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# Construction of a preoperative lymph node metastasis risk prediction model for colorectal cancer

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**Abstract: Objective** To investigate the independent risk factors among preoperative systemic inflammatory indicators associated with lymph node metastasis (LNM) in patients with colorectal cancer (CRC) and to construct and validate a related risk prediction model. **Methods** Retrospective analyzed clinical data of 241 patients with CRC who received surgery at Affiliated Xinhua Hospital of Dalian University from January 2012 to December 2017. Variable selection was performed using univariate analysis combined with Least Absolute Shrinkage and Selection Operator (LASSO) regression and 10-fold cross-validation. After constructing the best logistic regression model, multivariate analysis was conducted to determine the independent risk factors for preoperative LNM in CRC, and a nomogram was developed. The model was internally validated using the Bootstrap method and its predictive performance and clinical utility were evaluated through receiver operating characteristic (ROC) curve, calibration curve, and decision curve analysis (DCA). **Results** Univariate analysis and LASSO regression with cross-validation identified 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. Multivariate analysis using these factors showed that smoking history (*OR*=2.669, 95%*CI*: 1.158-6.150, *P*=0.021), high NLR(*OR*=1.895, 95%*CI*: 1.379-2.605, *P*<0.001), low LMR (*OR*=0.907, 95%*CI*: 0.823-0.999, *P*=0.048), high FAR (*OR*=1.145, 95%*CI*: 1.062-1.235, *P*<0.001), and positive fecal occult blood (*OR*=2.289, 95%*CI*: 1.132-4.630, *P*=0.021) were independent risk factors for LNM in CRC (*P*<0.05). The ROC curve, calibration curve, and DCA curve indicated that the nomogram constructed in this study provided benefits to patients. **Conclusion** The risk predictive model constructed in this study demonstrated good predictive performance and clinical utility for preoperatively identifying LNM in CRC patients.

**Keywords:** Colorectal cancer; Lymph node metastasis; Inflammatory index; Predictive model; Nomogram; Fecal occult blood; Smoking history

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Colorectal cancer (CRC) is a common malignant tumor. Data shows that CRC ranks third in incidence and second in mortality among malignant tumors [1-2], posing a severe threat to patients' lives and health. With advancements in technology, the outcomes of CRC surgical treatment have significantly improved [3]. However, recurrence and metastasis remain major causes of death for patients, with lymph node metastasis (LNM) being an important influencing factor [4]. Therefore, accurate preoperative assessment of LNM is crucial for subsequent treatment. Existing studies have constructed predictive models for CRC LNM, but these models mainly focus on factors such as imaging characteristic, past medical history, tumor differentiation [5-7], and tumor markers [8]. Few studies have used inflammatory indicators for modeling, and many have not considered multicollinearity between factors and model overfitting [6,9], leading to low credibility and generalizability. Research indicated that inflammatory indicators were closely related to LNM [10-13] and were more accessible and cost-effective compared to imaging indicator, tumor markers, and preoperative pathology, making them more suitable for predicting CRC preoperative LNM in hospitals of various levels.

This study aims to analyze the risk factors for preoperative CRC LNM, primarily exploring the relationship between inflammatory indicators and CRC LNM, and employs Least Absolute Shrinkage and Selection Operator (LASSO) regression to reduce multicollinearity and improve model performance. The goal is to construct a model using more accessible and widely available indicators to accurately identify patients at high risk of LNM, thereby formulating better surgical plans and avoiding unnecessary expansion of surgical scope or omission of metastatic lymph node removal.

## 1 Materials and methods

### *1.1 Study subjects*

The study subjects were CRC patients who were initially diagnosed at Affiliated Xinhua Hospital of Dalian University from January 2012 to December 2017 and underwent standard surgical tumor resection and lymph node dissection. All patients were confirmed CRC based on preoperative endoscopic biopsy and postoperative

pathological specimens. According to postoperative pathological results, patients were classified into LNM group and control group.

**Inclusion criteria:** (1) No antitumor treatment prior to surgery; (2) No treatment for leukocyte or platelet increase before surgery; (3) Postoperative pathology confirmed no cancer cells at the resection margins; (4) Complete clinical data.

**Exclusion criteria:** (1) Severe hematologic disorders or infections before surgery; (2) Serious heart, lung, or other major organ diseases and autoimmune diseases; (3) Other malignant tumors; (4) Distant metastasis.

According to these criteria, 241 CRC patients with complete clinical data were finally selected for modeling and validation.

### *1.2 Observational indicators*

Clinical information potentially related to CRC LNM was collected, including gender, age, alcohol history, smoking history, preoperative disease history (hypertension, diabetes, coronary heart disease), preoperative bowel obstruction, last preoperative inflammatory indicators [complete blood count, C-reactive protein (CRP)], tumor markers [carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9)], liver function, fibrinogen (FIB), fecal occult blood (FOB), and preoperative diagnosis [14-16].

Additionally, tumor location (left colon, right colon, and rectum), tumor size (measured by the largest diameter), tumor T stage, differentiation degree, and postoperative pathological data were recorded [9].

Based on current research reports [10-11,17], systemic inflammatory response indicators were calculated, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), fibrinogen-to-albumin ratio (FAR), and C-reactive protein-to-albumin ratio (CAR).

### *1.3 Process and methods*

After completing preoperative laboratory and imaging tests, excluding surgical contraindications, and obtaining informed consent, the surgery was performed by a senior physician from the same treatment group. The surgical plan strictly adhered to the principles of complete mesocolic excision and total mesorectal excision, ensuring the complete removal of CRC tumors and associated mesentery, as well as thorough dissection of vascular and mesenteric root lymph nodes, followed by bowel anastomosis. After tumor removal, specimens were processed for pathological slides and staining within the effective time frame. All resected tumor specimens were processed for pathological slides and staining within the specified time, and reports were issued after review and confirmation by two senior pathologists. Tumor staging was determined according to the 8th edition AJCC colorectal cancer TNM staging standards.

### *1.4 Statistical methods*

Data analysis was performed using SPSS 23.0 and R 4.2. Continuous variables with a normal distribution were expressed as $\bar{x} \pm s$, and intergroup comparisons were conducted using *t*-tests. Continuous variables with a non-normal distribution were expressed as *M* (*IQR*), and comparisons were made using rank-sum tests. Categorical variables were expressed as case (%), with chi-square tests used for binary and unordered multicategorical variables and rank-sum tests for ordered categorical variables.

