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Application of peripheral nerve invasion based nomogram model in Stage Ⅰ-Ⅲ early-onset colorectal cancer

ZHU Juntao, LIU Lei, YAO Jianan, WU Jie, PENG Anyi, JI Guozhong

Department of Gastroenterology, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210011, China

Corresponding author: JI Guozhong, E-mail: jgzzl@163.com

Abstract: Objective To evaluate the impact of peripheral nerve aggression (PNI) on prognosis in patients with stage Ⅰ-Ⅲ early-onset colorectal cancer (EO-CRC) and to create a PNI-based nomogram prediction model. **Methods** This study analyzed data on 5,920 EO-CRC patients aged 50 years and younger enrolled in the U.S. Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2015. The patients were divided into the training group (n=4,164) and the validation group (n=1,756) by a ratio of 7:3. Kaplan-Meier survival curve was drawn and Cox proportional risk model was used for univariate and multivariate prognosis analysis. Based on the significant variables of the multivariate model, a nomogram was constructed, and the predictive ability was evaluated by receiver operating characteristic (ROC) curve, calibration curve and decision curve analysis (DCA). **Results** Compared with PNI negative patients, PNI positive patients tended to be young, lesions located in the left colon, with poor differentiation, higher TNM stage, chemotherapy intervention, and higher CEA level (P<0.05). Kaplan-Meier curve suggested that PNI positive group had worse prognosis than PNI negative group. Cox univariate analysis suggested that age, sex, degree of tumor differentiation, TNM stage, T stage, N stage, whether to receive radiation therapy, whether to receive chemotherapy, CEA level, maximum tumor diameter and PNI status were variables affecting the survival and prognosis of patients. Multivariate analysis showed that PNI was an independent prognostic indicator for patients with stage Ⅰ to Ⅲ EO-CRC (HR=1.73, 95%CI:1.44-2.08, P<0.05). The area under ROC curve of nomogram model based on PNI was more than 0.7 in both 3-year and 5-year lifetime. **Conclusion** PNI can be used as an independent prognostic marker in patients with stage Ⅰ-Ⅲ EO-CRC, and PNI-based nomogram model can be used as an effective prognostic tool.

Keywords: Early-onset colorectal cancer; Peripheral nerve invasion; Nomogram; Overall survival; Prognosis

Colorectal cancer (CRC) is a common malignant tumor of the digestive tract. According to the World Cancer Report published by the International Agency for Research on Cancer (IARC), CRC ranks third in incidence and second in mortality rates of global cancers [1]. Since the mid-1990s, the incidence of CRC among individuals aged 50 and above in the United States has been decreasing. However, the incidence among individuals under 50 years old, known as early-onset colorectal cancer (EO-CRC), has been rising, from 5.9 cases per 100,000 to 8.4 cases per 100,000 [2]. Related risk studies indicated that obesity, hyperlipidemia, alcohol consumption, hypertension, metabolic syndrome, ulcerative colitis, and a family history of CRC were key risk factors for EO-CRC [3].

Peripheral nerve invasion (PNI) is a mode of malignant tumor spread defined by the presence of cancer cells within or surrounding nerves [4], typically involving more than 33% of the area around the nerves or infiltrating the nerve sheath [5]. Similar to invasion of blood vessels and lymphatic vessels, PNI may lead to reduced survival time and increased risk of local recurrence [6]. The incidence of PNI in CRC patients varies widely, typically ranging from 9% to 33%, with positive PNI results often indicating a tendency for rapid disease progression [7]. According to the *Chinese Society of Clinical Oncology (CSCO) Diagnosis and Treatment Guidelines for Colorectal Cancer 2018*, PNI, along with positive margins, poor differentiation, vascular invasion, T4 stage, and fewer than 12 lymph nodes examined, is considered a high-risk factor and an indication for chemotherapy in stage Ⅱ CRC patients [8].Positive PNI generally indicating a lower survival expectation [4]. The guidelines also mention that PNI is a reliable indicator for evaluating the efficacy of chemoradiotherapy [8]. The frequency of positive PNI in EO-CRC patients is often higher than in late-onset colorectal cancer (LO-CRC) patients [9], suggesting a stronger correlation between PNI and EO-CRC. Therefore, this study aimed to explore the impact of PNI on the prognosis of stage I to Ⅲ EO-CRC patients and to develop a corresponding nomogram prognostic model.

1 Materials and Methods

1.1 General Data

A retrospective analysis was conducted on EO-

CRC patients from the U.S. Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2015. In this study, EO-CRC was defined as colorectal cancer diagnosed in individuals aged ≤50 years old.

Inclusion criteria: (1) colorectal cancer as the only primary cancer; (2) underwent surgical treatment; (3) AJCC staging at stage I–Ⅲ; (4) complete survival information.

Exclusion criteria: (1) presence of distant metastases; (2) missing clinical pathological data.

Colorectal cancer patients were identified using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site codes (C18.0, C18.2-C18.7, C19.9, and C20.9) and cancer staging schemes. After applying the inclusion and exclusion criteria, a total of 5,920 eligible patients were identified. Patient information for this study was obtained from the SEER database, a public database, so informed consent was not required.

1.2 Study Variables

The variables included in this study were age, gender, primary tumor location, maximum tumor diameter, tumor differentiation, T stage, N stage, carcinoembryonic antigen (CEA) level, PNI status, radiotherapy (none, received), chemotherapy, and overall survival time. Overall survival time is defined as the time from diagnosis to death from any cause (in months) or the duration of follow-up for any reason (in months).

1.3 Statistical Methods

Patients meeting the inclusion criteria were randomly divided into two groups in a ratio of 7:3: the training group (4,164 patients) and the validation group (1,756 patients). The training group was used for variable screening and model construction; the validation group was used to validate the results obtained from the training group. Count data were expressed as case (%). Chi-square tests were used to assess differences in baseline data between groups. Survival analysis was performed using the Kaplan-Meier method, log-rank test, and Cox proportional hazards model. A two-step method was used to assess the relationship between baseline characteristics and survival time: first, univariate Cox regression analysis was conducted for all variables; second, variables with P<0.05 from univariate analysis were included in the multivariate Cox regression model. Significant variables from the training group were used to construct a nomogram model, which was then validated using the validation group. The nomogram model was created using R 4.3.2 and the identified significant variables. To assess the performance and predictive accuracy of the nomogram model, receiver operating characteristic (ROC) curve analysis was performed. A larger area under the ROC curve (AUC) indicates higher predictive accuracy. Additionally, calibration curves for 3-year and 5-year prognosis were plotted to compare predicted overall survival (OS) with actual observed OS. Finally, decision curve analysis (DCA) was used to evaluate the clinical utility of the nomogram. Statistical analyses were performed using IBM SPSS Statistics Version 21.0 and R 4.3.2, with all tests two-tailed and P<0.05 considered statistically significant.

