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ORIGINAL RESEARCH

Performance of a Nomogram Based on the Integration of Inflammation Markers with Tumor Staging in Prognosis Prediction of Stage III Colorectal Cancer

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Introduction: The aim of the present study was to evaluate a nomogram model for predicting the 5-year overall survival (OS) in lymph node-metastatic colorectal cancer (CRC) patients by combining inflammation markers with some traditional prognostic factors.
Methods: A total of 399 patients with stage III ($pT_XN_{1-3}M_0$) CRC operated from January 2007 to December 2012 were enrolled in this retrospective study. All patients underwent D_2 lymphadenectomy in the hospital. A prognostic nomogram based on the integration of traditional prognostic factors and NLR (neutrophil-to-lymphocyte ratio) and PLR (platelet-to-lymphocyte ratio) was established and compared with the nomogram based on the traditional prognostic factors alone. ROC curves were further applied to verify the predictive accuracy of the established model.
Results: Both NLR (P=0.00) and PLR (P=0.01) predicted the 5-year OS. In multivariate analysis, age, T3 category, T4 category, N2 category, N3 category, Pgp (P-glycoprotein), NLR and PLR are proven to be independent (all $P \leq 0.05$). The established nomogram showed better predictive power than that of traditional profile (c-index: 0.66 versus 0.63) in both training and validation cohorts. External assessment by ROC curve analysis demonstrated that the established model had a good prediction accuracy of 5-year OS in stage III CRC patients, with area under curve values of 0.657 and 0.629 in training and validating sets, respectively.
Conclusion: A nomogram based on the integration of traditional prognostic factors and inflammatory markers (NLR and PLR) could provide more precise long-term prognosis information for lymph node-metastatic CRC patients than the model based on traditional profile alone. This model might be useful for clinical application in personalized evaluation.
Keywords: nomogram, TNM staging system, lymph node metastasis, colorectal cancer, prognosis

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Introduction

Colorectal cancer (CRC) is the second most frequently diagnosed cancer in females and the third in males, accounting for approximately 1 in 10 cancer cases and cancer-related deaths.[1] For non-metastatic CRC, D_2 radical resection and regional lymphadenectomy are currently the main curative therapeutic approach. Clinically, conventional TNM staging is the key determining factor for the prognostic outcome of CRC patients. However, the TNM

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classification system only evaluates the clinicopathologic features of cancer patients, and the limitation of TNM-based prognosis role for CRC has been reported,[2] particular for patients with positive lymph node metastasis (stage III).[3] To date, several studies have shown that a combination of tumor biomarkers or treatment parameters with TNM staging significantly enhanced the predictive power of clinical outcome in CRC patients.[3–5]

Previous studies have reported that cancer progression and tumorigenesis are closely related to inflammation and are reflected by the host inflammation response.[6] This response could be represented by changes in white blood cell count and acute-phase proteins. Recently, the pretreatment levels of platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR), known inflammation markers, have been demonstrated as potential prognostic predictors in CRC.[7–9] Together these results suggested that systemic inflammation can be an additional factor that affects the prognosis of cancer patients. However, whether the combination of these inflammation markers with conventional TNM staging could enhance the predictive power for long-term survival in CRC patients remains unclear.

Nomograms are widely used to estimate prognosis in oncology and can estimate an individual numerical probability of a clinical event by incorporating various prognostic determinants. Recent studies have reported a rapid development of nomograms as prognostic tools in various types of malignancy.[10–16] This study was designed to evaluate the prognostic value of the combination of traditional prognostic factors with inflammation markers NLR and PLR in stage III CRC patients using the nomogram tool.

