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ORIGINAL RESEARCH

Preoperative Systemic Inflammatory Markers as a Significant Prognostic Factor After TURBT in Patients with Non-Muscle-Invasive Bladder Cancer

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Introduction: Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/monocyte ratio (LMR) have been widely proposed to have predictive value for the patient prognosis of many malignancies, including bladder cancer. However, the predictive value of their combination in non-muscle-invasive bladder cancer (NMIBC) is unclear.

Methods: Cases of NMIBC patients who underwent transurethral resection of the bladder tumor were recruited from two tertiary public medical centers. A systemic inflammatory marker (SIM) score was calculated based on comprehensive consideration of NLR, PLR, and LMR. Recurrence-free survival (RFS) and progression-free survival (PFS) were estimated by Kaplan-Meier analysis. The Log rank test was used to compare differences between the groups. Cox regression was used to screen risk factors affecting RFS and PFS. Nomogram models were established and validated, and patients were stratified based on the model scores.

Results: The study dataset was grouped according to a 7:3 randomization, with the training cohort consisting of 292 cases and the validation cohort consisting of 124 cases. Cox regression analysis showed that SIM score is an independent predictor of RFS and PFS in NMIBC patients. The novel models were established based on the SIM score and other statistically significant clinicopathological features. The area under the curve (AUC) for predicting 1-, 2-, and 3-year RFS was 0.667, 0.689, and 0.713, respectively. The AUC for predicting 1-, 2-, and 3-year PFS was 0.807, 0.775, and 0.862, respectively. Based on the risk stratification, patients at high risk of recurrence and progression could be accurately identified. The established models were applied to the patient evaluation of the validation cohort, which proved the great performance of the novel models.

Conclusion: The novel models based on the SIM score and clinicopathological characteristics can accurately predict the survival prognosis of NMIBC patients, and the models can be used by clinicians for individualized patient assessment and to assist in clinical decision-making.

Keywords: systemic inflammatory markers, risk factor, bladder cancer, NMIBC, tumor recurrence, nomogram

Introduction

The proportion of patients initially diagnosed with non-muscle-invasive bladder cancer (NMIBC) accounts for the majority of bladder cancers.[1] Patients with NMIBC have a relatively good prognosis compared to those who progress to muscle-invasive bladder cancer (MIBC).[2,3] Unfortunately, even after transurethral resection of the bladder tumor (TURBT) and regular postoperative intravesical instillation, tumor recurrence and progression seem to be inevitable.[4–6] The risk scoring models established by the European Association of Urology (EAU)[2] and the Spanish Urological Organization (Club Urologico Español de Tratamiento Oncologico, CUETO)[3] for NMIBC were proposed at the beginning of the 21st century and have proven to be clinically effective.[7,8]

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Numerous studies have shown that different sites of initial invasion have different risks of postoperative progression, and patients with bladder neck invasion (BNI) had the highest risk.[9–13] Mediators such as chemokines or cytokines induce an inflammatory state in the body and promote the proliferation and progression of tumor cells. On the other hand, activation of oncogenes can drive the carcinogenesis of an inflammatory state. Thus, inflammation and cancer are mutually reinforcing and closely related.[14–17] Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/monocyte ratio (LMR), as widely studied systemic inflammatory response indicators, have been widely proven to be valuable predictors of a variety of malignancies.[18–20] Some studies focused on NMIBC patients have also shown that these systemic inflammatory response indicators have great potential for application.[21–24] In 2018, Cantiello et al first proposed the concept of a "systemic inflammatory marker" (SIM) score, and analyzed it in a cohort of NMIBC patients, which showed that the SIM score can be an independent predictor of recurrence and progression in NMIBC patients.[25] This study was innovative, but not modeling it accordingly reduced its usefulness.

There are no studies that have validated the value of the SIM score and integrated the analysis of systemic inflammatory response indicators and BNI. The aim of our study is to comprehensively assess the prognostic role of SMI and BNI in patients with NMIBC who underwent TURBT.

Materials and Methods

Study Population

This study was performed in line with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University and the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. The medical record databases of two tertiary public medical centers were retrospectively searched to collect data on patients with a pathological diagnosis of "urothelial carcinoma of the bladder" from October 2018 to June 2021. The inclusion criteria were as follows: (1) the surgery was performed in a consistent fashion; (2) postoperative histopathology confirmed urothelial carcinoma of the bladder; (3) specific pathological staging records after surgery. The exclusion criteria were as follows: (1) patients who received adjuvant therapy other than adjuvant intravesical instillation before or after TURBT; (2) clinical, laboratory, and follow-up data were incomplete; (3) tumor recurrence, progression, or death that occurred within one month. The serum biomarkers were collected within one week before surgery. Recurrence-free survival (RFS) was defined as the time from TURBT to the first evidence of either recurrent (or progression), cancer-related death, or last follow-up. Progression-free survival (PFS) was defined as the time from TURBT to the first evidence of progression, cancer-related death, or last follow-up.

Statistical Analysis

Data were collected from a total of 416 patients, and 292 patients were included in the training group through a 7:3 randomization. SIM were transformed from continuous variables to categorical variables using the X-tile program based on the total study cohort. Assign a value of 0 to protective subgroups and 1 to risk subgroups; therefore, the SIM score ranges from 0 to 3. Continuous data are presented as mean (±standard deviation) or median (interquartile range, IQR), categorical data as frequency and percentage. The Chi-square tests were used for categorical variables, and the Mann–Whitney *U*-tests were used for non-normally distributed continuous variables. Kaplan–Meier analysis was applied with Log rank testing. The univariate and multivariate Cox regression analyses were used to calculate the hazard ratio (HR) with a 95% confidence interval (CI) to identify risk factors. The models validation was performed by the area under the receiver operating characteristics curve (AUC) for discrimination ability and calibration curves for calibration ability. Decision curve analysis (DCA) was performed to determine the clinical net benefit associated with using the predictive models at different threshold probabilities in the patient cohort. After the models were established, patients were stratified by calculating the total points of individual patients. X-tile 3.6.1 (http://tissuearray.org/), SPSS 26.0 (IBM Corp., Chicago, IL), and R 4.1.2 (http://www.R-project.org/) were used to statistically analyze the database. A P-value <0.05 was considered to denote statistical significance.

