Development and external validation of a model to predict recurrence in patients with non-muscle invasive bladder cancer

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Background: Most patients initially diagnosed with non-muscle invasive bladder cancer (NMIBC) still have frequent recurrence after urethral bladder tumor electrodesiccation supplemented with intravesical instillation therapy, and their risk of recurrence is difficult to predict. Risk prediction models used to predict postoperative recurrence in patients with NMIBC have limitations, such as a limited number of included cases and a lack of validation. Therefore, there is an urgent need to develop new models to compensate for the shortcomings and potentially provide evidence for predicting postoperative recurrence in NMIBC patients.

Methods: Clinicopathologic characteristics and follow-up data were retrospectively collected from 556 patients with NMIBC who underwent transurethral resection of bladder tumors by electrocautery (TURBT) from January 2014 to December 2023 at the Affiliated Hospital of Zunyi Medical University and 167 patients with NMIBC who underwent the same procedure from January 2018 to April 2024 at the Third Affiliated Hospital of Zunyi Medical University. Independent risk factors affecting the recurrence of NMIBC were screened using the least absolute shrinkage and selection operator (Lasso) and Cox regression analysis. Cox risk regression models and randomized survival forest (RSF) models were developed. The optimal model was selected by comparing the area under the curve (AUC) of the working characteristics of the subjects in both and presented as a column-line graph.

Results: The study included data from 566 patients obtained from the affiliated hospital of Zunyi Medical University and 167 patients obtained from the third affiliated hospital of Zunyi Medical University. Tumor number, urine leukocytes, urine occult blood, platelets, and red blood cell distribution width were confirmed as independent risk factors predicting RFS by Lasso-Cox regression analysis. The Cox proportional risk regression model and RSF model were constructed based on Lasso, which showed good predictive efficacy in both training and validation sets, especially the traditional Cox proportional risk regression model. In addition, the discrimination, consistency, and clinical utility of the column-line graph were assessed using C-index, area under the curve (AUC), calibration curve, and decision curve analysis (DCA). Patients at high risk of recurrence can be identified early based on risk stratification.

Conclusion: Internal and external validation has demonstrated that the model is highly discriminative and stable and can be used to assess the risk of early recurrence in NMIBC patients and to guide clinical decision-making.

1 Introduction

Approximately 75% of patients with bladder cancer are diagnosed with non-muscle invasive bladder cancer (NMIBC) at their initial visi (1). Transurethral resection of bladder tumor (TURBT) supplemented with intravesical instillation is the standard treatment for NMIBC. With the rapid development of medical technology in recent years, the surgical approach has gradually matured, and the use of some novel therapeutic strategies, such as targeted therapies and immune checkpoint inhibitors, has enhanced patient outcomes. However, the prognosis of NMIBC patients still faces great challenges, mainly due to their high recurrence rate. About 50–70% of NMIBC patients will recur after surgery (2), and 10–20% of patients finally progress to muscle-invasive bladder cancer (MIBC) or metastatic bladder cancer (3). The recurrence of NMIBC is affected by a variety of factors, such as the pathological stage of the tumor, the number of tumors, the size of the tumors, and the operating level of the surgeon. Therefore, it is crucial to comprehensively analyze the risk factors affecting the recurrence of NMIBC. The main scoring models that are widely used to predict recurrence in NMIBC patients are the European Association of Urology (EAU) scoring model, the European Organization for Research and Treatment of Cancer (EORTC) scoring model, and the Spanish Urological Oncology Treatment Group (CUETO) scoring model (4–6). These models, developed for different NMIBC populations (7), cannot be fully applied to all NMIBC patients and have not yet taken into account the possible presence of biomarker variables such as blood and urine.

Previous studies have shown that changes in the values of certain inflammatory markers in the blood are associated with the recurrence of NMIBC, such as systemic immunoinflammatory index (SII) (8–11), mean platelet volume to lymphocyte ratio (12), and neutrophil/lymphocyte ratio (11, 13). Platelets are important coordinators involved in inflammatory and immune responses (14) and play an important role in key aspects of tumor cell extravasation, tumor growth, immune escape, and distant metastasis (15). Thrombocytosis has been associated with poor prognosis in a variety of cancers, such as ovarian, lung, and gastrointestinal cancers (16–18), but the predictive value of platelet count in NMIBC has not been elucidated. In addition, certain urinary markers such as albumin, globulin, and Prognostic

Nutritional Index (PNI) have some predictive value for recurrence in patients with NMIBC (19). Some studies have shown that NMIBC patients with preoperative pyuria responded poorly to BCG treatment (20), and patients with pyuria had lower recurrence-free survival (RFS) and progression-free survival (PFS) than patients without pyuria (21, 22). In addition, hematuria of the naked eye (23), urine erythrocyte count (9), and urine leukocyte count may be potential predictors of RFS (24). Nonetheless, potential predictive biomarkers that may be present in urine have been rarely mentioned. These indicators obtained based on blood and urine are cost-effective, easy to obtain, and non-invasive to perform, and are expected to play an important predictive role in the prognosis of NMIBC.

Therefore, this study incorporated relevant parameters in urine and combined them with statistically significant predictors from previous studies for a comprehensive assessment. The development of a new predictive model using machine learning is dedicated to improving the predictive performance of recurrence outcomes in NMIBC patients, and external validation is used to demonstrate the accuracy and clinical applicability of the model in the real world, which will help to improve the treatment and clinical decision-making for NMIBC patients.

2 Methods

2.1 Study population

Diese Studie complied with the Declaration of Helsinki and the ethical requirements of the Institutional Ethics Research Committee and was approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical University (KLLY-2023-107). A total of 556 NMIBC patients who underwent initial TURBT from January 2014 to December 2023 at the Affiliated Hospital of Zunyi Medical University were selected as an internal validation cohort. In addition, 167 NMIBC patients who underwent the same procedure at the Third Affiliated Hospital of Zunyi Medical University from January 2018 to April 2024 were selected as the external validation cohort. Inclusion criteria for the study population: (1) Patients diagnosed with NMIBC by histopathologic findings after the first TURBT; (2) Patients with complete basic clinical information and data; and (3) Patients who did not receive relevant antitumor

treatments, such as radiotherapy, chemotherapy, and immunotherapy, prior to the operation. Exclusion Criteria: (1) Patients with combination of other cancers; (2) Patients with tumor recurrence, progression, or death within einem Monat nach Surgery. The case-screening process is shown in Figure 1.

2.2 Data collection

The data collected in this study included general information, laboratory findings, and clinicopathologic features of the patients. General Information: age, gender, blood type, smoking history, diabetes, hypertension, cerebrovascular disease, and urological disease; Clinicopathological Characteristics: number, size, growth location, growth mode of the tumor, bladder perfusion medication, histopathological staging and grading of the tumor; and peripheral blood laboratory test indexes in the week before the operation: blood glucose, creatinine, uric acid, albumin, globulin, total protein, A/G, platelets (PLT), hemoglobin, red blood cell distribution width (RDW), prothrombin time, and activated partial thromboplastin; and urinary laboratory indicators within 1 week before surgery: leukocytes in urine (LEU), leukocytes in urine (quantitative), urinary proteins, urinary occult blood (BLD), and urinary nitrite. NMIBC was staged according to the 8th edition of the TNM staging method, published by the International Union Against Cancer (UICC) in 2017.

