) and costs in these patient populations are high.

Methods: A retrospective longitudinal cohort design of adult (≥18 years) patients with bladder cancer and BCG treatment (01/01/2012–31/12/2017) was conducted using data from a representative subset of the German statutory health insurance database. During the follow-up period after last BCG, patients were categorized into subgroups of *No further NMIBC treatment, Continuous treatment for NMIBC*, or *MIBC evidence*; HCRU and costs were tabulated for each subgroup and for the entire cohort.

Results: A total of 1049 patients met the study inclusion criteria (mean age, 70.9 years; 84.8% male). Across the different subgroups, patients showing *MIBC evidence* had more than two times higher hospitalization rates compared to the other subgroups. Overall, the entire BCG-treated cohort's total direct medical cost including hospitalizations, outpatient care and drugs was €33.9 million and €9250 per patient-year. Cost for patients with *MIBC evidence* was much higher, at €17,983 per patient-year, than patients with *No further NMIBC treatment* (€6617) and patients with *Continuous treatment for NMIBC* (€7786). Across the subgroups, hospitalization was the largest driver of cost and contributed the most to cost for those with *MIBC evidence*.

Conclusion: The overall cost burden of this BCG-treated cohort of 1049 patients is high (€38 million whereof 4.1 million are indirect costs) over a mean follow-up of 3.9 years; economic burden is especially substantial for patients who fail BCG treatment and those who progress.

Keywords: urinary bladder neoplasm, retrospective study, healthcare cost, intravesical instillation, healthcare resource

Plain Language Summary

Bladder cancer (BC) is the most frequently occurring malignancy of the urinary tract, including muscle-invasive BC (MIBC) and non-muscle-invasive BC (NMIBC). Despite the high clinical burden that BC presents, bladder-preserving treatment options for NMIBC are limited, especially for patients for whom intravesical Bacillus Calmette–Guérin (BCG) immunotherapy failed. Due to the need for continuous surveillance, BC has one of the highest lifetime cancer treatment costs, which increases with the severity of the disease. This study describes healthcare resource utilization and cost burden in BCG-treated NMIBC patients in Germany and confirms the cost of managing patients with NMIBC after BCG instillation is substantial, with patients who progress to MIBC after BCG having the highest cost. The overall cost burden (mainly driven by hospital cost) of the BCG-treated cohort of 1049 patients studied here was €38 million over a mean follow-up of 3.9 years.

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Introduction

Bladder cancer (BC) is the most frequently occurring malignancy of the urinary tract.[1] The main symptom of BC is haematuria, and the disease is diagnosed by a cystoscopy, and biopsy confirmed by a transurethral resection of the bladder tumour (TURBT).[2,3] BC can be divided into muscle-invasive (MIBC) and non-muscle-invasive (NMIBC).[4] NMIBC (Ta, T1 and carcinoma in situ [CIS]) accounts for 70–75% of the cases of BC. In MIBC, the tumour has invaded deeper layers of the bladder wall or formed metastases.[1,3,5,6]

BC is more prevalent in developed countries, among elderly, and roughly four times more common in men.[1,2,7] In Germany, the 2018 age standardized incidence was 15.7 per 100,000 persons and was increasing (annual incidence change in women 1.99%, men 1.27%).[2,8] Although mortality in European countries appears to be decreasing, possibly due to increased awareness and earlier detection, incidence is projected to rise for countries such as Germany, which has an aging population and high rates of smoking.[1,2,8]

Treatment options for NMIBC are limited, and treatment guideline adherence is reportedly low.[9,10] NMIBC guidelines from the European Association of Urology (EAU), the National Comprehensive Cancer Network (NCCN), and the German S3 Guidelines recommend instillation of chemotherapy following TURBT for low-risk NMIBC and intravesical Bacillus Calmette–Guérin (BCG) immunotherapy for intermediate or high-risk NMIBC.[3,11,12]

