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Prognostic value of the preoperative prognostic nutritional and systemic immunoinflammatory indexes in patients with colorectal cancer

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Abstract

Introduction Colorectal cancer (CRC) is a common malignant tumor of the digestive tract. Although many prognostic indicators are currently available, it remains unclear which indicators are the most beneficial for patients with CRC. Therefore, there is a critical need to identify a simple, convenient and accurate prognostic indicator.

Purpose To investigate the clinical significance of the systemic immune-inflammation index (SII) and prognostic nutritional index (PNI) as prognostic indicators for the survival of patients with CRC.

Methods The clinical data of CRC patients admitted to the general surgery ward of Taizhou People's Hospital affiliated to Nanjing Medical University from January 2015 to January 2018 were retrospectively analyzed. Two prognostic indicators (SII and PNI) were compared to evaluate their prognostic value in CRC patients.

Results Based on these variables, we constructed a LASSO prediction model. The AUC (Area Under the Curve) value and 95% CI of the training group were 0.917 (0.858–0.976) compared to 0.932 (0.846–1.000) in the validation group. We found that CEA > 5 ng/mL, tumor stage, pathological type, postoperative complications, and PNI were associated with the five-year survival rate of CRC patients. Receiver Operating Characteristic Curves (ROC) were drawn to assess the prediction accuracy of the model. The AUC and 95% CI of the training group were 0.913 (0.854–0.972), while the AUC and 95% CI of the validation group were 0.954 (0.899–1.000).

Conclusions PNI is an independent risk factor for postoperative complications associated with CRC and a powerful tool for predicting survival outcomes in CRC patients.

Keywords Colorectal cancer, Systemic immune-inflammation index, Prognostic nutritional index, Prognosis

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Introduction

Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies in the world, with 800,000 deaths reported globally every year [1, 2]. In 2020, approximately 19.3 million new cancer cases and nearly 10 million cancer deaths worldwide were reported [3]. The main risk factor for CRC is age, although other inherent risk factors such as inflammatory bowel disease and Crohn's disease have also been identified as important risk factors [4–6]. The global increase in CRC can be attributed to an increasingly aging population, adverse modern dietary habits, and an association with increased risk factors such as smoking, physical inactivity, obesity, diabetes mellitus and accompanying inflammatory state [7–11].

The prognostic nutritional index (PNI) refers to the use of serum albumin and peripheral blood level lymphocyte counts, and was originally used to predict preoperative nutritional status by assessing postoperative complications in patients undergoing surgery [12–14]. Recent studies have shown that the PNI has high accuracy in predicting various cancers [15]. Immune system function plays a crucial role in tumor efficacy, and serum albumin and lymphocyte levels are important indicators of immune system function [16, 17]. Thus, the PNI is a comprehensive reflection of the nutritional and immune status of patients and is closely associated with the body's ability to clear tumor cells and reduce local recurrence [18].

The systemic immune-inflammation index (SII) is a valuable prognostic indicator that reflects the local immune response and systemic inflammation of the whole body [19]. The SII was first proposed by Hu et al. in [20] and has since been extensively studied [20]. The SII is often used as a predictor of mortality in cancer patients because higher SII values are associated with an increased risk of death [21]. In patients with tumors, both pro-tumor and anti-tumor factors are induced in the body, including increased neutrophil and platelet levels, decreased lymphocyte levels, and increased SII values [22–24]. In recent years, the application of the SII has expanded, such that it can also be used to predict the severity of various diseases and the effects of different treatments [25].

Carcinoembryonic antigen (CEA) and carbohydrate antigen 19 – 9 (CA19-9) are well-established tumor markers that are present at elevated levels in the serum of patients with various gastrointestinal tumors or in cases where tumor metastasis has already occurred [26, 27]. Although CEA and CA19-9 can be used to monitor CRC patients, abnormal changes may also occur in colorectal polyps, indicating that these markers lack specificity and sensitivity [28, 29]. Tumor Protein p53 (*TP53*) is the most commonly mutated gene in humans with CRC [30]. *TP53* is a key tumor suppressor, and loss of *TP53* function is often a prerequisite for cancer development [31]. However, the diagnosis and treatment of tumor patients harboring *TP53* mutations is expensive and places a financial burden on the patients and their families. Therefore, there is a critical need to find a simple, inexpensive and reliable prognostic index.

