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Original Article

Prediction of recurrence risk in patients with non-muscle-invasive bladder cancer

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Abstract *Objective:* Non-muscle-invasive bladder cancer (NMIBC) remains a common challenge in uro-oncology with conflicting reports on recurrence risk. This study aimed to elucidate the recurrence rate of NMIBC in the Cancer Clinic of Shahid Beheshti Hospital in Iran and to investigate related parameters affecting recurrence risk.
Methods: The data of 143 patients with NMIBC, who underwent treatment between January 2017 and January 2020 and were followed up from the initial transurethral resection of bladder tumor until November 30, 2020 in our institution, were retrospectively assessed. The Cox regression analysis and Kaplan–Meier plot of recurrence-free survival were used to determine independent contributing factors for tumor recurrence.
Results: Among patients with NMIBC, 83.9% were male, and 16.1% were female, with a mean age of 64.4 (standard deviation [SD] 12.9) years. During the follow-up, 71 (49.7%) patients showed tumor recurrence, with a mean recurrence time of 11.5 (SD 6.9) months. In the Chi-square test or Fisher's exact test, the age (≥65 years) ($p=0.037$), obesity (body mass index ≥30 kg/m^2) ($p=0.004$), no diabetes mellitus ($p=0.005$), smoking (current or former smoker) ($p=0.001$), immediate perfusion therapy ($p=0.035$), number of tumors (>3) ($p<0.001$), and tumor stage (Ta, T1, and Tis) ($p=0.001$) had independent significant effects on the recurrence of NMIBC. The multivariate Cox regression analysis indicated that preoperative obesity (hazards ratio [HR] 7.90; 95% confidential interval [CI] 4.01–15.55; $p<0.001$), current or former smoking (HR 1.85; 95% CI 1.07–3.20; $p=0.027$), and a high-grade tumor (HR 4.03; 95% CI 1.59–10.25; $p=0.003$) were significant predictors of tumor recurrence. The Kaplan–Meier plot of recurrence-free survival showed that obesity (log-rank $p<0.001$), current or former smoking (log-rank $p=0.001$), and a high-grade tumor (log-rank $p=0.006$) were associated with a shorter time interval until the first tumor recurrence.
Conclusion: The study found a high recurrence rate of NMIBC in Iran from January 2017 to January 2020, with the obesity, smoking history, and the high-grade tumor as contributing factors.

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1. Introduction

Bladder cancer (BCa) is the ninth most common cancer in the world and the seventh most common cancer in men. Every year, nearly 550 000 cases of BCa are diagnosed, and 200 000 deaths occur due to this cancer worldwide [1,2]. The majority of BCa cases (80%) are non-muscle-invasive BCa (NMIBC) and pathological staged as Ta, T1, and carcinoma *in situ* (CIS) in the primary diagnosis [3]. The main treatment option for NMIBC is the transurethral resection of bladder tumor (TURBT) via cystoscopy under anesthesia. The initial TURBT defines the appearance, size, and location of the tumor and facilitates tissue resection for a histopathological assay [4,5]. The second TURBT is commonly recommended in 2—6 weeks after the primary TURBT for improving the pathological accuracy [4].

The probability of NMIBC recurrence remains a challenge [6]. The probability of NMIBC recurrence ranges from 15% to 70% every year [7] and from 31% to 78% in 5 years [8]. A recent review study revealed that the primary management of patients with NMIBC involves risk-adapted treatment, complete removal of all tumors, and routine follow-up for the risk control of a recurrence [9]. The standard treatment for patients with NMIBC is TURBT with intravesical bacillus Calmette—Guerin (BCG) therapy and chemotherapy to reduce the recurrence of disease and facilitate bladder preservation for patients with rapid progression to muscle invasive BCa (MIBC) [9].

There are various nomograms for estimating the risk of a recurrence, each with particular limitations and challenges. Based on the Club Urologico Español de Tratamiento Oncologico nomogram which evaluates patients with NMIBC, BCG plus interferon alfa-2b was administered. The Club Urologico Español de Tratamiento Oncologico nomogram is based on CIS, tumor stage (T category), tumor status, sex, and age [10]. The European Organization for Research and Treatment of Cancer nomogram, which provides a simple scoring system according to CIS, tumor stage (T category), tumor grade, number of tumors, tumor size, and frequency of previous recurrences, does not use sex or age in the scoring model, while it evaluates the tumor size [8].