In up to 50% of NMIBC cases, patients become refractory or unresponsive to BCG treatment.[10,13] Radical cystectomy is the mainstay option for these patients, however there is no current optimal treatment option for patients who are unable or unwilling to undergo radical cystectomy.[1] The EAU guidelines recommend a clinical trial or "bladder-preserving strategies" for these BCG-unresponsive patients.[3] Potential new treatment options under study for patients failing BCG therapy include novel chemotherapy and drugs such as vaccines, augmented BCG immunotherapy, adenoviral and gene therapy, and combination systemic immunotherapy with intravesical agents.[10,14]

Due to the need for surveillance, BC has one of the highest lifetime cancer treatment costs.[15–17] A study conducted a decade ago estimated the total healthcare costs for BC in Europe to be €2.9 billion in 2012 (€3.8 billion in 2022 value).[18] Including indirect costs, cost increased to €4.9 billion (2012). In Germany, the cost was €610 million (informal care €170 million), some of the highest reported in Europe. Inpatient care was the primary driver of cost (58% of the total cost); primary care and outpatient care were also large drivers of cost.[18]

In NMIBC, healthcare costs and resource use are higher in patients with high-risk diseases.[19] Costs are also substantial for patients with high-intensity treatment, which is associated with increased healthcare resource utilization (HCRU) due to disease surveillance, follow-up physician visits, and intravesical treatment.[19] Disease progression to MIBC is also a key driver of cost.[19]

Up-to-date data on HCRU and cost reflecting a European treatment practice for BCG-treated patients is limited. Studies have identified clinical practice gaps and non-adherence to EAU and AUA guidelines in the treatment of intermediate- and high-risk NMIBC.[9,20,21] The objective of this study is to describe the HCRU and costs during and after BCG treatment in NMIBC patients, over the period 2012–2019 in Germany.

Materials and Methods

Data Source

This study used administrative claims from 1/1/2010 to 31/12/2019, extracted from a subset of the German statutory health insurance (GKV-Spitzenverband, *Gesetzliche Krankenversicherung*) database. This subset includes data for approximately 5 million insured persons from different sickness funds and presents good representativeness in terms of age/sex distribution and geography versus total GKV.[22] The anonymized data set includes detailed prescription, sickness record, inpatient hospitalization, outpatient treatment, special services, and registration/deregistration (including due to death) data.

Study Design

This was a retrospective longitudinal cohort design of adult (≥18 years) patients with a first diagnosis of BC (International Classification of Diseases 10th Revision [ICD-10] code C67* and/or CIS D09.0) between 1/1/2012 and 31/12/2017, who initiated treatment with BCG bladder instillation for the first time between 01/01/2012 and 31/12/2017.

This allowed a minimum of 2-year baseline period prior to index date during which patients' characteristics were described. Patients with metastases (ICD-10 codes C77*, C78*, C79*, C80*) or cancers to the liver (C22*), lung (C34*), and bone (C40*, C41*) at baseline were excluded. The index date was the dispensing date that BCG instillation was initiated. Intravesical BCG was identified by using Anatomical Therapeutic Chemical (ATC) codes and Pharma-Zentral-Nummer (PZN) codes, used in Germany to identify medications and their packaging information. Follow-up time was from index date to end of the study (31/12/2019), or an earlier date if the patient had died or was lost to follow-up.

Disease status after last BCG administration was defined based on subsequent records: *No further NMIBC treatment, Continuous treatment for NMIBC, MIBC evidence. Continuous treatment for NMIBC* – possibly indicating a recurrence – was defined as presence of an intravesical instillation of an agent other than BCG (ie, mitomycin C, epirubicin, gemcitabine or doxorubicin). *MIBC evidence*, including progression to MIBC/metastatic disease, was defined as radiotherapy, systemic antineoplastic agent, metastasis diagnosis, procedure (surgical excision or lesion destruction procedures to organs proximal to the bladder or lymph nodes), or death within 6 months of last BCG. As radical cystectomy is recommended for both BCG-unresponsive NMIBC and MIBC, this procedure was not used for outcome subgroup categorization.

