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ORIGINAL ARTICLE

Novel nomograms to predict recurrence and progression in primary non-muscle-invasive bladder cancer: validation of predictive efficacy in comparison with European Organization of Research and Treatment of Cancer scoring system

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Abstract

Purpose To develop and validate novel nomograms to predict recurrence and progression after transurethral resection of bladder tumor (TURBT) in Korean patients with non-muscle-invasive bladder cancer (NMIBC).

Methods We retrospectively analyzed the clinical data on 970 newly diagnosed NMIBC patients after TURBT between 2000 and 2013 in a single institution. We used multivariate Cox proportional hazard models to identify the significant predictors of recurrence and progression, which resulted in the construction of the nomograms predicting the 5-year probability of recurrence and progression. We internally validated the nomograms using the area under the receiver-operating characteristics' curves and calibration plots. In addition, the clinical usefulness of each nomogram was assessed and compared with that of the European Organization of Research and Treatment of Cancer (EORTC)-scoring system using decision curve analysis (DCA).

Results The significant factors related to recurrence were gross hematuria at diagnosis, previous or concomitant upper urinary tract urothelial carcinoma (UTUC), pT1 tumor, high tumor grade, multiple tumors, and intravesical therapy. The significant predictors of progression were previous or concomitant UTUC, pT1 tumor, high tumor grade, carcinoma in situ, and lymphovascular invasion. The 5-year predictive accuracy of each nomogram was 65% for recurrence and 70% for progression, respectively. Compared with the EORTC-scoring system, the nomograms were generally well calibrated. On DCA, each nomogram presented better net benefit gains than did the EORTC-scoring system across a wide range of threshold probabilities.

Conclusions Our novel nomograms are not completely accurate, but they show a reasonable level of discriminative ability, adequate calibration, and meaningful net benefit gain for the prediction of recurrence and progression after TURBT in Korean NMIBC patients. Additional external validation will be required to generalize the nomograms which we developed.

Keywords Urinary bladder neoplasms · Recurrence · Disease progression · Nomograms

Introduction

Urothelial carcinoma (UC) is the most common (more than 90%) histological type among primary tumors that originate in the bladder [1]. Most bladder UCs (70–80%) are initially diagnosed as non-muscle-invasive bladder cancer (NMIBC), which is confined to either the mucosa [Ta, carcinoma in situ (CIS)] or the submucosa (T1) [2]. NMIBC is primarily diagnosed and treated with transurethral resection of bladder tumor (TURBT) [1, 3]. However, these tumors are usually at risk for recurrence and progression, and thus, regular surveillance after TURBT is mandatory in nearly all NMIBC patients [4]. Furthermore, stratifying NMIBC

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patients according to the risk of disease recurrence and progression can aid in individualizing follow-up schedules and adjuvant treatment strategies, such as intravesical therapy, after TURBT [5–7].

In an effort to predict the risk of recurrence and progression after TURBT for NMIBC, investigators have developed a number of risk prediction tools [8–14]. Of these, the European Organization of Research and Treatment of Cancer (EORTC) scoring system and risk tables, which were initially introduced in the 2008 European Association of Urology guidelines on Ta and T1 bladder cancer, are widely used to estimate recurrence and progression risk in NMIBC [8]. This system assigns scores for degree of recurrence or progression for the six well-known prognostic factors in NMIBC: number of tumors, tumor size, prior recurrence rate, T category, and presence of CIS and grade. According to the total sums of the scores for each prognostic factor, risk tables provide the probabilities of 1- and 5-year recurrence and progression by classifying patients into four groups by total score and three groups by risk (low, intermediate, and high). Since the introduction of this system, clinical efficacy and applicability of the EORTC risk tables have been externally validated with focuses on Asian populations [15–17]. However, there are some limitations in applying the EORTC risk tables in the current clinical practice settings. First, the EORTC cohort (2596 patients) only consisted of European patients from Belgium and The Netherlands, and second, the EORTC risk tables involve complex calculations and imbalanced prevalences in individual risk groups [8].

In this study, we aimed to develop novel nomograms for easily predicting the probabilities of recurrence and progression after TURBT by incorporating relevant clinical and pathological factors in a Korean NMIBC cohort. In addition, we sought to assess the efficacy of the novel nomograms in predicting the risk of recurrence and progression by comparing them with the performance of the existing EORTC-scoring system and risk tables.

Materials and methods

Study population

After we obtained institutional review board approval from Seoul National University Hospital, we initially reviewed the medical records for 2218 patients who underwent TURBT by multiple surgeons from 2000 to 2013. The board waived written informed consent for each patient owing to the retrospective nature of the study. We excluded patients who had incomplete data, benign lesions (e.g., cystitis and papilloma), non-UC histological types, primary CIS only, and muscle-invasive or metastatic disease. For patients with UCs that recurred repeatedly during the evaluation period, we only included initially diagnosed cases. Consequently, a total of 970 patients who had been initially diagnosed with NMIBC (Ta or T1) following TURBT and for whom there were complete data without missing values for the included variables composed the eligible cohort for the development of the nomograms in this study.