2.3 Follow-up

Follow-up was mainly based on telephone follow-up and outpatient follow-up. Low-risk NMIBC patients underwent the 1st cystoscopy at the 3rd month postoperatively, and if the cystoscopy was negative, a second cystoscopy was performed at 1 year postoperatively, and then once a year for 5 years. Patients with high-risk NMIBC had a repeat cystoscopy every 3 months for 2 years after surgery and a repeat cystoscopy every 6 months thereafter for 5 years. The follow-up deadline was April 31, 2024. The follow-up included the drugs for bladder irrigation, the time of cystoscopy, abdominal ultrasound, and CT examination to observe postoperative tumor recurrence. If new organisms in the bladder were found on examination, a biopsy was taken under cystoscopy or tissue biopsy was taken by TURBT after admission to the hospital and sent to pathology to clarify whether the tumor was recurrent or not. Recurrence-free survival (RFS) was defined as the time to the first recurrence after surgery.

2.4 Statistical analysis

SPSS 29.0 software was used to statistically analyze the data. Measurement information that conformed to normal distribution was expressed as mean ± standard deviation (), and an independent samples t-test was used for comparison between groups; measurement information that did not conform to normal distribution was expressed as median (interquartile spacing), and the Mann-Whitney U test was used for comparison between groups; and counting information was described as frequency and percentile, and the $\chi2$ test was used for comparison between groups. Survival analysis was performed using Kaplan-Meier curves using the log-rank test. The data were randomly divided into training and validation sets in a ratio of 7:3. Multifactor analysis was performed using the backward stepwise method in COX regression analysis. Lasso-Cox regression models and RSF models were constructed using R software (version 4.2.1, https://www.r-project.org). Harrell's consistency index (C-index), area under the curve (AUC) of the subjects' work characteristics, calibration curves, and decision curve analysis (DCA) were used to evaluate the discriminability, accuracy, and clinical applicability of the COX regression models. Specificity, sensitivity, accuracy, precision, recall, and F1 value were used to evaluate the predictive performance of the RSF model.

3 Results

3.1 Patient characteristics

A total of 556 patients were enrolled, of which 249 (44.7%) had recurrence, 199 (35.8%) were male and 50 (9.0%) were female, 68 (12.2%) were younger than 60, and 181 (32.6%) were older than or equal to 60, with a mean follow-up of 22.8 months, ranging from 1 to 60 months, and a median RFS of 22.0 months. The 1-, 3-, and 5-year cumulative recurrence rates were 21.0% (117/556), 35.0% (193/556), and 45.0% (249/556), respectively, as shown in Supplementary Table 1. The two groups were characterized in terms of age, number of tumors, urinary leukocytes (qualitative), urinary leukocytes (quantitative), urinary occult blood, A/G, globulin, hemoglobin, PLT, erythrocytes, RDW, and prothrombin time; activated partial thromboplastin was statistically different (P < 0.05), as shown in Table 1.

3.2 Prediction model built based on Lasso-Cox regression

Using SPSS software, 556 patients were randomly divided into a training set (n = 385) and an internal validation set (n = 171) in a

FIGURE 1
The flow diagram shows the sample selection.

Flow diagram content:
- A total of 904 patients diagnosed with NMIBC in the Affiliated Hospital of Zunyi Medical University (n=706) + The Third Affiliated Hospital of Zunyi Medical University (n=198) were enrolled
- Excluded(n=142)
- Patients who refused TURBT(n=36) Patients with comorbid severe organic disease and other tumours (n=50) Patients with incomplete information (n=56)
- NMIBC patients receiving TURBT (n=762)
- Patients lost (n=39)
- Final enrolment of 723 (556 from the Zunyi Medical University Affiliated Hospital; 167 from the Third Affiliated Hospital of Zunyi Medical University)
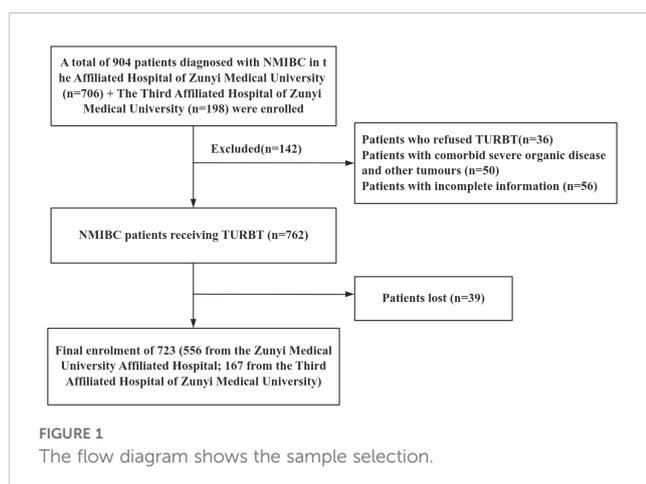
TABLE 1 The relationship between risk factors for recurrence and clinical pathological parameters after NMIBC electrocautery in the modeling group.

Variables	Total (n=385)	Recurrence (n=180)	Non- recurrence (n=205)	t/χ2/z	P value
Age				11.435	0.001
<60	132 (34.2)	46 (11.9)	86 (22.3)		
≥60	253 (65.7)	134 (34.8)	119 (30.9)		
Gender				0.065	0.798
Male	308 (80.0)	145 (37.7)	163 (42.3)		
Female	77 (20.0)	35 (9.1)	42 (10.9)		
Blood type				4.380	0.223
A	134 (34.8)	67 (17.4)	67 (17.4)		
B	104 (27.0)	49 (12.7)	55 (14.3)		
AB	41 (10.7)	13 (3.4)	28 (7.3)		
O	106 (27.5)	51 (13.2)	55 (14.3)		
Smoking				0.754	0.385
Yes	99 (25.7)	50 (13.0)	49 (12.7)		
No	286 (74.3)	130 (33.8)	156 (40.5)		
Diabetes mellitus				0.076	0.783
Yes	41 (10.6)	20 (5.2)	21 (5.5)		
No	344 (89.4)	160 (41.6)	184 (47.8)		
Hypertension				1.249	0.264
Yes	103 (26.8)	53 (13.8)	50 (13.0)		
No	282 (73.2)	127 (33.0)	155 (40.3)		
Cerebrovascular disease				0.008	0.930
Yes	11 (2.9)	5 (1.3)	6 (1.6)		
No	374 (97.1)	175 (45.5)	199 (51.7)		
Urinary system disease				1.262	0.261
Yes	168 (43.6)	84 (21.8)	84 (21.8)		
No	217 (56.4)	96 (24.9)	121 (31.4)		
Tumor number				128.447	<0.001
Single	248 (44.6)	45 (8.1)	203 (36.5)		
Multiple	308 (55.4)	204 (36.7)	104 (18.7)		
Tumor size				0.237	0.626
≤3cm	312 (81.0)	144 (37.4)	168 (43.6)		
>3cm	73 (19.0)	36 (9.4)	37 (9.6)		
Tumor location				4.358	0.225
Side wall	275 (71.4)	136 (35.3)	139 (36.1)		
Bladder neck	36 (9.4)	14 (3.7)	22 (5.7)		
Trigone	33(8.6)	16 (4.2)	17 (4.4)		
Other	41 (10.6)	14 (3.6)	27 (7.0)		

(Continued)

