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ORIGINAL ARTICLE

A nomogram of inflammatory indexes for preoperatively predicting the risk of lymph node metastasis in colorectal cancer

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Abstract

Purpose To investigate the independent risk factors associated with the development of lymph node metastasis (LNM) in patients with colorectal cancer (CRC), focusing on preoperative systemic inflammatory indicators, and to construct a corresponding risk predictive model.

Materials and Methods The clinical data of 241 patients with CRC who underwent surgery after the first diagnosis between January 2012 and December 2017 at our hospital were reviewed. A best logistic regression model was constructed by Lasso regression for multivariate analysis, from which a Nomogram was derived. Using bootstrap to conduct internal validation. The model's predictive performance and clinical practicability were evaluated using the receiver operating characteristic curve (ROC) curve, calibration curve, and decision curve analysis (DCA). External validation was conducted using retrospective data from 170 patients who underwent surgery between January 2020 and May 2022 at another hospital.

Results Cross-validation indicated smoking history, neutrophil–lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), fibrinogen-albumin ratio (FAR), and fecal occult blood (FOB) as variables with non-zero coefficients. These factors were included in the logistic regression, and multivariate analysis confirmed that smoking history, NLR, LMR, FAR, and FOB were independent risk factors ($P < 0.05$). The ROC and calibration curve of the original model and external validation indicated strong predictive power of the model. DCA suggested the model's favorable clinical utility.

Conclusions The model constructed in this study has robust predictive performance and clinical utility for the preoperative determination of CRC LMN, offering significant for clinical decision-making in patients with CRC.

Keywords Colorectal cancer · Lymph node metastasis · Prediction model · Nomogram

Introduction

According to the latest global cancer statistics, colorectal cancer (CRC) is one of the most common malignant tumors of the gastrointestinal tract. Its incidence and mortality rates have surged to third and second place, respectively, among malignant tumors. Furthermore, rough statistics indicate that the 5-year survival rate for late-stage patients with CRC with distant metastasis is less than 15% [1], posing a serious threat to the lives and health of those patients.

Current comprehensive clinical treatments for CRC include surgery, radiotherapy, targeted therapy, and immunotherapy [1]. With the development and application of laparoscopic techniques, surgical treatment of CRC has significantly improved, and postoperative complications have relatively reduced [2]. However, postoperative recurrence and metastasis remain major causes of death in advanced patients, with lymph node metastasis (LNM) being a critical factor leading to postoperative tumor recurrence and distant metastasis [3]. Although many studies have shown that endoscopic ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are important for the assessing CRC LNM, determining the presence of metastasis in lymph nodes less than 5 mm in diameter remains

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challenging [4–6]. Additionally, diagnostic results obtained through various examination methods for the same patient can vary, and conclusions drawn from the same examination may differ based on the experience and expertise of the examiners. Therefore, relying solely on these examinations to evaluate preoperative lymph node metastasis (LNM) in colorectal cancer (CRC) can introduce significant bias [6, 7].

In addition, while there are some studies on risk predictive models related to preoperative LNM in CRC, these studies possess many limitations. For instance, most models were constructed only to predict a specific tumor stage or to analyze the risk of postoperative LNM. Moreover, the factors considered in these studies primarily related to imaging examinations, past medical history, and the degree of tumor differentiation etc. [8, 9]. Although some predictive models use laboratory indices, most of them mainly focus on tumor markers, with inflammatory indicators rarely utilized for constructing models to predict preoperative LNM [10]. Additionally, many existing risk predictive emphasize internal validations and rarely conduct external validation, which limits their credibility and generalizability [9–11]. Therefore, there is an urgent need for more accurate, objective, inexpensive, and accessible predictive models for evaluating preoperative LNM in CRC to better support clinicians individualized treatment planning. Building on previous studies, this study intends to use the preoperative inflammatory indexes of patients with CRC to construct a predictive model for the risk of LNM. Both internal and external validations of the model were conducted to enhance its predictive performance and generalizability. This approach aims to facilitate early and accurate identification of high-risk patients with CRC with LNM. Consequently, clinicians can develop rigorous and appropriate surgical plans, avoiding unnecessary expansion of the surgical scope or omitting lymph node dissection in patients with LNM. This will benefit the patients and help prevent the waste of limited medical resources.