Methods

Patients

This retrospective study included 399 consecutive CRC cases who underwent D_2 lymphadenectomy at the

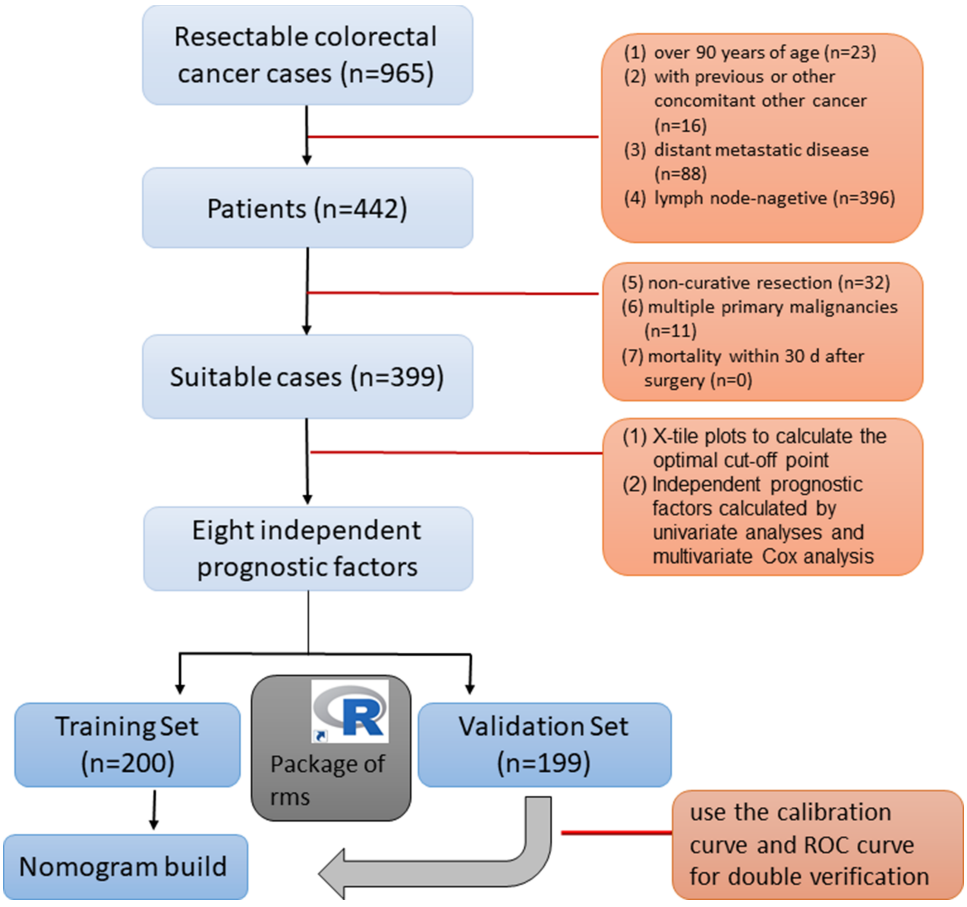

Figure 1 A flow chart for the study design.

Department of Gastrointestinal Surgery, Fujian Cancer Hospital & Fujian Medical University Cancer Hospital from January 2007 to December 2012. All CRC patients were diagnosed as $pT_XN_{1-3}M_0$ based on the American Joint Committee on Cancer (AJCC) 8th edition of the classification of TNM. Patients were excluded if they had received any cancer-specific pretreatment or concurrent hematologic, autoimmune, or infectious diseases. The flow chart for the study design is shown in Figure 1.

Dataset

The Ethics Committee of Fujian Medical University Cancer Hospital approved the study and waived the need for patient's informed consent, as the present study only retrospectively analyzed the existing data and do not include any personal confidential data or involve any commercial interests. All procedures were performed in accordance with the Declaration of Helsinki. The retrieved information from patient record includes demographic characteristics, clinicopathological features and circulating blood counts at the first assessment before operation. Based on the node grouping of the 8th classification of TNM, the number of metastatic lymph nodes was also counted. The NLR and PLR ratios were calculated by dividing the total number of neutrophils or platelet counts by the absolute number of lymphocyte counts. Follow-up information was gathered from the records of the hospital. The duration was calculated from the date of the surgery to the last date of follow-up (1st January 2019).

Statistical Analysis

SPSS version 19.0 (IBM Corp, Armonk, NY, USA) was used to perform the statistical analyses. The distributions of baseline characteristics were compared using either unpaired *t* test or ANOVA test. The cut-off values of NLR and PLR were determined and analyzed using *X*-tile program in terms of survival.