TABLE 1 Continued

Variables	Total (n=385)	Recurrence (n=180)	Non- recurrence (n=205)	t/χ2/z	P value
Growth pattern				2.252	0.813
Papilla	72 (18.7)	32 (8.3)	40 (10.4)		
Cauliflower	105 (27.3)	49 (12.7)	56 (14.5)		
Coralloid	45 (11.7)	25 (6.5)	20 (5.2)		
Carpet	14 (3.6)	5 (1.3)	9 (2.3)		
Waterweed	54 (14.0)	25 (6.5)	29 (7.5)		
Other	95 (24.7)	44 (11.4)	51 (13.2)		
Infusion medication				2.280	0.131
HydroxycamptotHecin	270 (70.1)	133 (34.5)	137 (35.6)		
Pirarubicin	115 (29.9)	47 (12.2)	68 (17.7)		
Tumor stage				0.009	0.922
Ta	155 (40.3)	72 (18.7)	83 (21.6)		
T1	230 (59.7)	108 (28.1)	122 (31.7)		
Tumor grade				3.712	0.156
Low malignant potential	112 (29.1)	50 (13.0)	62 (16.1)		
Low	203 (52.7)	90 (23.4)	113 (29.4)		
High	70 (18.2)	40 (10.4)	30 (7.8)		
LEU				136.454	**<0.001**
Positive	223 (40.1)	167 (30.0)	56 (10.1)		
Negative	333 (59.9)	82 (14.7)	251 (45.1)		
BLD				155.049	**<0.001**
Positive	114 (20.5)	110 (19.8)	4 (0.7)		
Negative	442 (79.5)	139 (25.0)	303 (54.5)		
Urinary protein				1.794	0.180
Positive	14 (3.6)	9 (2.3)	5 (1.3)		
Negative	371 (96.4)	171 (44.4)	200 (51.9)		
Urine nitrite				1.949	0.163
Positive	56 (14.5)	31 (8.1)	25 (6.5)		
Negative	329 (85.5)	149 (38.7)	180 (46.8)		
Blood sugar	-	4.9 (4.4~6.0)	4.8 (4.4~5.3)	-1.514	0.130
Creatinine	-	82.0 (73.0~94.8)	81.0 (71~91)	-0.911	0.362
Uric acid	-	346 (289~409)	340 (279.5~400.0)	-0.382	0.702
Total protein	-	65.3 ± 5.8	64.8 ± 5.6	0.752	0.452
Albumin	-	39.1 ± 4.0	39.8 ± 3.7	-1.736	0.083
Globulin	-	26.3 ± 4.3	25.0 ± 3.7	3.272	**0.001**
A/G	-	1.5 (1.3~1.7)	1.6 (1.4~1.8)	-3.301	**0.001**
Platelet	-	160.5 (114~191)	189 (161~230)	-6.630	**<0.001**
Leukocyte	-	5.9 (4.8~7.3)	5.8 (4.8~6.9)	-1.209	0.227

(Continued)

TABLE 1 Continued

Variables	Total (n=385)	Recurrence (n=180)	Non- recurrence (n=205)	t/χ2/z	P value
Urine nitrite				1.949	0.163
Erythrocyte	-	4.3 ± 0.6	4.4 ± 6.0	-2.355	**0.019**
Hemoglobin	-	133.5 (120~143)	138 (123~147)	-2.621	**0.009**
Thrombin time	-	19.5 (17.2~21.5)	17.9 (17.0~19.6)	-3.879	**<0.001**
Fibrinogen	-	2.8 (2.3~3.3)	2.7 (2.3~3.2)	-0.010	0.992
Red blood cell distribution width		13.4 (12.8~14.1)	13.1 (12.6~13.7)	2.771	**0.006**
U-LEU	-	10.0 (0.0~54.8)	5.0 (0.0~27.5)	-2.110	**0.035**
Activated partial Prothrombin	-	29.4 (25.9~34.3)	27.1 (25.0~31.9)	-3.152	**0.002**
Alanine aminotransferase	-	17.0 (12.0~24.0)	27.5 (13.0~27.5)	-1.785	0.074
Aspartate aminotransferase	-	23.0 (19.0~28.0)	24.0 (20.0~28.0)	-0.851	0.395
AST/ALT	-	1.3 (1.0~1.7)	1.3 (1.0~1.6)	-1.771	0.077

The meaning of bold values indicates P<0.05 and has statistical significance.

ratio of 7:3. In order to avoid omission of potentially important factors, 16 variables with P<0.1 in the modeling set (age, tumor number, LEU, urine leukocytes (quantitative), BLD, A/G, globulin, hemoglobin, PLT, erythrocytes, RDW, prothrombin time, activated partial thromboplastin, alanine aminotransferase, AST/ALT, albumin) were screened by Lasso regression (Figure 2). A 10-fold cross-validation method and 52 iterations of analysis were performed using the library (GLMNET) software package, and

the model with excellent performance but with the lowest number of variables was obtained at λ of 0.00352 (Log λ = 0.04342118). number of tumors: partial regression coefficient = 0.67593800, LEU: partial regression coefficient = -0.90570221, BLD: partial regression coefficient = -1.07517848, PLT: partial regression coefficient = -0.70723872, RDW: partial regression coefficient = -0.17083061 were included in Cox multifactor analysis. The results showed that BLD, LEU, RDW, and tumor number were
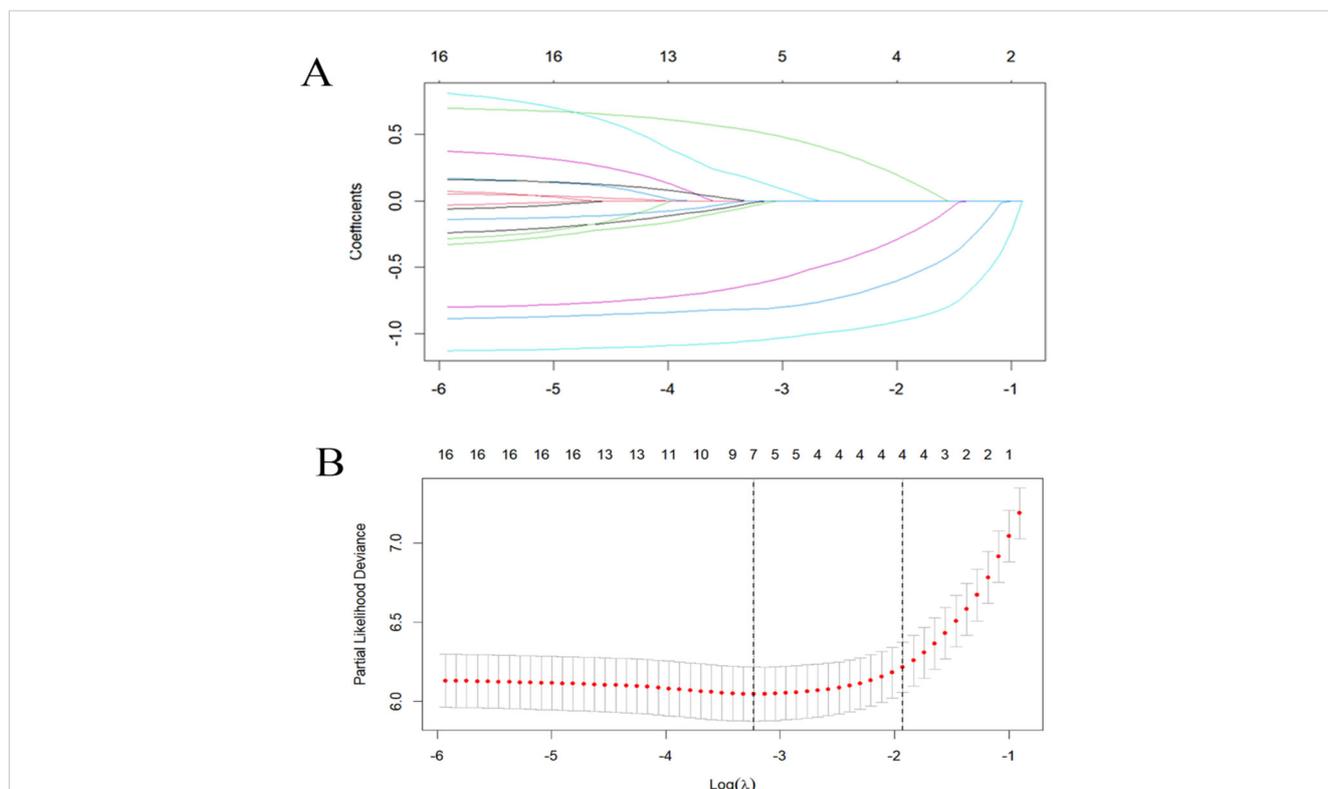