2 Results

2.1 Demographic and Pathological Characteristics

A total of 5,920 patients were included in the study, with a nearly equal number of male (52.1%, 3,086/5,920) and female (47.9%, 2,834/5,920) patients. The primary tumor was most commonly located in the left colon (72.4%, 4,289/5,920), with the majority of tumors being high-/moderate-differentiated (84.0%, 4,971/5,920). Some patients had significantly elevated CEA levels (32.2%, 1,904/5,920), and most tumors had a diameter≤5 cm (63.1%, 3,733/5,920). Patients were randomly assigned to the training group (n=4,164) and the validation group (n=1,756). The demographic and clinical pathological characteristics of the patients are shown in **Table 1**. PNI-positive patients accounted for 14.4% (n=600) in the training group and 13.2% (n=232) in the validation group, while PNI-negative patients accounted for 85.6% (n=3,564) and 86.8% (n=1,524), respectively. In the training group, there were statistically significant differences between PNI-negative and PNI-positive patients in multiple indicators (P<0.05), including age, tumor primary site, tumor differentiation, T stage, N stage, CEA level, chemotherapy, and radiotherapy. Similar results were observed in the validation group, except for age (P=0.14) and radiotherapy (P=0.86).

2.2 Univariate and Multivariate Cox Regression Analysis

In univariate analysis, PNI is a significant variable affecting patient survival prognosis (P<0.05), along with other variables such as sex, tumor differentiation, T stage, N stage, radiotherapy, chemotherapy, CEA levels, and maximum tumor diameter. Incorporating significant variables into the Cox multivariate survival analysis revealed that tumor differentiation, T stage, N stage, CEA levels, chemotherapy, radiotherapy, and PNI status were independent prognostic indicators **[Table 2]**. Kaplan-Meier survival curves and log-rank tests were used to evaluate the impact of PNI status on prognosis **[Figure 1]**. The survival curves show that the survival outcome for the PNI-positive group is significantly worse than that of the PNI-negative group (HR=2.63, 95%CI: 2.21–3.13).

Tab.1 Basic characteristics of PNI positive group and PNI negative group [case (%)]

Characteristic	Training group (*n*=4 164)				Verification group (*n*=1 756)			
	PNI positive group (*n*=600)	PNI negative group (*n*=3 564)	χ^2 value	*P* value	PNI positive group (*n*=232)	PNI negative group (*n*=1 524)	χ^2 value	*P* value
Age			14.27	0.01			5.49	0.14
11-20 years	2(0.3)	4(0.1)			0	4(0.3)		
21-30 years	39(6.5)	130(3.6)			14(6.0)	51(3.3)		
31-40 years	128(21.3)	701(19.7)			54(23.3)	323(21.2)		
41-50 years	431(71.8)	2,729(76.6)			164(70.7)	1,146(75.2)		
Gender			0.29	0.59			3.62	0.06
Male	305(50.8)	1,854(52.0)			109(47.0)	818(53.7)		
Female	295(49.2)	1,710(48.0)			123(53.0)	706(46.3)		
Site			5.73	0.01			6.10	0.01
Right	137(22.8)	983(27.6)			52(22.4)	459(30.1)		
Left	463(77.2)	2 581(72.4)			180(77.6)	1065(69.9)		
Differentiation			41.85	<0.01			20.77	<0.01
High/moderately	448(74.7)	3,037(85.2)			173(74.6)	1,313(86.2)		
Low/Un	152(25.3)	527(14.8)			59(25.4)	211(13.8)		
T stage			129.12	<0.01			50.87	<0.01
T_{1-2}	28(4.7)	914(25.6)			13(5.6)	414(27.2)		
T_{3-4}	572(95.3)	2,650(74.4)			219(94.4)	1,110(72.8)		
N stage			272.59	<0.01			136.19	<0.01
N_0	125(20.8)	1,878 (52.7)			40(17.2)	814(53.4)		
N_1	250(41.7)	1,169(32.8)			99(42.7)	492(32.3)		
N_2	225(37.5)	517(14.5)			93(40.1)	218(14.3)		
CEA level			52.48	<0.01			19.87	<0.01
Normal	328(54.7)	2,482(69.6)			130(56.0)	1,076(70.6)		
Ascend	272(45.3)	1,082(30.4)			102(44.0)	448(29.4)		
Chemotherapy			109.16	<0.01			52.09	<0.01
Unaccepted	94(15.7)	1,339(37.6)			34(14.7)	595(39.0)		
Accepted	506(84.3)	2,225(62.4)			198(85.3)	929(61.0)		
Radiation therapy			4.10	0.04			0.03	0.86
Unaccepted	430(71.7)	2,692(75.5)			176(75.9)	1,164(76.4)		
Accepted	170(28.3)	872(24.5)			56(24.1)	360(23.6)		
Maximum diameter of tumor			2.64	0.10			1.89	0.17
≤5 cm	398(66.3)	2,241(62.9)			154(66.4)	940(61.7)		
>5 cm	202(33.7)	1,323(37.1)			78(33.6)	584(38.3)		

2.3 Construction of Prognostic Nomogram

The nomogram model including significant variables (including PNI) from the multivariate analysis was seen in **Figure 2**. The nomogram method involved mapping patients' specific variable data to corresponding score points on the model, finding the score value for each variable on the score line above, and summing the scores of all relevant variables to obtain a total score. This total score could then be used to directly find the predicted 3-year and 5-year overall survival probabilities at the bottom of the nomogram.

2.4 Validation of the Nomogram Model

In both the training and validation groups, the AUC for 3-year and 5-year survival exceeded 0.7 **[Figure 3]**. Calibration curves revealed that the model's predicted survival probabilities were highly consistent with observed survival outcomes in both the training and validation groups **[Figure 4]**. The DCA plot showed two standard lines representing two extreme situations, where the slanted line (All) represents all factors being positive, and the horizontal line (None) represents all factors being negative. Results suggested that the nomogram provides clinical net benefit and practicality for predicting 3-year and 5-year OS in EO-CRC patients in the training group, but in the validation group, the curves are close to the highest clinical cost threshold line, indicating moderate clinical net benefit **[Figure 5]**.