Healthcare Resource Utilization

HCRU data were captured for the following categories: inpatient care (overnight stays and day cases); outpatient care; medication used; and sick leave. Procedures related to BC treatment were also captured separately: systemic treatment; intravesical treatment; radiotherapy; and surgery (TURBT and cystectomy). HCRU was presented for the entire cohort and per each outcome subgroup category, per patient and per patient-year.

Cost

Total cost and cost for each HCRU category and sickness leave were computed based on the actual costs reimbursed in euros during the study period. Costs were presented for the entire cohort and for each subgroup, per patient and per patient-year.

Statistical Analysis

Patient demographic and clinical characteristics were summarized using percentages for categorical variables, and mean, median, interquartile range (IQR), and standard deviation (SD) for continuous variables. Means were computed among patients with at least one record. Outliers were included in description as part of presenting ranges and IQR. Results were presented for the entire cohort and each post-BCG outcome subgroup category: 1) Patients with *No further NMIBC treatment* were followed up from date of last BCG to end of follow-up; 2) Patients with *Continuous treatment for NMIBC* were followed up from first evidence of intravesical instillation of an agent other than BCG to end of follow-up, death, date of MIBC evidence, or date of radical cystectomy, whichever occurs first; and 3) Patients with *MIBC evidence* were followed up from MIBC evidence to end of follow-up.

Results

A total of 1049 patients met the inclusion criteria (Figure 1). The mean age of the overall cohort was 70.9 years at BCG initiation, and on average the time between first BC diagnosis evidence and BCG initiation was 6 months. Most of the cohort were males and the most common baseline comorbidity was urinary tract infection (Table 1). The mean number of TURBTs was 2.2, which could include either a confirmatory TURBT and/or recurrence of a tumour. Patients had many comorbidities, as reflected by the high mean Charlson comorbidity index.

The mean (SD) and median (IQR) follow-up times for the cohort were 3.9 (1.7) and 3.5 (2.6, 4.9) years, respectively. Overall, patients received a mean of 13.1 (7.1) BCG instillations over a mean duration of 13.6 (12.8) months. This includes any re-challenge with BCG within a two-year period. After last BCG, 603 patients (57.5%) did not receive further BC treatment (including cystectomy) nor presented MIBC evidence during the remaining follow-up period; 115 patients (10.9%) showed continuous treatment for NMIBC (as potential evidence of NMIBC recurrence); 316 patients (30.1%) presented MIBC evidence; and 145 patients had cystectomy (13.8%) (Figure S1).

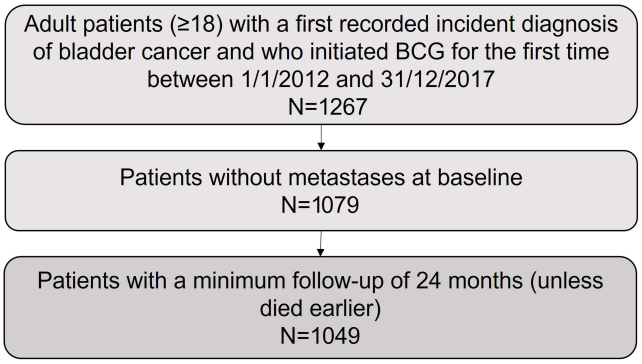

Figure 1 Patient selection chart.
Abbreviation: BCG, Bacillus Calmette–Guérin.

Healthcare Resource Utilization

HCRU results are presented in Table 2. For the main cohort, most patients had at least one hospitalization (including 89.2% patients with at least an overnight stay and 27.4% with at least one-day case admission). The mean (SD) number

Table 1 Baseline Characteristics

Number of patients initiating BCG, N		1049
Age at first recorded BC diagnosis, years – Mean (SD)		70.4 (10.1)
Age at first BCG instillation, years – Mean (SD)		70.9 (10.1)
Gender, Male – n (%)		890 (84.8)
Number of TURBTs prior to first BCG instillation – Mean (SD)		2.2 (1.2)
Comorbidities,[a] n (%)		
Viral infection		324 (30.9)
Urinary tract infection		758 (72.3)
Diabetes mellitus		241 (23.0)
Mild liver disease		299 (28.5)
History of malignancy[b] of other organs than the bladder		382 (36.42)
Renal diseases (or renal failure)		291 (27.7)
Congestive heart failure		298 (28.4)
Coronary artery disease		181 (17.3)
Chronic pulmonary disease		479 (45.7)
Peripheral vascular disease		419 (39.9)
Cerebrovascular disease		347 (33.1)
Charlson Comorbidity Index		
Mean (SD)		4.5 (2.8)
Score, n (%)	3–4	287 (27.4)
	≥5	486 (46.3)