FIGURE 2
Lasso regression analysis was used to select screening variables. **(A)** The variation characteristics of variable coefficients; **(B)** The optimal λ-value process is screened by a 10-fold cross-validation process.
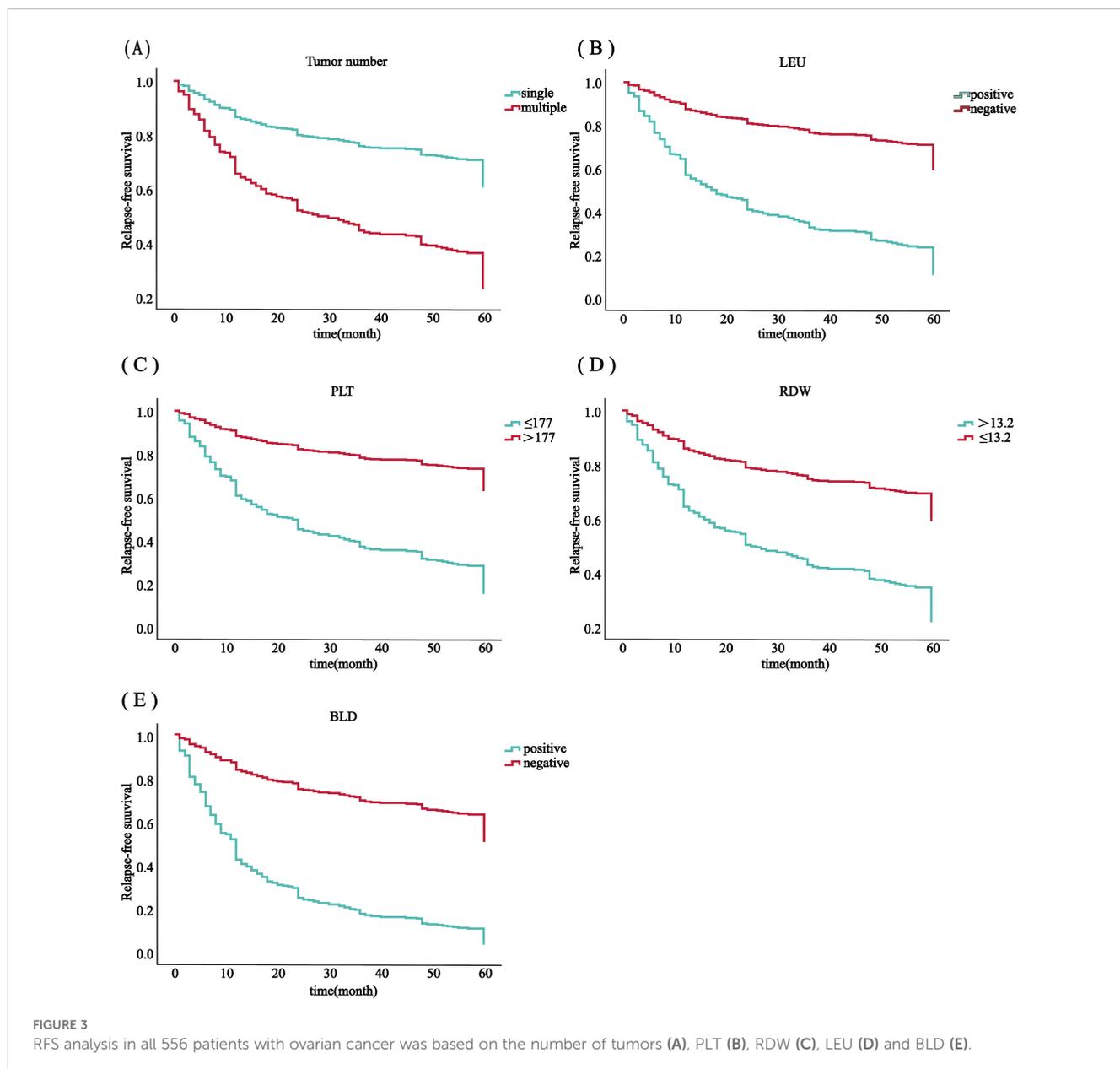
independent risk factors for NMIBC recurrence, and PLT was a protective factor (Table 2). Time-dependent recurrence curves of the K-M method were plotted based on the above five indicators to see whether they predicted poor patient outcomes (Figure 3). A prognostic model for predicting recurrence was also constructed for screening people at high risk of recurrence for timely intervention.

3.3 Evaluation of the Lasso-Cox regression prediction model

The C-index for the training set and internal validation set of the COx regression model was calculated to be 0.821 (95% CI: 0.792~0.850) and 0.726 (95% CI: 0.669~0.783), respectively, by calling the library(survival) package. The model was trained by a

TABLE 2 Cox proportional hazards regression to predict recurrence based on Lasso regression.

Variables	B	SE	Wald	HR (95.0% CI)	P value
BLD	-0.718	0.187	14.817	2.051 (1.423-2.956)	0.004
PLT	-0.007	0.001	29.695	0.993 (0.990-0.995)	<0.001
LEU	0.528	0.151	13.368	1.695 (1.261-2.279)	<0.001
RDW	0.120	0.050	5.742	1.128 (1.022-1.244)	0.017
Number of tumors	0.749	0.171	19.150	2.114 (0.998-1.801)	<0.0011

FIGURE 3
RFS analysis in all 556 patients with ovarian cancer was based on the number of tumors (A), PLT (B), RDW (C), LEU (D) and BLD (E).
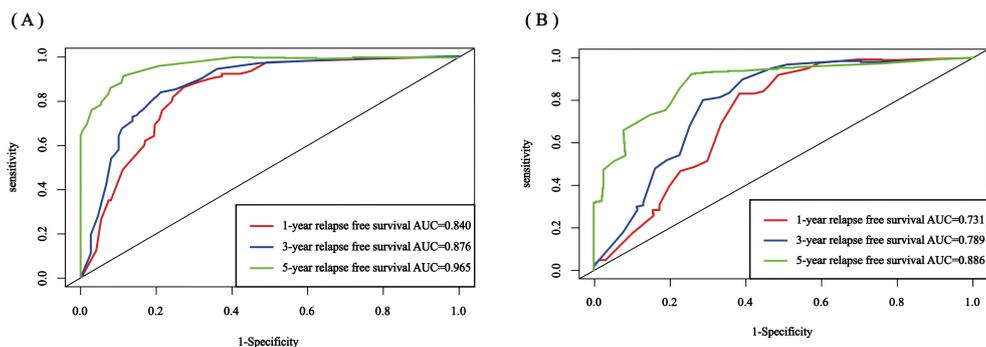
FIGURE 4
Nomogram ROC curves for 1-, 3-, and 5-year RFS for the training set and internal validation set. **(A)** training set; **(B)** internal validation set. ROC, receiver operating characteristic; AUC, area under the curve; RFS, recurrence-free survival.