Assessed clinical and pathological variables

We extracted the following clinical variables from the final NMIBC database: age at the time of surgery, gender, presence or absence of gross hematuria as a presenting symptom, previous or concomitant upper urinary tract urothelial carcinoma (UTUC), tumor size (<3 cm vs. ≥ 3 cm), and number of tumors (single vs. 2–7 vs. ≥ 8) and intravesical treatment. The tumor size and number of each case were assessed based on the findings in preoperative computed tomography or cystoscopic examination. To facilitate analysis, we dichotomized number of tumors into single (1) or multiple (2 or more). Intravesical treatment included adjuvant bacillus Calmette–Guerin (BCG) and/or any types of chemotherapeutic agents following TURBT.

All TURBT specimens had been processed following our institutional pathology procedures and examined by experienced genitourinary pathologists in accordance with a standardized reporting protocol. The tumor stage was determined using the 2010 American Joint Committee on Cancer staging system. The tumor grade was based on the 1973 and 2004 World Health Organization systems. Therefore, we reevaluated the tumor stage and grade of patients who received TURBT before the updated guidelines were applied. A single pathologist with genitourinary expertise deciphered again the previous classified stage and grade in a blinded manner. Other pathological variables were as follows: concomitant CIS, lymphovascular invasion (LVI), and variant histology of UC. We considered LVI as the presence of tumor cells within an endothelium-lined space without underlying muscular walls.

In addition, we compared our study cohort with the existing EORTC cohort, which consists of 2596 Ta or T1 bladder cancer, by stratifying the patients into risk groups according to the total scores for the six clinico-pathological factors based on the EORTC-scoring system for recurrence and progression [8].

Follow-up protocol

The follow-up for patients after TURBT was usually every 3–4 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter with urine analysis, urine cytology, and cystoscopic examination. Radiologic assessments, such as intravenous pyelography, computed tomography, and magnetic resonance imaging, were optionally performed at the discretion of the surgeon if recurrence or metastasis was suspected. The events of interest in this study were time to first recurrence and progression, with recurrence considered the first tumor relapse within the bladder or prostatic urethra regardless of tumor stage. We defined progression as the first development of muscle-invasive disease (T2 or more) or metastatic disease at the time of tumor recurrence during follow-up period.

Statistical analyses

To assess the significant clinical and pathological factors related to recurrence and progression, we used univariate and multivariate Cox proportional hazard models. We ultimately incorporated the identified significant factors to construct nomograms that predicted the probabilities of 1- and 5-year recurrence and progression after TURBT.

We quantitatively evaluated the discriminative abilities of the developed nomograms and the EORTC-scoring system to distinguish patients with events from those without events using the area under the receiver-operating characteristics (ROC) curve, which also corresponds concordance index (*C*-index) ranging from 0.5 (50%) to 1 (100%) [18]. A score of 1 implies that the model can perfectly discriminate between patients who will have recurrence and progression, whereas a score of 0.5 suggests that the model has no discriminative ability. We internally validated all area under the ROC curve estimates using 1000 bootstrap samples. We evaluated statistical differences in the area under the ROC curves using the nonparametric method [19].

To explore model performance, we evaluated general calibration using a calibration plot, which is applied to elucidate the relationships between model-derived predicted probabilities and actual event risks. We internally validated the models using 200 bootstrap resamples to decrease overfit bias. The calibration plot was characterized by intercept, which indicates the extent that predictions are systemically too low or too high, and calibration slope, which should be 1 [20].

To explore the clinical value of each nomogram for predicting recurrence and progression, we conducted decision curve analysis (DCA), which is a method for assessing the clinical usefulness of prediction models by quantifying the net benefits when various threshold probabilities are considered; you sum the benefits (true positives) and subtract the harms (false positives) [21, 22].

All statistical analyses were two-sided, and we considered *p* values less than 0.05 to be statistically significant. We prepared the nomograms (models), statistics, and figures using the SPSS software, version 21.0 (SPSS, Chicago, IL, USA) and R package 2.13.2.