Based on LASSO regression variable selection results and univariate analysis results, further multivariate binary logistic regression analysis was conducted to identify independent risk factors for preoperative LNM in CRC. Independent risk factors were used as predictors to construct a nomogram model. The model's predictive performance and accuracy were evaluated using receiver operating characteristic (ROC) curves and calibration curves. Internal validation of the model was performed using the bootstrap method to avoid overfitting. Additionally, decision curve analysis (DCA) was used to assess the clinical utility of the risk prediction model. The significance level was set at $\alpha = 0.05$.

## 2 Results

### *2.1 Univariate analysis*

According to the inclusion and exclusion criteria, a total of 241 patients were included in the study, with the age of 69 (21–89) years. Of these, 150 were male and 91 were female. Based on postoperative pathological results, patients were divided into a LNM group (90 cases; 54 males, 36 female) and a control group (151 cases; 96 males, 55 female). There were statistically significant differences in age, smoking history, NLR, PLR, LMR, FAR, CAR, CEA, CA19-9, FOB, and tumor T stage between two groups ($P<0.05$). **See Table 1.**

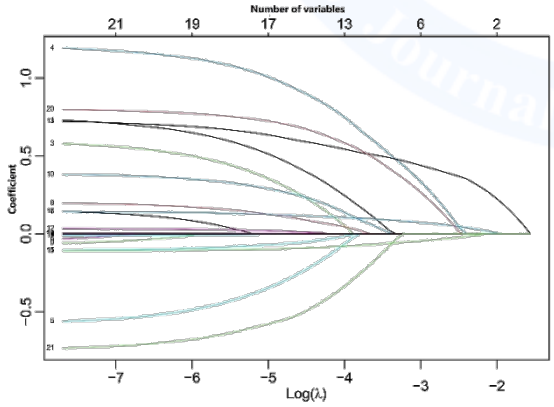
### *2.2 Determination of potential risk factors*

Due to the large number of independent variables, univariate analysis alone was difficult to reduce issues such as multicollinearity and model overfitting. Therefore, this study employed LASSO regression (**Figure 1)** and 10-fold cross-validation (**Figure 2**) to achieve a more efficient variable selection, aiming to obtain a model with the fewest variables and the best fitting performance [Results of the Hosmer-Lemeshow (HL) test for the model constructed with variables showing statistical differences in univariate analysis: $\chi^2 = 13.176$, $P = 0.105\ 9$; HL test results for the model constructed with non-zero coefficients selected by LASSO regression: $\chi^2 = 8.8076$, $P = 0.358\ 8$). The non-zero coefficient variables identified in the final optimal model were: smoking history, NLR, PLR, LMR, FAR, and FOB.

**Tab. 1** Comparison of basic characteristics between LNM group and control group patients

| Indicator | Lymph node metastasis group (*n*= 90) | Control group (*n*= 151) | $\chi^2/Z/t$ value | *P* value |
|---|---|---|---|---|
| **Gender** | | | 0.307 | 0.580 |
| **male** | 54 (60.0) | 96 (63.6) | | |
| **female** | 36 (40.0) | 55 (36.4) | | |
| **Age(year)** [b] | 65.50 (17.00) | 70.00 (15.50) | 2.001 | 0.045 |
| **BMI(kg/m$^2$)** [c] | 23.84±3.26 | 23.80±3.49 | 0.084 | 0.933 |
| **Smoking history** | 27 (30.0) | 17 (11.3) | 13.272 | <0.001 |
| **Drinking history** | 17 (18.9) | 19 (12.6) | 1.765 | 0.184 |
| **Hypertension** | 24 (26.7) | 44 (29.1) | 0.170 | 0.680 |
| **Coronary heart disease** [a] | 8 (8.9) | 12 (7.9) | 0.066 | 0.798 |
| **Diabetes** [a] | 17 (18.9) | 26 (17.2) | 0.107 | 0.743 |
| **NLR** [b] | 3.36 (1.658) | 2.01 (1.463) | 6.943 | <0.001 |
| **PLR** [b] | 177.4 (95.26) | 137.4 (80.25) | 5.052 | <0.001 |
| **LMR** [b] | 2.09 (1.880) | 4.75 (3.871) | 7.476 | <0.001 |
| **FAR (%)** [b] | 12.36 (6.940) | 8.84 (5.569) | 5.104 | <0.001 |
| **CAR (%)** [b] | 8.22 (7.242) | 6.77 (8.323) | 2.145 | 0.032 |
| **CEA (ng/mL)** [b] | 9.66 (19.21) | 3.17 (5.795) | 5.889 | <0.001 |
| **CA19-9 (u/mL)** [b] | 16.25 (25.69) | 12.87 (16.07) | 2.066 | 0.039 |
| **FOB positive** | 37 (41.1) | 31 (20.5) | 11.793 | 0.001 |
| **Tumor location** | | | 1.048 | 0.592 |
| **Right hemi-colon** | 18 (20.0) | 36 (23.8) | | |
| **Left hemi-colon** | 9 (10.0) | 19 (12.6) | | |
| **Rectum** | 63 (70.0) | 96 (63.6) | | |
| **CRP (mg/L)** [b] | 3.10 (2.645) | 2.19 (2.515) | 2.393 | 0.017 |
| **Albumin (g/L)** [c] | 35.95±5.82 | 36.41±6.80 | 0.528 | 0.598 |
| **FIB(g/L)** [b] | 4.45 (2.400) | 3.17 (1.960) | 5.305 | <0.001 |
| **Intestinal obstruction** | 17 (18.9) | 35 (23.2) | 0.613 | 0.434 |
| **Tumor diameter (cm)** | 4.75 (2.50) | 4.50 (2.60) | 1.008 | 0.313 |
| **Differentiation degree** [a] | | | 0.564 | 0.573 |
| **Low** | 7 (7.8) | 17 (11.3) | | |
| **Moderate** | 83 (92.2) | 124 (82.1) | | |
| **High** | 0 | 10 (6.6) | | |
| **T stage** | | | 2.179 | 0.029 |
| **1** | 3 (3.3) | 9 (6.0) | | |
| **2** | 6 (6.7) | 23 (15.2) | | |
| **3** | 8 (8.9) | 15 (9.9) | | |
| **4** | 73 (81.1) | 104 (68.9) | | |