Multiple studies have reported significant associations between the recurrence of NMIBC and the use of dietary and nutritional supplements, diabetic drugs, statins, and lifestyle factors. However, there are some gaps in previous research. Ferro et al. [11] revealed that statins may have beneficial effects on the recurrence of NMIBC. Moreover, a recent study summarized the literature on the association between lifestyle factors and NMIBC outcomes and found that dietary and nutritional supplements, diabetic drugs, or statins did not affect outcomes of NMIBC [12]. Moreover, demographic characteristics or anthropometric indices of patients are not completely used to stratify the recurrence risk in patients with NMIBC. Some studies have reported that parameters, such as demographic and anthropometric profiles, smoking, and diabetes mellitus, influence the recurrence and progression of disease [13—17]. There are also conflicting reports on the clinical features and recurrence risk prediction of BCa [18—20]. It is potentially important to assess patients with NMIBC based on these factors and to understand their impact on the prediction of recurrence.

2. Patients and methods

A total of 180 patients with BCa, aged 25—95 years old, who underwent treatment between January 2017 and January 2020, were retrospectively assessed in our institution. Patients with secondary bladder tumor or renal cell cancer ($n=19$) , or MIBC patients with tumor stage T2 or higher ($n=6$), as well as patients who were not compliant with the consultant's recommendations or did not return for continued care ($n=12$), were excluded from the study. Therefore, 143 patients were ultimately selected for inclusion in the study. Written informed consents were obtained from all of them.

The primary TURBT was routinely performed for all patients, and the first TURBT pathology was retrospectively recorded. Almost all patients had a biopsy report in their medical records. The initial diagnosis was determined according to the biopsy report. Tumor staging was performed using cystoscopy and histological assessment of tissue obtained via TURBT or multiple bladder biopsies for CIS. The tumors were classified as Ta, T1, and Tis (CIS), according to the European Association of Urology (EAU) guidelines [21]. The tumors were also divided into two categories based on the histological grade, namely, low or high grades [22,23].

The patients' demographic characteristics, body mass index (BMI), history of diabetes mellitus, and smoking status before the primary diagnosis were collected. Additionally, the pathological characteristics, including the tumor stage, tumor grade, tumor number, and tumor size (defined as the largest diameter during cystoscopy) were obtained from their medical records. The patient's cause of death and time of death were also obtained from Iran's Death Registration System. Permission for use information from a database or repository was obtained by our institution. The time until the first tumor recurrence was measured from the date of the initial diagnosis until the date of the first malignant event in the analysis. Patients with benign recurrences were not classified in the recurrence group.

In our institution, the treatment for patients with bladder tumors is based on the EAU NMIBC risk guidelines. Typically, the follow-up of patients with an initial diagnosis of low-grade NMIBC involves TURBT after 3 months and then every year. For patients with high-grade NMIBC, restage TURBT is performed 2—6 weeks after the initial diagnosis

and intravesical chemotherapy or BCG instillations, according to the surgeon's decision and compliance with the medical care conditions of the patients. Patients with high-grade NMIBC were followed-up by cystoscopy every 3 months in the first year, every 6 months in the second year, and then once a year [9].

In the current study, all the patients were followed up from the initial TURBT until November 30, 2020. Twelve patients were also excluded due to loss to the follow-up and non-compliance with the consultant's recommendations. Finally, the complete data of 143 patients were collected in the study. All patients were categorized into two groups (<65 years age group and ≥65 years age group), according to the patient's age in the primary TURBT for pathology.

The smoking status of the patients was categorized as follows: never-smokers, former smokers who quit smoking before the first TURBT, and current regular smokers at the time of the first TURBT. Diabetes mellitus was also assessed in the first admission. Patients who had a diagnosis of diabetes mellitus by a physician and/or had received oral antidiabetic drug treatments, insulin therapy, or nutrition therapy were classified as Type 1 or Type 2 diabetes mellitus. Moreover, the BMI of the patient in the first admission was calculated using the patient's weight and height. The BMI of ≥30 kg/m^2 was defined as obesity.