The Kaplan-Meier approach was used to generate the 5-year overall survival (OS) curves and the Log rank test was used to compare the difference of variables. Covariates that showed significance ($P<0.05$) in univariate analysis were entered into the Cox regression model for multivariate analyses. $P<0.05$ was considered statistically significant.

Based on the influence weight of each factor, nomogram model was developed by R 4.0. Novel prognostic nomograms for OS and AJCC 8th staging system were established. Concordance index (C-index), the receiver operating characteristic (ROC) curve was further used to evaluate predictive performance.[17] The values of $P<0.05$ were considered statistically significant.

Results

Patients' Information

A total of 399 patients categorized as $pT_XN_{1-3}M_0$ CRC who had undergone D_2 radical resection qualified for the study. The patient group included 235 male and 164 female patients, with an age ranging from 20 to 87 years old (Table 1). Among the 399 patients, the average follow-up time was 87.6 months, ranging from 63 to 114 months. The 5-year OS rate was 64.02%.

Table 1 Demographic Data

Characteristics	(n=399)	%
Age (years)	56.00 (20–87)	NS
Gender		
Female	164	41.10%
Male	235	58.90%
Location		
Right	60	15.04%
Left	91	22.80%
Rectum	248	62.16%
T category		
T1	5	1.25%
T2	30	7.52%
T3	177	44.36%
T4	187	46.87%
N category		
N1	266	66.67%
N2-3	133	33.33%
NLR level	2.51(0.54–14.33)	NS
PLR level	139.91(0–683.50)	NS
Pgp level		
Negative	323	80.95%
+	33	8.27%
++	41	10.28%
+++	2	0.50%

Abbreviations: NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; Pgp, P-glycoprotein.
PLR: platelet–lymphocyte ratio,
Pgp: P-Glycoprotein.