Results

Characteristics of the study cohort

Table 1 summarizes the characteristics of the present study cohort and the existing EORTC cohort; the study population consisted of 970 patients with initially diagnosed pTa or T1 tumors after TURBT. Unlike the EORTC cohort, several clinical and pathological variables, such as gross hematuria, history of UTUC, LVI, and variant histology of UC, were included only in the present study cohort. The median age of enrolled patients was 65.9 years [interquartile range (IQR): 57.2–72.4], the male-to-female ratio was approximately 5:1, most patients, 77.5%, complained of gross hematuria as a presenting symptom, and 11.2% had the previous or concomitant UTUC. A majority of patients, 73.4%, had tumors of less than 3 cm in size and 62.6% showed two or more tumors. Nearly three quarters of the patients (693, 71.4%) received an additional intravesical treatment, mainly BCG based-therapy (61.5%), after TURBT. On pathological evaluation, 43.9% presented pT1 tumors, 34.4% showed high-grade disease, 5.7% had accompanying CIS, 2.2% displayed LVI, and 3.4% demonstrated variant UC histology. Among the entire study population, recurrence occurred in 541 (55.8%) patients and progression developed in 90 (9.3%) patients, with a median follow-up duration of 38 months (IQR 19–54). In the EORTC cohort, 47.8% showed recurrence and 10.7% presented progression, a median follow-up of 3.9 years. When we applied the EORTC risk classification to the study population, most patients, 97.4%, were at intermediate risk for recurrence and none were allocated to the low-risk group. In terms of progression, 5.8% were at low risk, 46.2% were at intermediate risk, and 48% at high risk (Table 1).

Construction and internal validation of the nomograms

The regression analysis results using univariate and multivariate Cox proportional hazard models are summarized in Table 2 and 3. Gross hematuria [hazard ratio (HR): 1.394, $p = 0.002$], UTUC (HR: 2.060, $p < 0.001$), pT1 tumor (HR: 1.229, $p = 0.049$), high-grade tumor (HR: 1.249, $p = 0.036$), multiple tumors (HR: 1.848, $p < 0.001$), and no intravesical treatment (HR: 1.700, $p < 0.001$) were the independent predictive factors for disease recurrence. In addition, UTUC (HR: 1.814, $p = 0.045$), pT1 tumor (HR: 2.407, $p = 0.003$), high-grade tumor (HR: 1.822, $p = 0.042$), CIS (HR: 2.720, $p = 0.005$), and LVI (HR: 3.876, $p < 0.001$) were the significant predictors

Table 1 Patient characteristics

Variables	Present series, numbers (%)	The EORTC series, numbers (%)
Age (years), median (IQR)	65.9 (57.2–72.4)	65 (–)
≤ 60	332 (34.2)	859 (33.1)
61–70	350 (36.1)	890 (34.3)
71–80	249 (25.7)	690 (26.6)
> 80	39 (4.0)	118 (4.5)
Gender		
Male	812 (83.7)	2044 (78.7)
Female	158 (16.3)	515 (19.8)
Gross hematuria		
No	218 (22.5)	–
Yes	752 (77.5)	–
Previous or concomitant UTUC		
No	861 (88.8)	–
Yes	109 (11.2)	–
Prior recurrence rate		
Primary	970 (100.0)	1405 (54.1)
Recurrent, ≤ 1 rec/year	0 (0.0)	505 (19.5)
Recurrent, > 1 rec/year	0 (0.0)	645 (24.8)
T stage		
pTa	544 (56.1)	1451 (55.9)
pT1	426 (43.9)	1108 (42.7)
Tumor grade (1973 WHO system)		
1	70 (7.2)	1121 (43.2)
2	712 (73.4)	1139 (43.9)
3	188 (19.4)	271 (10.4)
Tumor grade (2004 WHO/ISUP system)		
Low grade	636 (65.6)	–
High grade	334 (34.4)	–
Carcinoma in situ		
Present	55 (5.7)	113 (4.4)
Absent	915 (94.3)	2440 (94.0)
Lymphovascular invasion		
Present	21 (2.2)	–
Absent	949 (97.8)	–
Variant histology of urothelial carcinoma		
Present	33 (3.4)	–
Absent	937 (96.6)	–
Tumor size (cm)		
< 3	712 (73.4)	2087 (80.4)
≥ 3	258 (26.6)	464 (17.9)
Number of tumors		
1	363 (38.4)	1465 (56.4)
2–7	542 (55.9)	836 (32.2)
≥ 8	65 (6.7)	255 (9.8)
Intravesical treatment		
No	277 (28.6)	561 (21.6)

Table 1 (continued)

Variables	Present series, numbers (%)	The EORTC series, numbers (%)
Yes	693 (71.4)	2035 (78.4)
BCG only	215 (22.1)	
Chemotherapy + BCG	382 (39.4)	
Chemotherapy only	96 (9.9)	
Recurrence		
No	429 (44.2)	1356 (52.2)
Yes	541 (55.8)	1240 (47.8)
Progression		
No	880 (90.7)	2317 (89.3)
Yes	90 (9.3)	279 (10.7)
EORTC recurrence risk classification		
0 (low)		271 (10.9)
1–4 (intermediate–low)	511 (52.7)	1022 (40.9)
5–9 (intermediate–high)	434 (44.7)	944 (37.8)
10–17 (high)	25 (2.6)	259 (10.4)
EORTC progression risk classification		
0 (low)	56 (5.8)	431 (17.2)
2–6 (intermediate)	448 (46.2)	1238 (49.6)
7–13 (high–low)	421 (43.4)	712 (28.5)
14–23 (high–high)	45 (4.6)	119 (4.7)