Tab.2 Cox univariate and multivariate regression analysis of EO-CRC patients in stage I-III training group

Characteristic	Univariate analysis		Multivariant analysis	
	HR (95%*CI*)	*P* value	*HR* (95%*CI*)	*P* value
Age		0.62		
11-20 years	1.00			
21-30 years	0.42(0.10-1.76)	0.23		
31-40 years	0.39(0.09-1.60)	0.19		
41-50 years	0.39(0.09-1.58)	0.19		
Gender				
Male	1.00		1.00	
Female	0.85(0.73-0.99)	<0.05	0.92(0.78-1.07)	0.28
Site				
Right	1.00			
Left	1.04(0.87-1.24)	0.69		
Differentiation				
High/moderate	1.00		1.00	
Low/Un	1.91(1.60-2.28)	<0.01	1.59(1.33-1.91)	<0.01
T stage				
T_1-T_2	1.00		1.00	
T_3-T_4	2.64(2.06-3.39)	<0.01	1.67(1.15-2.45)	0.01
N stage				
N_0	1.00		1.00	
N_1	2.23(1.84-2.70)	<0.01	2.06(1.65-2.57)	<0.01
N_2	3.96(3.24-4.85)	<0.01	3.12(2.47-3.96)	<0.01
CEA level				
Normal	1.00		1.00	
Ascend	1.86(1.59-2.18)	<0.01	1.49(1.28-1.75)	<0.01
PNI				
Negative	1.00		1.00	
Positive	2.60(2.19-3.09)	<0.01	1.73(1.44-2.08)	<0.01
Chemotherapy				
Unaccepted	1.00		1.00	
Accepted	1.79(1.49-2.15)	<0.01	0.70(0.55-0.88)	0.01
Radiation therapy				
Unaccepted	1.000		1.00	
Accepted	1.49(1.26-1.75)	<0.01	1.41(1.18-1.69)	<0.01
Maximum tumor diameter				
≤5 cm	1.00		1.00	
>5 cm	1.23(1.05-1.44)	0.01	1.08(0.92-1.27)	0.38

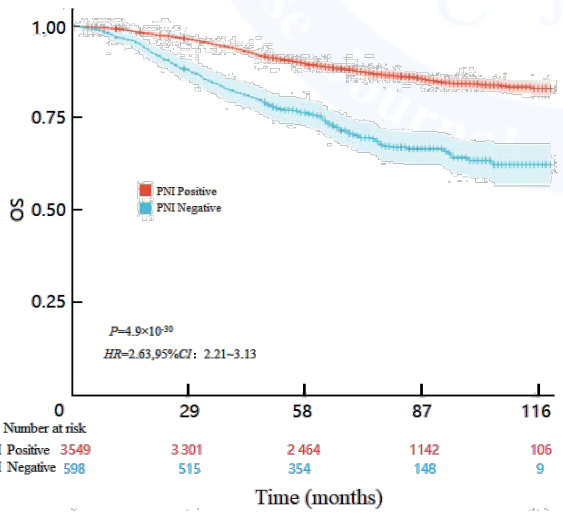


Fig. 1 Kaplan-Meier survival curves of PNI-positive and PNI-negative in training group

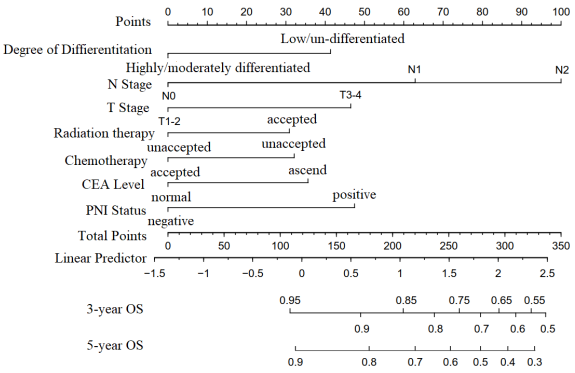
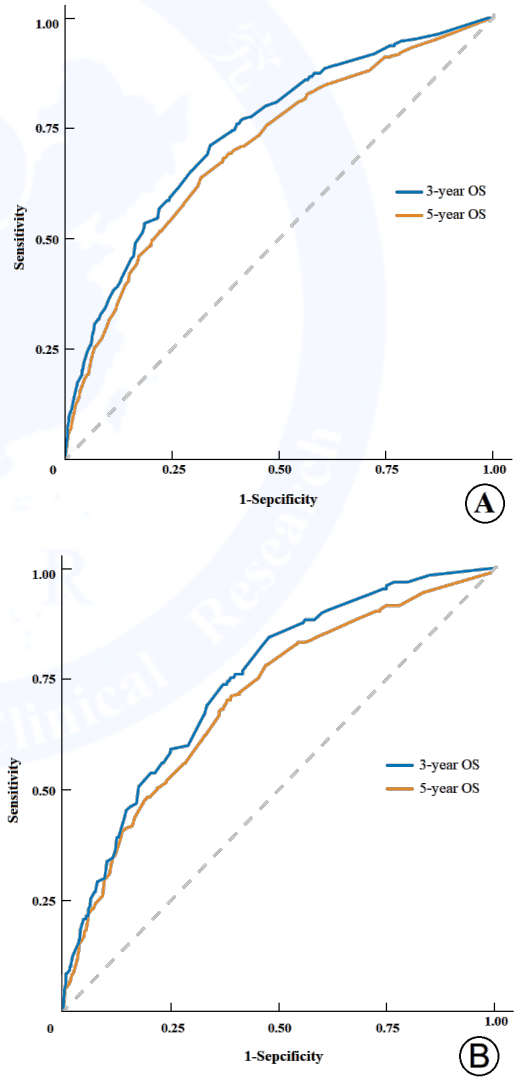
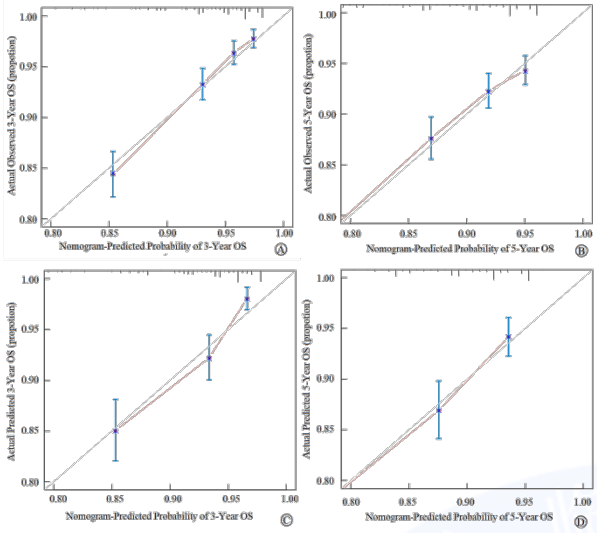