Notes: [a]Comorbidities are not mutually exclusive. [b]History of malignancy excluding C67*, D09.0, C68, basal cell carcinoma, squamous cell carcinoma of the skin, leukaemia, lymphoma, and multiple myeloma.
Abbreviations: BC, bladder cancer; BCG, Bacillus Calmette–Guérin; SD, standard deviation; TURBT, transurethral resection of the bladder tumour.

Table 2 Healthcare Resource Utilization Among BCG-Treated Bladder Cancer Patients

	All BCG Treatment Recipients (Main Cohort)	Outcome Subgroup Category[†]		
		No Further NMIBC Treatment	Continuous Treatment for NMIBC	MIBC Evidence
Number of patients, N	1049	603	115	316
Mean (SD) follow-up duration, years	3.9 (1.7)	3.9 (1.5)	4.5 (1.8)	3.8 (2)
Number of patients who died, n (%)	222 (21.2)	63 (10.4)	22 (19.1)	139 (44.0%
Hospital admissions – All (overnight stays and/or day cases)				
Number of patients with a hospital admission, n (%)	947 (90.3)	392 (65.0)	92 (80.0)	256 (81.0)
Total number of hospital admissions, N	5905	1549	336	1524
Mean per patient* (SD)	6.2 (6.2)	4.0 (3.9)	3.7 (3.2)	6.0 (5.8)
Hospital admission rate, per 100 patient-year	145.25	103.09	103.19	257.19
Hospital admissions (overnight stays)				
Number of patients with an overnight hospital admission, n (%)	936 (89.2)	375 (62.2)	90 (78.3)	254 (80.4)
Total number of overnight hospital admissions, N	4845	1284	281	1266
Mean per patient* (SD)	5.2 (4.4)	3.4 (3.0)	3.1 (2.6)	5.0 (4.7)
Overnight hospital admission rate, per 100 patient-year	119.17	85.45	86.30	213.65
Cumulative duration of overnight hospital stays, days				
Mean per patient (SD)	50.0 (78.7)	30.1 (37.0)	30.0 (40.1)	68.3 (110.0)
Hospital admissions (day cases)				
Number of patients with a day case hospital admission, n (%)	287 (27.4)	99 (16.4)	25 (21.7)	83 (26.3)
Total number of day case hospital admissions, N	1060	265	55	258
Mean per patient* (SD)	3.7 (5.5)	2.7 (3.4)	2.2 (2.3)	3.1 (3.9)
Day case hospital admission rate, per 100 patient-year	26.07	17.64	16.89	43.54
Hospitalizations with bladder cancer-related[a] procedures (overnight stays and/or day cases)				
Number of patients with a hospital admission, n (%)	687 (65.5)	173 (28.7)	44 (38.3)	113 (35.8)
Number of TURBTs, N	1384			

(*Continued*)

Table 2 (Continued).

	All BCG Treatment Recipients (Main Cohort)	Outcome Subgroup Category[†]		
		No Further NMIBC Treatment	Continuous Treatment for NMIBC	MIBC Evidence
Number of patients with at least 1 TURBT during BCG, n (%)	382 (36.4)			
Mean (SD) number of TURBTs per patient*	1.6 (1.0)			
Number of patients with at least 1 TURBT after BCG, n (%)	454 (43.3%)	173 (28.7%)	43 (37.4%)	59 (18.7%)
Mean (SD) number of TURBTs per patient*	1.7 (1.4)	1.7 (1.5)	1.7 (1.1)	1.3 (0.6)
Outpatient care records				
Number of patients with an outpatient care record, n (%)	1049 (100.0)	603 (100.0)	115 (100.0)	288 (91.1)
Total number of outpatient care records, N	132,821	40,964	11,257	21,755
Mean per patient* (SD)	126.6 (75.0)	67.9 (57.2)	97.9 (106.7)	75.5 (63.2)
Outpatient care record rate, per 100 patient-year	3267	2726	3457	3671