Results

Patient Characteristics

As shown in Table 1, in the training cohort, the median age at diagnosis was 66 years old (IQR 58–74), median tumor size was 20 millimeter (mm) (IQR 15–30), median NLR was 1.863 (IQR 1.429–2.670), median PLR was 113.7 (IQR 90–151.429), and median LMR was 4.348 (IQR 3.265–5.510). The majority of NMIBC patients were male (83.904%) and non-overweight (60.616%). Most tumors status were in Ta stage (59.932%), primary status (86.986%), high pathology grade (57.534%) and multiple lesions (54.110%). Over half of the patients denied a smoking history. The cut-off value for NLR, PLR and LMR was 2.12, 175.71, and 4.58, respectively. Most patients had preoperative NLR and PLR less than the cut-off value (61.643%, 85.616%, respectively), and with LMR greater than or equal to the cut-off value (56.507%) (Table 2). According to the maker cutoffs, we found that patients with NLR≥2.12 or LMR<4.58 have a higher percentage of older patients (p=0.008, p=0.016, respectively); and patients with PLR≥175.71 have a higher percentage of larger tumor size (p=0.02). Table 3 lists the clinical and pathologic variables according to the SIM score. Based on the results in our pre-analysis (Figure 1), elevated NLR, elevated PLR and decreased LMR were identified as risk factors for NMIBC

Table 1 Baseline Demographics & Clinical Characteristics of Study Population

Variables	Level	Training Cohort (n=292)	Validation Cohort (n=124)
Gender, n (%)	Female	47(16.096)	15(12.097)
	Male	245(83.904)	109(87.903)
BMI (kg/m^2), n (%)	<25	177(60.616)	70(56.452)
	≥25	115(39.384)	54(43.548)
T category, n (%)	Ta	175(59.932)	73(58.871)
	T1	117(40.068)	51(41.129)
Prior recurrence status, n (%)	Primary	254(86.986)	105(84.677)
	Recurrent	38(13.014)	19(15.323)
Pathology grade, n (%)	Low-grade	124(42.466)	49(39.516)
	High-grade	168(57.534)	75(60.484)
Tumor number, n (%)	Single	134(45.890)	52(41.935)
	Multiple	158(54.110)	72(58.065)
Bladder neck invasion, n (%)	No	246(84.247)	101(81.452)
	Yes	46(15.753)	23(18.548)
Smoking status, n (%)	No	185(63.356)	76(61.290)
	Yes	107(36.644)	48(38.710)
Smoking years, n (%)	0	185(63.356)	76(61.290)
	<30	49(16.781)	18(14.516)
	≥30	58(19.863)	30(24.194)
Cigarettes per day, n (%)	0	185(63.356)	76(61.290)
	<30	96(32.877)	38(30.645)
	≥30	11(3.767)	10(8.065)
Age (year), median [IQR]		66[58, 74]	69[58, 75]
Maximum tumor diameter (millimeter), median [IQR]		20[15, 30]	20[14, 29]
Neutrophil count (×10^9/L), median [IQR]		3.480[2.790, 4.630]	3.480[2.780, 4.290]
Lymphocyte count (×10^9/L), median [IQR]		1.800[1.400, 2.300]	1.800[1.400, 2.400]
Monocyte count (×10^9/L), median [IQR]		0.430[0.340, 0.530]	0.450[0.340, 0.570]
Platelet count (×10^9/L), median [IQR]		217[181, 255]	204[175, 241]
NLR, median [IQR]		1.863[1.429, 2.670]	1.776[1.443, 2.640]
PLR, median [IQR]		113.700[90, 151.429]	115.130[83.125, 148.800]
LMR, median [IQR]		4.348[3.265, 5.510]	4.167[3.110, 5.806]

Abbreviations: BMI, body mass index, weight/height^2; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; IQR, inter-quartile range.

Table 2 Demographics & Clinical Characteristics According to NLR, PLR and LMR in the Training Cohort

Variables	Level	NLR<2.12 (n=180)	NLR≥2.12 (n=112)	p	PLR<175.71 (n=250)	PLR≥175.71 (n=42)	p	LMR<4.58 (n=165)	LMR≥4.58 (n=127)	p
Gender, n (%)	Female	33(18.333)	14(12.500)	0.187	37(14.800)	10(23.810)	0.142	22(13.333)	25(19.685)	0.143
	Male	147(81.667)	98(87.500)		213(85.200)	32(76.190)		143(86.667)	102(80.315)	
BMI (kg/m^2), n (%)	<25	104(57.778)	73(65.179)	0.208	148(59.200)	29(69.048)	0.227	107(64.848)	70(55.118)	0.092
	≥25	76(42.222)	39(34.821)		102(40.800)	13(30.952)		58(35.152)	57(44.882)	
T category, n (%)	Ta	114(63.333)	61(54.464)	0.133	153(61.200)	22(52.381)	0.281	91(55.152)	84(66.142)	0.057
	T1	66(36.667)	51(45.536)		97(38.800)	20(47.619)		74(44.848)	43(33.858)	
Prior recurrence status, n (%)	Primary	157(87.222)	97(86.607)	0.879	216(86.400)	38(90.476)	0.468	142(86.061)	112(88.189)	0.592
	Recurrent	23(12.778)	15(13.393)		34(13.600)	4(9.524)		23(13.939)	15(11.811)	
Pathology grade, n (%)	Low-grade	74(41.111)	50(44.643)	0.553	105(42)	19(45.238)	0.694	70(42.424)	54(42.520)	0.987
	High-grade	106(58.889)	62(55.357)		145(58)	23(54.762)		95(57.576)	73(57.480)	
Tumor number, n (%)	Single	86(47.778)	48(42.857)	0.412	120(48)	14(33.333)	0.078	71(43.030)	63(49.606)	0.264
	Multiple	94(52.222)	64(57.143)		130(52)	28(66.667)		94(56.970)	64(50.394)	
Bladder neck invasion, n (%)	No	153(85)	93(83.036)	0.654	212(84.800)	34(80.952)	0.527	139(84.242)	107(84.252)	0.998
	Yes	27(15)	19(16.964)		38(15.200)	8(19.048)		26(15.758)	20(15.748)	
Smoking status, n (%)	No	109(60.556)	76(67.857)	0.208	153(61.200)	32(76.190)	0.062	110(66.667)	75(59.055)	0.181
	Yes	71(39.444)	36(32.143)		97(38.800)	10(23.810)		55(33.333)	52(40.945)	
Smoking years, n (%)	0	109(60.556)	76(67.857)	0.443	153(61.200)	32(76.190)	0.167	110(66.667)	75(59.055)	0.407
	<30	32(17.778)	17(15.179)		45(18)	4(9.524)		25(15.152)	24(18.898)	
	≥30	39(21.667)	19(16.964)		52(20.800)	6(14.286)		30(18.182)	28(22.047)	
Cigarettes per day, n (%)	0	109(60.556)	76(67.857)	0.407	153(61.200)	32(76.190)	-	110(66.667)	75(59.055)	0.232
	<30	63(35)	33(29.464)		86(34.400)	10(23.810)		51(30.909)	45(35.433)	
	≥30	8(4.444)	3(2.679)		11(4.400)	0(0)		4(2.424)	7(5.512)	
Age (year), median [IQR]		65[55, 73]	68[63, 76]	0.008	66[57, 74]	64[59, 76]	0.867	67[59, 76]	65[55, 72]	0.016
Maximum tumor diameter (mm), median [IQR]		20[14, 30]	21[15, 30]	0.1	20[14, 30]	25[17, 35]	0.02	20[15, 30]	20[14, 27]	0.172