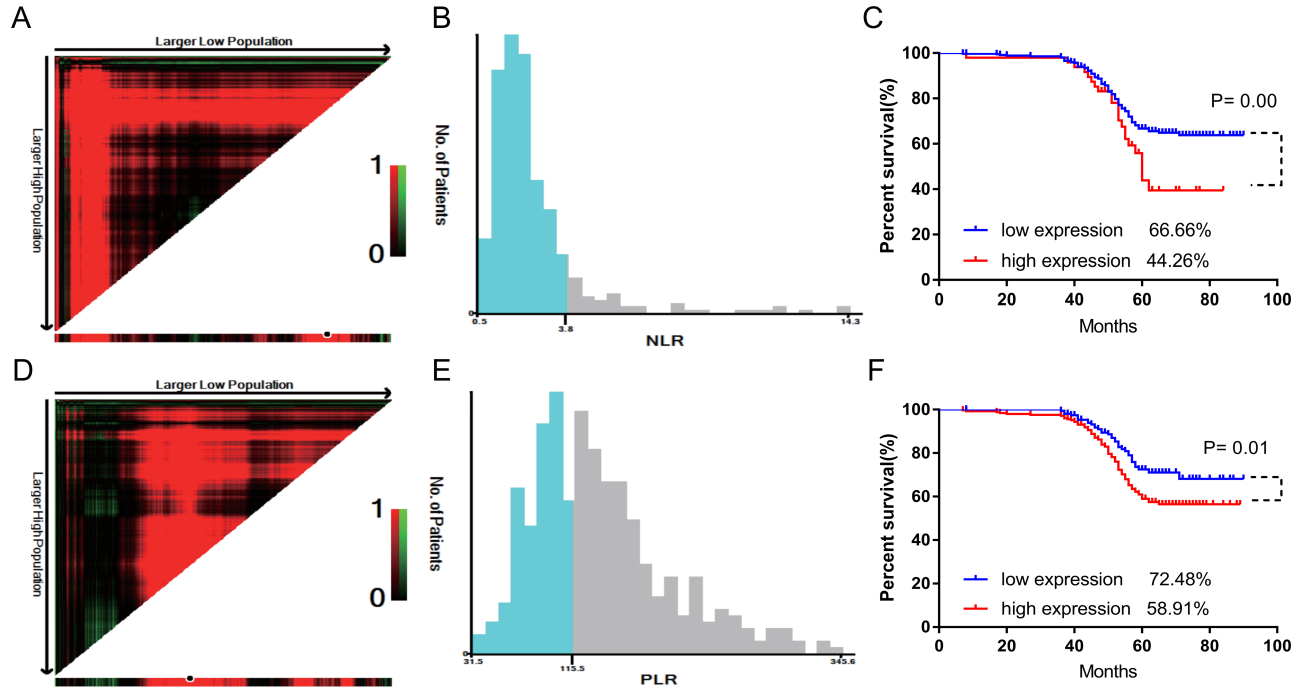

Figure 2 Determination of optimal cut-off values of NLR and PLR and survival analysis. (**A, B**) Identification of optimal cut-off value of NLR by X-tile. (**C**) Survival analysis for low NLR (less than 3.8) and high NLR (more than 3.8) groups. (**D, E**) Identification of optimal cut-off value of PLR by X-tile. (**F**) Survival analysis for low PLR (less than 115.5) and high PLR (more than 115.5) groups.

Identification of Optimal Cut-Off Values for NLR and PLR

According to the X-tile plots, the optimal cut-off point for NLR was 3.8 (Figure 2A and B) and PLR was 115.5 (Figure 2D and E). As shown in Figure 2C, the 5-year OS rate of CRC patients in the NLR-low group (less than 3.8) was 66.66% compared with 44.26% in the NLR-high group (more than 3.8). In the PLR-low group (less than 115.5), the 5-year OS rate was 72.48%, while the OS rate was 58.91% in the PLR-high group (more than 115.5) (Figure 2F).

Table 2 Univariate and Cox Multivariate Analyses of Prognostic Factors for Overall Survival

	Univariate Analysis	P value	COX Analysis	P value
Age	1.05(1.01–1.27)	0.00	1.03(1.02–1.05)	0.00
T category				
T1	1(reference)	NS	1(reference)	NS
T2	0.46(0.09–2.56)	0.51	0.44(0.06–2.22)	0.43
T3	1.16(1.05–1.72)	0.03	1.17(1.04–1.73)	0.02
T4	1.98(1.57–2.02)	0.00	1.89(1.55–1.92)	0.01
N category				
N1	1(reference)	NS	1(reference)	NS
N2	1.96(1.59–2.37)	0.07	1.93(1.56–2.34)	0.01
N3	2.32(1.76–3.09)	0.01	2.23(1.79–3.11)	0.00
NLR	2.04(1.90–3.91)	0.02	2.02(1.95–3.95)	0.00
PLR	2.01(1.46–3.12)	0.01	2.06(1.44–3.03)	0.00
Pgp	1.89(1.54–2.37)	0.00	1.87(1.52–2.35)	0.01
Location	1.81(1.61–2.98)	0.00	1.79(1.62–2.95)	0.03
Gender	1.06(0.79–1.24)	0.45	1.04(0.73–1.23)	0.20

Identification of Prognostic Factors

To evaluate the association of the individual clinicopathological parameters and pretreatment levels of NLR and PLR with prognosis, univariate analyses were performed. Age, T category, N category, NLR and PLR level, Pgp (P-glycoprotein) and tumor location were significantly associated with 5-year OS, while gender showed no association (all P value <0.05, Table 2).

The seven covariates that showed significance were entered into the multivariate Cox analysis. Age, T category, N category, NLR and PLR level, Pgp and tumor location were independent prognostic factors (all P value <0.05, Table 2).