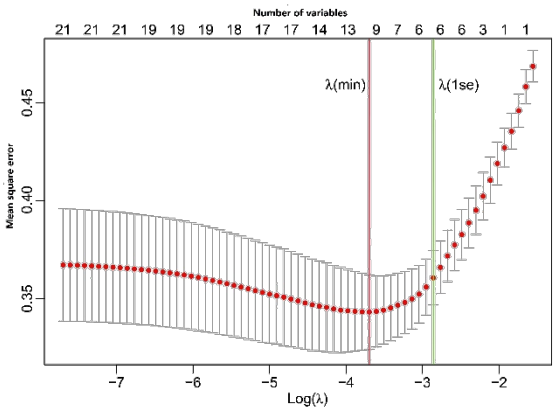
Note: [a] Data expressed as cases (%), [b] data expressed as *M(IQR)*, [c] data expressed as $\bar{x}$±s.




Note: Each colored curve represented the trend of the coefficient of a variable separately.

**Fig.1** Trend of coefficient changes during variable screening using LASSO regression

Note: λ (min) referred to the value of λ relative to the smallest mean square error among all the values of λ; λ (1se) referred to the value of λ




corresponding to the best model after 10-fold cross-validation in a variance range of λ (min).

**Fig.2** Results of 10-fold cross validation

## *2.3 Multivariate analysis*

The non-zero coefficient variables selected above were used to construct the optimal logistic model. Smoking history, NLR, LMR, FAR, and FOB were independent risk factors for preoperative LNM in CRC ($P < 0.05$). **See Table 2.**

## *2.4 Development and internal validation of the nomogram model*

The independent risk factors identified in the previous steps were used as predictors to create a nomogram model using R software (**Figure 3**). The ROC curve for the model was plotted, and the AUC was 0.8396 (**Figure 4**).

Internal validation of the model was performed using the Bootstrap method with 1,000 resampling iterations, yielding a concordance index of 0.8392. The calibration curve showed that the predicted probability curve was close to the actual probability curve, with the model's C-index (ROC) being 0.840, S:p = 0.965 > 0.05 (**Figure 5**). According to the DCA curve, when the threshold probability for preoperative LNM in CRC patients is >11%, using the nomogram model constructed in this study for predicting preoperative LNM can yield accurate results and benefit patients (**Figure 6**).

**Tab.2** Multivariate analysis results of preoperative LNM in CRC patients

| Variate | *β* | *SE* | *Wald* | *OR* | 95%*CI* | *P* |
|---|---|---|---|---|---|---|
| **Smoking history** | 0.982 | 0.426 | 5.315 | 2.669 | 1.158-6.150 | 0.021 |
| **NLR** | 0.639 | 0.162 | 15.546 | 1.895 | 1.379-2.605 | <0.001 |
| **PLR** | 0.004 | 0.003 | 2.699 | 1.004 | 0.999-1.010 | 0.100 |
| **LMR** | -0.098 | 0.050 | 3.923 | 0.907 | 0.823-0.999 | 0.048 |
| **FAR** | 0.136 | 0.039 | 12.360 | 1.145 | 1.062-1.235 | <0.001 |
| **FOB positive** | 0.828 | 0.359 | 5.307 | 2.289 | 1.132-4.630 | 0.021 |

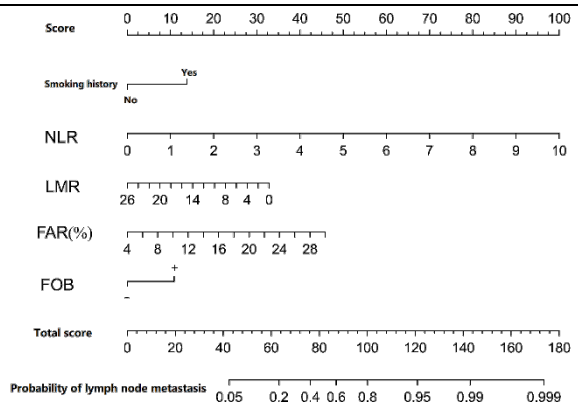



**Fig.3** Nomogram of inflammatory factors predicting LNM

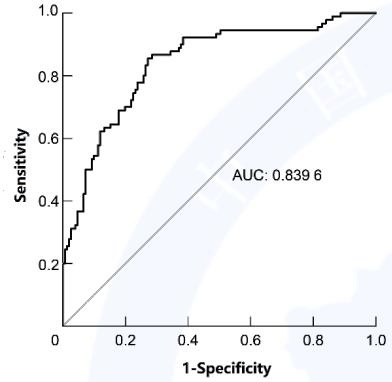



**Fig.4** ROC curve of the prediction model

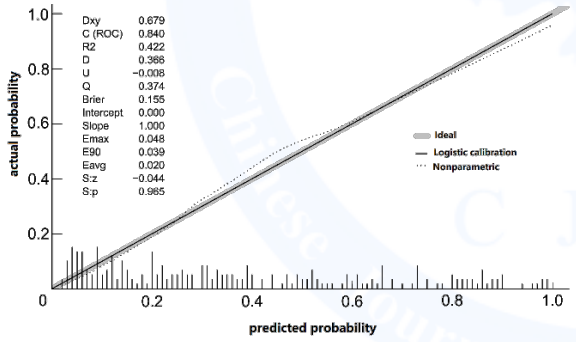



**Fig.5** Calibration curve of prediction model

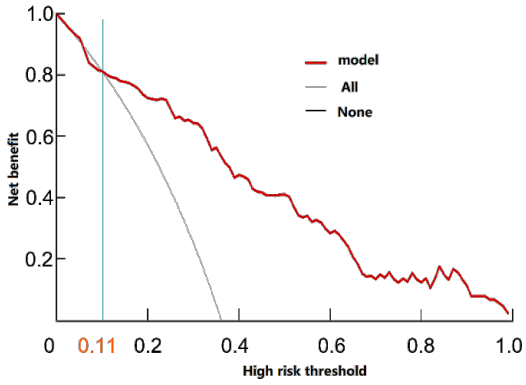



**Fig.6** DCA of prediction model

## 3 Discussion

Accurate preoperative assessment of LNM is crucial for determining surgical strategies, the extent of lymph node dissection, and adjusting postoperative treatment. Existing evaluation methods for preoperative CRC LNM are prone to considerable bias [19]. Therefore, there is an urgent need to develop more objective, cost-effective, and accessible evaluation indicators and predictive models for preoperative CRC LNM. Traditional inflammatory markers are well-established, widely used, and accurate. However, relying solely on a single marker still makes it challenging to provide an accurate assessment. Thus, multiple markers need to be evaluated to identify more valuable indicators.