Fig. 2 A nomogram model for predicting 3-year and 5-year OS of stage Ⅰ-Ⅲ EO-CRC



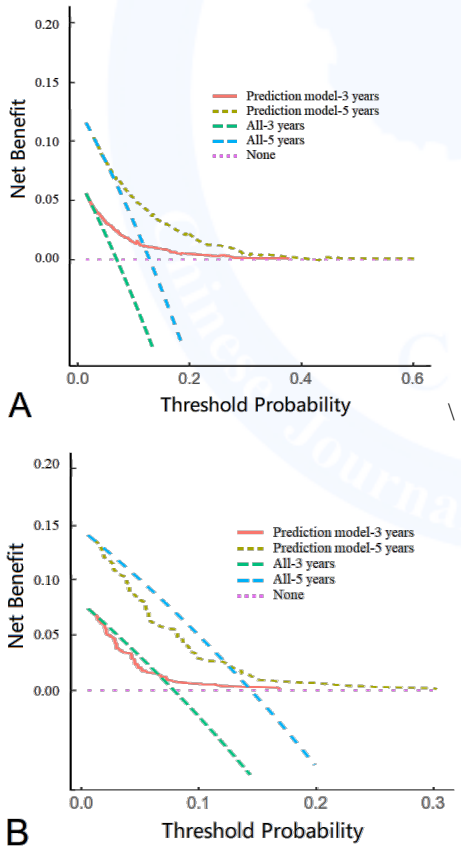
Note: A is training group; B is verification group.

Fig. 3 ROC curves of training group and verification group



Note: A and B are the calibration curves of 3-year and 5-year OS for EO-CRC patients in the training group; C and D are the calibration curve for the 3-year and 5-year OS of EO-CRC patients in the validation group. The gray line represents the ideal reference line, where the predicted probability will match the observed survival rate. The red dots represent the performance of the column chart. The closer the red solid line is to the gray line, the more accurate the model's prediction of survival rate.

Fig. 4 Calibration curve of the nomogram



Note: A was the 3-year and 5-year DCA of the training group column chart; B was the 3-year and 5-year DCA for the validation group column chart.

Fig. 5 DCA of the nomogram

3 Discussion

EO-CRC is often diagnosed at a later stage with poorer tumor differentiation and predominantly affects the left colon [1]. The result of this study indicated that age, gender, and primary tumor site did not significantly affect the prognosis of EO-CRC patients, which was similar to the conclusion of Wang *et al.* [10]. But some research suggested that younger patients might have similar or even better prognosis compared to older patients [11]. Differences in study populations, such as racial background, customs, and lifestyle, may account for these variations. Some studies revealed that non-Hispanic Black and Hispanic individuals were more prone to EO-CRC, with non-Hispanic Black patients showed significant differences in clinical pathological features [12]. This study also found that T stage, N stage, tumor differentiation, CEA levels, PNI status, and radiotherapy and chemotherapy significantly impacted prognosis. The conclusion was consistent with previous research [13-14], that high AJCC stage, poorly differentiated tumors, and high CEA levels were considered risk factors for poor prognosis in EO-CRC.

PNI is considered an indicator of local tumor progression and a form of metastasis, observed in various cancers, including head and neck, pancreatic, prostate, bile duct, stomach, and colorectal cancers [6]. In this study, PNI-positive patients had more primary tumors located in the left colon, with lower tumor differentiation, predominantly poorly differentiated or undifferentiated types. PNI-positive patients were more frequently in T3–T4 stages and had higher CEA levels. Most PNI-positive patients received chemotherapy. Some studies have pointed out that PNI was closely related to tumor differentiation and AJCC staging [15]. PNI is an independent prognostic risk factor for CRC, particularly for EO-CRC [16]. This study confirmed similar findings, with Kaplan-Meier survival curves and Cox regression models validating PNI's prognostic value in stage I–Ⅲ EO-CRC, showing a significantly increased risk of mortality in PNI-positive patients.

This study constructed a PNI-based nomogram to predict OS in stage I–Ⅲ EO-CRC patients. This model included seven variables: tumor differentiation, T stage, N stage, CEA levels, PNI status, chemotherapy, and radiotherapy. We found that poorly differentiated tumors, high T and N stages, high CEA levels, PNI positivity, and receiving radiotherapy were associated with poorer survival outcomes, while receiving chemotherapy was associated with better survival outcomes. ROC curve analysis shows high accuracy for predicting 3-year and 5-year OS (AUC>0.7). DCA demonstrated significant clinical benefit from the nomogram model.

However, this study has limitations: first, the SEER database may have differences in race, region, lifestyle, and health beliefs compared to Asian patients.

Second, the SEER database lacks detailed information on individual patient radiotherapy and chemotherapy, which may necessitate reliance on other clinical trials or studies for specific interventions or treatment effects.

In summary, PNI shows potential as a prognostic marker in stage I–Ⅲ EO-CRC patients and can serve as an independent prognostic indicator. The PNI-based nomogram model is a valuable tool for quantifying prognosis in EO-CRC patients.

Conflicts of Interest: None

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·论　著·

基于周围神经侵犯的列线图模型在预测Ⅰ~Ⅲ期早发性结直肠癌预后中的应用

朱俊韬，刘雷，姚家楠，吴洁，彭安易，季国忠
南京医科大学第二附属医院消化内科，江苏 南京 210011

摘要：目的　评估周围神经侵犯(PNI)对Ⅰ~Ⅲ期早发性结直肠癌(EO-CRC)患者预后的影响,并构建基于 PNI 的列线图预测模型。**方法**　本研究分析了 2010 年至 2015 年美国监测、流行病学和最终结果(SEER)数据库中登记的 50 岁及以下 5 920 例 EO-CRC 患者数据。通过 7∶3 比例分为训练组(n=4 164)和验证组(n=1 756),运用 Kaplan-Meier 绘制生存曲线,Cox 比例风险模型进行单变量及多变量预后分析。基于多变量模型显著变量构建列线图,通过受试者工作特征曲线(ROC)、校准曲线、决策曲线分析(DCA)评估其预测能力。**结果**　相较于 PNI 阴性患者,PNI 阳性患者更年轻、病变位于左侧结肠、分化程度更低、TNM 分期更高、接受化学治疗、CEA 水平偏高(P<0.05)。Kaplan-Meier 曲线提示 PNI 阳性组较 PNI 阴性组有更差的预后。COX 单变量分析提示年龄、性别、肿瘤分化程度、TNM 分期、T 分期、N 分期、是否接受放射治疗、是否接受化学治疗、CEA 水平、肿瘤最大直径以及 PNI 状态为影响患者生存预后的变量(P<0.05)。多变量分析显示 PNI 是Ⅰ~Ⅲ期 EO-CRC 患者的独立预后指标(HR=1.73,95%CI:1.44~2.08,P<0.01)。基于 PNI 构建的列线图模型在 3 年与 5 年生存期的 ROC 曲线下面积均超过 0.7。**结论**　PNI 可作为Ⅰ~Ⅲ期 EO-CRC 患者的独立预后标志,基于 PNI 的列线图模型可作为一个有效的预测预后工具。