Nomogram Established for Predicting Prognosis of CRC Patients

To evaluate the predictive power of the established nomogram for prognosis, approximately half of the patients

Table 3 Demographics and Clinicopathologic Characteristics of Stage III CRC Patients in the Training Set and Validation Set

	Training Set(n=200)		Validation Set(n=199)		P
Age	54 (20–82)	NS	59 (31–87)		NS
Gender					
Female	80	40.00%	84	42.21%	0.654
Male	120	60.00%	115	57.79%	
Location					
Right	35	17.50%	25	12.56%	0.166
Left	39	19.50%	52	26.13%	
Rectum	126	63.00%	122	61.31%	
T category					
T1-2	15	7.50%	20	10.05%	0.368
T3-4	185	92.50%	179	89.95%	
N category					
N1	129	64.50%	137	68.84%	0.357
N2-3	71	35.50%	62	31.16%	
NLR level	2.05 (0.85–14.14) NS		2.04 (0.54–14.33)		NS
PLR level	132.08 (31.48–345.56) NS		137.62 (37.92–337.14)		NS
Pgp					
Negative	160	80.00%	163	81.91%	0.727
+	16	8.00%	17	8.54%	
++ - +++	24	12.00%	19	9.55%	

(200, 50.12%) were assigned to a training set, while the other 199 cases were assigned to the validation set. Both subgroups had comparable patient demographics and clinicopathologic characteristics (Table 3).

The new nomogram model was created and compared: one was a combination of inflammation markers (NLR and PLR level) and the traditional prognostic factors, including TNM stage system (T category and N category), patient basic information (age, and tumor location) and Pgp status, and the other was only based on the traditional prognostic factors.

The new nomogram was initially established in the training set by bootstrap validation, resulting in an unadjusted

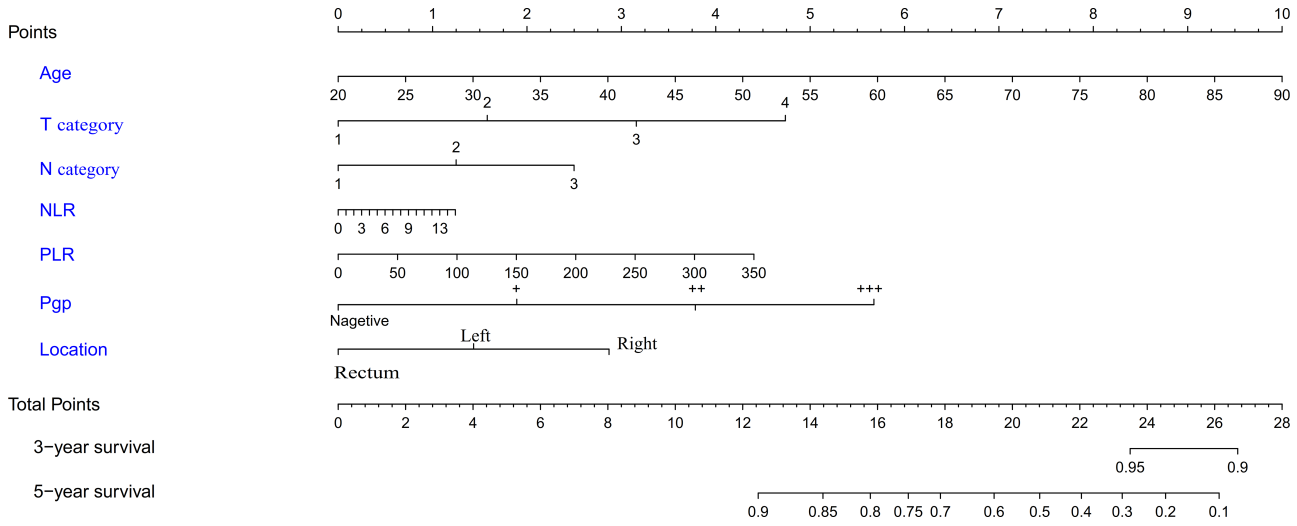

Figure 3 Integration model for predicting the 5-year survival probability in stage III CRC patients using nomogram. The 5-year probability of death for a patient is located on the Total Points axis (bottom) by summing up the total points assigned to each variable at the scales shown above, as indicated with the lines drawn downward to each axis.