All statistical analyses were performed in SPSS version 20.0 (IBM Co., Chicago, IL, USA). The Chi-square test or Fisher's exact test was used for comparing categorical variables between the two groups (with and without a recurrence). A univariate Cox regression analysis was performed to examine the independent effects of significant variables on the risk of NMIBC. Subsequently, a multivariate Cox regression analysis was carried out on the selected variables for further identification of the risk of NMIBC recurrence. Moreover, the Kaplan–Meier plot was used to plot the recurrence-free survival curves. The log-rank test was separately performed for the effects of age, obesity, diabetes mellitus, smoking history, immediate perfusion therapy, and clinic pathological characteristics of tumors, immediate on the recurrence-free survival. All statistical tests were two-sided, and a p-value of <0.05 was considered significant.

This study was completed in accordance with the Helsinki Declaration as revised in 2013. This research was additionally approved by the ethics committee of Babol University of Medical Sciences (Ethic ID: IR.MUBABOL.HRI.REC.1399.088).

3. Results

Out of 143 patients with NMIBC, the majority (83.9%) was male and the mean age was 64.4 (standard deviation [SD] 12.9; range 27–94) years. Upon the diagnosis, 75 (52.4%) patients were younger than 65 years old, and 68 (47.6%) patients were 65 years old or above. The mean follow-up time was 29.0 (SD 8.7) months. Overall, 25.9% of the patients had BMI of 30 kg/m^2 or higher, and 46.2% of the patients were current or former smokers at the time of BCa diagnosis. Most of the patients (84.6%) had diabetes mellitus. The characteristics of the patients were stratified by the initial malignant recurrence age in the follow-up as "non-recurrent tumor" and "recurrent tumor". During the follow-up, 71 (49.7%) patients showed NMIBC recurrence, and the mean time until tumor recurrence was 11.5 (SD 6.9) months. At the time of the study, 21 (14.7%) patients were dead; however, four deaths were not related to BCa.

The Chi-square test or Fisher's exact test revealed significant differences between recurrent and non-recurrent tumor groups in terms of preoperative old age (56.3% *vs.* 38.9%; $p=0.037$), obesity (36.6% *vs.* 15.3%; $p=0.004$), no diabetes mellitus (23.9% *vs.* 6.9%; $p=0.005$), smoking (60.6% *vs.* 31.9%; $p=0.001$), and immediate infusion therapy on restage TURBT (63.4% *vs.* 45.8%; $p=0.035$). No significant difference was found regarding sex between patients with recurrent and non-recurrent tumors ($p=0.849$) (Table 1).

Of all patients with NMIBC, the majority (59.4%) had Ta tumors; 19.6% had T1 tumors; and 21.0% had Tis (CIS) tumors. Tumor size in 55.9% of the patients was 3 cm or larger, and more than three tumors were found in 61.5% of the patients. High-grade BCa accounted for 81.1% of all cases. The univariate analysis revealed a significant difference between patients with recurrent and non-recurrent tumors in terms of the number of tumors (>3 tumors) (80.3% *vs.* 43.1%; $p<0.001$) and all stage BCa ($p=0.001$, such as T1 31.0% *vs.* 8.3%). The evaluation of the tumor grade revealed no significant difference between patients with recurrent and non-recurrent tumors regarding the tumor grade ($p=0.060$); and the analysis revealed a significant difference between patients with recurrent and non-recurrent tumors in terms of tumor size ($p=0.001$) (Table 1).

The results of the univariate Cox regression analysis indicated that preoperative obesity (hazards ratio [HR] 4.31, 95% CI 2.47–7.53; $p<0.001$), being a current or former smoker (HR 2.30, 95% CI 1.35–3.90; $p=0.002$), and a high-grade tumor (HR 2.58; 95% CI 1.21–5.53; $p=0.014$) were associated with tumor recurrence. The results of the multivariate Cox regression analysis, in agreement with the results of univariate Cox regression, showed that preoperative obesity was associated with tumor recurrence (HR 7.90, 95% CI 4.01–15.55; $p<0.001$) (Table 2).