IQR, interquartile range; UTUC, upper urinary tract urothelial carcinoma; EORTC, European Organization of Research and Treatment of Cancer

Table 2 Univariate Cox proportional hazard models for time to first recurrence and time to progression in the entire cohort

Variables	Recurrence		Progression	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (continuous)	1.038 (1.009–1.051)	**< 0.001**	2.024 (1.980–2.587)	**< 0.001**
Gender: male vs. female	1.023 (0.868–1.225)	0.084	1.350 (0.864–2.216)	0.185
Gross hematuria: no vs. yes	1.620 (1.381–1.901)	**< 0.001**	1.230 (0.752–2.012)	0.420
UTUC: no vs. yes	2.060 (1.617–2.625)	**< 0.001**	2.326 (1.578–3.451)	**< 0.001**
T stage: Ta vs. T1	1.218 (1.159–1.485)	**< 0.001**	2.374 (1.679–3.371)	**< 0.001**
Tumor grade (2004): HG vs. LG	1.540 (1.349–1.778)	**< 0.001**	2.671 (1.825–3.938)	**< 0.001**
CIS: absent vs. present	1.260 (1.016–1.583)	**0.039**	1.986 (1.358–2.271)	**< 0.001**
LVI: absent vs. present	0.894 (0.751–1.061)	0.203	3.058 (1.976–4.048)	**< 0.001**
Variant histology of UC: absent vs. present	0.950 (0.837–1.096)	0.508	1.032 (0.732–1.465)	0.851
Tumor size: < 3 cm vs. ≥ 3	1.286 (1.187–1.498)	**0.001**	1.113 (1.098–1.636)	**0.045**
Number of tumors: single vs. multiple	1.297 (1.138–1.475)	**< 0.001**	1.374 (1.437–1.856)	**0.035**
Intravesical treatment: yes vs. no	1.237 (1.165–2.115)	**< 0.001**	1.340 (0.831–1.641)	0.674

Bold indicates statistical significance

HR, hazard ratio; CI, confidence interval; UTUC, upper urinary tract urothelial carcinoma; HG, high grade; LG, low grade; CIS, carcinoma in situ; LVI, lymphovascular invasion; UC, urothelial carcinoma

of disease progression. On the basis of these analytic results, we developed two nomograms for predicting the 5-year probabilities of disease recurrence and progression after TURBT (Fig. 1a, b). On internal validation, the 5-year predictive accuracy of each nomogram, which was measured as the area under ROC curve, was 0.65 (65%) for recurrence (Fig. 2a) and 0.70 (70%) for progression (Fig. 2c), respectively. Whereas, the 5-year predictive accuracy of the EORTC-scoring system was 0.56 (56%) for recurrence (Fig. 2b) and 0.70 (70%) for progression

Table 3 Multivariate Cox proportional hazard models for time to first recurrence and time to progression in the entire cohort

Variables	Recurrence		Progression	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (continuous)	1.004 (0.996–1.1012)	0.325	1.020 (0.998–1.042)	0.073
Gross hematuria: no vs. yes	1.394 (1.126–1.726)	**0.002**	–	–
UTUC: no vs. yes	2.060 (1.617–2.625)	**< 0.001**	1.814 (1.012–3.249)	**0.045**
T stage: Ta vs. T1	1.229 (1.001–1.508)	**0.049**	2.407 (1.358–4.266)	**0.003**
Tumor grade (2004): HG vs. LG	1.249 (1.015–1.537)	**0.036**	1.822 (1.022–3.247)	**0.042**
CIS: absent vs. present	0.821 (0.534–1.260)	0.366	2.720 (1.358–5.451)	**0.005**
LVI: absent vs. present	–	–	3.876 (1.823–8.241)	**< 0.001**
Tumor size: < 3 cm vs. ≥ 3	1.033 (0.839–1.272)	0.760	0.951 (0.575–1.571)	0.844
Number of tumors: single vs. multiple	1.848 (1.519–2.248)	**< 0.001**	1.174 (0.742–1.856)	0.493
Intravesical treatment: yes vs. no	1.700 (1.365–2.115)	**< 0.001**	–	–

Bold indicates statistical significance

HR, hazard ratio; CI, confidence interval; UTUC, upper urinary tract urothelial carcinoma; HG, high grade; LG, low grade; CIS, carcinoma in situ; LVI, lymphovascular invasion; UC, urothelial carcinoma

(Fig. 2d), respectively. In comparison with the EORTC-scoring system (Fig. 2b, d), the calibration plot for each nomogram demonstrated good correspondence between predicted and actual risks of recurrence (Fig. 2a) and progression (Fig. 2c) at 5 years, suggesting that the developed nomograms functioned well for predicting recurrence and progression. The results of the DCA depicted in Fig. 3 suggested that each nomogram showed better net benefit gains than the EORTC-scoring system across a wide range of threshold probabilities (Fig. 3a, b).