Abbreviations: BMI, body mass index, weight/height^2; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; IQR, inter-quartile range.

Table 3 Demographics & Clinical Characteristics According to SMI Score in the Training Cohort

Variables	Level	SIM Score=0 (n=111)	SIM Score=1 (n=77)	SIM Score=2 (n=70)	SIM Score=3 (n=34)	p
Gender, n (%)	Female	21(18.919)	12(15.584)	8(11.429)	6(17.647)	0.602
	Male	90(81.081)	65(84.416)	62(88.571)	28(82.353)	
BMI, n (%)	<25	60(54.054)	48(62.338)	46(65.714)	23(67.647)	0.313
	≥25	51(45.946)	29(37.662)	24(34.286)	11(32.353)	
T category, n (%)	Ta	74(66.667)	46(59.740)	37(52.857)	18(52.941)	0.236
	T1	37(33.333)	31(40.260)	33(47.143)	16(47.059)	
Prior recurrence status, n (%)	Primary	99(89.189)	64(83.117)	60(85.714)	31(91.176)	0.548
	Recurrent	12(10.811)	13(16.883)	10(14.286)	3(8.824)	
Pathology grade, n (%)	Low-grade	44(39.640)	37(48.052)	27(38.571)	16(47.059)	0.557
	High-grade	67(60.360)	40(51.948)	43(61.429)	18(52.941)	
Tumor number, n (%)	Single	60(54.054)	28(36.364)	33(47.143)	13(38.235)	0.084
	Multiple	51(45.946)	49(63.636)	37(52.857)	21(61.765)	
Bladder neck invasion, n (%)	No	92(82.883)	69(89.610)	58(82.857)	27(79.412)	0.471
	Yes	19(17.117)	8(10.390)	12(17.143)	7(20.588)	
Smoking status, n (%)	No	66(59.459)	47(61.039)	45(64.286)	27(79.412)	0.195
	Yes	45(40.541)	30(38.961)	25(35.714)	7(20.588)	
Smoking years, n (%)	0	66(59.459)	47(61.039)	45(64.286)	27(79.412)	0.358
	<30	20(18.018)	16(20.779)	9(12.857)	4(11.765)	
	≥30	25(22.523)	14(18.182)	16(22.857)	3(8.824)	
Cigarettes per day, n (%)	0	66(59.459)	47(61.039)	45(64.286)	27(79.412)	-
	<30	39(35.135)	27(35.065)	23(32.857)	7(20.588)	
	≥30	6(5.405)	3(3.896)	2(2.857)	0(0)	
Age, median [IQR]		65[55, 71]	69[58, 75]	67[63, 78]	64[59, 76]	0.029
Maximum tumor diameter, median [IQR]		20[13, 27]	20[15, 30]	20[15, 30]	25[18, 35]	0.084

Abbreviations: BMI, body mass index, weight/height^2; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; SMI, systemic inflammatory markers; IQR, inter-quartile range.

patient prognosis. Therefore, we assigned a value of 0 to the subgroup with NLR and PLR less than the cut-off point and a value of 1 to the subgroup with LMR less than the cut-off point. The majority of patients had a SIM score of 0. The proportion of patients with scores of 0, 1, 2, and 3 was 38.014%, 26.370%, 23.973%, and 11.644%, respectively.

Associations of SIM Score with Recurrence-Free Survival and Progression-Free Survival

We used Kaplan-Meier survival analysis to examine whether the SIM score correlated with patients' RFS and PFS. Patients were divided into four groups based on the SIM score. As shown in Figure 2, the SIM score can accurately distinguish NMIBC patients with different risks of recurrence and progression (p=0.0013 in RFS, p=0.00015 in PFS). The higher the SIM score, the worse the prognosis of the patients.

Screening for Predictive Factors

In univariate regression (Tables 4 and 5), T category (HR=1.729, p=0.013 for RFS, and HR=2.642, p=0.002 for PFS), prior recurrence status (HR=2.461, p=0.001 for RFS, and HR=3.188, p<0.001 for PFS), pathology grade (HR=1.628, p=0.039 for RFS, and HR=3.395, p=0.001 for PFS), tumor number (HR=2.045, p=0.003 for RFS, and HR=3.220, p=0.001 for PFS), BNI (HR=2.133, p=0.003 for RFS, and HR=3.447, p<0.001 for PFS), and SIM score (p=0.003 for RFS, and p=0.001 for PFS) were suggested to be associated with both RFS and PFS. The statistically significant variables in the univariate analysis were then assessed by using the multivariate Cox regression. Ultimately, prior recurrence status (HR=2.564, p=0.001), tumor number (HR=1.968, p=0.008), and SIM score (p=0.002) proved to be independent