Materials and methods

Research subjects

In this study, we reviewed the clinical data of patients initially diagnosed with CRC and treated surgically at Dalian University Affiliated Xinhua Hospital and Affiliated Zhongshan Hospital of Dalian University. CRC were confirmed in patients on the basis of preoperative endoscopic biopsies and postoperative pathological specimens, and lymph node dissection was performed intraoperatively. The patients were divided into an LNM group and a non-LNM group on the basis of postoperative pathological findings. The inclusion criteria were as follows: (1) all patients were confirmed to have CRC by preoperative endoscopy, (2) no preoperative antitumor therapy, (3) no preoperative leukocyte-raising and platelet-raising therapy, (4) postoperative pathology confirmed the absence of tumor cells at the resection margin, and (5) complete clinical data of patients were available. The exclusion criteria were as follows: (1) preoperative presence of serious hematologic diseases and infections; (2) the presence of serious heart, lung, or other significant organ diseases, as well as immune disorders; (3) presence of other malignant tumors; and (4) distant metastasis of tumors.

Following this inclusion and exclusion criteria, 241 patients with CRC in our hospital from January 2012 to December 2017 were selected and used as a training cohort for model construction and internal verification in this study. Further, another 170 patients with CRC from January 2020 to May 2022 from Affiliated Zhongshan Hospital of Dalian University were screened and used as the validation cohort for external validation of the model.

Observation indicators

Clinical data were collected from patients, including sex, age, history of alcohol consumption, history of smoking, preoperative diagnosis, past medical history (hypertension, diabetes, history of coronary heart disease, etc.), presence of preoperative intestinal obstruction, last preoperative inflammatory indices (including blood count, C-reactive protein, etc.), tumor markers [e.g., carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19-9), etc.], albumin, fibrinogen (FIB), and fecal occult blood (FOB). Additionally, data on tumor site (left colon, right colon, and rectum), tumor size (based on the largest diameter of the tumor), tumor stage, grade of tumor differentiation, and postoperative pathological data were collected. The systemic inflammatory response indicators reported as predictors of CRC LNM in recent studies [12–15], including neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), lymphocyte–monocyte ratio (LMR), fibrinogen–albumin ratio (FAR), and C-reactive protein–albumin ratio (CAR), were also determined.

Process and methodology

Preoperative laboratory indices, imaging examinations and other relevant tests were completed, and surgical treatment was performed after excluding any contraindications and obtaining informed consent from patients. The surgeries were performed by senior physicians within the same treatment group at the respective hospitals. Complete resection of the tumor and associated mesentery, clearance of blood vessels and mesenteric root lymph nodes, and intestinal anastomosis were conducted following the principles of complete mesocolic excision and total mesorectal excision. The tumor specimens were promptly

stained and sectioned. The pathological specimen sections of all patients were reviewed by two senior pathologists, who issued detailed reports. The tumor staging was conducted in accordance with the 8th edition of the American Joint Committee on Cancer Classification of Malignant Tumors (AJCC TNM) staging system for colorectal cancer [16].

Statistical analysis

The data were statistically analyzed, and correlation pictures were drawn using IBM SPSS Statistics software (version 23.0) and R software (×64 version 4.2.1). Initially, univariate analysis of potential preoperative risk factors for LNM in CRC was conducted. Continuous variables following a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$), and compared using the *t*-test between groups. Non-normally distributed continuous variables were presented as the median (interquartile range) [M (IQR)], and compared using the rank sum test. Categorical variables were expressed as the number of cases (%) [*n* (%)], and compared using the Chi-square test.

In R software, the least absolute shrinkage and selection operator (Lasso) method was employed for variable screening and tenfold cross-validation to develop a risk predictive model with the least variables and the optimal performance. At the same time, Hosmerand–Lemeshow (HL) test was utilized to compare the fitting performance of the models obtained from univariate analysis and Lasso regression, confirming the optimal model derived from Lasso regression and cross validation. Variables with non-zero coefficients in the cross-validation were included in multivariate binary logistic regression to screen for independent risk factors for preoperative LNM. Using the "rsm" package, a Nomogram was drawn to visualize the complex logistic regression equations. Internal validation of the model was performed using 1000 times bootstrap self-sampling with the "caret" package. Utilizing the "pROC," "rsm," and "rmda" packages to plot receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA) curves to assess the discrimination, calibration, and clinical usefulness of the model.

Calculating the total score for each patient in the validation cohort based on the plotted Nomogram, then performing logistic regression again using these scores as predictors. Finally, plotting ROC curves and calibration curves based on this regression analysis to complete external validation of the model [17]. The significance level was set at $\alpha = 0.05$.