Systemic inflammatory response (SIR) plays a critical role in different stages of tumor development, progression, and metastasis [20]. Key markers of SIR include NLR and LMR [21]. Studies have found that intense neutrophil infiltration into tumors can lead to immune suppression, excessive tumor cell proliferation, and angiogenesis, thus promoting tumor metastasis [21-22]. Conversely, lymphocytes, as host cell-mediated immune agents, play a significant role in inhibiting tumor cell proliferation and metastasis [23]. Khan *et al.* [17] demonstrated that high preoperative NLR levels were positively correlated with CRC LNM, indicating that NLR could serve as a marker for lymph node involvement in CRC patients. This study's results similarly confirmed that NLR was an independent risk factor for LNM in CRC patients. In summary, a high NLR suggested a strong inflammatory response and/or immune suppression, reflecting a reduced ability to combat tumor cells, which leads to tumor LNM.

Tumor burden increases with elevated peripheral blood monocyte counts, leading to tumor progression and metastasis. When accompanied by lymphocyte reduction-induced immune suppression, the body's ability to combat tumor cells is diminished, making the tumor more prone to metastasis [23]. Our study also suggested that LMR served as an independent risk factor for LNM in CRC patients.

Studies found that elevated FAR was a risk factor for preoperative LNM in cervical squamous cell carcinoma patients [11]. Yang *et al.* [10] confirmed that high preoperative FAR was an independent risk factor for LNM in CRC. High FIB levels indicated a chronic inflammatory state, and the inflammatory microenvironment played an important role in tumor metastasis. Additionally, FIB can promote angiogenesis in the tumor microenvironment, increasing the tumor's blood supply. Low albumin levels typically indicate malnutrition and immune suppression, which reduces the body's ability to fight tumors, thus increasing the likelihood of tumor cell survival and spread in lymph nodes. This study confirmed that FAR was an independent risk factor for LNM in CRC, though being a retrospective study, further research is needed to clarify the relationship between FAR and CRC LNM.

Research confirmed that nicotine in tobacco promoted LNM in esophageal cancer by mediating the downregulation of *OTUD3* and inhibiting the degradation of vascular endothelial growth factor-C mRNA [24].

However, there is limited research on smoking and CRC LNM. This study showed that smoking history was an independent risk factor for LNM in CRC. Smoking can cause chronic inflammation and immune suppression, weakening the body's immune surveillance and clearance of tumor cells, creating favorable conditions for CRC development and LNM. Nicotine and polycyclic aromatic hydrocarbons in tobacco not only induce DNA damage and gene mutations but also promote angiogenesis, inhibit apoptosis, and enhance tumor cell invasiveness, thus increasing the risk of LNM.

Currently, FOB is primarily used for early screening of CRC and less frequently for prognostic assessment [25]. This study was the first to include FOB as a potential risk factor for CRC LNM. The analysis revealed that FOB was an independent risk factor affecting CRC LNM. However, as a retrospective study with a relatively small sample size, and given that interpretation of FOB results should be individualized, further research is needed to explore and explain the relationship between FOB and CRC LNM.

Previous studies related to risk factors often conducted univariate analysis to screen variables before performing multivariate analysis, which is prone to issues like multicollinearity and model overfitting. This study, based on previous research experience [26-27], used LASSO regression and cross-validation for screening potential risk factors, reducing the impact of multicollinearity on the model. The results were visualized using a nomogram, making it more convenient for clinical prediction of preoperative LNM probability.

In conclusion, a history of smoking, high preoperative NLR, low LMR, high FAR, and positive FOB are high-risk factors for preoperative LNM in CRC. The predictive model constructed with these factors has good prediction performance and clinical applicability. Applying this model can help identify high-risk CRC patients for preoperative LNM early and develop more personalized and effective treatment plans to improve patient outcomes.

**The authors report no conflict of interest**

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·论　著·

# 结直肠癌术前淋巴转移风险预测模型的构建

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**摘要：目的**　探究术前系统性炎症指标与结直肠癌（CRC）患者淋巴结转移的关系，并构建和验证相关风险预测模型。**方法**　回顾性分析 2012 年 1 月至 2017 年 12 月于大连大学附属新华医院行手术治疗的 241 例 CRC 患者的临床资料，通过单因素分析结合最小绝对收缩和选择算子（LASSO）回归及 10 折交叉验证进行变量筛选。构建最佳 logistic 回归模型后，进行多因素分析以确定术前 CRC 淋巴结转移的独立危险因素，并绘制列线图。采用 Bootstrap 法对模型进行内部验证，并通过受试者工作特征（ROC）曲线、校准曲线及决策曲线分析（DCA）评估模型的预测性能与临床实用性。**结果**　单因素分析及 LASSO 回归交叉验证显示，吸烟史、中性粒细胞与淋巴细胞比值（NLR）、血小板与淋巴细胞比值（PLR）、淋巴细胞与单核细胞比值（LMR）、纤维蛋白原与白蛋白比值（FAR）和粪便潜血（FOB）是非零系数变量。将上述因素纳入二元 logistic 回归进行多因素分析，结果显示吸烟史（*OR*=2.669，95%*CI*：1.158~6.150，*P*=0.021）、高 NLR（*OR*=1.895，95%*CI*：1.379~2.605，*P*<0.001）、低 LMR（*OR*=0.907，95%*CI*：0.823~0.999，*P*=0.048）、高 FAR（*OR*=1.145，95%*CI*：1.062~1.235，*P*<0.001）和 FOB 阳性（*OR*=2.289，95%*CI*：1.132~4.630，*P*=0.021）是 CRC 淋巴结转移的独立危险因素（*P*<0.05）。ROC 曲线、校准曲线以及 DCA 曲线显示，应用本研究构建的列线图可使患者获益。**结论**　本研究构建的风险预测模型对于术前判断 CRC 淋巴结转移具有较好的预测性能及临床实用性。