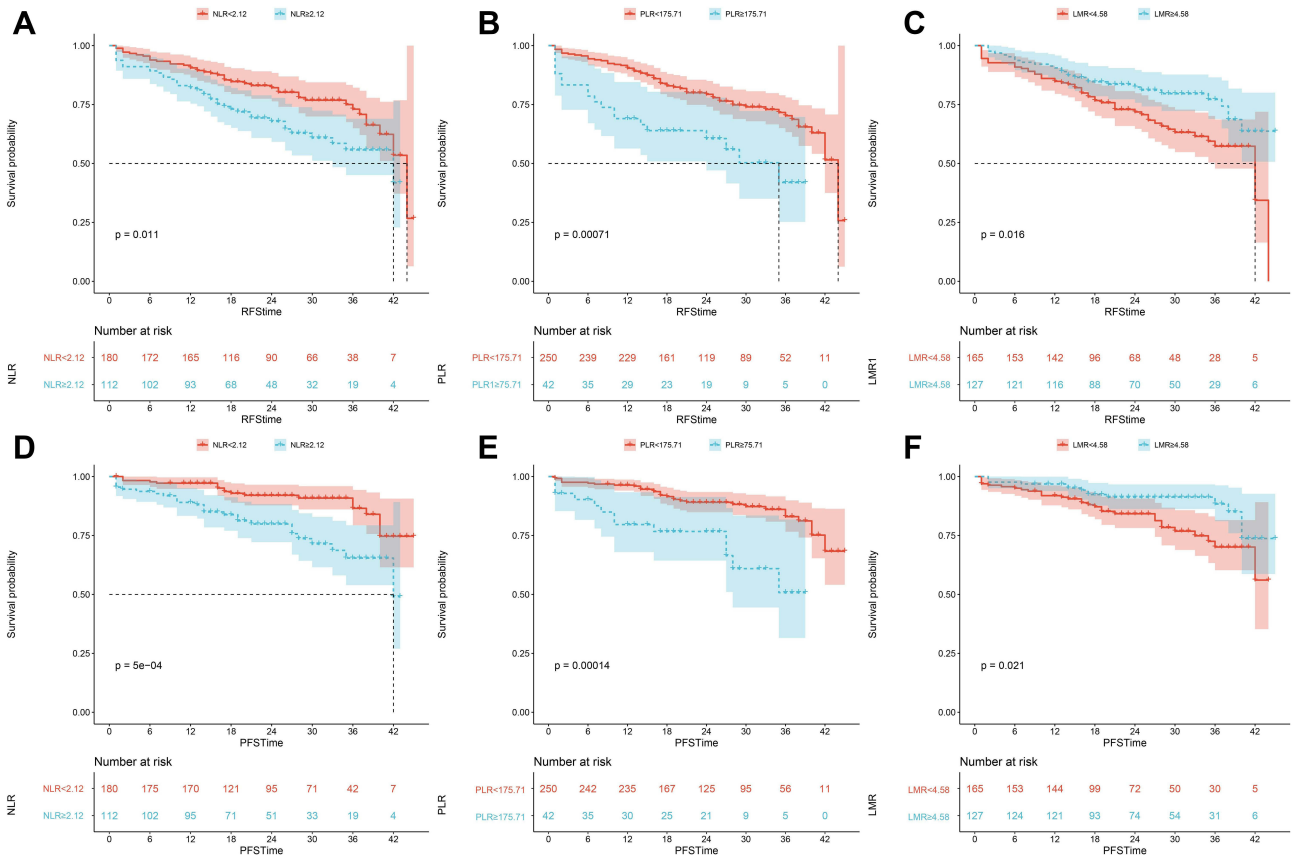

Figure 1 The Kaplan-Meier analysis of RFS stratified by (**A**) NLR, (**B**) PLR, (**C**) LMR; and the Kaplan-Meier analysis of PFS stratified by (**D**) NLR, (**E**) PLR, (**F**) LMR in the training cohort.

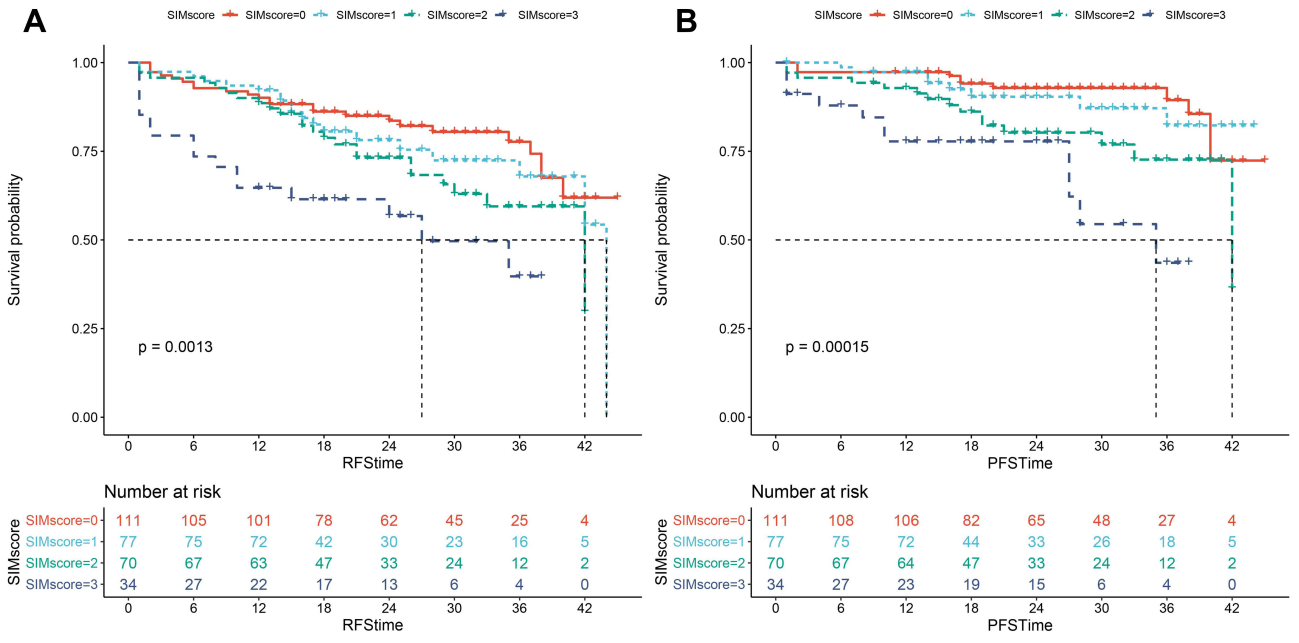

Figure 2 The Kaplan-Meier analysis of (**A**) RFS and (**B**) PFS stratified by SIM score in the training cohort.