Discussion

NMIBC generally shows varying natural history and prognosis depending on the recurrence and progression potential of underlying UC [1]. Therefore, it is important to recognize the factors that predict recurrence and progression in managing NMIBC [4]. Although the prognostic significance of different factors has not always been consistent among the previous studies, the well-known factors related to the prognosis of NMIBC are as follows [9–14, 23–26]: (1) clinical factors, including age, gender, number of tumors, tumor size, recurrence rate/year, and recurrence, at the first 3 months after initial TURBT, intravesical therapy, re-staging TURBT, and muscle layer inclusion in TURBT specimen and (2) pathological factors, such as tumor stage and grade, positive urine cytology result prior to TURBT, CIS, variant UC histology, and LVI.

In recent years, many investigators have developed models for predicting NMIBC prognosis by incorporating the well-known factors mentioned above [8–14]. Among these, the EORTC-scoring system and risk tables have played a role as representative predictive tools for short-and long-term risks of recurrence and progression after TURBT. Based on 2596 patients with TaT1 tumors, the scoring system is derived from six clinical and pathological factors: number of tumors, tumor size, prior recurrence rate, T category, CIS, and grade. The risk tables suggest that the probabilities of recurrence and progression at 1 year ranged from 15 to 61% and from < 1 to 17%, respectively. At 5 years, the probabilities of recurrence and progression ranged from 31 to 78% and from < 1 to 45% according to the total sums of the scores assigned for each factor [8].

Although applicability and efficiency of the EORTC risk tables were externally validated by many investigators in various Asian countries [15–17] and their use is currently recommended by the international guidelines [2], this predictive tool may show some limitations in applying to Asian populations considering the differences in geographic location, ethnic background, treatment algorithm, and malignant potential, resulting in the need for novel predictive models for Asian NMIBC patients.

We identified the relevant significant factors to construct the nomograms that predict the probabilities of recurrence and progression in Korean NMIBC patients (Table 2). We also incorporated well-established predictors of recurrence and progression identified in the previous risk predictive models, including number of tumors [9, 10, 12–14], tumor stage [10–12] and grade [9–12, 14], CIS [9, 10], LVI [23], and intravesical treatment [9, 11–14] to develop our nomograms. On multivariable analyses, gross hematuria, which is the most common presenting symptom in NMIBC [2], was also predictive of recurrence. Notably, this correlation may be a new finding, considering that there have been no relevant articles to report the prognostic value of gross hematuria in NMIBC [9–13]. We assume that, owing to the retrospective feature of our study, the well-known prognostic factors of NMIBC not examined in the current study, which include re-staging TURBT, preoperative positive