**关键词：**结直肠癌；淋巴结转移；炎症指标；预测模型；列线图；粪便隐血；吸烟史

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# Construction of a preoperative lymph node metastasis risk prediction model for colorectal cancer

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**Abstract: Objective**　To investigate the independent risk factors among preoperative systemic inflammatory indicators associated with lymph node metastasis (LNM) in patients with colorectal cancer (CRC) and to construct and validate a related risk prediction model. **Methods**　Clinical data of 241 patients with CRC who received surgery at Affiliated Xinhua Hospital of Dalian University from January 2012 to December 2017 were retrospective analyzed. Variable selection was performed using univariate analysis combined with Least Absolute Shrinkage and Selection Operator (LASSO) regression and 10-fold cross-validation. After constructing the best logistic regression model, multivariate analysis was conducted to determine the independent risk factors for preoperative LNM in CRC, and a nomogram was developed. The model was internally validated using the Bootstrap method and its predictive performance and clinical utility were evaluated through receiver operating characteristic (ROC) curve, calibration curve, and decision curve analysis (DCA). **Results**　Univariate analysis and LASSO regression with cross-validation identified smoking history, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR),

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fibrinogen-to-albumin ratio (FAR), and fecal occult blood (FOB) as variables with non-zero coefficients. Multivariate analysis using these factors showed that smoking history (*OR*=2.669, 95%*CI*: 1.158-6.150, *P*=0.021), high NLR (*OR*=1.895, 95%*CI*: 1.379-2.605, *P*<0.001), low LMR (*OR*=0.907, 95%*CI*: 0.823-0.999, *P*=0.048), high FAR (*OR*=1.145, 95%*CI*: 1.062-1.235, *P*<0.001), and positive FOB (*OR*=2.289, 95%*CI*: 1.132-4.630, *P*=0.021) were independent risk factors for LNM in CRC (*P*<0.05). The ROC curve, calibration curve, and DCA curve indicated that the nomogram constructed in this study provided benefits to patients. **Conclusion** The risk predictive model constructed in this study demonstrated good predictive performance and clinical utility for preoperatively identifying LNM in CRC patients.

**Keywords**: Colorectal cancer; Lymph node metastasis; Inflammatory index; Predictive model; Nomogram; Fecal occult blood; Smoking history

**Fund program**: Dalian Medical Science Research Program (2022006)

结直肠癌(colorectal cancer, CRC)是常见的恶性肿瘤,数据显示 CRC 发病率及死亡率分别居恶性肿瘤第 3 位和第 2 位[1-2],严重威胁患者生命健康。随着技术的进步,CRC 手术治疗效果显著改善[3],但复发和转移仍是患者主要死亡原因,且淋巴结转移是重要影响因素[4]。虽然已有研究构建 CRC 淋巴结转移的预测模型,但研究的主要因素多为影像学检查、既往病史、肿瘤分化程度[5-7]、肿瘤标志物等指标[8-9],较少应用炎症性指标进行建模,且多未考虑因素间的多重共线性和模型过拟合[6,10],致使可信度和普适性偏低。研究表明,炎症性指标与淋巴结转移息息相关[11-14],且比影像学、肿瘤标志物、术前病理等指标更易获得、价格更低,更适用于各层次医院对 CRC 术前淋巴结转移的预测。本研究拟对术前 CRC 淋巴结转移的危险因素进行分析,主要探究炎症性指标与 CRC 淋巴结转移的关系,并采用最小绝对收缩和选择算子(Least Absolute Shrinkage and Selection Operator, LASSO)回归减少因素间的多重共线性并提高模型拟合性能。以期实现术前利用更易获得、普及率更高的指标构建模型精准识别淋巴结转移高危患者,从而制定更优的手术方案,避免出现不必要的手术范围扩大或遗漏已转移淋巴结的清扫。

## 1　材料与方法

1.1　*研究对象*　研究对象为 2012 年 1 月至 2017 年 12 月在大连大学附属新华医院初诊为 CRC 并接受标准外科肿瘤切除手术治疗和淋巴结清扫术的患者。所有患者于术前内镜下活检的病理标本和术后病理标本均确诊 CRC。根据术后病理检查结果,确定患者是否发生淋巴结转移,并将患者分为淋巴结转移组和对照组。纳入标准:(1) 术前未接受任何抗肿瘤治疗;(2) 术前未接受升白细胞、升血小板等治疗;(3) 术后病理证实切缘无肿瘤细胞;(4) 患者临床资料完整。排除标准:(1) 术前存在严重血液系统疾病、感染;(2) 合并严重心、肺等重要器官疾病及免疫性疾病;(3) 合并其他恶性肿瘤;(4) 肿瘤已发生远处转移。根据上述纳排标准,最终筛选出 241 例具有完整临床数据的 CRC 患者进行建模和验证。

1.2　*观察指标*　收集与 CRC 淋巴结转移潜在相关的临床信息[包括性别、年龄、饮酒史、吸烟史、术前疾病史(如高血压、糖尿病、冠状动脉粥样硬化性心脏病史等)]、术前是否合并肠梗阻、术前最后一次炎症性指标[如血常规、C 反应蛋白(C-reactive protein, CRP)等]、肿瘤标志物[癌胚抗原(carcinoembryonic antigen, CEA)和糖类抗原 19-9(carbohydrate antigen 19-9, CA19-9)等]、肝功能、纤维蛋白原(fibrinogen, FIB)、粪便隐血(faecal occult blood, FOB)、术前诊断等[15-17],此外,还记录患者的肿瘤位置(左半结肠、右半结肠和直肠)、肿瘤最大径、肿瘤 T 分期、分化程度、术后病理资料等[10]。并根据当前的一些研究报道[11-12, 18],计算可能作为预测 CRC 淋巴结转移的系统性炎症反应指标,包括中性粒细胞与淋巴细胞比值(neutrophil-to-lymphocyte ratio, NLR)、血小板与淋巴细胞比值(platelet-to-lymphocyte ratio, PLR)、淋巴细胞与单核细胞比值(lymphocyte-to-monocyte ratio, LMR)、纤维蛋白原与白蛋白比值(fibrinogen-to-albumin ratio, FAR)以及 C-反应蛋白与白蛋白比(C-reactive protein-to-albumin ratio, CAR)。