Table 4 Univariable and Multivariable Analysis for Predicting Recurrence-Free Survival

Variables	Univariate HR	95% CI	p	Multivariate HR	95% CI	p
Age	0.998	[0.982, 1.015]	0.843			
Maximum tumor diameter	1.016	[1.000, 1.033]	0.056			
Gender			0.259			
Female	1(reference)					
Male	1.491	[0.745, 2.982]				
BMI			0.189			
<25	1(reference)					
≥25	0.732	[0.459, 1.167]				
T category			0.013			0.294
Ta	1(reference)			1(reference)		
T1	1.729	[1.120, 2.669]		1.291	[0.801, 2.08]	
Prior recurrence status			0.001			0.001
Primary	1(reference)			1(reference)		
Recurrent	2.461	[1.465, 4.134]		2.564	[1.479, 4.446]	
Pathology grade			0.039			0.217
Low-grade	1(reference)			1(reference)		
High-grade	1.628	[1.024, 2.589]		1.379	[0.828, 2.299]	
Tumor number			0.003			0.008
Single	1(reference)			1(reference)		
Multiple	2.045	[1.274, 3.283]		1.968	[1.196, 3.237]	
Bladder neck invasion			0.003			0.533
No	1(reference)			1(reference)		
Yes	2.133	[1.295, 3.513]		1.194	[0.684, 2.083]	
SIM score			0.003			0.002
0	1(reference)			1(reference)		
1	1.235	[0.675, 2.258]	0.494	1.118	[0.601, 2.083]	0.724
2	1.672	[0.942, 2.966]	0.079	1.583	[0.881, 2.844]	0.124
3	3.265	[1.726, 6.177]	<0.001	3.323	[1.732, 6.375]	<0.001
Smoking status			0.256			
No	1(reference)					
Yes	1.292	[0.830, 2.009]				
Smoking years			0.419			
0	1(reference)					
<30	1.447	[0.830, 2.523]	0.193			
≥30	1.167	[0.670, 2.033]	0.585			
Cigarettes per day			0.209			
0	1(reference)					
<30	1.204	[0.758, 1.914]	0.432			
≥30	2.238	[0.887, 5.648]	0.088			

Abbreviations: BMI, body mass index, weight/height^2; SMI, systemic inflammatory markers; N, number of patients; HR, hazard ratio; CI, confidence interval.

predictors of RFS, while prior recurrence status (HR=3.172, p=0.003), pathology grade (HR=2.644, p=0.016), tumor number (HR=3.325, p=0.002), and SIM score (p=0.001) were independent predictors of PFS.

Development and Validation of the Nomogram Models

The nomogram models were constructed based on the results in the Cox regression (Figures 3A and 4A). The receiver operating characteristic (ROC) curves showed the great predictive accuracy regarding 1-, 2-, and 3-year PFS rates of the models, with the AUC reaching 0.807, 0.775 and 0.862, respectively (Figure 4B). Meanwhile, when predicting patient's 1-, 2-, and 3-year RFS rates, the AUC was 0.667, 0.689 and 0.713, respectively (Figure 3B). The calibration plots validated by 1000 bootstrap

Table 5 Univariable and Multivariable Analysis for Predicting Progression-Free Survival

Variables	Univariate HR	95% CI	p	Multivariate HR	95% CI	p
Age	0.999	[0.978, 1.021]	0.94			
Maximum tumor diameter	1.026	[1.004, 1.048]	0.018	1.01	[0.988, 1.033]	0.382
Gender			0.106			
Female						
Male	2.633	[0.815, 8.502]				
BMI			0.908			
<25						
≥25	0.965	[0.527, 1.767]				
T category			0.002			0.353
Ta				1(reference)		
T1	2.642	[1.444, 4.835]		1.371	[0.705, 2.67]	
Prior recurrence status			<0.001			0.003
Primary				1(reference)		
Recurrent	3.188	[1.665, 6.104]		3.172	[1.491, 6.75]	
Pathology grade			0.001			0.016
Low-grade				1(reference)		
High-grade	3.395	[1.631, 7.067]		2.644	[1.195, 5.851]	
Tumor number			0.001			0.002
Single				1(reference)		
Multiple	3.22	[1.592, 6.516]		3.325	[1.551, 7.129]	
Bladder neck invasion			<0.001			0.329
No				1(reference)		
Yes	3.447	[1.865, 6.370]		1.415	[0.704, 2.844]	
SIM score			0.001			0.001
0				1(reference)		
1	1.171	[0.470, 2.916]	0.735	1.139	[0.443, 2.934]	0.787
2	2.459	[1.129, 5.357]	0.024	2.564	[1.143, 5.755]	0.022
3	5.098	[2.190, 11.871]	<0.001	5.354	[2.185, 13.121]	<0.001
Smoking status			0.144			
No						
Yes	1.549	[0.862, 2.784]				
Smoking years			0.261			
0	1(reference)					
<30	1.798	[0.880, 3.676]	0.108			
≥30	1.344	[0.643, 2.813]	0.432			
Cigarettes per day			0.192			
0	1(reference)					
<30	1.448	[0.785, 2.669]	0.236			
≥30	2.682	[0.801, 8.973]	0.109			

Abbreviations: BMI, body mass index, weight/height^2; SMI, systemic inflammatory markers; N, number of patients; HR, hazard ratio; CI, confidence interval.

resampling proved the appreciable reliability of new models (Figures 3C and 4C). The DCA curve demonstrated a greater clinical benefit of the new models (Figures 3D and 4D). The AUC and calibration curves of the established models in the validation cohort for predicting RFS and PFS also showed great performance (Figure 5). Patients were then classified into low-risk group or high-risk group based on the models (cutoff-value=149.95 for RFS and 180.84 for PFS). The Kaplan–Meier survival analysis showed the patients in the high-risk group had a clearly worse survival outcomes than patients in the low-risk group (both $p < 0.0001$) (Figure 6).