Notes: *Mean per patient was computed among patients with at least one record. [†]Subgroups non-mutually exclusive. [a]Related to cystectomy or TURBT.
Abbreviations: BCG, Bacillus Calmette–Guérin; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer; SD, standard deviation; TURBT, transurethral resection of the bladder tumour.

of hospital admissions (overnight stay or day case) per patient was 6.2 (6.2) and a rate of 145.3 per 100 patient-year. The mean (SD) and median (IQR) duration of an overnight hospital stay per admission were 9.7 (13.3) and 5.0 (3.0, 9.0) days, respectively. The length of stay per overnight hospital admission ranged from 2 days to 119 days; 46% exceeded a duration of 5 days and the top Diagnosis-Related Groups for these cases were transurethral intervention, bladder surgery, or very severe infection. In the overall cohort, 687 (65.5%) patients had a BC-related procedure during hospitalization, among whom 382 (55.6%) had a TURBT during BCG (mean of 1.6 (1.0) TURBT per patient). All patients in the main cohort had at least one outpatient care record.

Across the outcome subgroup categories, the number of patients with at least one hospitalization (overnight or day case) was the lowest for patients without further BC treatment after BCG nor MIBC evidence. The hospitalization rates (overall, overnight stays and day cases separately) were similar for patients with *No further NMIBC treatment* and patients with *Continuous treatment for NMIBC*; compared with these two subgroups, patients showing *MIBC evidence* had more than twice as high hospitalization rates (Table 2). Mean number of TURBTs per patient after last BCG was lowest for the *MIBC evidence* group (1.3 vs 1.7 for subgroups without MIBC evidence), as they were probably performed prior to the MIBC diagnosis and therefore within a shorter timeframe. Proportion of patients with at least one TURBT was slightly higher (37.4% vs 28.7%) for patients with *Continuous treatment for NMIBC* rather than for those with *No further NMIBC treatment*. Few cystectomies were observed in the group with *Continuous treatment for NMIBC*; there was a total of 72 cystectomies in the *MIBC evidence* group.

Costs

The entire BCG-treated cohort's total direct medical cost including hospitalizations, outpatient care and drugs was €33.9 million. After adding the €3.7 million in social security transfers, the total cost was €37.6 million (Table 3). This translates into an average cost per patient of €35,852 during the 3.9-year follow-up period, or €9250 per patient-year.

Table 3 Healthcare and Sickness Leave Cost for BCG-Treated Bladder Cancer Patients