1000-time resampling method through a library (PEC) software package. The area under the ROC curve AUCs of the RFS for 1, 3, and 5 years in the training and internal validation sets were plotted using the library (survival ROC) and library (foreign) software packages were 0.840, 0.876, and 0.965; and 0.731, 0.789, and 0.886, respectively (Figures 4A, B). The results showed that the model exhibited high accuracy in predicting recurrence in patients within 5 years. The calibration curves and clinical decision curves for RFS at 1, 3, and 5 years in the training and internal validation sets were plotted using the library(rms) and library(survival) software packages, and the predicted probabilities were closer to the actual direction, indicating a high consistency of the model (Figures 5A–F). In addition, we also assessed the clinical applicability of the model, and DCA demonstrated that patients achieved better net clinical benefit (Figures 6A–F).
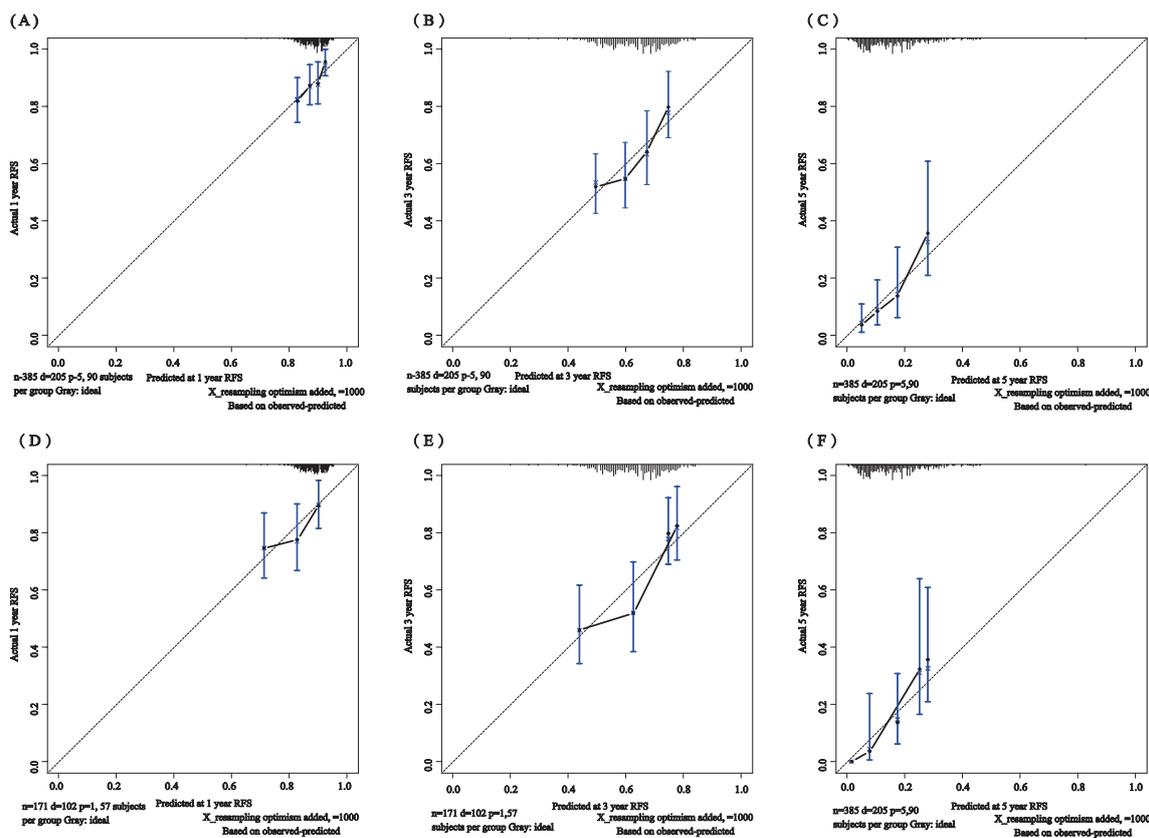

FIGURE 5
Calibration curves of the training set for 1-year **(A)**, 3-year **(B)**, and 5-year **(C)** and the internal validation set for 1-year **(D)**, 3-year **(E)**, and 5-year **(F)**. The blue curve is the prediction curve, and the dashed line is the reference curve.

FIGURE 6
Decision curve analysis of the training set for 1-year **(A)**, 3-year **(B)**, and 5-year **(C)** and the internal validation set for 1-year **(D)**, 3-year **(E)**, and 5-year **(F)**.
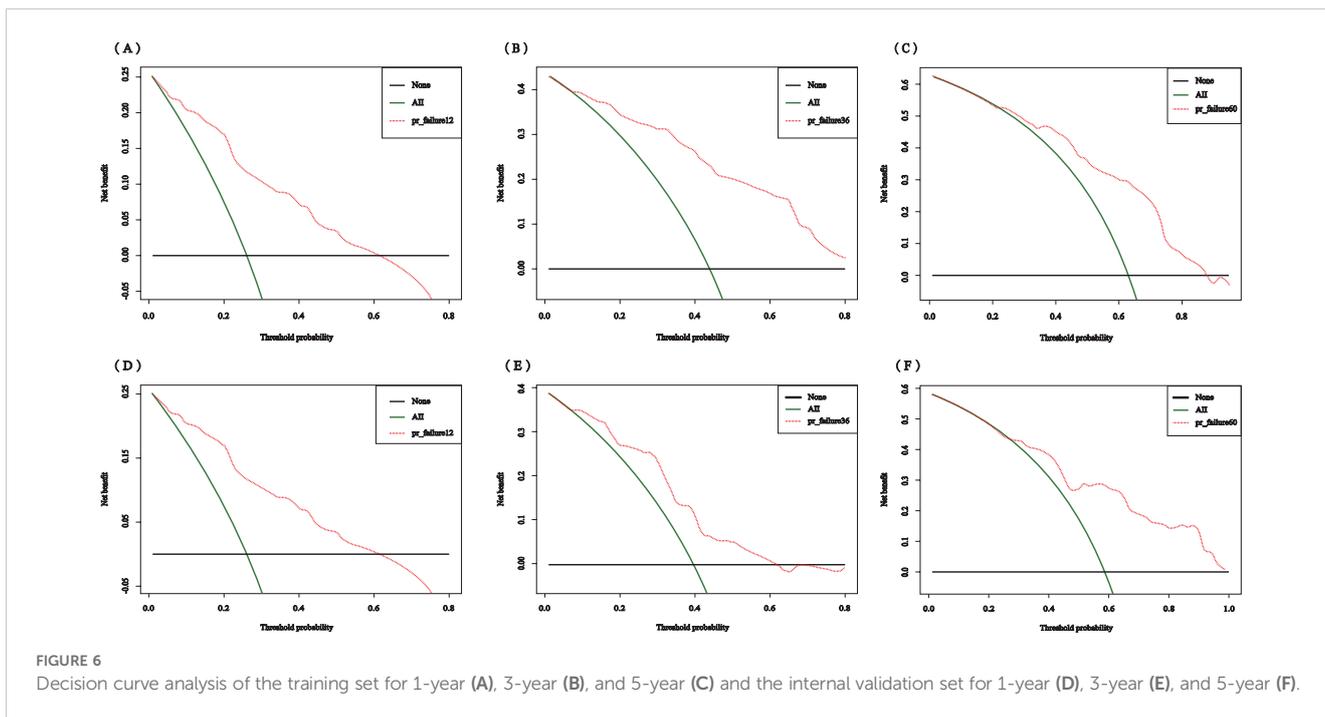
3.4 Prediction model built based on a random survival forest