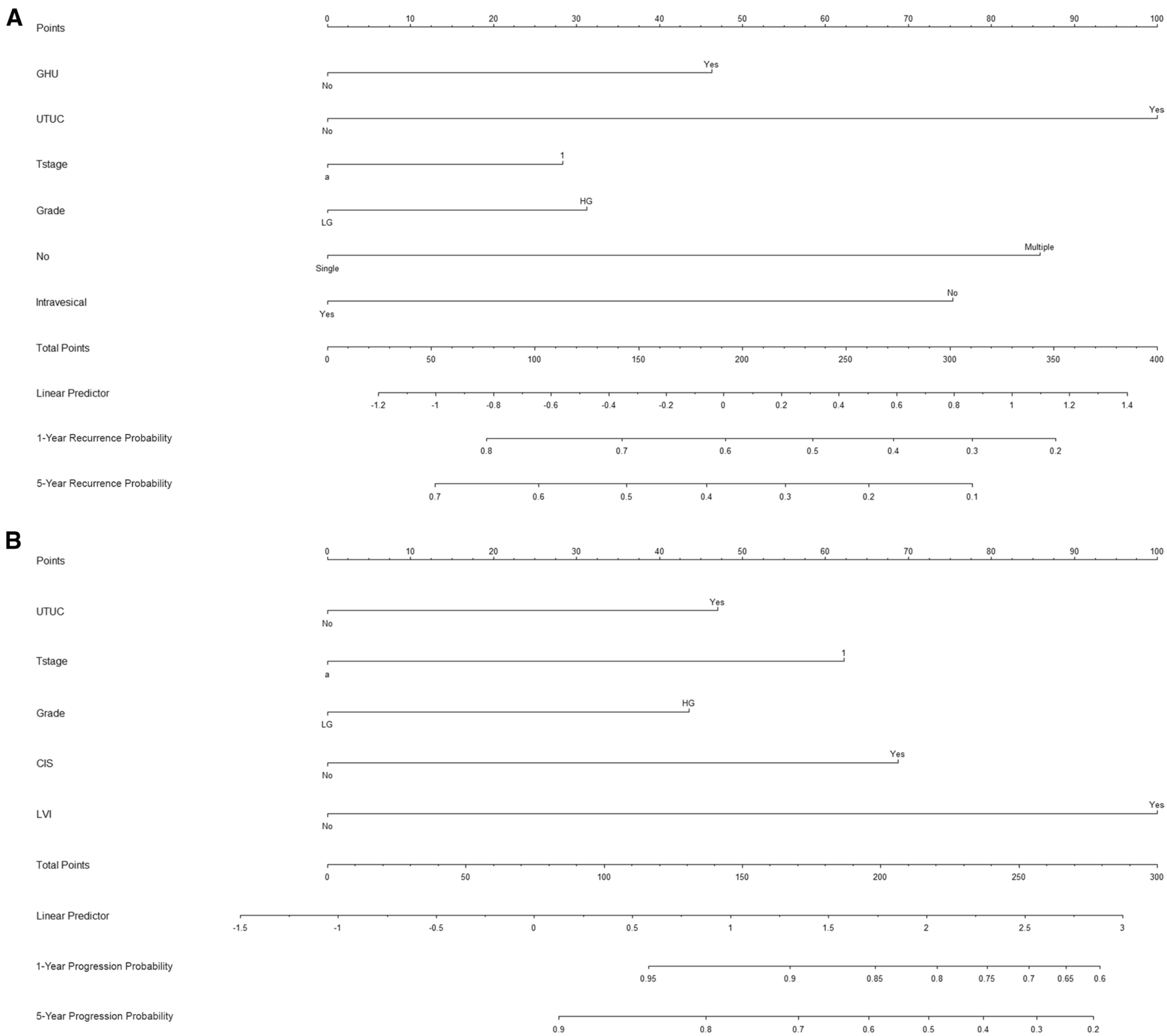

Fig. 1 Nomograms to predict recurrence and progression at 1 and 5 years. **a** Probability of recurrence. **b** Probability of progression. GHU, gross hematuria; UTUC, upper urinary tract urothelial carcinoma; LG, low grade; HG, high grade, No, number of tumors; Intravesical, intravesical treatment; CIS, carcinoma in situ; LVI, lymphovascular invasion

urine cytology result, and smoking history [24–26], could be more included in gross hematuria group, and therefore, gross hematuria might have acted as a negative predictor for NMIBC recurrence. Separately, the presence of UTUC was the significant predictor of both recurrence and progression. This association, especially in terms of recurrence, partially corresponds to the observations in the recent studies [27, 28]. Unlike the EORTC cohort that included recurrent cases (44.3%), our study cohort only included initially diagnosed NMIBC patients without prior recurrence (Table 1), and this inclusion of study subjects was also found in the previous studies [9, 11, 13]. In the EORTC cohort, 78.7% and 33.2% of all patients were assigned in the intermediate recurrence and high progression risk groups, respectively [8]. In contrast, using the EORTC risk classification in the present study, nearly all, 97.4%, and 48% of all subjects were classified into the intermediate-risk recurrence and high-risk progression groups, respectively (Table 1). In short, our study cohort included a higher proportion of intermediate- and high-risk NMIBC patients than the EORTC cohort. In the current study, each nomogram predicting recurrence and progression showed modest predictive accuracy, with a *C*-index of 0.65 and 0.70, respectively. However, in calibration plots, our nomograms were better functioned than the EORTC-scoring system for the prediction of recurrence and progression. In addition, we conducted a DCA that