关键词：早发性结直肠癌；周围神经侵犯；列线图；总生存期；预后
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Application of peripheral nerve invasion based nomogram model in predicting the prognosis of stage Ⅰ-Ⅲ early-onset colorectal cancer

ZHU Juntao, LIU Lei, YAO Jianan, WU Jie, PENG Anyi, JI Guozhong
Department of Gastroenterology, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210011, China
Corresponding author: JI Guozhong, E-mail: jgzzl@163.com

Abstract: Objective　To evaluate the impact of peripheral nerve aggression (PNI) on prognosis in patients with stage Ⅰ-Ⅲ early-onset colorectal cancer (EO-CRC) and to create a PNI-based nomogram prediction model. **Methods**　This study analyzed data on 5 920 EO-CRC patients aged 50 years and younger enrolled in the U.S. Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2015. The patients were divided into the training group (n=4 164) and the validation group (n=1 756) by a ratio of 7∶3. Kaplan-Meier survival curve was drawn and Cox proportional risk model was used for univariate and multivariate prognosis analysis. Based on the significant variables of the multivariate model, a nomogram was constructed, and the predictive ability was evaluated by receiver operating characteristic curve (ROC), calibration curve and decision curve analysis (DCA). **Results**　Compared with PNI negative patients, PNI positive patients tended to be young, lesions located in the left colon, with poorer differentiation, higher TNM stage, chemotherapy intervention, and higher CEA level (P<0.05). Kaplan-Meier curve suggested that PNI positive group had a worse prognosis than PNI negative group. Cox univariate analysis suggested that age, sex, degree of tumor differentiation, TNM stage, T stage, N stage, whether to receive radiation therapy, whether to receive

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通信作者：季国忠，E-mail：jgzzl@163.com
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chemotherapy, CEA level, maximum tumor diameter and PNI status were variables affecting the survival and prognosis of patients. Multivariate analysis showed that PNI was an independent prognostic indicator for patients with stage Ⅰ to Ⅲ EO-CRC (*HR*=1.73, 95%*CI*: 1.44-2.08, *P*<0.01). The area under ROC curve of nomogram model based on PNI was more than 0.7 in both 3-year and 5-year lifetime. **Conclusion** PNI can be used as an independent prognostic marker in patients with stage Ⅰ-Ⅲ EO-CRC, and PNI-based nomogram model can be used as an effective prognostic tool.

Keywords: Early-onset colorectal cancer; Peripheral nerve invasion; Nomogram; Overall survival; Prognosis

结直肠癌(colorectal cancer, CRC)是一种消化道常见的恶性肿瘤。根据世界卫生组织国际癌症研究机构(International Agency for Research on Cancer, IARC)发布的全球癌症统计数据报告,CRC 在全球癌症发病率中排名第三,死亡率位列第二[1]。自 20 世纪 90 年代中期起,美国 50 岁以上人群的 CRC 发病率有所下降。然而,在 50 岁以下人群,即早发性 CRC(early-onset colorectal cancer, EO-CRC)的发病率却呈上升趋势,由 5.9 例/每十万人升至 8.4 例/每十万人[2]。相关风险研究表明,肥胖、高脂血症、饮酒、高血压、代谢综合征、溃疡性结肠炎以及一级亲属的 CRC 病史等,都是 EO-CRC 的关键危险因素[3]。

周围神经浸润(peripheral nerve invasion, PNI)是一种恶性肿瘤的扩散方式,被定义为肿瘤细胞存在于神经内、神经周围[4],一般占据神经周围的 33%以上或侵犯神经鞘[5]。与血管和淋巴管受侵犯相似,PNI 可能导致患者的生存时间减少以及局部复发的风险增加[6]。PNI 在 CRC 患者中的发生率通常在 9%~33%,PNI 的阳性结果通常表明 CRC 可能呈现快速进展的趋势[7]。根据 2018 年 CRC 的诊疗指南,PNI 与阳性切缘、分化差和脉管浸润、T4 期、术中淋巴结<12 个等指标共同作为Ⅱ期 CRC 患者的高危因素和化疗适应证[8]。当 PNI 阳性时,通常预示着更低的生存预期[4]。指南中同样提到,在评估放化疗的疗效方面,PNI 也是可靠指标之一[8]。在 EO-CRC 患者中,PNI 阳性率往往高于晚发性 CRC 患者[9],这提示 PNI 可能与 EO-CRC 有更强的相关性。鉴于此,本研究的目的是探讨 PNI 对Ⅰ至Ⅲ期 EO-CRC 患者预后的影响,并构建相应的列线图预后预测模型。

1　资料与方法

1.1　*研究资料*　从 2010 年至 2015 年美国监测、流行病学和最终结果(Surveillance, Epidemiology, and End Results, SEER)数据库中筛选 EO-CRC 患者进行分析。本研究中 EO-CRC 被定义为诊断时年龄≤50 岁的 CRC。纳入标准:(1) CRC 为唯一的原发性肿瘤;(2) 进行手术治疗;(3) AJCC 分期在Ⅰ~Ⅲ期;(4) 有完整的生存信息。排除标准:(1) 存在远处转移;(2) 临床病理资料缺失。CRC 患者通过《国际肿瘤疾病分类第三版》[International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3)]站点代码(C18.0, C18.2~C18.7, C19.9 和 C20.9)和肿瘤分期方案确定。根据纳入和排除标准筛选后,共 5 920 例合格患者。本研究患者信息均来自 SEER 数据库,为公开数据库,故无需患者知情同意书。

1.2　*研究变量*　纳入的变量包括年龄、性别、原发肿瘤位置、肿瘤最大直径、肿瘤分化程度、T 分期、N 分期、癌胚抗原(carcinoembryonic antigen, CEA)水平、PNI 状态、放射治疗、化学治疗以及总生存时间。总生存时间定义为从诊断到因任何原因死亡的时间(月)或任何原因停止对患者随访所持续的时间(月)。