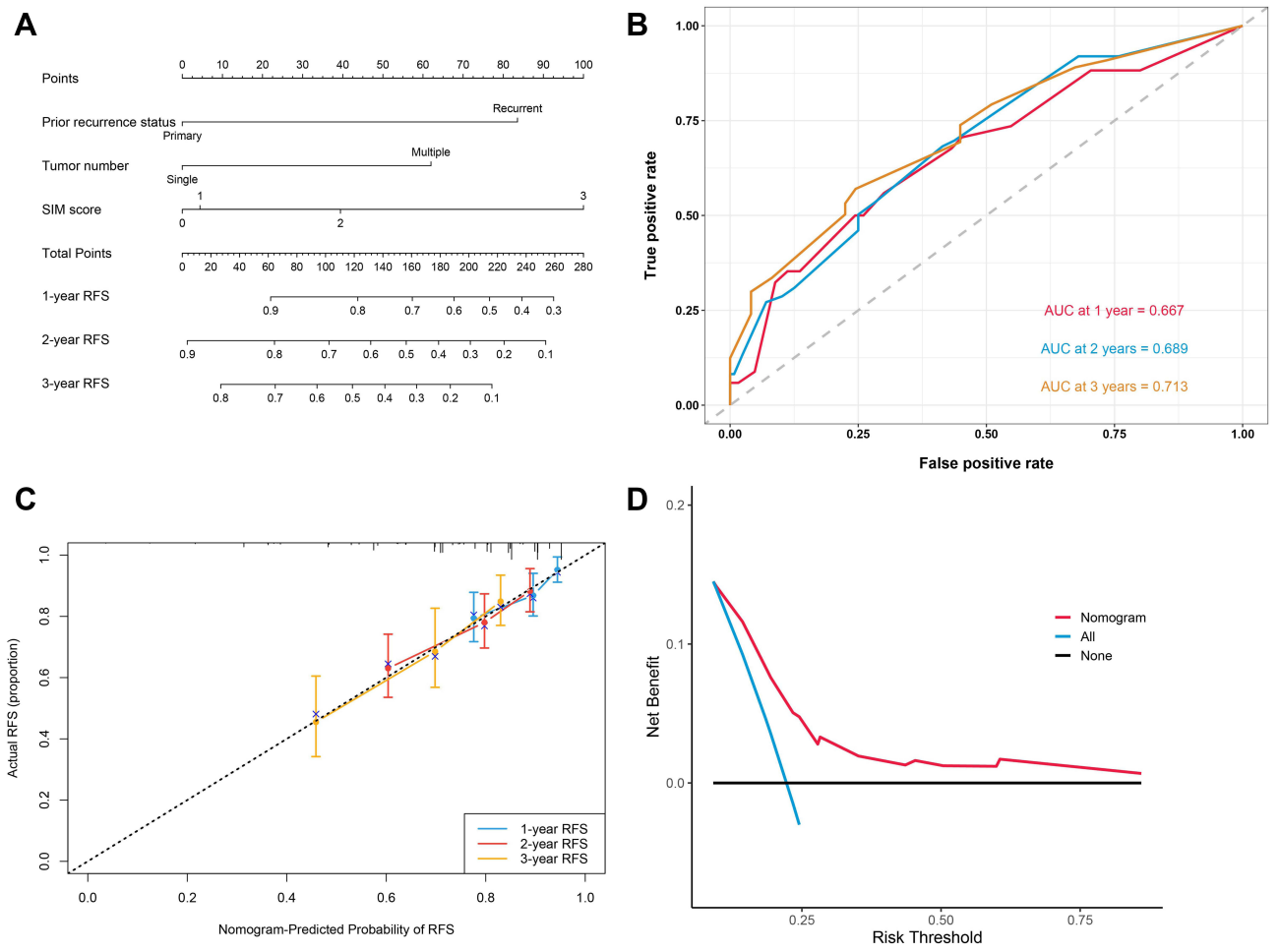

Figure 3 (**A**) The nomogram for predicting RFS after TURBT for NMIBC. (**B**) Time-dependent ROC curves of the nomogram for predicting RFS in the training cohort. (**C**) Calibration plot of the nomogram by bootstrapping with 1000 resamples for predicting RFS in the training cohort. (**D**) Decision-curve analyses demonstrating the net benefit associated with the use of the model for predicting RFS.

Discussion

Our study explored the value of the SIM score in predicting RFS and PFS in NMIBC patients who underwent TURBT. The results showed that the SIM score remained a statistically significant independent predictor even after adjusting for common clinicopathological variables and tumor status data such as BNI. The models based on variables, including the SIM score, had great accuracy and stability. To our knowledge, this is the first predictive models constructed for bladder cancer that includes the SIM score.

Systemic inflammatory response markers have been widely demonstrated to play an important role in assessing the prognosis of patients with a variety of malignancies.[18,26–29] NLR, PLR, and LMR are the most well-studied of these factors. In 2018, a review of previous literature by Vartolomei et al In six studies that used multivariate analysis to assess the value of NLR in tumor recurrence and progression in patients with NMIBC, all confirmed that elevated NLR was associated with reduced RFS and PFS.[21] A study by Wu et al demonstrated that, for NMIBC patients receiving BCG immunotherapy, the PLR levels before and during induction treatment may serve as indicators of disease progression and recurrence.[30] Yıldız et al showed that reduced LMR was an independent risk factor for predicting tumor recurrence in NMIBC patients.[22] By inducing cytotoxic cell death and preventing tumor cell growth and metastasis, lymphocytes play a critical role in the host's ability to fight tumors. A reduction in lymphocytes affects the body's ability to fight tumors, which raises the chance of cancer development and recurrence.[31] While neutrophils emit huge amounts of vascular endothelial growth factor, which speeds up tumor angiogenesis and encourages tumor carcinogenesis and metastasis,[16]