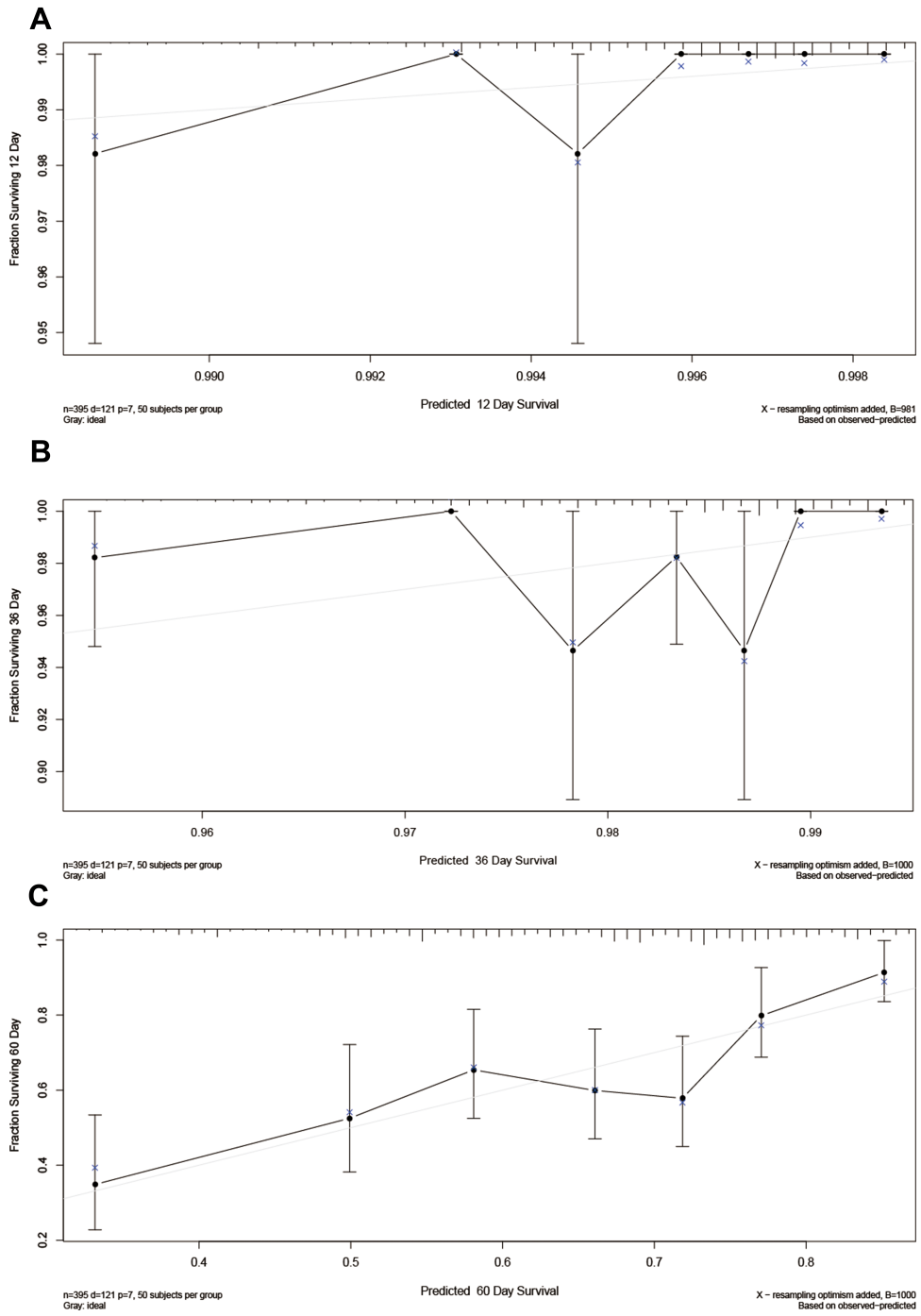

Figure 4 Calibration curves of the established nomogram model for 5-year OS. (**A**) The calibration curve for the new nomogram model in the training set for 1 year; (**B**) in the training set for 3 years; and (**C**) in the training set for 5 years. The nomogram-predicted probability for OS is plotted on the x-axis, while the actual OS is plotted on the y-axis.