1.3　*流程与方法*　患者在完善术前实验室指标和影像学等检查,排除手术禁忌并签署手术知情同意书后,由同一治疗组高年资医师进行手术治疗。手术方案严格遵循完整的结肠系膜切除术和全直肠系膜切除术原则,确保 CRC 患者的肿瘤及相关肠系膜得到完整切除,并彻底清扫血管及肠系膜根部淋巴结,最终实施肠管吻合术。所有切除的肿瘤标本

在规定时间内进行病理切片和染色,并经过两位高年资病理医师审阅确认无误后出具报告。肿瘤的分期依据第 8 版 AJCC 结直肠癌 TNM 分期标准进行确定[19]。

1.4　统计学方法　数据分析采用 SPSS 23.0 和 R 4.2。对于服从正态分布的连续变量,表示为 $\bar{x}\pm s$,组间比较采用 $t$ 检验;非正态分布的连续变量以 $M$($IQR$)表示,组间比较则采用秩和检验。分类变量以例(%)表示,二分类变量和无序多分类变量采用 $\chi^2$ 检验、有序分类变量则采用秩和检验进行组间比较。基于 LASSO 回归的变量筛选结果和单因素分析结果,进一步行多因素二元 logistic 回归分析,以筛选出 CRC 术前发生淋巴结转移的独立危险因素。以独立危险因素作为预测因子,绘制列线图模型。模型的预测性能与准确性则通过受试者工作特征曲线(receiver operating characteristic, ROC)和校准曲线进行评估。Bootstrap 法进行模型的内部验证。使用决策曲线分析(decision curve analysis, DCA)评估风险预测模型的临床实用性。检验水准 $\alpha$ = 0.05。

## 2　结　果

2.1　单因素分析　本研究根据纳排标准共计纳入 241 例患者,年龄为 69(21~89)岁,其中男性 150 例,女性 91 例。根据术后病检结果,将患者分为淋巴结转移组 90 例(男性 54 例,女性 36 例),对照组 151 例(男性 96 例,女性 55 例)。两组年龄、吸烟史、NLR、PLR、LMR、FAR、CAR、CEA、CA-199、FOB、肿瘤 T 分期差异有统计学意义($P$<0.05)。见表 1。

2.2　潜在危险因素的确定　由于自变量数量较多,仅进行单因素分析,难以减少变量间的多重共线性以及模型过拟合等问题,因此本研究采用 LASSO 回归(图 1)和 10 折交叉验证(图 2)实现更为高效的变量筛选,以获得变量最少且拟合性能最佳的模型(单因素分析有统计学差异的变量所构建的模型的拟合优度检验结果:$\chi^2$ = 13.176, $P$ = 0.105 9;LASSO 回归筛选出的非零系数所构建的模型的拟合优度检验结果:$\chi^2$ = 8.807 6, $P$ = 0.358 8)。最终筛选出非零系数变量有:吸烟史、NLR、PLR、LMR、FAR 和 FOB。

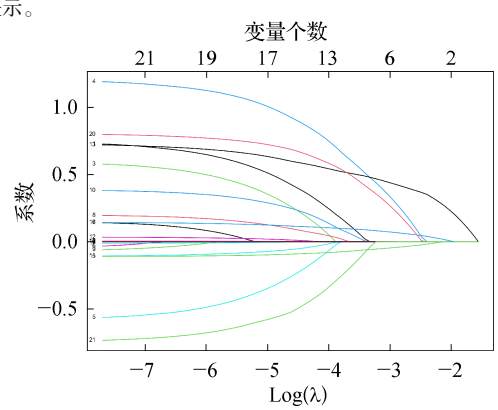
2.3　多因素分析　上述筛选出的非零系数变量构建最佳 logistic 模型,进行多因素分析后的结果显示吸烟史、NLR、LMR、FAR、FOB 是 CRC 术前淋巴结转移的独立危险因素($P$<0.05)。见表 2。

**表 1**　淋巴结转移组和对照组患者基本特征比较

**Tab. 1**　Comparison of basic characteristics between lymph node metastasis group and control group patients

| 项目 | 淋巴结转移组($n$=90) | 对照组($n$=151) | $\chi^2/Z/t$ 值 | $P$ 值 |
|---|---|---|---|---|
| 性别[a] | | | 0.307 | 0.580 |
| 　男 | 54 (60.0) | 96 (63.6) | | |
| 　女 | 36 (40.0) | 55 (36.4) | | |
| 年龄(岁)[b] | 65.50(17.00) | 70.00(15.50) | 2.001 | 0.045 |
| BMI(kg/m$^2$)[c] | 23.84±3.26 | 23.80±3.49 | 0.084 | 0.933 |
| 吸烟史[a] | 27(30.0) | 17(11.3) | 13.272 | <0.001 |
| 饮酒史[a] | 17(18.9) | 19(12.6) | 1.765 | 0.184 |
| 高血压[a] | 24(26.7) | 44(29.1) | 0.170 | 0.680 |
| 冠心病[a] | 8(8.9) | 12(7.9) | 0.066 | 0.798 |
| 糖尿病[a] | 17(18.9) | 26(17.2) | 0.107 | 0.743 |
| NLR[b] | 3.36(1.658) | 2.01(1.463) | 6.943 | <0.001 |
| PLR[b] | 177.4(95.26) | 137.4(80.25) | 5.052 | <0.001 |
| LMR[b] | 2.09(1.880) | 4.75(3.871) | 7.476 | <0.001 |
| FAR(%)[b] | 12.36(6.940) | 8.84(5.569) | 5.104 | <0.001 |
| CAR(%)[b] | 8.22(7.242) | 6.77(8.323) | 2.145 | 0.032 |
| CEA(ng/mL)[b] | 9.66(19.21) | 3.17(5.795) | 5.889 | <0.001 |
| CA19-9(u/mL)[b] | 16.25(25.69) | 12.87(16.07) | 2.066 | 0.039 |
| FOB 阳性[a] | 37(41.1) | 31(20.5) | 11.793 | 0.001 |
| 肿瘤位置[a] | | | 1.048 | 0.592 |
| 　右半结肠 | 18(20.0) | 36(23.8) | | |
| 　左半结肠 | 9(10.0) | 19(12.6) | | |
| 　直肠 | 63(70.0) | 96(63.6) | | |
| CRP(mg/L)[b] | 3.10(2.645) | 2.19(2.515) | 2.393 | 0.017 |
| 白蛋白(g/L)[c] | 35.95±5.82 | 36.41±6.80 | 0.528 | 0.598 |
| 纤维蛋白原(g/L)[b] | 4.45(2.400) | 3.17(1.960) | 5.305 | <0.001 |
| 术前肠梗阻[a] | 17(18.9) | 35(23.2) | 0.613 | 0.434 |
| 肿瘤最大径(cm) | 4.75(2.50) | 4.50(2.60) | 1.008 | 0.313 |
| 肿瘤分化程度[a] | | | 0.564 | 0.573 |
| 　低分化 | 7(7.8) | 17(11.3) | | |
| 　中分化 | 83(92.2) | 124(82.1) | | |
| 　高分化 | 0 | 10(6.6) | | |
| T 分期[a] | | | 2.179 | 0.029 |
| 1 | 3(3.3) | 9(6.0) | | |
| 2 | 6(6.7) | 23(15.2) | | |
| 3 | 8(8.9) | 15(9.9) | | |
| 4 | 73(81.1) | 104(68.9) | | |