1.3　*统计学方法*　所有符合纳入标准的患者按照 7∶3 的比例随机分入两个组别:训练组(共 4 164 例患者)和验证组(共 1 756 例患者)。训练组用于筛选变量并构建模型;验证组用于验证训练组获得的结果。计数资料以例(%)表示,采用 χ^2 检验比较组间差异。生存分析通过 Kaplan-Meier 法、log-rank 检验以及 Cox 比例风险模型进行。采用两步法评估基线特征与生存时间之间的关系:首先是对所有的变量进行单变量 Cox 回归分析;其次,将单变量分析中 *P*<0.05 的变量纳入到多变量 Cox 回归模型中。训练组中显著变量被用于构建列线图模型,验证组用来对该模型进行验证。列线图模型利用 R 软件以及确定的显著变量来创建的。通过受试者工作特征(receiver operating characteristic, ROC)曲线分析评估列线图模型的性能以及预测准确性。ROC 曲线下的面积(area under curve, AUC)越大,预测的准确性就越高。此外,绘制预后的 3 年和 5 年时点的列线图校准曲线,用以比较预测的总生存率(overall survival, OS)与实际观察到的 OS。最后,用决策曲线分析(decision curve analysis, DCA)评估列线图在临床应用中的实用性。采用 IBM SPSS Statistics 21.0 统计软件及 R 4.3.2 进行统计学处理,统计检验均在双侧进行,以 *P*<0.05 为差异有统计学意义。

2　结　果

2.1　人口学及病理学特征　共有 5 920 例患者被纳入研究,男性(52.1%,3 086/5 920)和女性(47.9%,2 834/5 920)患者数量基本相当,原发肿瘤多见于左侧结肠(72.4%,4 289/5 920),肿瘤分化程度以高分化/中分化为主(84.0%,4 971/5 920),部分患者 CEA 水平显著升高(32.2%,1 904/5 920),且大多数肿瘤直径≤5 cm(63.1%,3 733/5 920)。患者被随机分配到训练组 (n=4 164)和验证组(n=1 756)。患者的人口统计学和临床病理特征见表 1。PNI 阳性患者占训练组的 14.4%(n=600),占验证组的 13.2%(n=232),而 PNI 阴性患者分别占 85.6%(n=3 564)和 86.8%(n=1 524)。在训练组中,PNI 阴性组与 PNI 阳性组的患者在多个指标上存在统计学差异(P<0.05),包括年龄、肿瘤原发部位、肿瘤分化程度、T 分期、N 分期、CEA 水平、化学治疗、放射治疗。在验证组中结果相似,除了年龄(P=0.14)和放射治疗(P=0.86)。

2.2　单变量和多变量 Cox 回归分析　在单变量分析中,PNI 是影响患者生存预后的显著变量(P<0.05),其他显著变量包括性别、肿瘤分化程度、T 分期、N 分期、放射治疗、化学治疗、CEA 水平以及肿瘤最大直径。将显著变量纳入 Cox 多变量生存分析发现,肿瘤分化程度、T 分期、N 分期、CEA 水平、化学治疗、放射治疗以及 PNI 状态是影响生存预后的独立预后指标(表 2)。使用 Kaplan-Meier 生存曲线和 log-rank 检验来评估 PNI 状态对预后的影响(图 1)。生存曲线显示 PNI 阳性组的生存结局显著较 PNI 阴性组差(HR=2.63, 95%CI: 2.21~3.13)。

2.3　预后列线图的构建　包含 PNI 在内的多变量分析中显著变量的列线图模型见图 2。该列线图使用方法为:将患者的具体变量数据对应到模型中相应的得分点,并在上方的分数线找到此变量的得分值,将所有相关变量的得分累加后得到的总分值,可直接在

表 1　PNI 阳性组与 PNI 阴性组患者的基本特征　[例(%)]

Tab. 1　Basic characteristics of PNI positive group and PNI negative group　[case (%)]

特征	训练组(n=4 164)				验证组(n=1 756)			
	PNI 阳性组(n=600)	PNI 阴性组(n=3 564)	χ^2 值	P 值	PNI 阳性组(n=232)	PNI 阴性组(n=1 524)	χ^2 值	P 值
年龄			14.27	0.01			5.49	0.14
11~20 岁	2(0.3)	4(0.1)			0	4(0.3)		
21~30 岁	39(6.5)	130(3.6)			14(6.0)	51(3.3)		
31~40 岁	128(21.3)	701(19.7)			54(23.3)	323(21.2)		
41~50 岁	431(71.9)	2 729(76.6)			164(70.7)	1 146(75.2)		
性别			0.29	0.59			3.62	0.06
男	305(50.8)	1 854(52.0)			109(47.0)	818(53.7)		
女	295(49.2)	1 710(48.0)			123(53.0)	706(46.3)		
部位			5.89	0.02			5.79	0.02
右侧	137(22.8)	983(27.6)			52(22.4)	459(30.1)		
左侧	463(77.2)	2 581(72.4)			180(77.6)	1 065(69.9)		
分化程度			41.85	<0.01			20.77	<0.01
高分化/中分化	448(74.7)	3 037(85.2)			173(74.6)	1 313(86.2)		
低分化/未分化	152(25.3)	527(14.8)			59(25.4)	211(13.8)		
T 分期			129.12	<0.01			50.87	<0.01
T1~T2	28(4.7)	914(25.6)			13(5.6)	414(27.2)		
T3~T4	572(95.3)	2 650(74.4)			219(94.4)	1 110(72.8)		
N 分期			272.59	<0.01			136.19	<0.01
N0	125(20.8)	1 878 (52.7)			40(17.2)	814(53.4)		
N1	250(41.7)	1 169(32.8)			99(42.7)	492(32.3)		
N2	225(37.5)	517(14.5)			93(40.1)	218(14.3)		
CEA 水平			52.48	<0.01			19.87	<0.01
正常	328(54.7)	2 482(69.6)			130(56.0)	1 076(70.6)		
升高	272(45.3)	1 082(30.4)			102(44.0)	448(29.4)		
化学治疗			109.16	<0.01			52.09	<0.01
未接受	94(15.7)	1 339(37.6)			34(14.7)	595(39.0)		
接受	506(84.3)	2 225(62.4)			198(85.3)	929(61.0)		
放射治疗			4.09	0.04			0.03	0.86
未接受	430(71.7)	2 692(75.5)			176(75.9)	1 164(76.4)		
接受	170(28.3)	872(24.5)			56(24.1)	360(23.6)		
肿瘤最大直径			2.64	0.10			1.89	0.17
≤5 cm	398(66.3)	2 241(62.9)			154(66.4)	940(61.7)		
>5 cm	202(33.7)	1 323(37.1)			78(33.6)	584(38.3)		

列线图的下方找到对应的 3 年及 5 年的 OS 预测值。

表 2　训练组患者生存预后的 Cox 单变量与多变量回归分析

Tab. 2　Cox univariate and multivariate regression analysis of survival prognosis in training group