The Kaplan–Meier plot of recurrence-free survival showed that obesity was associated with a shorter time until the initial tumor recurrence compared to the non-obese group (6.50 months *vs.* 14.40 months; log-rank $p<0.001$) (Fig. 1). The estimated time until initial tumor recurrence was 10 months in young patients less than 30 kg/m^2 and 6 months in patients with BMI ≥30 kg/m^2 following NMIBC treatment (Fig. 1). Additionally, in the multivariate Cox regression analysis, being a current or former smoker was associated with tumor recurrence (HR 1.85, 95% CI 1.07–3.20; $p=0.027$) (Table 2). The Kaplan–Meier plot of the recurrence-free survival showed that being a current or former smoker was associated with a shorter time until the first tumor recurrence compared to never smokers (9.05 months *vs.* 15.29 months; log-rank $p=0.001$). Besides, the estimated time until initial tumor recurrence was 7 months in current or former smokers and 15 months in never smokers after NMIBC treatment (Fig. 2). Based on the multivariate Cox regression analysis, a high-grade tumor was associated with tumor recurrence (HR 4.03, 95% CI 1.59–10.25; $p=0.003$) (Table 2) and

Table 1 Descriptive statistics of patients with non-muscle invasive bladder cancer between January 2017 and January 2020 at a tertiary referral center.

Characteristic	Patient ($n=143$)	Non-recurrence tumor ($n=72$)	Recurrence tumor ($n=71$)	p-Value[a]
Age, year				
<65	75 (52.4)	44 (61.1)	31 (43.7)	NR
≥65	68 (47.6)	28 (38.9)	40 (56.3)	0.037
Gender				0.849
Female	23 (16.1)	12 (16.7)	11 (15.5)	
Male	120 (83.9)	60 (83.3)	60 (84.5)	
BMI, kg/m^2				
<30	106 (74.1)	61 (84.7)	45 (63.4)	NR
≥30	37 (25.9)	11 (15.3)	26 (36.6)	0.004
Diabetes mellitus				
Yes	121 (84.6)	67 (93.1)	54 (76.1)	NR
No	22 (15.4)	5 (6.9)	17 (23.9)	0.005
Smoking history				
Current or former smoker	66 (46.2)	23 (31.9)	43 (60.6)	0.001
Never smoker	77 (53.8)	49 (68.1)	28 (39.4)	NR
Tumor size, cm				0.001
<3	63 (44.1)	42 (58.3)	21 (29.6)	
≥3	80 (55.9)	30 (41.7)	50 (70.4)	
Number of tumor				
1–3	55 (38.5)	41 (56.9)	14 (19.7)	NR
>3	88 (61.5)	31 (43.1)	57 (80.3)	<0.001
Tumor grade				0.060
Low	27 (18.9)	18 (25.0)	9 (12.7)	
High	116 (81.1)	54 (75.0)	62 (87.3)	
Tumor stage				0.001
Ta	85 (59.4)	52 (72.2)	33 (46.5)	
T1	28 (19.6)	6 (8.3)	22 (31.0)	
Tis (CIS)	30 (21.0)	14 (19.4)	16 (22.5)	
Immediate infusion therapy				
Yes	78 (54.5)	33 (45.8)	45 (63.4)	0.035
No	65 (45.5)	39 (54.2)	26 (36.6)	NR

CIS, carcinoma *in situ*; BMI, body mass index; NR, not reported.
Note: data were presented as *n* (%).
[a] The Chi-square test or Fisher's exact test.

correlated with a shorter interval until initial tumor recurrence compared to the low-grade tumor group (10.44 months *vs.* 18.89 months; log-rank $p=0.006$). The estimated time until initial tumor recurrence was 9 months in the patients with high-grade tumors and 17 months in those with low-grade tumors following NMIBC treatment (Fig. 3). However, the results of Cox regression analysis indicated no significant association between tumor recurrence and age, diabetes mellitus, tumor size, immediate infusion therapy, or number of tumors (Table 2).