注:[a] 为数据以例(%)表示,[b] 为数据以 $M$($IQR$)表示,[c] 为数据以 $\bar{x}\pm s$ 表示。

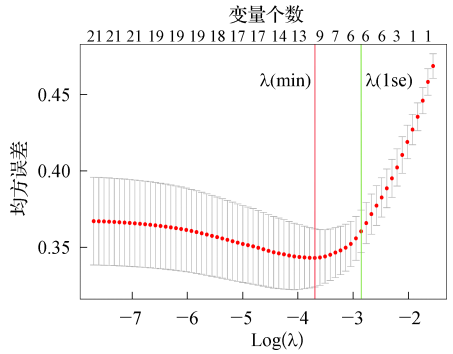



注:每一条彩色曲线分别代表一个变量系数的变化趋势。

**图 1**　LASSO 回归进行变量筛选时系数变化趋势图

**Fig. 1**　Trend of coefficient changes during variable screening using LASSO regression

2.4　列线图模型的建立与内部验证　上述步骤筛得的独立危险因素作为预测因子,利用 R 软件绘制列线图模型(图 3)。进而绘制模型的 ROC 曲线,并求得 AUC 为 0.839 6(图 4)。Bootstrap 法完成1 000次自助抽样对模型进行随机抽样内部验证,得出模型的一致性指数是 0.839 2。校准曲线显示预测概率曲线和实际概率曲线较为接近,模型的 C(ROC)指数为0.840,S:p=0.965>0.05(图 5)。根据 DCA 曲线所示,当 CRC 患者术前淋巴结转移发生的阈值概率>11%时,应用本研究构建的列线图模型对患者术前淋巴结转移进行预测,可以获得较为准确的结果(图 6)。




注:λ(min)指在所有的 λ 值中,最小均方误差相对的 λ 值;λ(1se)指在 λ(min)一个方差范围内经过 10 折交叉验证后得到最优异模型对应的 λ 值。

**图 2**　10 折交叉验证结果图
**Fig. 2**　Results of 10-fold cross-validation

**表 2**　CRC 患者术前淋巴结转移多因素分析结果
**Tab. 2**　Multivariate analysis results of preoperative lymph node metastasis in CRC patients

| 变量 | *β* | *SE* | *Wald* 值 | *OR* | 95%*CI* | *P* 值 |
|---|---|---|---|---|---|---|
| 有吸烟史 | 0.982 | 0.426 | 5.315 | 2.669 | 1.158~6.150 | 0.021 |
| NLR | 0.639 | 0.162 | 15.546 | 1.895 | 1.379~2.605 | <0.001 |
| PLR | 0.004 | 0.003 | 2.699 | 1.004 | 0.999~1.010 | 0.100 |
| LMR | −0.098 | 0.050 | 3.923 | 0.907 | 0.823~0.999 | 0.048 |
| FAR | 0.136 | 0.039 | 12.360 | 1.145 | 1.062~1.235 | <0.001 |
| FOB 阳性 | 0.828 | 0.359 | 5.307 | 2.289 | 1.132~4.630 | 0.021 |