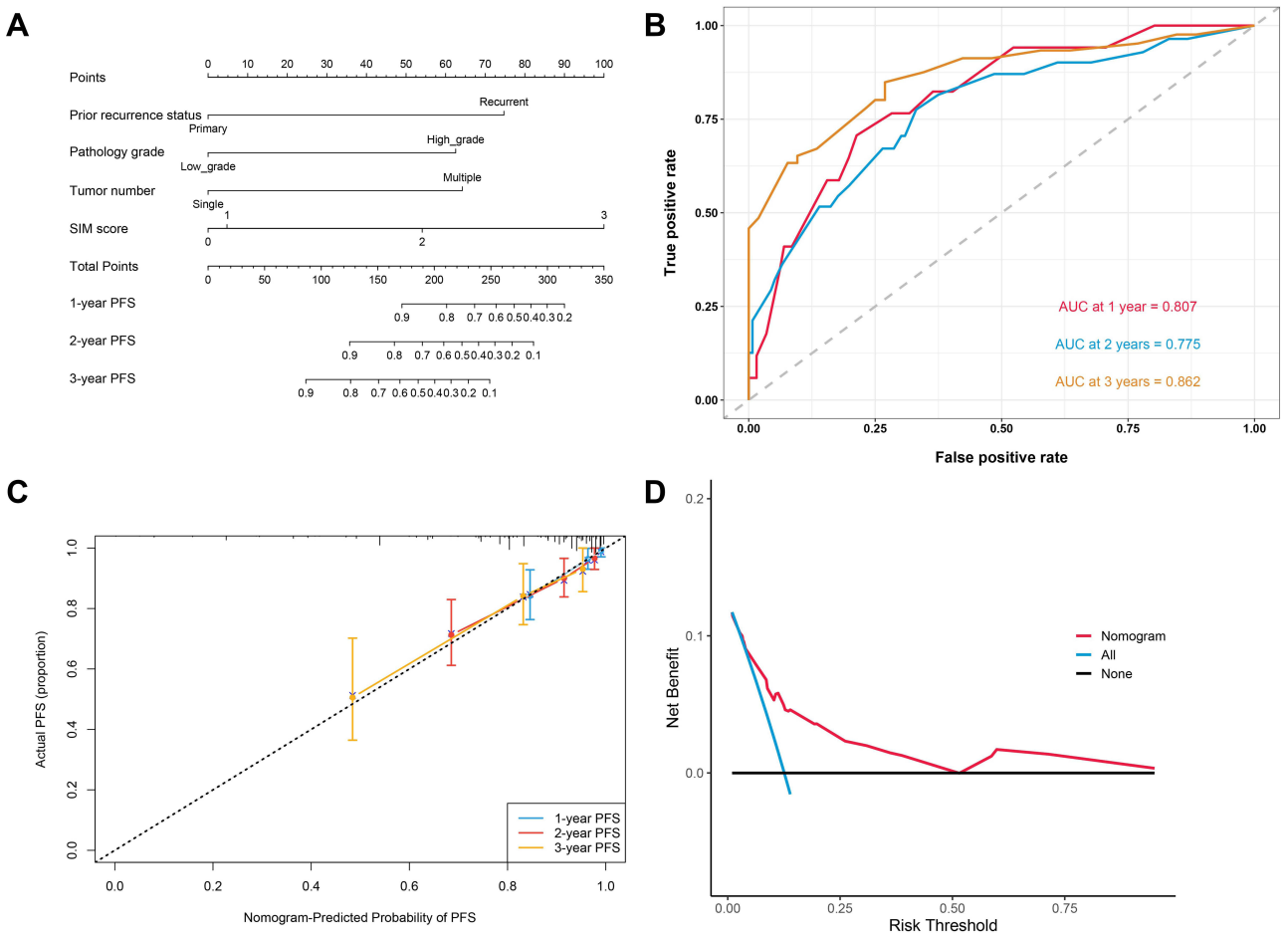

Figure 4 (**A**) The nomogram for predicting PFS after TURBT for NMIBC. (**B**) Time-dependent ROC curves of the nomogram for predicting PFS. (**C**) Calibration plot of the nomogram by bootstrapping with 1000 resamples for predicting PFS. (**D**) Decision-curve analyses demonstrating the net benefit associated with the use of the model for predicting PFS.

platelets boost the production of angiogenic factors, which stimulate tumor angiogenesis and protect tumor cells from cytolysis.[14] In the tumor microenvironment, monocytes can differentiate into tumor-associated macrophages, which promote tumor infiltration and metastasis. An increase in serum monocyte count can reflect the activity of tumor-associated macrophages.[28] Previous studies have shown that the anatomical location of the tumor at the time of the first electrosurgery is closely related to tumor recurrence and progression. This may be related to factors such as the pathological and histological characteristics of the different sites and intraoperative visualization. Intraoperatively, patients with BNI have a greater risk of tumor residuals.[32,33] In recent years, the emergence of the field of molecular biomarkers[34–36] may have been of further help in predicting treatment response in patients with bladder cancer. Also, liquid biopsy[37] has potential as a new technique in the therapeutic evaluation of patients with bladder cancer, factors that have not been fully demonstrated clinically have great value for future research. Despite the attractiveness of these metrics, prospective large studies of these metrics in the clinical setting are difficult due to the high cost of the tests required, especially in countries and regions where genetic testing is not yet widely available. Hematologic markers such as the SIM score, for example, have better utility as essential tests in the perioperative period with the advantages of low price, easy access, and stable values, even if the disadvantage of their lower specificity cannot be ignored.

Based on our study, the SIM score was a strong predictor of survival prognosis in NMIBC patients, with higher scores associated with a poorer prognosis. Although BNI was a significant variable in predicting RFS and PFS in the univariate regression analysis, unfortunately, it was not significant in any of the multivariate analyses. We believe this may be due to the small sample size. Although smoking has been shown to be the most important causal factor in the development of