C-index of 0.63 (assessment by the traditional prognostic factors) and a bootstrap-adjusted C-index of 0.66 (assessment by the new nomogram model). In the validating set, the C-index was 0.66, which is kept in line with the training set. As shown in Figure 3, nomograms enabled the prediction of a 5-year probability of death for a patient on the lowest scale by summing up the total points assigned to each variable that was indicated at the top of scale.

Calibration curves for three models revealed the calibration plot for the probability of 1, 3 and 5-year OS had a great agreement with the actual observed outcomes (Figure 4A–C).

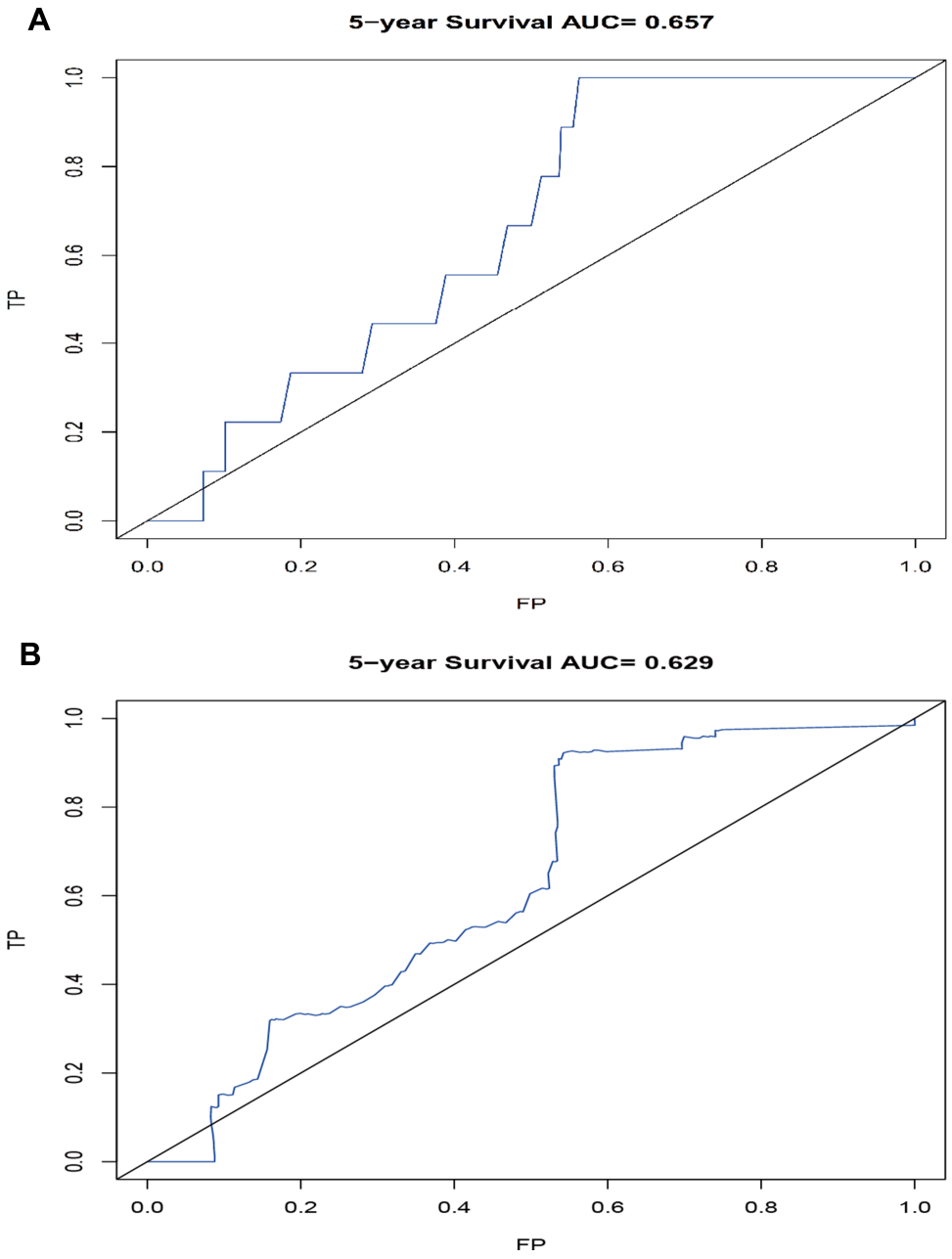

Figure 5 Internal validation of the established model using ROC analysis for 5 years. The area under the receiver operating characteristic (ROC) curve (AUC) values were 0.657, and 0.629 for the training set (**A**) and the validation set (**B**) respectively.