4. Discussion

NMIBC is known as a heterogeneous disease, characterized by a wide range of adverse oncologic outcomes after treatment. To improve the patient outcomes, understanding the risk of recurrence is critical. This study was performed on patients with NMIBC, undergoing treatment in our institution. Expectedly, the overall rate of NMIBC recurrence was relatively high in our institution. The Ta tumors (mostly high-grade) had a higher recurrence rate compared to other tumor stages, while CIS was the lower recurrent type of NMIBC in this study. So far, various studies have been performed to identify the recurrence rate of NMIBC, ranging from 40% to 90% [9,15,24–26].

It is generally accepted that different diagnostic techniques and several important factors can account for different recurrence rates and predict the recurrence of NMIBC; consequently, its diagnosis remains a major challenge [27,28]. In our institution, several recurrence risk factors have been investigated for NMIBC in patients undergoing treatment between January 2017 and January 2020. NMIBC was about five times more frequent in males than in females. The incidence of this disease in our study was closer to that reported in China. They reported that the incidence of NMIBC was 4.6 times more common in males than in females [29]. A possible explanation for the relatively higher incidence of NMIBC in males compared with

Table 2 The Cox regression analyses predicting for the risk of recurrence in patients with non-muscle-invasive bladder cancer between January 2017 and January 2020 at a tertiary referral center.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age, year				
<65	1.00	Ref	NA	NA
≥65	0.92 (0.58–1.48)	0.743	NA	NA
BMI, kg/m^2				
<30	1.00	Ref	1.00	Ref
≥30	4.31 (2.47–7.53)	<0.001	7.90 (4.01–15.55)	<0.001
Diabetes mellitus				
Yes	1.03 (0.58–1.82)	0.917	NA	NA
No	1.00	Ref	NA	NA
Smoking history				
Current or former smoker	2.30 (1.35–3.90)	0.002	1.85 (1.07–3.20)	0.027
Never smoker	1.00	Ref	1.00	Ref
Alcohol intake				
Yes	1.38 (0.751–2.54)	0.299	NA	NA
No	1.00	Ref	NA	NA
Tumor size, cm				
<3	1.00	Ref	NA	NA
≥3	1.32 (0.773–2.25)	0.310	NA	NA
Number of tumor				
1–3	1.00	Ref	NA	NA
>3	1.22 (0.68–2.21)	0.506	NA	NA
Tumor grade				
Low	1.00	Ref	1.00	Ref
High	2.58 (1.21–5.53)	0.014	4.03 (1.59–10.25)	0.003
Tumor stage				
Ta	1.00	Ref	NA	NA
T1	1.41 (0.81–2.45)	0.222	NA	NA
Tis (CIS)	1.62 (0.87–3.01)	1.30	NA	NA
Immediate infusion therapy				
Yes	0.90 (0.55–1.48)	0.688	NA	NA
No	1.00	Ref	NA	NA

CIS, carcinoma *in situ*; HR, hazard ratio; CI, confidence interval; BMI, body mass index; Ref, reference.
Note: NA means that the multivariate analysis was not performed on the variables that were not significantly associated with survival in the univariate analysis.

females may be their higher exposure to cigarette smoking and the lower prevalence of cigarette smoking in women [30,31].

In the present study, smoking history was associated with tumor recurrence (HR 1.85; $p=0.027$). However, Freedman et al. [32] reported that cigarette smoking is a strong risk factor for BCa. Shiota et al. [33] showed that androgen and androgen receptors are important risk factors, increasing the risk of BCa in males. Despite the higher incidence of NMIBC in males, our findings showed that sex is not an important risk factor for the NMIBC recurrence. While several studies, contrary to our research, have shown that women have higher recurrence rates than males [29,30], further assessment of the association between sex and NMIBC recurrence may be needed. Moreover, emphasis should be placed on cigarette smoking cessation to decrease the risk of NMIBC recurrence [34].

Expectedly, patients who were obese had a higher tumor recurrence rate compared to non-obese patients. Also, obese patients experienced a shorter time to a recurrence. This finding is consistent with the results of several studies, suggesting that obesity was associated with a higher tumor recurrence rate [15,17,35,36]. Therefore, health professionals should focus on appropriate intervention planning to decrease obesity; this strategy may reduce the risk of recurrence in patients with NMIBC. Nonetheless, further research is essential to understand what leads to higher tumor recurrence rates in obese patients with NMIBC.