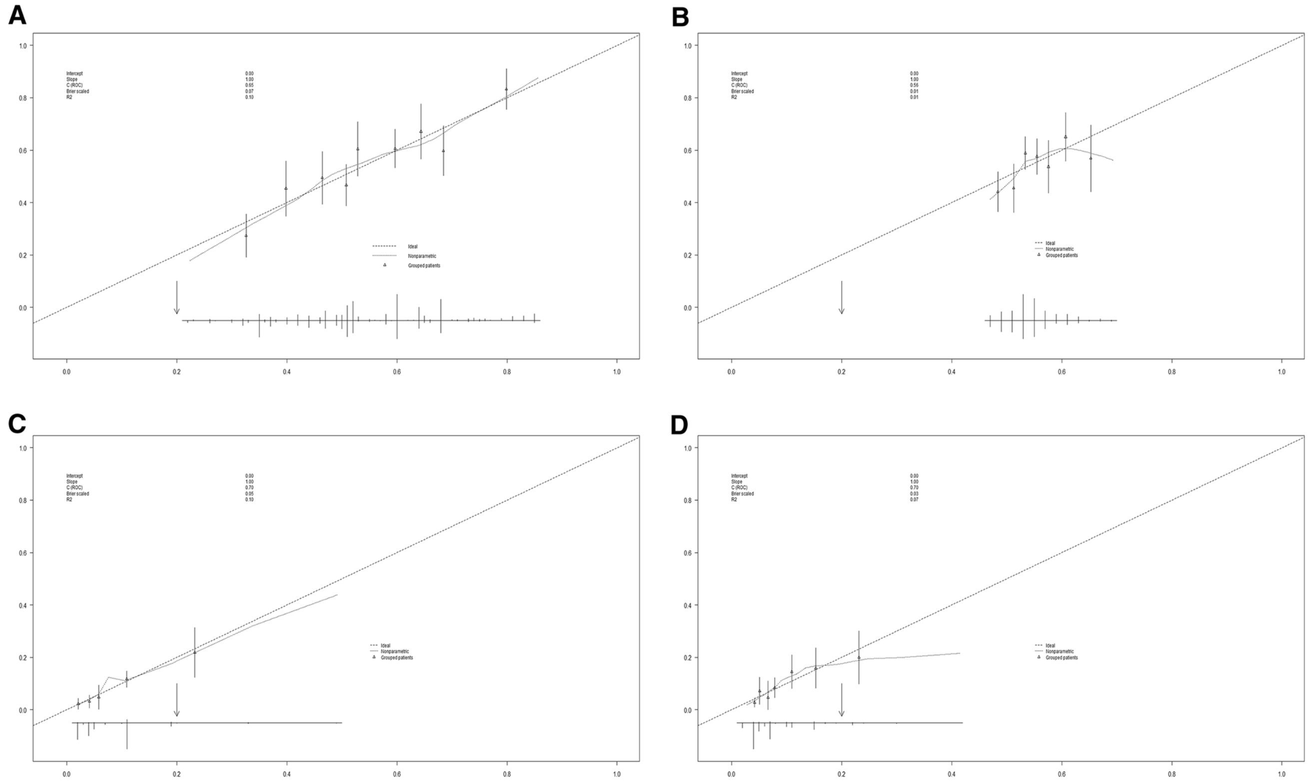

Fig. 2 Calibration plots. **a** Nomogram for recurrence. **b** EORTC-scoring system for recurrence. **c** Nomogram for progression. **d** EORTC-scoring system for progression

evaluates the consequences of clinical decisions to investigate the potential clinical impact of using our nomograms and the EORTC-scoring system (Fig. 3). Net benefits of two prediction models were superior at wide range of decision to treat thresholds. For recurrence, our nomogram showed a greater net benefit than the EORTC-scoring system in threshold probabilities of 40% or more (Fig. 3a). In terms of progression, developed nomogram had a more net benefit compared to the EORTC-scoring system in most ranges of threshold probabilities except for narrow range of threshold probabilities between 12 and 15% (Fig. 3b). In summary, although our developed nomograms are not completely accurate, they achieved a modest level of discrimination, adequate calibration, and meaningful net benefit gain for the prediction of recurrence and progression after TURBT in Korean NMIBC patients. Therefore, we postulate that our nomograms may be used as a potential decision-making tool in counseling patients, determining follow-up schedules, and selective enrollment into clinical trials of experimental novel therapies in primary NMIBC patients [7].

However, the results of our study should be cautiously interpreted due to several limitations. Above all, there might be inherent bias resulting from the retrospective nature of the current study. Other potential prognostic factors that we did not include in our data, such as preoperative positive urine cytology, re-staging TURBT, and muscle layer inclusion, which were suggested as significant prognostic factors of NMIBC in the recent studies [24–26], could be added to the nomograms to improve their usefulness in clinical practice. Given that our study cohort consisted of TURBT cases performed by multiple surgeons, there could have been considerable variation in the surgeons' expertise with TURBT, determining the performance of intravesical therapy and which instillation drug (BCG or chemotherapeutic agents) was used. In addition, owing to the limitation of the retrospective analysis, it is difficult to identify the exact information about the regimen of intravesical therapy (e.g., induction BCG only/maintenance BCG; type of chemotherapeutic agent; MMC/epirubicin/thiotepa/etc.) and sub-classification of UC histologic variants (e.g., micropapillary/sarcomatoid/plasmacytoid/etc.) Consequently, we considered these variables as one entity without subdivision when constructing nomogram by performing multivariable regression analyses, and these factors might have affected the prognosis of NMIBC patients after TURBT. Next, a DCA was used to evaluate and compare the clinical usefulness of the prediction models. A limitation of DCA is that the concept of net benefit is difficult to be clinically applied, because it is a mathematically derived definition and does