Results

Comparison of baseline characteristics of patients in different cohorts

A total of 411 patients were included in this study according to the specified inclusion and exclusion criteria. the median age was 68 years (range: 21–89 years), including 246 males and 165 females. Among them, 241 patients comprised the training cohort, while 170 patients formed the validation cohort. When comparing the characteristics of the training and validation cohorts, differences were noted only in body mass index (BMI), tumor site, and hemoglobin (Hb) level, with no other significant disparities ($P < 0.05$) observed, indicating that the data from both cohorts were generally comparable. The incidence of LNM was 37.34% and 38.82% in the training and validation cohorts, respectively (Table 1).

Comparison of patients' characteristics in the training cohort

The training cohort was divided into 90 cases in the LNM group (54 males and 36 females) and 151 cases in the control group (96 males and 55 females) according to postoperative pathological examination. Comparisons between both groups revealed statistically significant differences in age, smoking history, NLR, PLR, LMR, FAR, CAR, CEA, CA-199, FOB, CRP, FIB, NE, LY, MO, PLT, and tumor differentiation grade. (Table 2).

Variable screening using Lasso regression

Owing to the large number of independent variables, addressing multicollinearity and model overfitting was challenging through univariate analysis alone. Therefore, this study employed Lasso regression and tenfold cross-validation for efficient variable screening in order to yield a model with the minimal variables and the optimal performance (HL test of the model constructed from variables with significant univariate analysis: $\chi^2 = 11.889$, $P = 0.1562$; HL test for the model constructed with non-zero coefficients screened by Lasso regression: $\chi^2 = 8.8076$, $P = 0.3588$). The non-zero coefficient variables in the final optimal model were smoking history, NLR, PLR, LMR, FAR, and FOB (Fig. 1).

Results of multivariate analysis

The variables with non-zero coefficients screened above were included in the best logistic regression model for multivariate analysis. The results of the multivariate analysis indicated

Table 1 Comparison of baseline characteristics between the training and validation cohorts

Variables	Derivation cohort ($n=241$)	Validation cohort ($n=170$)	P
Sex			
Male	150 (62.2%)	96 (56.5%)	0.240
Female	91 (37.8%)	74 (43.5%)	
Age (years)	69.00 (17.00)	67.00 (11.75)	0.208
BMI	23.70 (4.255)	24.59 (4.424)	0.003
Smoking history			
Yes	44 (18.3%)	38 (22.4%)	0.306
No	197 (81.7%)	132 (77.6%)	
Drinking history			
Yes	36 (14.9%)	37 (21.8%)	0.075
No	205 (85.1%)	133 (78.2%)	
Hypertension			
Yes	68 (28.2%)	58 (34.1%)	0.201
No	173 (71.8%)	112 (65.9%)	
Coronary atherosclerotic heart disease			
Yes	20 (8.3%)	9 (5.3%)	0.241
No	221 (91.7%)	161 (94.7%)	
Diabetes mellitus			
Yes	43 (17.8%)	23 (13.5%)	0.241
No	198 (82.2%)	147 (86.5%)	
NLR	2.634 (1.759)	2.381 (1.560)	0.143
PLR	155.3 (92.86)	148.4 (85.17)	0.412
LMR	3.407 (3.863)	3.716 (4.080)	0.774
FAR (%)	9.967 (6.682)	9.610 (4.595)	0.451
CAR (%)	7.121 (7.535)	7.429 (13.43)	0.526
CEA (ng/ml)	5.130 (12.01)	4.100 (6.768)	0.093
CA19-9 (U/ml)	14.02 (18.30)	12.00 (14.03)	0.100
FOB			
Positive	68 (28.2%)	53 (31.2%)	0.517
Negative	173 (71.8%)	117 (68.8%)	
Site			
Right colon	54 (22.4%)	22 (12.9%)	< 0.001
Left colon	28 (11.6%)	46 (27.1%)	
Rectum	159 (66.0%)	102 (60.0%)	
CRP (mg/L)	2.550 (2.720)	2.465 (4.775)	0.376
Alb (g/L)	36.50 (8.500)	38.00 (9.050)	0.232
FIB (g/L)	3.550 (2.310)	3.460 (1.603)	0.785
WBC	6.500 (2.600)	5.965 (2.638)	0.142
NE	3.810 (2.100)	3.485 (1.745)	0.156
LY	1.500 (0.800)	1.600 (0.730)	0.457
MO	0.480 (0.450)	0.460 (0.618)	0.569
PLT	228.0 (87.00)	235.5 (91.00)	0.735
Hb	121.0 (32.00)	132.0 (26.00)	< 0.001
Preoperative intestinal obstruction			
Yes	52 (21.6%)	27 (15.9%)	0.149
No	189 (78.4%)	143 (84.1%)	
Maximum tumor diameter	4.500 (2.500)	4.000 (2.500)	0.126
Tumor differentiation grade			
Low	24 (10.0%)	10 (5.9%)	0.257
Middle	207 (85.9%)	155 (91.2%)	
High	10 (4.1%)	5 (2.9%)	
T grade			
1	12 (5.0%)	14 (8.2%)	0.081
2	29 (12.0%)	26 (15.3%)	
3	23 (9.5%)	25 (14.7%)	
4	177 (73.4%)	105 (61.8%)	
Lymph node metastasis			
LNM group	90 (37.3%)	66 (38.8%)	0.761
Control group	151 (62.7%)	104 (61.2%)	