In the present study, diabetic patients showed a higher percentage of recurrence-free cases compared to non-diabetic patients (76.1% *vs.* 23.9%). However, the results of the Cox analysis revealed no significant association between diabetes mellitus and the risk of recurrence. This finding is consistent with the results of one study, which reported that diabetes mellitus is not associated with a higher tumor recurrence rate [37]. However, there is a strong biological link between diabetes mellitus and many cancers, such as bladder, breast, uterine, and kidney

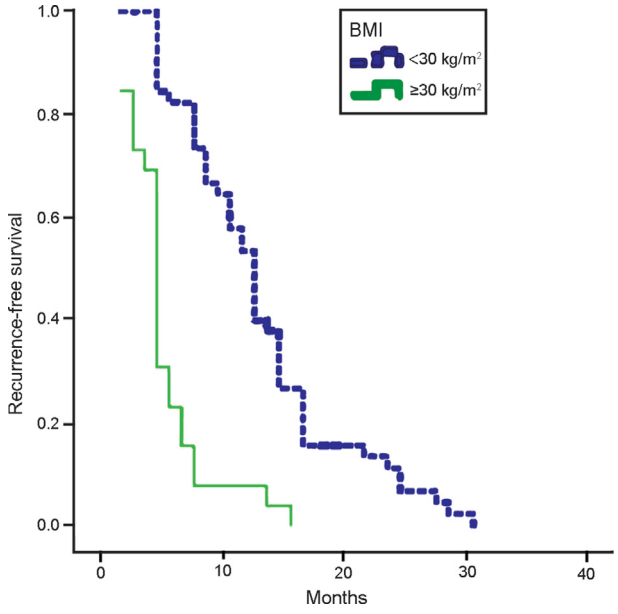

Figure 1 The Kaplan–Meier plot of recurrence-free survival of patients with non-muscle-invasive bladder cancer with obesity (log-rank $p<0.001$). BMI, body mass index.

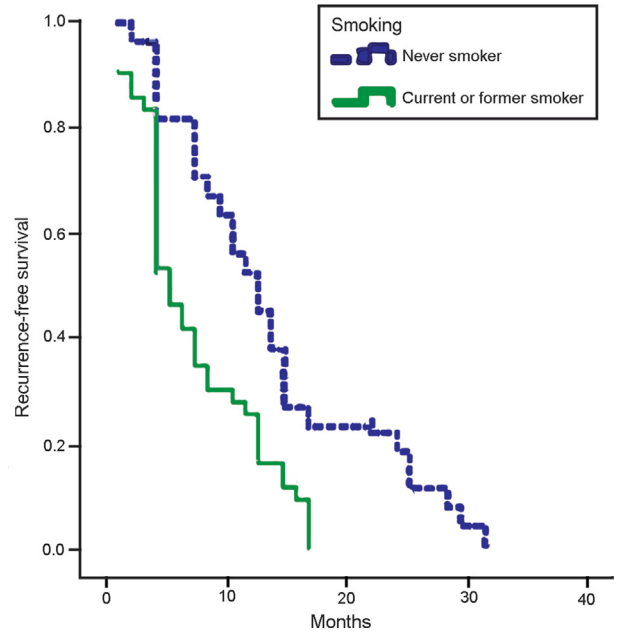

Figure 2 The Kaplan–Meier plot of recurrence-free survival of patients with non-muscle-invasive bladder cancer with and without history of cigarette smoking (log-rank $p=0.001$).

cancers [38]. A meta-analysis showed that use of metformin could improve the prognosis of patients with BCa [39]. However, further prospective studies with a larger sample size are still required to better identify the association between diabetes mellitus and the risk of recurrence.