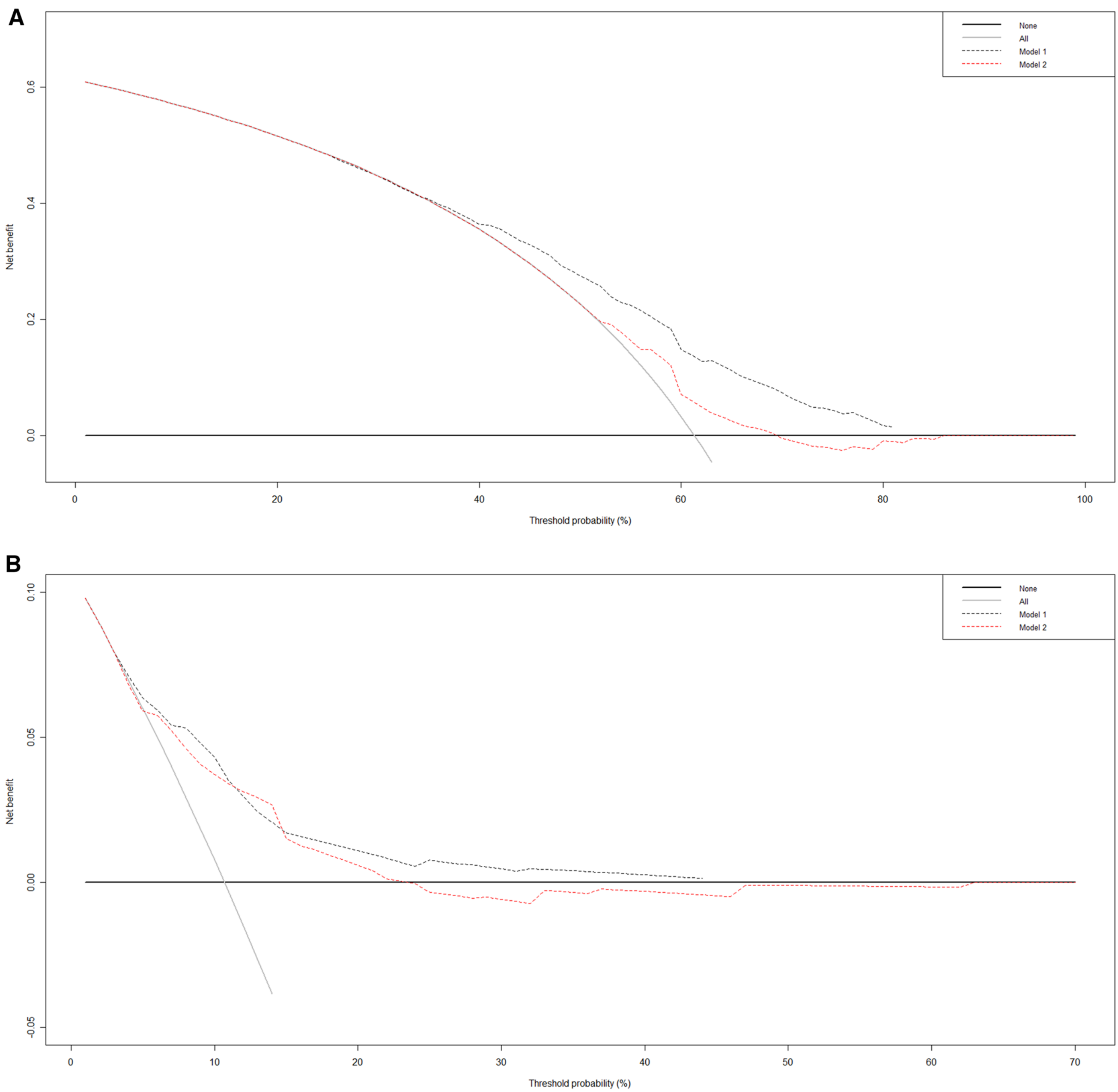

Fig. 3 Decision curve analysis: **a** recurrence. **b** Progression. Model 1 = nomogram. Model 2 = the EORTC-scoring system

not help to determine an acceptable probability threshold [21, 22]. Therefore, our results do not always mean that our nomograms have an absolute superiority over the EORTC-scoring system for the prediction of recurrence and progression when applying in real clinical practice. Finally, although we identified the efficacy of our novel nomograms in Korean patients through internal validation, we did not perform external validation. To generalize their use in clinical practice, the applicability of our novel nomograms should be externally validated with other NMIBC patient cohort.

Conclusions

Our novel nomograms, which were constructed based on single institutional database, are not perfectly accurate, but they attained a reasonable level of discrimination, adequate calibration, and meaningful net benefit gain on an internal validation. Therefore, our nomograms may serve as another potential predictive tool for the prediction of recurrence and progression after TURBT in Korean NMIBC patients. Further validation using the other external patient cohort is needed to generalize the applicability of the developed nomograms in real clinical practice.

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Compliance with ethical standards

Conflict of interest There is no any conflict of interest to disclose among all authors.

Research involving human participants and/or animals Prior to the initiation of the study, the use of patients' data in this study was approved from institutional review board (IRB) of Seoul National University Hospital (IRB number: H-1506-063-679).

Informed consent Owing to the retrospective feature of this study, the requirement for obtaining written informed consent from each patient was waived by the IRB of Seoul National University Hospital.

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