BMI body mass index, *NLR* neutrophil–lymphocyte ratio, *PLR* platelet–lymphocyte ratio, *LMR* lymphocyte–monocyte ratio, *FAR* fibrinogen–albumin ratio, *CAR* C-reactive protein–albumin ratio, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19-9, *FOB* fecal occult blood, *CRP* C-reactive protein, *Alb* albumin, *FIB* fibrinogen, *WBC* white blood cell, *NE* neutrophil, *LY* lymphocyte, *MO* monocyte, *PLT* platelet, *Hb* hemoglobin, *LNM* lymph node metastasis

that smoking history, NLR, LMR, FAR, and FOB were independent risk factors for LNM of CRC ($P<0.05$) (Details are provided in Table 3).

Construction and validation of Nomogram

The nomogram model was constructed using the five independent risk factors obtained from the multivariate analysis as predictors (Fig. 2). The ROC curve of the model was plotted, and demonstrated an area under the curve (AUC) of 0.8396 (Fig. 3a). A bootstrap was used to conduct 1000 times self-sampling for internal validation of the model, yielded a concordance index of 0.8392. The calibration curve indicated close alignment between the predicted and actual probability curves (HL test: $\chi^2=14.99$, $P=0.59$) (Fig. 3b). The DCA curve revealed that when the threshold probability of preoperative LNM occurrence in patients with CRC exceeded 11%, using the nomogram model could be beneficial for patients (Fig. 4). The results of the external validation ROC curve showed an AUC of 0.8317 (95% confidence interval: 0.7705–0.8930) (Fig. 5), and the calibration curve proved close alignment between the predicted probability curve and the actual probability curve (HL test: $\chi^2=11.320$, $P=0.1842$) (Fig. 5b).

Table 2 Comparison of patients' characteristics in the training cohort

Variables	LNM group ($n=90$)	Control group ($n=151$)	*P*
Sex			
Male	54 (60.0%)	96 (63.6%)	0.580
Female	36 (40.0%)	55 (36.4%)	
Age (years)	65.50 (17.00)	70.00 (15.50)	0.045
BMI	23.84 ± 3.26	23.80 ± 3.49	0.933
Smoking history			
Yes	27 (30.0%)	17 (11.3%)	< 0.001
No	63 (70.0%)	134 (88.7%)	
Drinking history			
Yes	17 (18.9%)	19 (12.6%)	0.184
No	73 (81.1%)	132 (87.4%)	
Hypertension			
Yes	24 (26.7%)	44 (29.1%)	0.680
No	66 (73.3%)	107 (70.9%)	
Coronary atherosclerotic heart disease			
Yes	8 (8.9%)	12 (7.9%)	0.798
No	82 (91.1%)	139 (92.1%)	
Diabetes mellitus			
Yes	17 (18.9%)	26 (17.2%)	0.743
No	73 (81.1%)	125 (82.8%)	
NLR	3.356 (1.658)	2.014 (1.463)	< 0.001
PLR	177.4 (95.26)	137.4 (80.25)	< 0.001
LMR	2.089 (1.880)	4.750 (3.871)	< 0.001
FAR (%)	12.36 (6.940)	8.837 (5.569)	< 0.001
CAR (%)	8.206 (7.242)	6.772 (8.323)	0.032
CEA (ng/ml)	9.660 (19.21)	3.170 (5.795)	< 0.001
CA19-9 (U/ml)	16.25 (25.69)	12.87 (16.07)	0.039
FOB			
Positive	37 (41.1%)	31 (20.5%)	0.001
Negative	53 (58.9%)	120 (79.5%)	
Site			
Right colon	18 (20.0%)	36 (23.8%)	0.592
Left colon	9 (10.0%)	19 (12.6%)	
Rectum	63 (70.0%)	96 (63.6%)	
CRP (mg/L)	3.100 (2.645)	2.190 (2.515)	0.017
Alb (g/L)	35.95 ± 5.82	36.41 ± 6.80	0.598
FIB (g/L)	4.450 (2.400)	3.170 (1.960)	< 0.001
WBC	6.400 (2.575)	6.500 (2.600)	0.744
NE	4.190 (1.855)	3.550 (2.070)	0.015
LY	1.255 (0.423)	1.800 (0.975)	< 0.001
MO	0.5900 (0.623)	0.4000 (0.335)	< 0.001
PLT	214.5 (61.50)	250.0 (92.50)	0.049
Hb	121.2 ± 22.89	120.7 ± 23.65	0.894
Preoperative intestinal obstruction			
Yes	17 (18.9%)	35 (23.2%)	0.434
No	73 (81.1%)	116 (76.8%)	
Maximum tumor diameter (mm)	4.75 (2.50)	4.50 (2.60)	0.313
Tumor differentiation grade			
Low	7 (7.8%)	17 (11.3%)	0.026
Middle	83 (92.2%)	124 (82.1%)	
High	0 (0%)	10 (6.6%)	
T grade			
1	3 (3.3%)	9 (6.0%)	0.143
2	6 (6.7%)	23 (15.2%)	
3	8 (8.9%)	15 (9.9%)	
4	73 (81.1%)	104 (68.9%)	