The RSF model was constructed using the randomForest, caret, and pROC software packages. When setting the random seed to 123 and adjusting the parameter Mtry = 2, the training set ntree was 400, Out of bag (OOB) = 8.83%, and the squared mean of residuals (MSE) = 0.07; the validation set ntree was 250, OOB = 18.34%, and the MSE = 0.14, and the error rate of the model was stabilized (Figures 7). The importance of the variables was ranked according to the VIMP method, and they were, in order, tumor number, LEU, BLD, PLT, and RDW (Figure 8). Among them, tumor number had the strongest importance, and RDW had the weakest importance.

3.5 Evaluation of random forest prediction models

The accuracy, precision, recall, F1 value, sensitivity, and specificity values of the RSF model were calculated by calling the caret software package to draw the confusion matrix (Figure 9) to assess the accuracy and generalization ability of the RSF model (Supplementary Table 2). The results show that the model exhibits good prediction and generalization ability in both the training and validation sets. In addition, the AUC values (0.697, 0.855, and 0.801; 0.640, 0.845, and 0.820, respectively) at 1, 3, and 5 years for the training and validation sets indicated that the model had good accuracy in predicting the RFS of the patients at 1, 3, and 5 years after the operation (Figure 10).
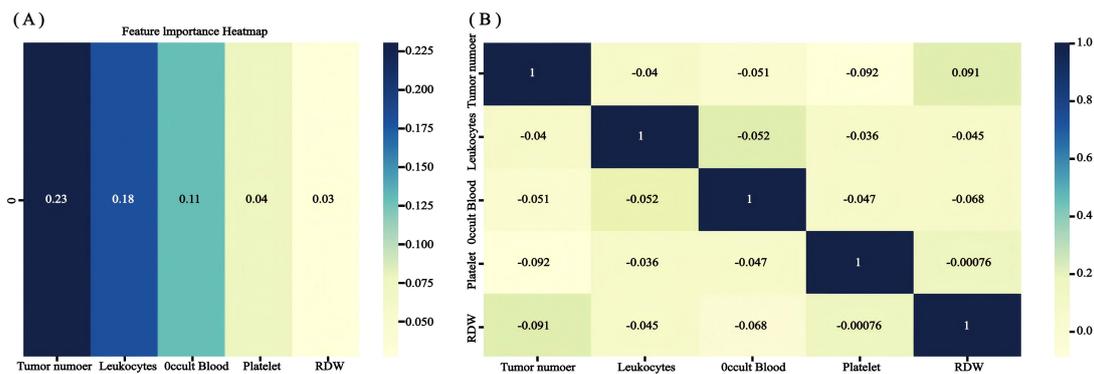

FIGURE 7
The error rate of a random survival forest. **(A)** training set; **(B)** validation set.
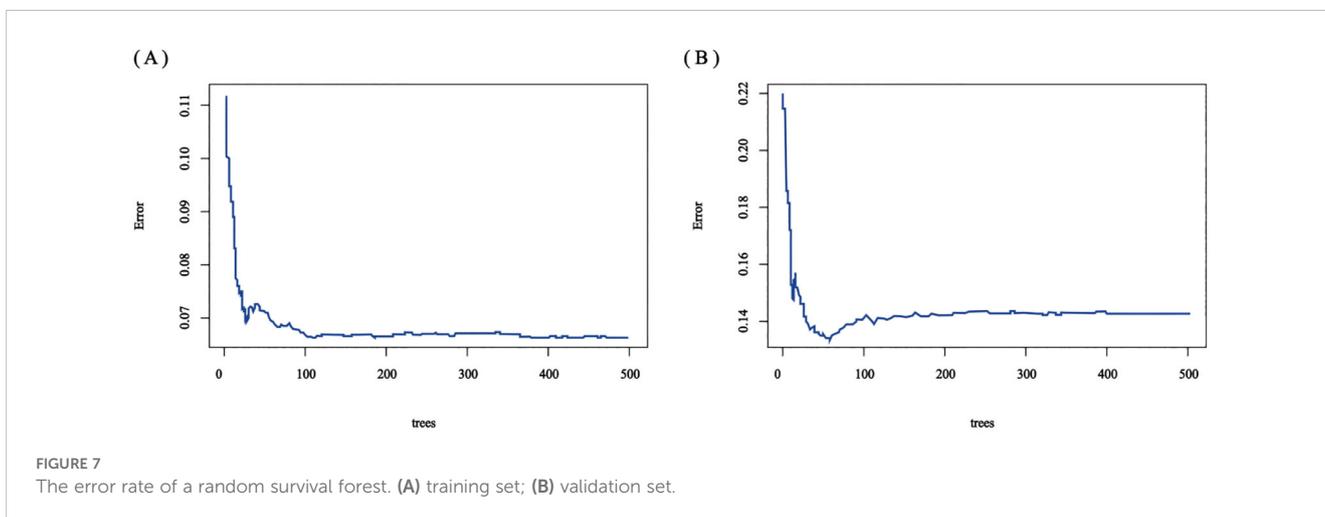
FIGURE 8
The recurrence risk analysis of NMIBC is based on a random survival forest. **(A)** Out-of-bag variable importance ranking. **(B)** correlation heat map.
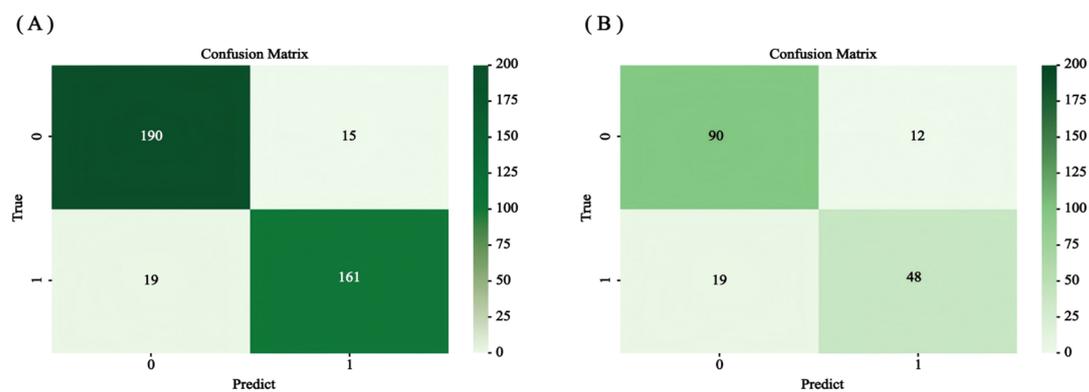