	All BCG Recipients (Main Cohort) N= 1049			
	Per patient*		Total cost (€), study cohort study period	Cost (€) per person-year (%**)
	Mean (SD)	Median		
Direct medical cost				
Total hospital cost	19,046 (21,913)	12,586	19,979,181	4914 (53.1)
Hospitalization with TURBT[a]	3696 (4784)	2491	3,876,613	954 (10.3)
Overnight stay	18,857 (21,789)	12,466	19,781,513	4866 (52.6)
Hospital day case	188 (603)	NA	197,669	49 (0.5)
Outpatient care cost	5254 (6,123)	4353	5,511,489	1356 (14.7)
Drug cost	8064 (16,710)	4417	8,458,946	2081 (22.5)
Other cost				
Sick leave cost	1099 (5387)	NA	1,153,053	284 (3.1)
Remedies and other benefits[b]	2389 (5822)	463	2,506,106	616 (6.7)
Total cost*	35,852 (34,341)	26,335	37,608,775	9251 (100)
	Outcome subgroup category: *No further NMIBC treatment*[c] N = 603			
	Per patient*		Total cost (€), subcohort study period	Cost (€) per person-year (%**)
	Mean (SD)	Median		
Direct medical cost				
Total hospital cost	8672 (15,292)	2882	5,229,414	3480 (52.6)
Hospitalization with TURBT[a]	1411 (3427)	NA	850,599	566 (8.6)
Overnight stay	8587 (15,233)	2865	5,177,879	3446 (52.1)
Hospital day case	86 (324)	NA	51,535	34 (0.5)
Outpatient care cost	2879 (3497)	2220	1,736,110	1155 (17.5)
Drug cost	3139 (9207)	1473	1,893,063	1260 (19)
Other cost				
Sick leave cost	219 (1834)	NA	131,745	88 (1.3)
Remedies and other benefits[b]	1580 (5027)	62	952,810	634 (9.6)
Total cost*	16,489 (22,725)	7913	9,943,142	6617 (100)
	Outcome subgroup category: *Continuous treatment for NMIBC*[d] N = 115			
	Per patient*		Total cost (€), subcohort, study period	Cost (€) per person-year (%**)
	Mean (SD)	Median		
Direct medical cost				
Total hospital cost	9534 (12,105)	4633	1,096,383	3367 (43.2)
Hospitalization with TURBT[a]	1644 (2752)	NA	189,100	581 (7.5)
Overnight stay	9438 (12,079)	4476	1,085,312	3333 (42.8)
Hospital day case	96 (268)	NA	11,070	34 (0.4)
Outpatient care cost	5057 (15,019)	3078	581,538	1786 (22.9)
Drug cost	5393 (5296)	3690	620,193	1905 (24.5)
Other cost				
Sick leave cost	473 (3267)	NA	54,392	167 (2.1)
Remedies and other benefits[b]	1590 (4945)	104	182,842	562 (7.2)
Total cost*	22,047 (28,029)	14,689	2,535,349	7786 (100)

(*Continued*)

Table 3 (Continued).

	Outcome subgroup category: *MIBC evidence*[e] N = 316			
	Per patient		Total cost (€), subcohort, study period	Cost (€) per person-year (%**)
	Mean (SD)	Median		
Direct medical cost				
Total hospital cost	19,249 (21,820)	13,960	6,082,535	10,265 (57.1)
Hospitalization with TURBT[a]	947 (2363)	NA	299,280	505 (2.8)
Overnight stay	19,075 (21,724)	13,960	6,027,723	10,172 (56.6)
Hospital day case	174 (468)	NA	54,811	92 (0.5)
Outpatient care cost	3215 (3405)	2296	1,015,898	1714 (9.5)
Drug cost	8376 (21,175)	1403	2,646,736	4467 (24.8)
Other cost				
Sick leave cost	773 (4829)	NA	244,329	412 (2.3)
Remedies and other benefits[b]	2109 (5356)	411	666,575	1125 (6.3)
Total cost*	33,722 (36,980)	22,578	10,656,073	17,983 (100)

Notes: *Among all cohort patients; if the patient did not have the corresponding cost, it is recorded as 0. **% = Cost per person-year for each cost component/Cost per person-year for total cost. [a]Hospitalization with an OPS code for transurethral resection of bladder tumour (TURBT). [b]Remedies and other benefits include non-medical or non-drug prescriptions dispensed by pharmacies, preventive care, health promotion activities, cures, rehabilitation, physiotherapies delivered by other health professionals than physicians. [c]Cost time period would be from last BCG date to end of follow-up. [d]Cost time period would be from date of recurrence to end of follow-up or date of MIBC for those who progressed. [e]Cost time period would be from MIBC to end of follow-up.
Abbreviations: BCG, Bacillus Calmette–Guérin; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer; SD, standard deviation; TURBT, transurethral resection of the bladder tumour; NA, non-applicable (median could not be estimated for cost items for which >50% patients had no cost recorded).