特征	单因素分析		多因素分析	
	HR(95%*CI*)	*P* 值	*HR*(95%*CI*)	*P* 值
年龄		0.62		
11~20 岁	1.00			
21~30 岁	0.42(0.10~1.76)	0.23		
31~40 岁	0.39(0.09~1.60)	0.19		
41~50 岁	0.39(0.09~1.58)	0.19		
性别				
男	1.00		1.00	
女	0.85(0.73~0.99)	<0.05	0.92(0.78~1.07)	0.28
部位				
右侧	1.00			
左侧	1.04(0.87~1.24)	0.69		
分化程度				
高分化/中分化	1.00		1.00	
低分化/无分化	1.91(1.60~2.28)	<0.01	1.59(1.33~1.91)	<0.01
T 分期				
T1~T2	1.00		1.00	
T3~T4	2.64(2.06~3.39)	<0.01	1.67(1.15~2.45)	0.01
N 分期				
N0	1.00		1.00	
N1	2.23(1.84~2.70)	<0.01	2.06(1.65~2.57)	<0.01
N2	3.96(3.24~4.85)	<0.01	3.12(2.47~3.96)	<0.01
CEA 水平				
正常	1.00		1.00	
升高	1.86(1.59~2.18)	<0.01	1.49(1.28~1.75)	<0.01
PNI 状态				
无	1.00		1.00	
有	2.60(2.19~3.09)	<0.01	1.73(1.44~2.08)	<0.01
化学治疗				
未接受	1.00		1.00	
接受	1.79(1.49~2.15)	<0.01	0.70(0.55~0.88)	0.01
放射治疗				
未接受	1.000		1.00	
接受	1.49(1.26~1.75)	<0.01	1.41(1.18~1.69)	<0.01
肿瘤最大直径				
≤5 cm	1.00		1.00	
>5 cm	1.23(1.05~1.44)	0.01	1.08(0.92~1.27)	0.38

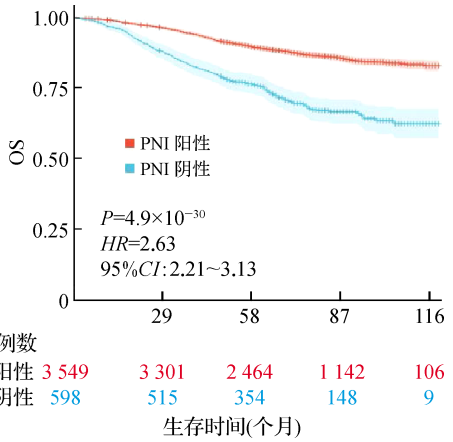


图 1　训练组 PNI 阳性和 PNI 阴性的 Kaplan-Meier 生存曲线

Fig. 1　Kaplan-Meier survival curves of PNI-positive and PNI-negative in training group

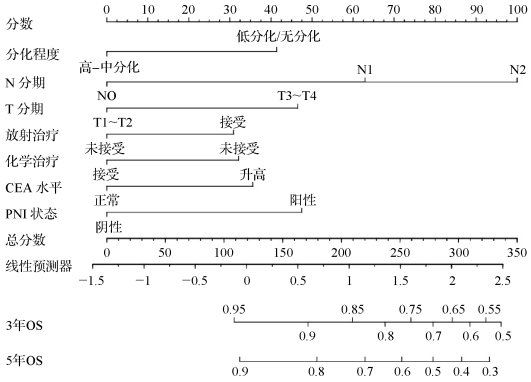
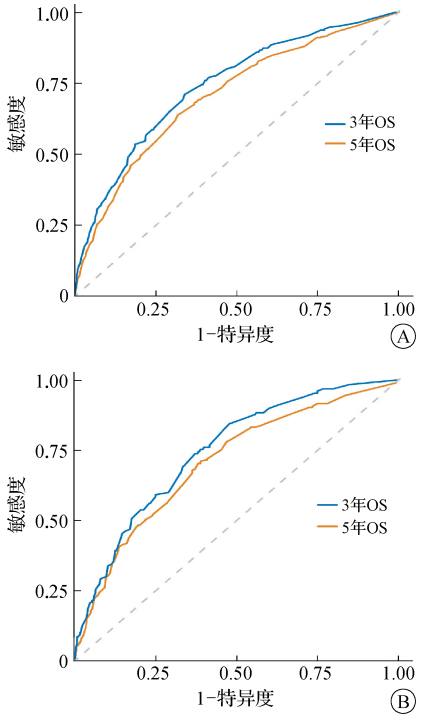