FIGURE 9
The confusion matrix is **(A)** the training set and **(B)** the validation set.
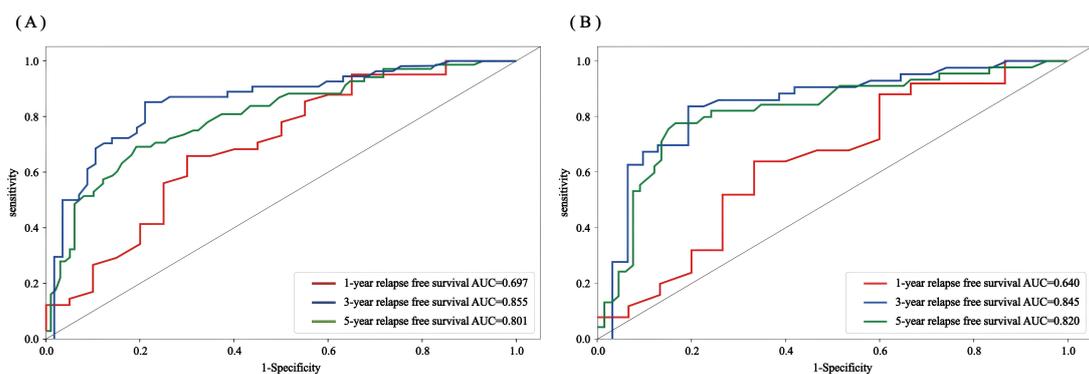

FIGURE 10
Random forest ROC curves of the 1-, 3-, and 5-year RFS for the training set and validation set **(A)** training set; **(B)** validation set.

3.6 Nomogram as a tool for visualization

The empirical validation found that both models showed good predictive efficacy, so we finally chose the Lasso-COX risk-proportionality-based model as the optimal model by comparing the AUC values of the 2 models and visualizing the model in the form of a column-line graph (Figure 11). When using the model to assess individual risk, each variable score in the model needs to be summed. A vertical line is first drawn at the total score so that it intersects the three lines representing the predicted RFS. The values corresponding to the intersection points are the individual's predicted 1-, 3-, and 5-year RFS. For example, an NMIBC patient with multiple tumors, positive urinary occult blood, negative urinary leukocytes, platelets of 177×10^9/L, and erythrocyte distribution width of >13.2% would have a total score of approximately 238, a 1-year RFS of approximately 67%, a 3-year RFS of approximately 42%, and a 5-year RFS of approximately 13%. It can be seen that a nomogram can intuitively assess the weight of each variable and help clinicians make better diagnostic and therapeutic decisions to better serve the clinic.

3.7 External validation of Lasso Cox regression prediction model

The C-index in the external validation cohort was 0.776 (95% CI: 0.721-0.830). The 1-, 3-, and 5-year AUC values for patients were 0.807, 0.736, and 0.725, respectively (Figure 12), indicating good predictive performance of the RSF model. The calibration curves showed that the predicted probabilities in the external validation cohort were close to the same direction as the actual results (Figures 13A–C). The DCA confirmed the clinical validity of our column-line graphs for RFS Figures 13D–F), which shows that our model yielded a better net clinical benefit. In summary, the column-line diagram we developed has better predictive performance.

4 Discussion

The high recurrence rate is one of the main reasons plaguing the treatment of NMIBC. The postoperative recurrence rate of NMIBC in our study was 44.7%, which is within the reported range of 31-78% (25). Therefore, early identification of predisposing factors for recurrence is crucial for the treatment of NMIBC.

The number of tumors as an independent risk factor for recurrence in NMIBC is not controversial and will not be discussed here (26, 27). Elevated PLT counts have been reported to be positively correlated with more advanced stages of solid tumors, such as ovarian and lung cancer (28, 29). In hepatocellular carcinoma, patients with PLT counts $\geq 148 \times 10^9$/L have a higher recurrence rate (30). PLT is also an independent risk factor for lymph node metastasis in MIBC (31). However, in our study, PLT was a protective rather than a risk factor for NMIBC recurrence, and patients with PLT $\leq 152 \times 10^9$/L had a shorter RFS than patients with $>152 \times 10^9$/L. This suggests that reduced PLT is associated with a poor prognosis in BCa, but a large number of studies are needed to confirm our view.

RDW is an important parameter corresponding to the degree of homogeneity of erythrocyte volume and is one of the potential inflammatory markers to predict the prognosis of various cancers. Some studies have shown that elevated RDW is significantly and positively correlated with endometrial cancer stage, lymph node metastasis and recurrence (32). In addition, elevated RDW has been associated with lung cancer (33) and metastatic renal cell carcinoma (34), which are associated with a poorer prognosis and with ICU mortality in critically ill cancer patients (35). However, the relationship between RDW and BCa remains controversial. One study found that RDW was not associated with the recurrence of NMIBC (36, 37), which contradicts the study by Fukuoka et al (38). In the present study, we showed that the risk of BCa recurrence in the high RDW group was approximately twice that of the low RDW group, and patients with RDW > 13.2% had a shorter RFS, which is consistent with the study by Fukuoka et al.

Due to the strong association between urine and bladder tumors, urine-based diagnostic biomarkers (e.g. urine pH, urine protein, urine glucose, and BLD) have been developed for the diagnosis and prognosis of BCa. Lower urine pH and higher urine protein, urine glucose, and urinary occult blood levels were found to be strongly associated with an increased risk of BCa in a case-control study (39). Our results showed that BLD positivity was strongly associated with recurrence in patients with NMIBC, and the positive group had a shorter RFS compared to the BLD-negative
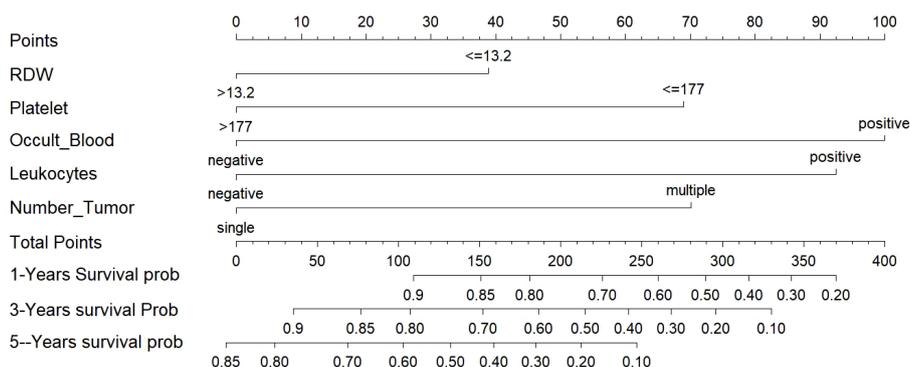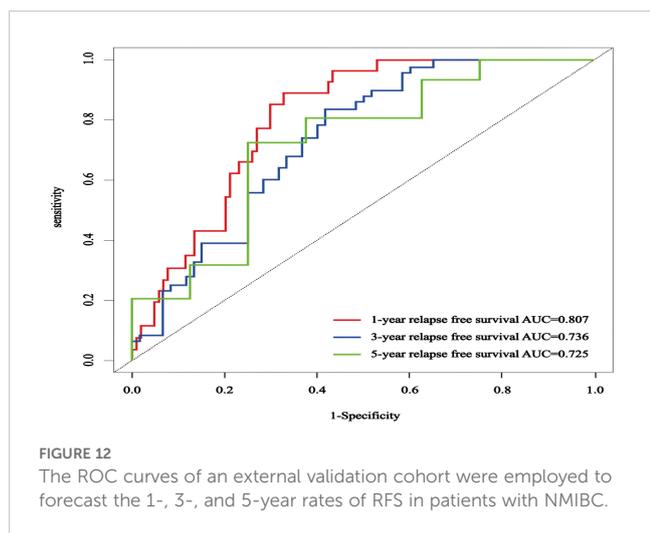

FIGURE 11
Nomogram for predicting NMIBC patients at 1-, 3-, and 5-years. NMIBC: non-muscle-invasive bladder cancer.