For patients with *No further NMIBC treatment* and patients with *Continuous treatment for NMIBC*, the total cost was €6617 and €7786 per patient-year, respectively, while the cost for patients with *MIBC evidence* was much higher, at €17,983 per patient-year. Across all three subgroups, hospitalization was the largest cost driver. Hospital costs comprised almost 60% of the direct costs and expressed a skewed cost distribution with a median of €12,586 and a mean of €19,046 per patient in the main cohort. Patients in the *MIBC evidence* category had a greater share of hospital costs in relation to total costs (57%) than the other two subgroups. Likewise, drug cost in the *MIBC evidence* category was higher than outpatient costs and the second largest driver of cost for this group. In both the *No further NMIBC treatment* group and the *Continuous NMIBC treatment* group, outpatient and drug costs were the next largest drivers of cost, with values (Table 3, Figure 2). For patients undergoing cystectomy, the mean total cost per patient was €21,957 in the first 3 months post cystectomy including peri-surgical complications; the cost per person-year was €10,657 after month 4 of cystectomy.

Discussion

In this study, we estimated the HCRU and costs of NMIBC patients treated with BCG instillation in a real-world German population using claims data from a representative subset of the statutory health insurance. The results show the cost burden of this patient population is high compared to other cancers such as prostate cancer,[18] with overall costs of nearly €38 million for the 1049 patients followed up for a mean of 3.9 years, or an average cost per patient-year of €9251. From a national perspective, assuming an incidence of 2336 BCG-treated patients per year,[23] there is an annual cost impact of €21.6 million for each new cohort of patients, and an overall cost impact of €84.3 million considering a mean follow-up time of 3.9 years.

When examining cost across outcome subgroups, per patient mean costs were highest for the subgroup with *MIBC evidence* (€17,983) while the groups with *No further NMIBC treatment* and *Continuous treatment for NMIBC* had costs that were lower by more than half (€6617 and €7786, respectively). Hospital admission rates were highest for patients who progressed to MIBC, which explains in part the higher overall cost in this group. The *MIBC evidence* group had the highest number of cystectomies, which in a German study of claims data (2011–2016) was identified as an important driver of cost.[6] Hospital cost related to TURBT hospital cost was non-negligible for the NMIBC subgroups, confirming its impact on the