Internal Validation of Predictive Models by ROC Curve

The predictive accuracy of the established models for 5-year OS was further assessed by ROC curves. The values of area under curve (AUC) were 0.657, and 0.629 in the training set (Figure 5A), the validation set (Figure 5B), respectively.

Discussion

Previous studies have suggested the advantages of the nomogram model in cancer prognosis prediction, particularly when combined with other disease characteristics rather than TNM staging alone.[18] A previous report on CRC indicated that the prognosis assessment of node-positive CRC patients by TNM classification is suboptimal.[5] Both NLR and PLR

inflammation markers have demonstrated prognostic values in previous studies.[19,20] In the present study, we evaluated the new nomogram model for prognosis prediction in stage III CRC patients. We found that both PLR and NLR were independent prognostic factors affecting lymph node metastasis in CRC. We also showed that the established the new nomogram model had higher predictive power than traditional TNM staging for 5-year survival (C-index: 0.62 for the traditional prognostic factors and 0.66 for the new nomogram model).

The correlation between NLR and prognosis in patients with CRC has been demonstrated in several studies,[11–13] although cut-off values varied. In contrast, the role of PLR remains controversial.[21] This difference may be ascribed to the choice of the PLR cut-off point and the heterogeneous nature of the study population. In the present study, we identified optimal cut-off values of inflammatory biomarkers using a robust graphical tool of X-tile program. Moreover, the study population was limited to stage III CRC patients, which was more homogeneous than those of previous studies. Thus, we believe that our results are reliable. The worse prognosis associated with higher PLR might also reflect an important role of platelet dominant inflammation response in the process of lymph node metastasis in CRC, except for the neutrophil dominant inflammation effects that were confirmed by NLR in a previous study.[22] Moreover, we also found that T4 stage and N stages were independent prognosis factors in stage III CRC patients, which is consistent with the latest NCCN guideline recommendations[23] and previous reports.[24,25]

P-glycoprotein (P-GP), a member of the ATP binding box (ABC) superfamily, extrudes chemotherapeutic drugs out of cells. In the present study, Pgp was also an independent prognostic variable for survival. This observation was not consistent with the findings reported by Tokunaga et al.[26] This discrepancy might result from differences in the patient characteristics or treatment regimen.

Based on the above findings, a nomogram was constructed based on the integration of NLR and PLR with tumor staging features. Using training and validating sets, we found a great agreement between the predictive probability for the 5-year OS with the actual observed outcomes, indicating the good reliability of our established model. The value of adjusted C-index for this model is comparable that in a similar recent report[27] and was significantly higher than that the C-index based on TNM staging features (0.58). To further confirm the performance of the new nomogram model, an additional statistical tool of ROC curve was applied. The result also showed that the AUC values were 0.657 and 0.629 for the training set and the validation set, respectively. The data show the new model has good and stabled accuracy as an evaluation system.

This study had several limitations. First, the sample size is small, which may limit the statistical power of this study. Second, this model only included TNM staging, inflammation markers (NLR and PLR level), inflammation markers (NLR and PLR level), patient basic information (age, and tumor location) and immunohistochemical index (Pgp status), but ignored other potential factors such as differentiation grade of tumor and other factors. Thus, this nomogram is worth for further improvement by including other parameters.

Conclusion

We construct a new prognostic evaluation model based on TNM staging, pretreatment inflammation markers (NLR and PLR level), patient basic information (age, and tumor location) and Pgp status for stage III CRC patients. The nomogram integrated with both markers into some traditional prognostic factors could enhance the prediction accuracy of 5-year outcome in these patients. Since NLR and PLR are easily available parameters that could be obtained from routine blood counts, the model might have clinical value for prognosis purpose in CRC patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; 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 in this work.

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