Patients with malignant tumors often have cachexia, severe malnutrition and chronic inflammatory stimulation, which have negative effects on the treatment of patients. Therefore, the aim of this study was to examine further the prognostic value of the SII and PNI in CRC patients before and/or before treatment.

Methods

Study participants

This study was approved by the Ethics Committee of Taizhou People's Hospital Affiliated to Nanjing Medical University and was strictly screened according to the inclusion and exclusion criteria. The clinical data of patients with CRC admitted to the general surgery ward of Taizhou People's Hospital Affiliated to Nanjing Medical University (Taizhou, China) from January 2015 to January 2018 were retrospectively collected.

The inclusion criteria included: (1) aged 18–80 years old; (2) CRC was diagnosed after biopsy; (3) no other forms of treatment such as radiotherapy or chemotherapy were received after diagnosis; (4) written informed consent of the patient and their family was obtained; and (5) the complete medical records and follow-up data of patients were available. The exclusion criteria included: (1) CRC patients with tumors at other sites; (2) CRC patients with a severe bleeding tendency; (3) CRC patients with serious medical diseases; (4) CRC patients that had undergone other treatment options; and (5) patients with incomplete medical records.

Data collection

General information was collected including the patient's age, sex, height, weight, Body Mass Index (BMI), hypertension, diabetes, tumor location, surgical method, preoperative albumin, preoperative lymphocytes, preoperative neutrophils, preoperative platelets, preoperative monocytes, preoperative white blood cells, preoperative hemoglobin, CEA, CA125, CA19-9, maximum tumor diameter, tumor stage, the presence of lymph node metastasis, pathological type, five-year overall survival (OS), PNI, SII and other clinical data. Patients were followed up through outpatient clinics and telephone calls. A total of 221 CRC patients were followed. By December 2023, data regarding the survival status of patients diagnosed with CRC after surgical treatment in our hospital and five-year follow-up data were obtained.

The SII value was calculated as follows: SII = platelet count (P) × neutrophil count (N)/lymphocyte count (L). The PNI value was calculated as follows: PNI = neutrophil count (N)/lymphocyte count (L).

Statistical analysis

Key variables were screened using LASSO and a LASSO prediction model was developed based on the selected variables. Next, COX regression analysis was performed on the selected variables. The validity of the LASSO-Cox regression model was assessed by generating receiver operating characteristic (ROC) curves on the prediction models of the training and validation groups. $P < 0.05$ indicated that differences were statistically significant.

Results

Baseline characteristics of five-year survival in patients with CRC

First, we examined the potential factors associated with five-year survival or death in CRC patients to identify the risk factors associated with mortality in CRC patients. As shown in Table 1, CEA > 5 ng/mL ($P = 0.001$), tumor stage ($P = 0.001$), lymph node metastasis ($P = 0.001$), pathological type ($P = 0.001$), postoperative complications ($P = 0.001$), intraoperative bleeding > 100 ml ($P = 0.035$), intraoperative blood transfusion ($P = 0.004$), leukocyte ($P = 0.028$), albumin ($P = 0.028$), prealbumin ($P = 0.001$), lymphocytes ($P = 0.001$), PNI ($P = 0.001$) and SII ($P = 0.001$) were significantly different between the surviving and deceased groups. Therefore, we hypothesized that these risk factors were associated with the five-year survival of CRC patients.