LNM lymph nodes metastasis, *BMI* body mass index, *NLR* neutrophil–lymphocyte ratio, *PLR* platelet-lymphocyte ratio, *LMR* lymphocyte–monocyte ratio, *FAR* fibrinogen–albumin ratio, *CAR* C-reactive protein–albumin ratio, *CEA* carcinoembryonic antigen, *CA19-9* carbohydrate antigen 19–9, *FOB* fecal occult blood, *CRP* C-reactive protein, *Alb* albumin, *FIB* fibrinogen, *WBC* white blood cell, *NE* neutrophil, *LY* lymphocyte, *MO* monocyte, *PLT* platelet, *Hb* hemoglobin

Discussion

The occurrence of lymph node metastasis (LNM) is a significant factor contributing to poor prognosis in patients with CRC. Accurate preoperative assessment of LNM not only dominates the preoperative treatment plan, surgical approach, and extent of intraoperative lymph node dissection but also has an important impact on the postoperative treatment adjustment. Currently, the clinical examinations commonly lack of specificity, objectivity, and/or sensitivity, and some are invasive, which makes widespread screening for preoperative LNM in CRC challenging. Therefore, there is a critical need to develop a new tool that can objectively and accurately predict preoperative LNM. Such a tool would greatly benefit patients with CRC by providing more precise diagnostic information, facilitating better treatment decisions, and ultimately improving patient outcomes.

The systemic inflammatory response (SIR), including markers, such as NLR and LMR [18, 19], plays a crucial role throughout different stages of tumorigenesis, progression, invasion, and metastasis. Owing to the advantages of objectivity, accessibility, and affordability, an increasing number of studies have focused on the role of SIR in tumorigenesis and development in recent years [20]. Previous studies have highlighted that increased NLR correlates with poorer prognosis in patients with CRC [21], while elevated NLR was typically caused by increased neutrophils and/or decreased lymphocytes. Strong infiltration of neutrophils within tumors can lead to immunosuppression, excessive proliferation of tumor cells, and promote angiogenesis, thus promoting tumor metastasis [18, 20]. In contrast, lymphocytes, act as host cell-mediated immune substitutes, play a role in inhibiting tumor cell proliferation and metastasis