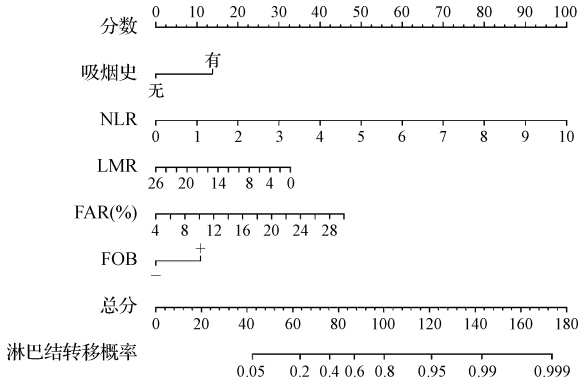



**图 3**　炎症性因子预测术前淋巴结转移的列线图
**Fig. 3**　Nomogram of inflammatory factors predicting preoperative lymph node metastasis

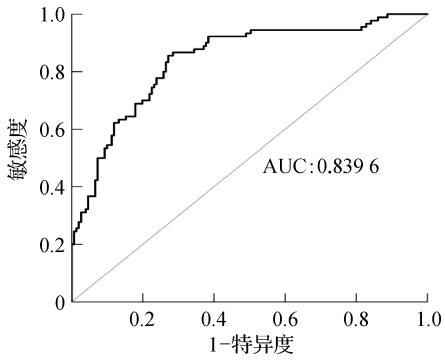



**图 4**　预测模型的 ROC 曲线
**Fig. 4**　ROC curve of the prediction model

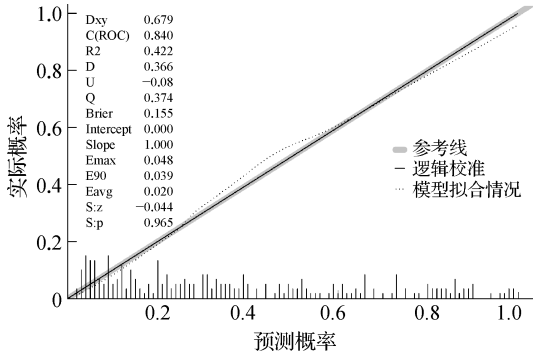



**图 5**　预测模型的校准曲线
**Fig. 5**　Calibration curve of prediction model

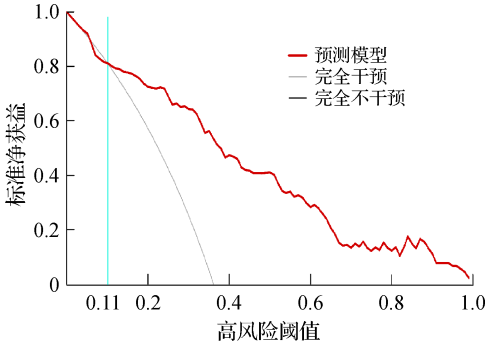



**图 6**　预测模型的 DCA
**Fig. 6**　DCA of prediction model

## 3　讨　论

术前准确评估淋巴结转移情况事关手术方案的制定、淋巴结清扫范围的确定,还对患者术后治疗方式的调整产生重要影响。根据现有的检查结果评估术前 CRC 淋巴结转移存在较大偏倚[20]。故亟需开发更加客观、廉价、可及性更强的 CRC 术前淋巴结转移的评价指标和预测模型。传统的炎症性指标技术成熟、普及面广,结果准确,但仅靠单一指标仍难以作

出准确评估,故需对多指标进行筛查,以发现更有价值的指标。

全身炎症反应(systemic inflammatory response, SIR)在肿瘤发生、发展和转移等不同阶段发挥至关重要的作用[21]。SIR 的主要标志物包括 NLR 和 LMR[22]。研究发现中性粒细胞对肿瘤的强烈浸润可导致免疫抑制、肿瘤细胞的过度增殖和血管生成,从而促进肿瘤转移[22-23]。而淋巴细胞作为宿主细胞介导的免疫替代物,在抑制肿瘤细胞增殖和转移方面发挥显著作用[24]。Khan 等[18]研究发现术前高 NLR 水平与患者 CRC 淋巴结转移情况呈正相关,说明 NLR 可作为 CRC 患者淋巴结受累的标志物。本研究分析结果同样证实 NLR 是 CRC 患者发生淋巴结转移的独立危险因素。高 NLR 提示机体存在较为强烈的炎症反应和(或)免疫抑制,反映机体对肿瘤细胞杀伤能力减弱,从而导致肿瘤淋巴结转移。

肿瘤负荷会随着外周血中单核细胞数量的升高而增加,进而导致肿瘤恶化、转移,在合并淋巴细胞减少导致的免疫抑制时,机体对肿瘤细胞的杀伤能力降低,肿瘤更易出现转移[24],本研究结果也表明,LMR 可作为 CRC 患者淋巴结转移的独立危险因素。

有研究发现 FAR 升高是宫颈鳞状细胞癌患者术前淋巴结转移的危险因素[12]。杨文昶等[11]则证实术前高 FAR 是 CRC 发生淋巴结转移的独立危险因素。高 FIB 水平多提示慢性炎症状态,而炎症微环境在肿瘤的转移中发挥重要作用,且 FIB 还可促进肿瘤微环境中血管生成,增加肿瘤的血液供应,而白蛋白水平低下常提示营养不良和免疫抑制,此时机体对抗肿瘤的能力下降,共同增加了肿瘤细胞在淋巴结中的存活和扩散概率。本研究结果证实 FAR 是 CRC 发生淋巴结转移的独立危险因素,但本研究系回顾性研究,需基础研究加以明确 FAR 与 CRC 淋巴结转移之间的关系。

研究证实,烟草中的尼古丁通过介导 OTUD3 下调抑制血管内皮细胞生长因子-C 的 mRNA 降解以促进人食管癌的淋巴转移[25]。然而,鲜有吸烟与 CRC 淋巴结转移的相关研究,本研究结果显示吸烟史是 CRC 发生淋巴结转移的独立危险因素。吸烟可导致慢性炎症和免疫抑制,削弱机体对肿瘤细胞的免疫监视和清除能力,为 CRC 的发展和淋巴结转移创造了有利条件。烟草中的尼古丁和多环芳烃等,不仅可以诱导 DNA 损伤和基因突变,还可以促进血管生成、抑制细胞凋亡并增强肿瘤细胞的侵袭性,从而增加淋巴结转移风险。

目前,FOB 多用于 CRC 的早期筛查,较少用于预后判断[26],本研究将其纳入 CRC 淋巴结转移的潜在危险因素中进行研究,发现其可作为独立危险因素影响 CRC 的淋巴结转移,但作为样本量不是很大的回顾性研究,加之对 FOB 结果的解读需结合患者个体情况进行具体分析,因此未来仍需更多的研究来探索和解释 FOB 与 CRC 淋巴结转移之间的关系。

既往与危险因素相关的研究中,多先进行单因素分析筛查变量,再进行多因素分析,难以避免多重共线性和模型过拟合等问题。本研究结合既往研究经验[27-28],利用 LASSO 回归及交叉验证进行潜在危险因素的筛查,降低了变量间多重共线性对模型的影响,并以更直观的列线图进行结果的可视化处理,使临床上更加方便地预测术前淋巴结转移发生的概率。

综上,既往吸烟史、术前高 NLR、低 LMR、高 FAR 和 FOB 阳性是 CRC 术前发生淋巴结转移的高危因素。以上述因子构建的风险预测模型的预测性能和临床实用性较好,应用本模型可对术前淋巴结转移的高危 CRC 患者进行早期识别,并为这些患者制定更具个性化、更优质的诊疗方案以改善患者预后。

**利益冲突**　无

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