图 2　预测Ⅰ~Ⅲ期 EO-CRC 3 年及 5 年 OS 的列线图模型

Fig. 2　A nomogram model for predicting 3-year and 5-year OS of stage Ⅰ-Ⅲ EO-CRC

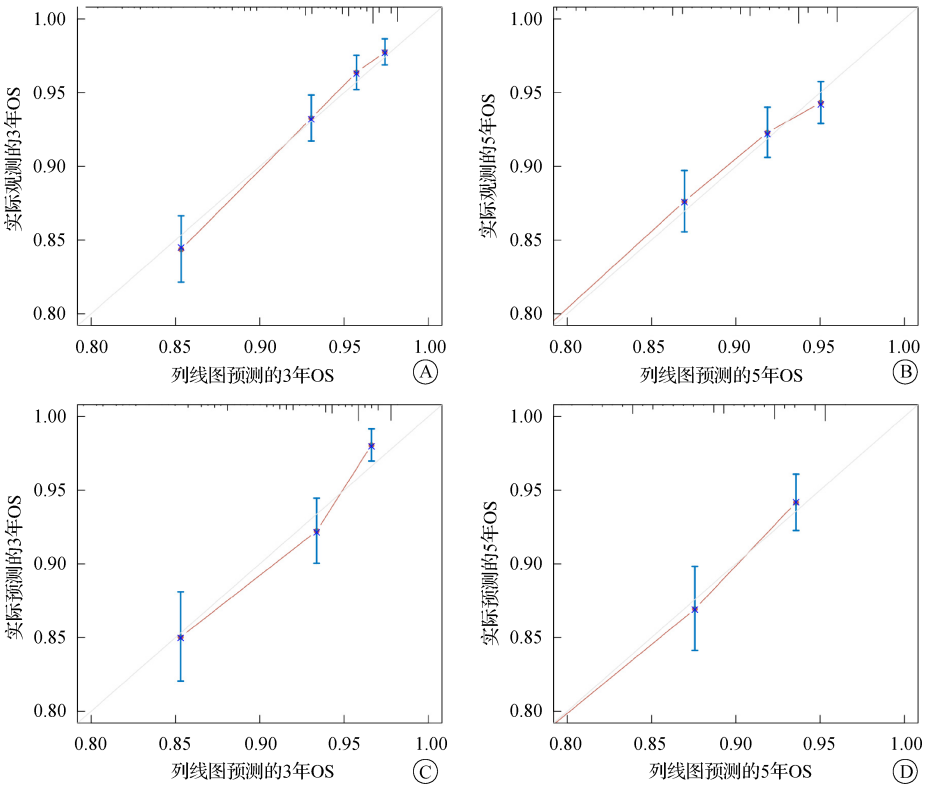


注:A 为训练组 3 年及 5 年 OS 的 ROC 曲线;B 为验证组 3 年及 5 年 OS 的 ROC 曲线。

图 3　训练组与验证组的 ROC 曲线

Fig. 3　ROC curves of training group and verification group

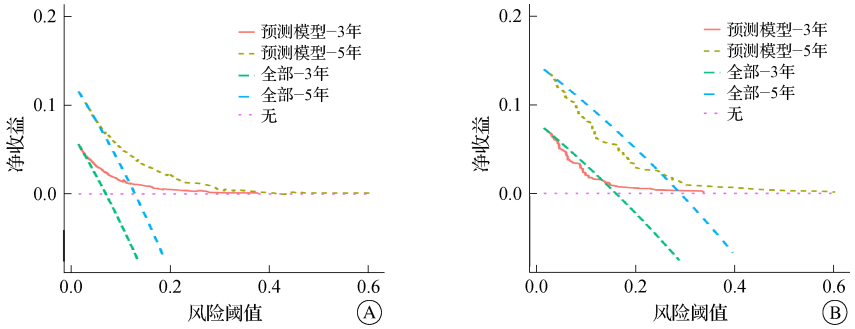
2.4　列线图模型的验证　在训练组与验证组中,预测 3 年、5 年 OS 的 AUC 均超过 0.7(图 3)。校准曲线显示在训练组和验证组中,模型预测的 OS 与观察到的生存结果具有较高的符合度(图 4)。DCA 图中,两条标准线代表两种极端情况,其中斜线代表所有因素均为阳性,而横线代表所有因素均是阴性。其结果表明,在训练组中该列线图对于 EO-CRC 患者的 3 年及 5 年 OS 预测提示具有临床净收益和实用性,但在验证组中两条曲线与最高临床成本阈值线相近,预测临床净收益一般(图 5)。



注:A、B 为训练组中 EO-CRC 患者的 3 年和 5 年 OS 的校准曲线;C、D 为验证组中 EO-CRC 患者的 3 年和 5 年 OS 的校准曲线。灰色线表示理想的参考线,其中预测的概率将与观察到的存活率相匹配。红点代表列线图的性能。红色实线越接近灰色线,模型预测生存率就越准确。

图 4　列线图校准曲线

Fig. 4　Calibration curve of the nomogram



注:A 为训练组列线图的 3 年与 5 年 DCA;B 为验证组列线图的 3 年与 5 年 DCA。

图 5　列线图的 DCA

Fig. 5　DCA of the nomogram

3　讨　论

EO-CRC 通常在诊断时已经发展到较晚期,肿瘤分化程度较差,并且多发于左侧结肠[1]。本研究结果表明,年龄、性别、肿瘤原发部位对 EO-CRC 患者的预后无显著影响。与王廉源等[10]的研究结论相似,但也有研究发现,较年轻的患者与老年患者相比,预后可能相似甚至更好[11]。这些研究数据来源不同,可能存在研究对象的种族背景、风俗习惯、生活方式等差异。有研究结果揭示,相较于其他人群,非拉丁裔黑人及拉丁裔个体更容易罹患 EO-CRC。此外,非拉丁裔黑人 EO-CRC 患者在临床病理特征上表现出显著的不同[12]。另外,本研究的结果提示,T 分期、N 分期、肿瘤分化水平、CEA 水平、PNI 状态及放疗和化疗显著影响预后,与高丹丹[13]、潘朝敏[14]等研究结果相似,高 AJCC 分期、肿瘤低分化及高 CEA 水平被认为是 EO-CRC不良预后的风险因素。

PNI 被视为肿瘤局部进展的一种表现,同时也是

一种转移方式,已在多种肿瘤中被观察到,包括头颈癌、胰腺癌、前列腺癌、胆管癌、胃癌和结直肠癌等[6]。本研究观察到,与 PNI 阴性患者相比,阳性患者的原发肿瘤更多位于左侧结肠,肿瘤多为低分化或未分化类型。PNI 阳性患者多在 T3~T4 期,CEA 水平上也普遍较高。绝大多数 PNI 阳性患者接受过化学治疗。有研究指出 PNI 与肿瘤分化程度、AJCC 分期密切相关[15]。PNI 是 CRC 的独立预后风险因素,尤其是对 EO-CRC 的影响更为显著[16]。本研究得出相似的结论,Kaplan-Meier 生存曲线、COX 回归模型均证实了 PNI 在Ⅰ~Ⅲ期 EO-CRC 中的预后价值,其阳性患者的生存预期劣于阴性患者。

本研究构建了一个基于 PNI 的列线图模型,旨在预测Ⅰ~Ⅲ期 EO-CRC 患者的 OS。该模型纳入了七个变量:肿瘤分化程度、T 分期、N 分期、CEA 水平、PNI 状态、化学治疗以及放射治疗。结果发现,低分化程度、高 T 分期、高 N 分期、高 CEA 水平、PNI 阳性以及接受放射治疗与较差的生存结果相关联,而接受化学治疗则与更好的生存结果相关。ROC 曲线分析显示,模型在预测 3 年和 5 年 OS 方面具有较高的准确性(AUC 值均>0.7)。校准曲线的走势表明模型的预测准确性较高。DCA 结果显示列线图模型带来了显著的临床益处。

然而,本项研究也有其局限性:第一,SEER 数据库可能与亚洲患者存在种族、地域、生活习惯、健康观念等差异。第二,SEER 数据库未提供个体患者接受放射治疗和化学治疗的详细信息,故对于特定干预措施或治疗效果的研究,可能需要依赖于其他的临床试验或研究。

综上所述,PNI 在Ⅰ~Ⅲ期的 EO-CRC 患者中展现出了预测预后的潜力,可作为独立预后标志。基于 PNI 构建的列线图模型能够作为一种有价值的预后预测工具,可对Ⅰ~Ⅲ期 EO-CRC 患者的生存预后进行量化预测。

利益冲突　无

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