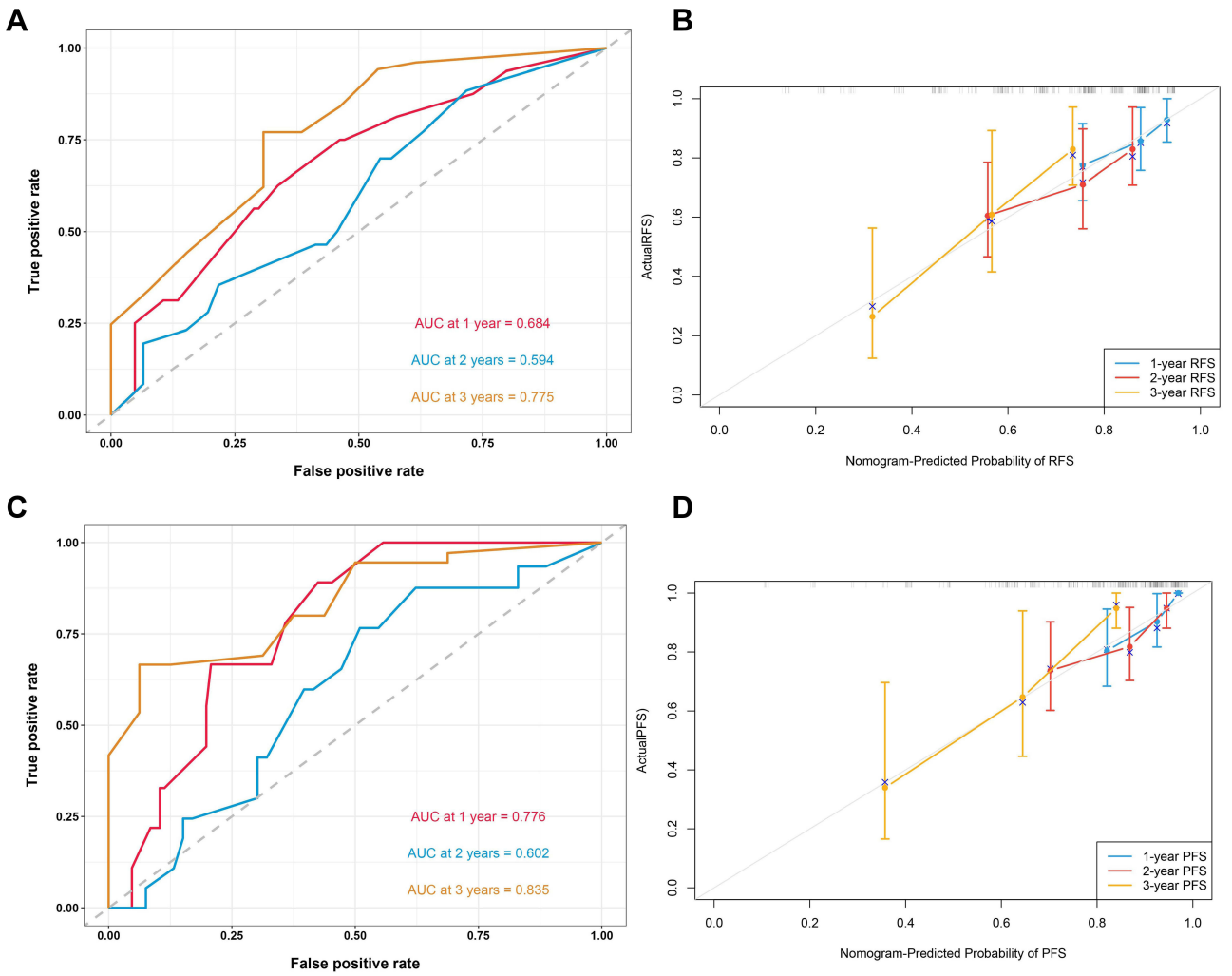

Figure 5 (**A**) Time-dependent ROC curves of the nomogram for predicting RFS in the validation cohort in the validation cohort. (**B**) Calibration plot of the nomogram by bootstrapping with 1000 resamples for predicting RFS in the validation cohort in the validation cohort. (**C**) Time-dependent ROC curves of the nomogram for predicting PFS in the validation cohort in the validation cohort. (**D**) Calibration plot of the nomogram by bootstrapping with 1000 resamples for predicting PFS in the validation cohort in the validation cohort.

bladder cancer, the relationship between smoking intensity and tumor recurrence and progression remains unclear.[38,39] Our study could not confirm that smoking status was associated with recurrence or progression of NMIBC, which may be explained by several reasons: due to social factors, some patients may conceal their smoking history at the time of initial diagnosis or follow-up, while our sample size was still not large enough to influence the results of the study.

There are inevitable limitations to our study. First, there may be some heterogeneity in the samples from the two medical centers. Second, conclusions might have been more reliable if preoperative serological indicators could have been collected the exact day before surgery. Also, although the vast majority of subjects included in the study received adjuvant intravesical instillation and subsequent further intravesical chemotherapy or BCG treatment, we have not included this variable in our analysis. Whereas, as the first study to build predictive models based on the SIM score, our study has some positive implications for the prognostic analysis of NMIBC patients.

Conclusion

We constructed novel models for predicting the survival prognosis of NMIBC patients based on the SIM score and clinicopathological features. Due to the inherent drawbacks of a retrospective design, more prospective studies are needed to confirm this result in the future.

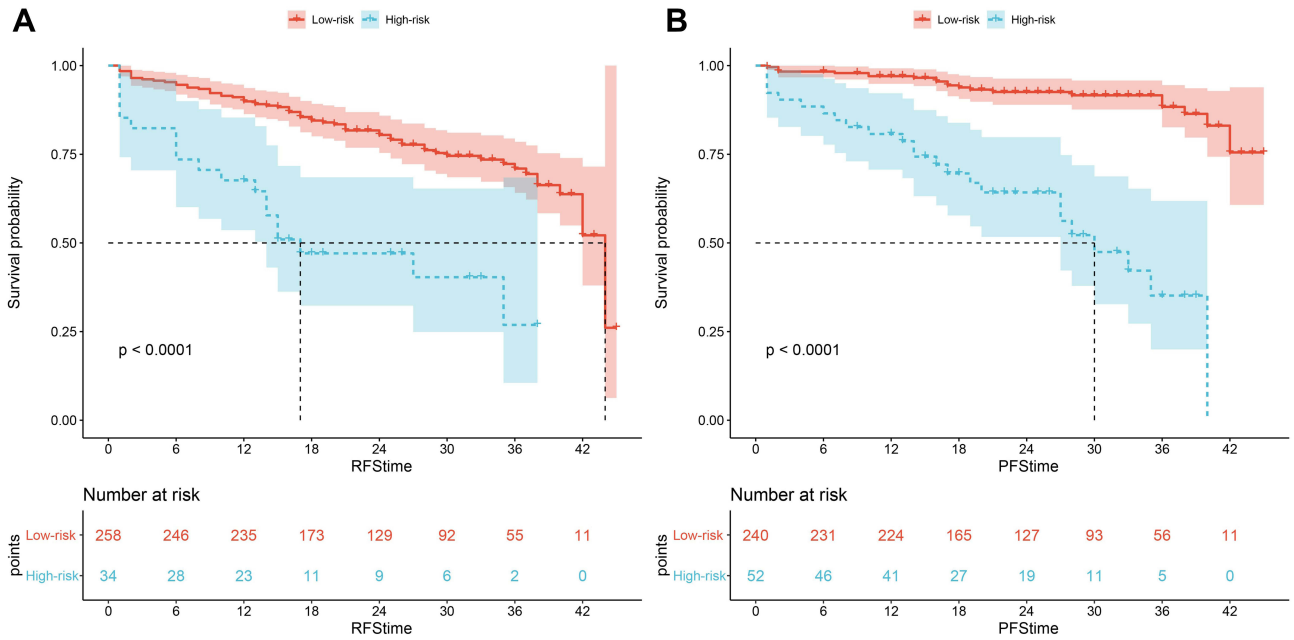

Figure 6 The Kaplan-Meier curves of low-risk and high-risk groups based on the prediction of the nomogram models for (**A**) RFS and (**B**) PFS.

Ethics Approval and Consent to Participate

This study was performed in line with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFT2022-KL340-01) and the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (2022-E318-01). The requirement for written informed consent has been accordingly waived due to the retrospective study design. Patient data involved in the study are confidential. Due to ethical restrictions, the raw data underlying this paper are available upon request to the corresponding author.

Author Contributions

All authors made a significant contribution to the work reported, whether it was in the conception, study design, execution, data acquisition, analysis and interpretation, or in all these areas. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests for this work.

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