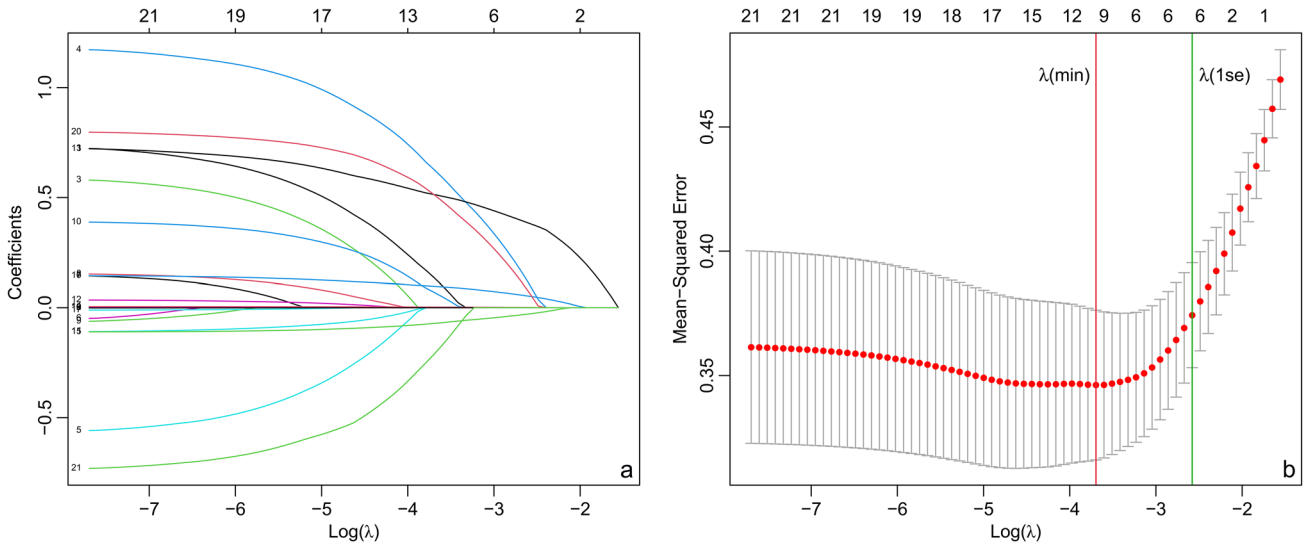

Fig. 1 Graph of the results of Lasso regression. **a** Coefficient trends of the variable screening. Each colored curve represents one variable coefficient change. **b** Results of cross-validation. λ min refers to the λ value corresponding to the minimum mean squared error (MSE) among all λ values; λ 1se refers to the λ value corresponding to the simplest and optimal model obtained after tenfold cross-validation within a square difference range of λ min

Table 3 Results of multivariate analysis related to preoperative lymph node metastasis in patients with CRC

Variables	β	OR	95% CI	*P*
Smoking history				
Yes	Reference			
No	0.982	2.669	1.158–6.150	0.021
NLR	0.639	1.895	1.379–2.605	< 0.001
PLR	0.004	1.004	0.999–1.010	0.100
LMR	–0.098	0.907	0.823–0.999	0.048
FAR	0.136	1.145	1.062–1.235	< 0.001
FOB				
Positive	Reference			
Negative	0.828	2.289	1.132–4.630	0.021

β Correlation coefficient, *OR* Odds ratio, *CI* Confidence interval

[22]. Consequently, the NLR is significant in determining patients' prognosis. In a retrospective study, Khan et al.[23] found that high preoperative NLR levels were positively correlated with pathologically confirmed LNM in patients after surgery, suggesting that NLR 's potential utility as a marker for lymph node involvement in patients with CRC. In this study, univariate analysis demonstrated that NLR was significantly higher in the LNM group than in the control group, and the results of subsequent multivariate analysis similarly confirmed NLR as an independent risk factor for LNM in patients with CRC ($P < 0.05$). Therefore, our findings support NLR could be used as predictor for LNM in CRC.

Monocytes play a crucial role in the progression of malignant tumors. Elevated levels of peripheral blood monocytes are associated with an increased tumor burden, which can lead to a higher likelihood of tumor spread, metastasis, and deterioration. Therefore, tumors are more likely to deteriorate and metastasis when lymphocytes are also decreased [22]. The results of this study also suggest that the LMR may serve as an independent risk factor for LNM in patients with CRC.

In recent years, numerous studies have focused on investigating the prognostic impact of FAR on malignant tumors. An et al. [24] identified elevated FAR was a risk factor for preoperative LNM in patients with cervical squamous cell carcinoma. Zhang et al. [25] highlight that the prechemotherapy FAR was a reliable indicator for predicting the efficacy and prognosis of chemotherapy in patients with metastatic CRC. Additional studies have confirmed that in patients with CRC liver metastasis and hepatectomy, the overall survival (OS) and disease-free survival (DFS) rates of patients with a high preoperative FAR index were significantly lower than those of the control group, indicating that the preoperative FAR index is an independent predictor of OS and DFS in patients with CRC liver metastasis and hepatectomy [26]. Paik et al. [27] also corroborated that high preoperative FAR was an independent risk factor for LNM in CRC. Nonetheless, given the retrospective nature of these studies, which limits the strength of the evidence, further research is required to definitively elucidate the relationship between FAR and LNM in CRC.