FIGURE 12

The ROC curves of an external validation cohort were employed to forecast the 1-, 3-, and 5-year rates of RFS in patients with NMIBC.

group. Hematuria is the most common symptom of BCa, and although there is no direct correlation between hematuria and the extent of the disease, our results suggest a relationship between urinary parameters and the biological behavior of the tumor. Further cystoscopy is recommended for patients presenting with symptoms of BCa, particularly those with recurrent hemorrhagia or recurrent disease.
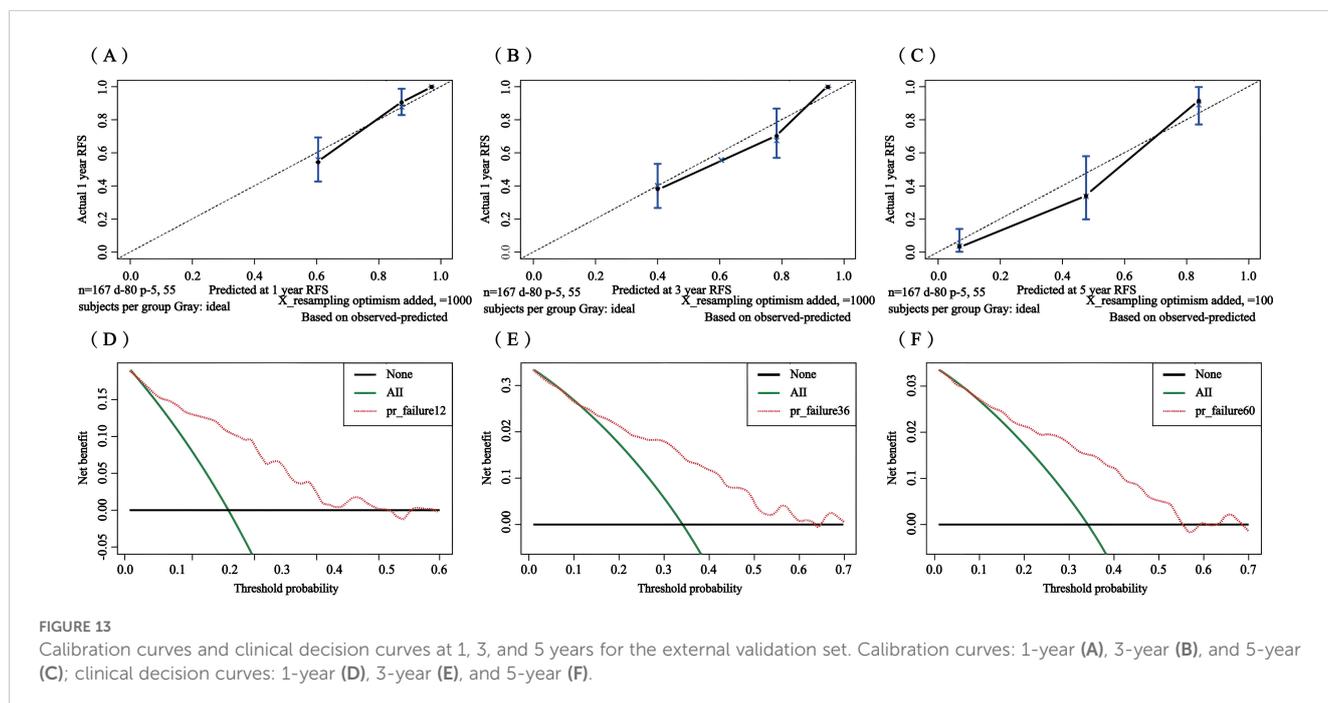
Tumor-inflammation interactions offer new immunotherapeutic avenues for cancer treatment (40). Inflammatory factors in serum and urine have also been widely used to predict the prognosis of various tumors, including BCa (41, 42). Qu (43) et al. analyzed peripheral blood leukocytes and 112 urine samples from 100 patients with NMIBC and found that interleukin-8 (IL-8) levels were high in both blood and urine in patients with recurrence. Patients with high

blood IL-8 levels had a more than 2.5-fold increased risk of recurrence, and IL-8 predicted a shorter RFS, while patients with high urinary IL-8 levels had an almost 4-fold increased risk of tumor recurrence, and their RFS was similar to that of patients with low urinary IL-8 levels. This suggests that elevated levels of IL-8, both in blood and urine, are associated with BCa recurrence. In our study, we found that LEU was associated with BCa recurrence, and the positive group had a 1.7-fold higher risk of BCa recurrence and shorter RFS compared to the negative LEU group, suggesting that LEU may be a promising biomarker for predicting recurrence in NMIBC patients.

However, our research has certain limitations. Firstly, due to the retrospective nature of the study, there may be selection bias in data collection. Secondly, the data collection time span is too long, and due to the continuous updates of detection technology, there may be deviations in the test results. In addition, we only collected preoperative test results from patients and did not observe any changes in them after surgery. Finally, more clinical trials and prospective studies are needed to further demonstrate the clinical value of my research findings for the prognosis of NMIBC patients.

5 Conclusion

In this study, the traditional Cox proportional hazards model and the RSF model based on Lasso regression were constructed, and both models showed good predictive performance. Since the RSF model was inferior to the traditional linear regression model in predicting the recurrence rate of patients at 1 year, the Lasso-Cox model was finally selected as the optimal model, and a column chart was constructed to predict the recurrence of patients with early NMIBC. The column chart has a significant risk stratification effect and is a useful guide for screening people at high risk of recurrence.

FIGURE 13

Calibration curves and clinical decision curves at 1, 3, and 5 years for the external validation set. Calibration curves: 1-year **(A)**, 3-year **(B)**, and 5-year **(C)**; clinical decision curves: 1-year **(D)**, 3-year **(E)**, and 5-year **(F)**.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

This study adhered to the Declaration of Helsinki and the ethical requirements of the Institutional Ethics Research Committee and was approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical University (KLLY-2023-107). The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from primarily isolated as part of your previous study for which ethical approval was obtained. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JT: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. LF: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. TH: Methodology, Writing – original draft, Writing – review & editing. RY: Methodology, Writing – original draft, Writing – review & editing. XY: Methodology, Writing – original draft, Writing – review & editing. YL: Formal analysis, Software, Writing – original draft, Writing – review & editing. MZ: Formal Analysis, Writing – original draft, Writing – review & editing. NZ: Funding acquisition, Writing – original draft, Writing – review & editing. JZ: Funding acquisition, Writing – original draft, Writing – review & editing.

Funding

Acknowledgments

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1467527/full#supplementary-material

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