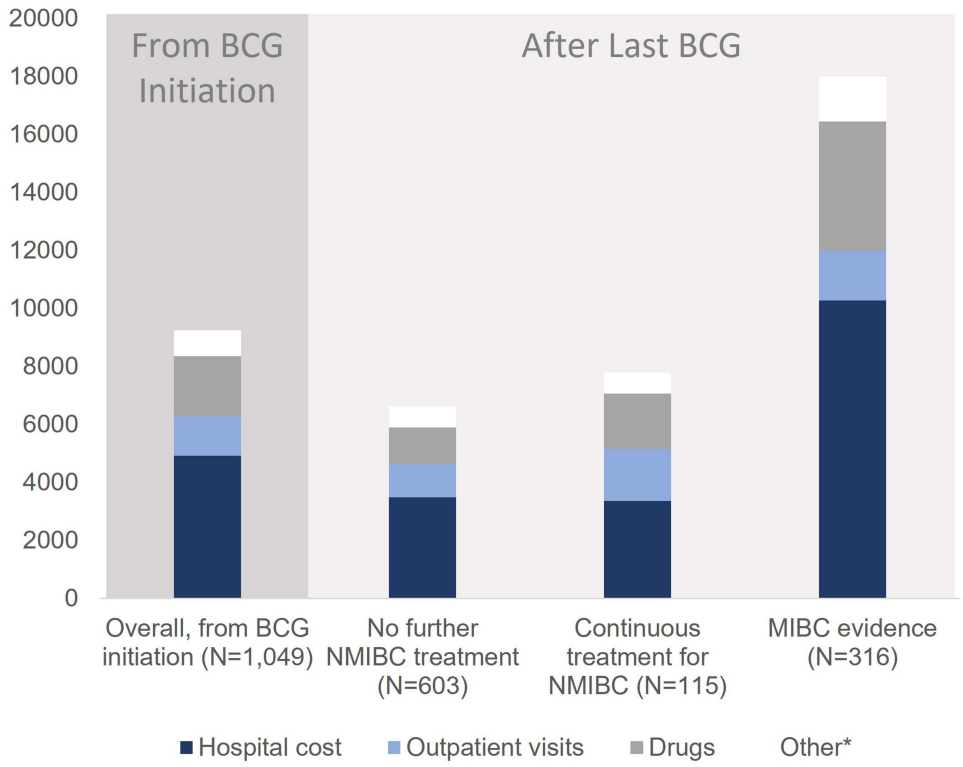

Figure 2 Costs (€) per patient-year, overall and in patient subgroups.
Notes: Hospital cost was mainly driven by overnight stays, including 19%, 16%, 17%, and 5% of the costs accounting for TURBT-related hospitalizations for the overall, no further NMIBC treatment, continuous treatment for NMIBC, and MIBC evidence subgroups, respectively. *Other includes sick leave costs, remedies (i.e., non-medical or non-drug prescriptions dispensed by pharmacies) and other benefits including the reimbursement information related to preventive care, health promotion activities, cures, rehabilitation, physiotherapies delivered by other health professionals than physicians.
Abbreviations: BCG, Bacillus Calmette–Guérin; MIBC, muscle-invasive bladder cancer; NMIBC, non-muscle-invasive bladder cancer.

overall economic burden of NMIBC treatment and follow-up, in addition to its critical impact on the psychological health and quality of life of patients.[24] Drug costs for the MIBC group were also roughly twice the costs for the NMIBC subgroups. Similar findings have been reported in two studies of cost in NMIBC. Mossanen et al reported that the primary cost driver for intermediate- and high-risk NMIBC in a Markov model was progression to MIBC requiring definitive therapy.[25] And a US veteran study showed disease progression was significantly associated with higher costs, largely due to increased outpatient, pharmacy and surgery-related costs.[16] Ultimately, the findings of the current study indicate that timely and effective treatment may reduce the resource use and costs among NMIBC patients if progression to MIBC can be avoided or delayed.

To our knowledge, only one study has examined the real-world costs following BCG treatment among patients with NMIBC. Patients with high-grade NMIBC (2008–2015) in the US SEER-Medicare database who progressed had higher hospitalization admissions and more outpatient/emergency visits; mean annualized costs per patient after BCG were double for patients who progressed (USD $65,668) compared with patients who did not (USD $29,780).[26]

The present study's strengths include the use of recent data from a representative subset of GKV German data; demographic distribution is similar to the general population, and results are generalisable to the German population. However, miscoding or coding delays may have introduced biases in this study. Cancer staging, morphology and grading were unavailable in this data source; hence, the true disease stage was unknown. Finally, this study includes costs reimbursed by the health insurance; indirect and patient-related costs were not included (including those reimbursed by employers or other insurance funds), and the overall humanistic and economic burden of the disease may be higher than estimated in our study.[27]

There is a substantial unmet need for new therapies in NMIBC; over the last 30 years, only three drugs have been approved by the EMA.[28] Although radical cystectomy remains the primary treatment option, there remains an unmet need for patients who are unable or unwilling to undergo surgery after BCG treatment failure.[29,30] Novel and future

treatments under investigation may offer alternatives to surgery and options for patients who have not responded to BCG and may potentially avoid the cost of high-intensity therapy in patients with disease progression.[31] Obviously, due to the cost of such novel gene therapies and immunotherapies, the optimal treatment approach should consider patient selection, efficacy, safety, cost and ease of administration.[32]

Ethics Approval

This study was conducted in accordance with legal and regulatory requirements and followed accepted international research practices described in Guidelines for Good Pharmaceutical Practices issued by the International Society for Pharmacoepidemiology; Good Practices for Outcomes Research; International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences; and the European Medicines Agency, European Network of Centres for Pharmacoepidemiology, and Pharmacovigilance Guide on Methodological Standards in Pharmacoepidemiology. Patient-level data used in this study are anonymized to comply with German data protection regulations, and use of such data for health services research is fully compliant with German Federal Data Protection Act of 30 June 2017, as last amended by Article 10 of the Act of 23 June 2021. Accordingly, Institutional Review Board/ethical approval was not required. Informed consent does not apply to this analysis of de-identified claims data.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

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