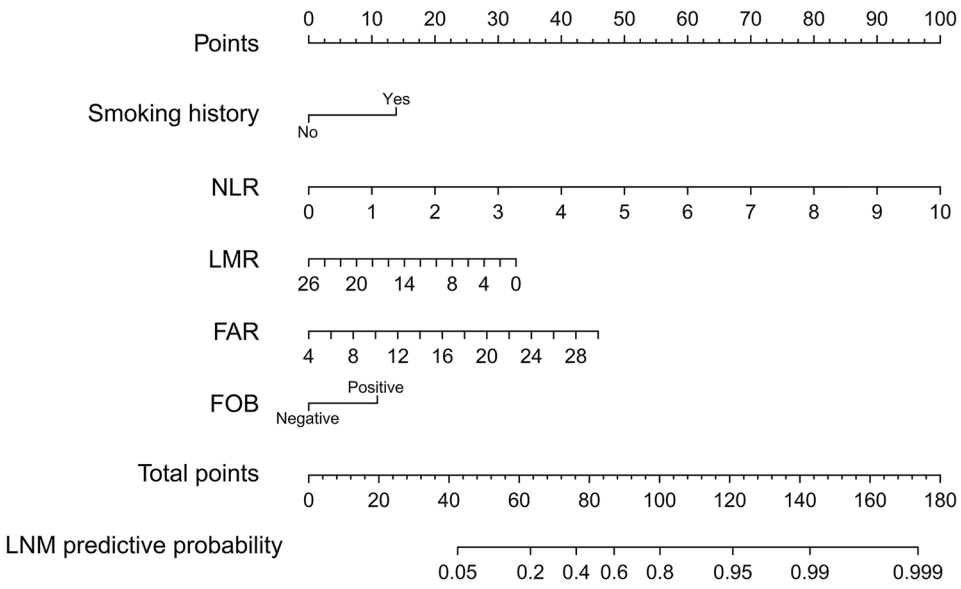

Fig. 2 Visualization nomogram of logistic regression for preoperative lymph node metastasis in CRC. *NLR* neutrophil–lymphocyte ratio, *LMR* lymphocyte–monocyte ratio, *FAR* fibrinogen–albumin ratio, *FOB* fecal occult blood

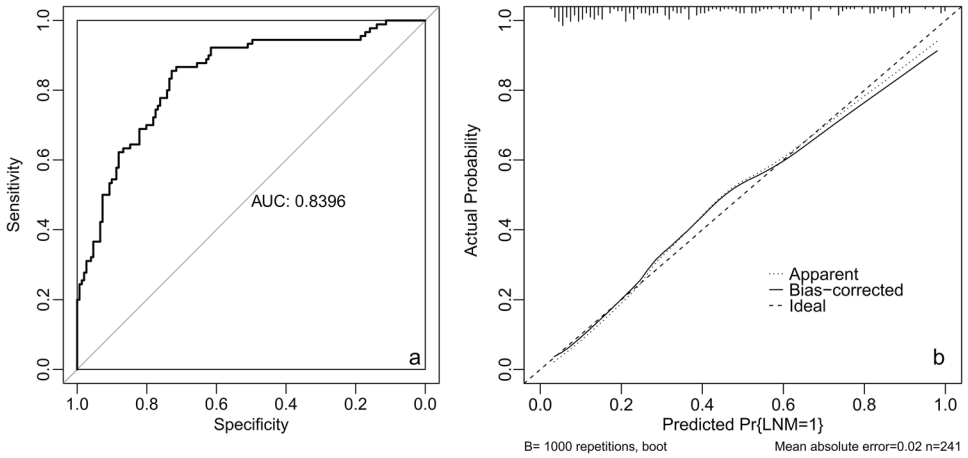

Fig. 3 ROC curves and calibration curves of the prediction model. **a** ROC curve **b** Calibration curve

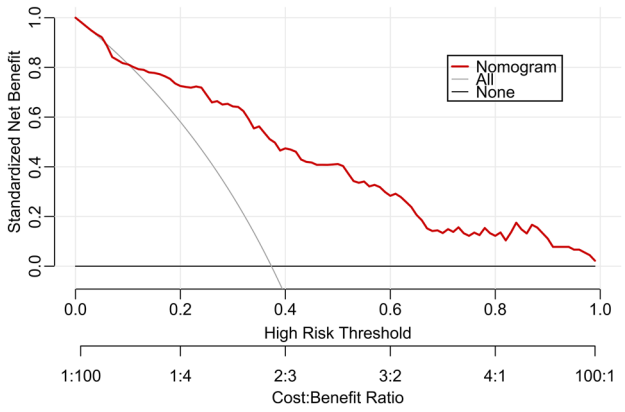

Fig. 4 DCA curves of the prediction model

Researches have demonstrated that smoking elevates the risk of CRC [28]. Botteri, et al. [29] through an analysis and synthesis of data from 188 original studies, concluded that the risk of CRC is positively associated with smoking. Furthermore, another study confirmed that nicotine present in tobacco could enhance lymphatic metastasis in human esophageal cancer by downregulating OTUD3, which in turn inhibit the expression of vascular endothelial growth factor-C mRNA [30]. Despite these findings, there is limited research specifically investigating the relationship between smoking and lymph node metastasis (LNM) in CRC. In this study, univariate analysis revealed a statistically significant difference in smoking history between the LNM group and the control group. Additionally, multivariate analysis also