In the current study, patients aged ≥65 years had a higher recurrence rate (56.3% *vs.* 38.9%). Nonetheless, the results of the multivariate Cox regression analysis showed no significant associations between old age (≥65 years) and

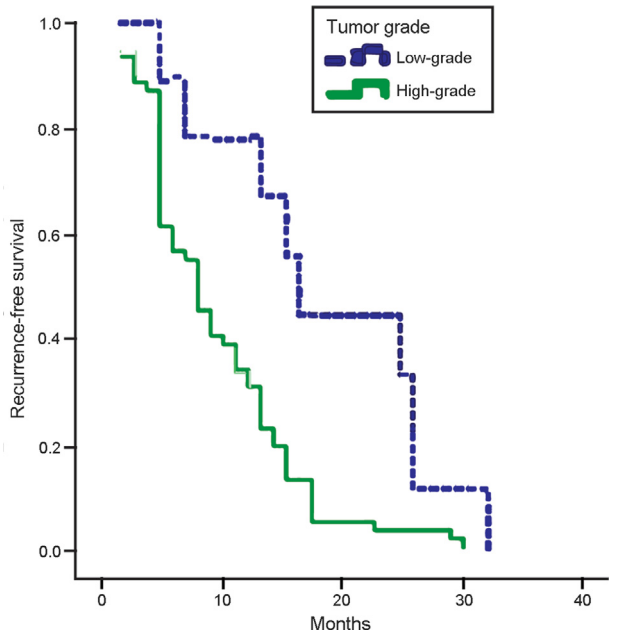

Figure 3 The Kaplan–Meier plot of recurrence-free survival of patients with non-muscle-invasive bladder cancer with high-grade tumor and low-grade tumor (log-rank $p=0.006$).

the risk of NMIBC recurrence. Overall, previous studies on age in relation to the NMIBC recurrence are limited, and the results are inconsistent. In this regard, Kocan and Kadihasanoglu [40] assessed the effects of sex and age on the NMIBC recurrence. They found that sex and age were not associated with the first recurrence in patients with NMIBC. Additionally, in a study on 1252 cases, Yuge et al. [41] showed that age was not related to the tumor recurrence in patients with NMIBC. On the other hand, Ferro et al. [42] found that the older age (>70 years) was associated with an increased risk of a recurrence in patients with bladder CIS. Further evaluation of a largest population is required to better understand the relationship between the age and tumor recurrence.

In contrast to other studies [8,43–45], we found no significant difference in the rate of recurrence considering the size of tumor, number of tumors, or stage of tumor based on the Cox regression analysis and log-rank test. However, both our Cox regression (univariate and multivariate) analysis and log-rank results revealed that the recurrence risk of high-grade tumors was obviously higher than that of low-grade tumors (HR 4.03; $p=0.003$) and associated with a shorter interval until the first tumor recurrence; also, high-grade tumors were independent factors for the prediction of the NMIBC recurrence. Beside, an important study by Ho et al. [46] revealed that the tumor grade was not an independent predictor of the NMIBC recurrence. Conversely, Ferro et al. [47] have shown that high-grade tumors were independent predictors of response to BCG treatment in patients undergoing restaging TURBT.

There are possible limitations to the present study. In this study with a retrospective design, a small sample size was evaluated for the risk prediction of a recurrence in patients with NMIBC. No follow-up data were found for 7.7%

of patients, and they were missing from the study. Nonetheless, future prospective cohort studies with a larger population are likely to provide stronger evidence on these predictors. Also, the present study could not assess the tumor progression rate or association between variables and tumor progression. Overall, our findings were not unexpected based on the results reported in the literature.

5. Conclusion

The present results indicated a 4-year NMIBC rate of 49.7% in Iran during January 2017 and January 2020. The old age, obesity, diabetes mellitus, being a current or former smoker, immediate infusion therapy, size of tumors, number of tumors, and a high-grade tumor were factors significantly affecting tumor recurrences in patients with NMIBC. Among these factors, obesity, smoking history, and the high-grade tumor were contributing factors for the tumor recurrence in patients with NMIBC. Our prediction model of recurrence risk may provide evidence for healthcare decisions in patients with NMIBC.

Author contributions

Study concept and design: Emaduddin Moudi, Niloufar Ahmadi.
Data acquisition: Emaduddin Moudi, Niloufar Ahmadi, Hamid Shafee.
Data analysis: Niloufar Ahmadi.
Drafting of manuscript: Emaduddin Moudi, Niloufar Ahmadi, Hamid Shafee.
Critical revision of the manuscript: Emaduddin Moudi, Niloufar Ahmadi, Hamid Shafee.

Conflicts of interest

The authors declare no conflict of interest.

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