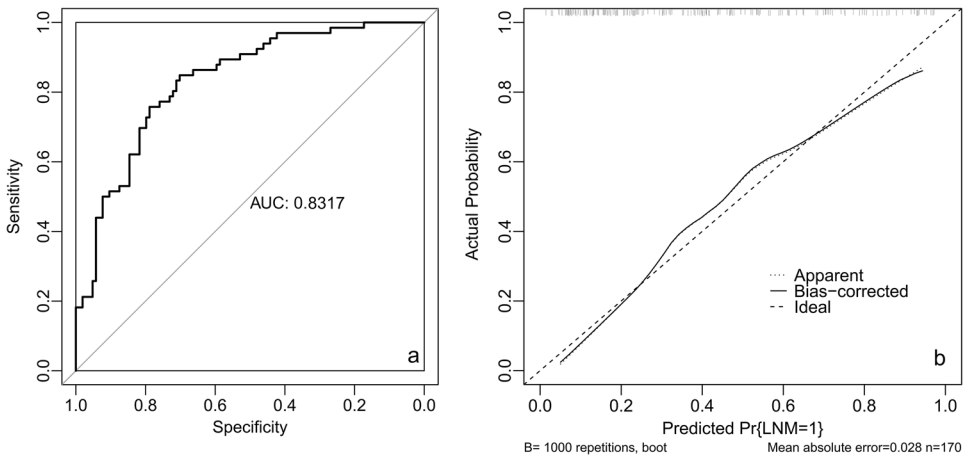

Fig. 5 Externally validated ROC curves and calibration curves. **a** ROC curve **b** Calibration curve

confirmed that smoking history was an independent risk factor for LNM in CRC. The precise mechanism by which smoking influences LNM in CRC remains to be elucidated.

At present, FOB is mostly utilized for the early screening of CRC, but its use in prognostication being relatively uncommon [31]. This study is the first to include FOB as a potential risk factor for lymph node metastasis (LNM) in CRC. Interestingly, univariate analysis revealed a statistically significant difference in FOB results between the two groups. It was also shown in the multivariate analysis that it could serve as an independent risk factor for LNM in CRC. However, given this study was retrospective and involves a small sample size, the credibility of this conclusion may be limited. Further studies are needed to verify the relationship between FOB and LNM in CRC.

Previous studies on risk factors have primarily conducted univariate analysis to screen variables followed by multivariate analysis. This approach is extremely inefficient for studies with a large number of variables, as it often leads to issues such as multicollinearity and model overfitting. Therefore, to address these challenges, our study applied Lasso regression and cross-validation, techniques commonly used in high-throughput screening, to identify potential risk factors for lymph node metastasis (LNM) in colorectal cancer (CRC) from inflammatory indicators. This method minimized the impact of multicollinearity among variables in the final model and resulted in a predictive model with superior fitting performance [32, 33]. Furthermore, since logistic regression equation is complex and difficult to generalize in clinical practice, we translated the complex logistic regression equation into a more intuitive nomogram. So that each independent risk factor is represented by a certain weight (or score), which can be read directly on the "points" scale, allowing the calculation of a total score for each patient. By referencing the "total points" scale, clinicians can determine the probability of preoperative LNM on the "LNM predictive probability" scale. This facilitates the formulation of a lymph node dissection plan for high-risk patients, potentially improving their prognosis and survival, and making the model convenient for clinical use. In the meantime, this study also supported that the model possesses good clinical utility using DCA analysis, indicating that patients could benefit from its application. However, this study also had some limitations: first, being a retrospective study, the results may carry inherent biases. Second, the sample size was relatively small, necessitating further studies to validate the model in the future.

Conclusions

Smoking history, preoperative NLR, LMR, CAR, and FOB have been identified as independent risk factors for the development of LNM in patients with CRC. The risk predictive model constructed in this study possesses robust predictive performance and clinical utility, enabling clinicians to preoperatively identify patients at high risk of CRC LNM at an early stage, providing a valuable reference for developing individualized treatment plans for these patients.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interests The other authors declare that they have no conflicts of interest.

Ethical approval This study was approved by the ethics committee of Dalian University Affiliated Xinhua Hospital and Affiliated Zhongshan Hospital of Dalian University and was conducted in accordance with the Declaration of Helsinki. This retrospective study did not involve the privacy of patients, so informed consent was waived.

Informed Consent Informed consent is not required for this retrospective study.

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