Table 1 Baseline characteristics of the surviving and deceased sets

	Survival	Death	*P* value
	N = 172	*N* = 49	
Age > 60years(%)	76(44.2)	27(55.1)	0.234
Gender, male(%)	103(59.9)	27(55.1)	0.663
Hypertension(%)	50(29.1)	15(30.6)	0.975
Diabetes(%)	13(7.6)	6(12.2)	0.457
Obesity(%)	71(41.3)	22(44.9)	0.773
Tumor position, rectum (%)	57(33.1)	17(34.7)	0.975
Surgical approach, knife(%)	72(41.9)	16(32.7)	0.319
CEA > 5ng/mL(%)	46(26.7)	30(61.2)	< 0.001
Diameter ≥ 5 cm((%)	70(40.7)	23(46.9)	0.537
Stage, III(%)	42(24.4)	31(63.3)	< 0.001
Transfer(%)	42(24.4)	31(63.3)	< 0.001
Pathological type, mid-to-high polarization(%)	132(76.7)	24(49.0)	< 0.001
Complications(%)	7(4.1)	14(28.6)	< 0.001
CA125>35U/mL(%)	23(13.4)	10(20.4)	0.321
CA199>37KU/L(%)	15(8.7)	6(12.2)	0.641
Anemic(%)	73(42.4)	22(44.9)	0.886
Bleeding > 100 ml(%)	54(31.4)	24(49.0)	0.035
Transfusion(%)	8(4.7)	9(18.4)	0.004
Neutrophil,10^9/L	5.68 ± 7.33	6.10 ± 3.87	0.698
Platelet,10^9/L	187.71 ± 70.74	185.22 ± 58.42	0.822
Monocyte,10^9/L	0.54 ± 0.52	0.65 ± 0.90	0.304
WBC,10^9/L	7.20 ± 2.61	8.34 ± 4.71	0.028
Pre-albumin, mg/L	191.37 ± 56.72	168.65 ± 67.09	0.019
HGB, g/L	116.06 ± 22.65	113.00 ± 25.40	0.417
Age, years	62.98 ± 12.04	67.29 ± 8.98	0.021
Albumin, g/L	40.35 ± 4.64	36.65 ± 4.20	< 0.001
Lymphocyte,10^9/L	2.59 ± 1.63	1.45 ± 0.66	< 0.001
PNI	53.29 ± 8.85	43.91 ± 5.62	< 0.001
SII	441.89 ± 360.15	923.75 ± 727.27	< 0.001

Construction of a five-year survival prediction model for patients with CRC

The variables were screened using the LASSO regression model (Figs. 1 and 2; Table 2). A death prediction model was constructed by randomly assigning the total population to a training group consisting of 70% of the patients (159 cases) and a validation group consisting of 30% of the patients (62 cases).

The training group was set up to predict the model, while the validation group was used for validation. The LASSO model for screening key variables was evaluated using ROC curves with the training group ROC curve shown in Fig. 3 and that of the validation group shown in Fig. 4. We found that the AUC values and 95% CI were 0.917 (0.858–0.976) in the training group and 0.932 (0.846–1.000) in the validation group, suggesting that the LASSO model had an excellent ability to screen for key variables.

Survival analysis of prognosis of patients with CRC

Survival analysis was performed on the selected key variables. We found that CEA ($P = 0.006$), tumor stage ($P = 0.016$), pathological type ($P = 0.033$), postoperative complications ($P = 0.047$) and PNI ($P = 0.000$) were all significant (Table 3).

Establishment and efficacy evaluation of a prognostic predictive model for CRC

The key variables (CEA, tumor stage, pathological type, complications and PNI) were selected by survival analysis and a nomogram was constructed. As shown in Fig. 5, the nomogram had certain clinical practicability. Each predicted risk factor was given a corresponding score. A total score was then calculated for each patient based on the predicted risk factor score for each of the patient's risk factors. The numbers corresponding to the total score were plotted vertically to obtain the predicted survival rates of CRC patients at 12, 36 and 60 months.

The predictive ability of the nomogram was further evaluated by drawing ROC curves. The ROC curves of the training group predicted model and validation group

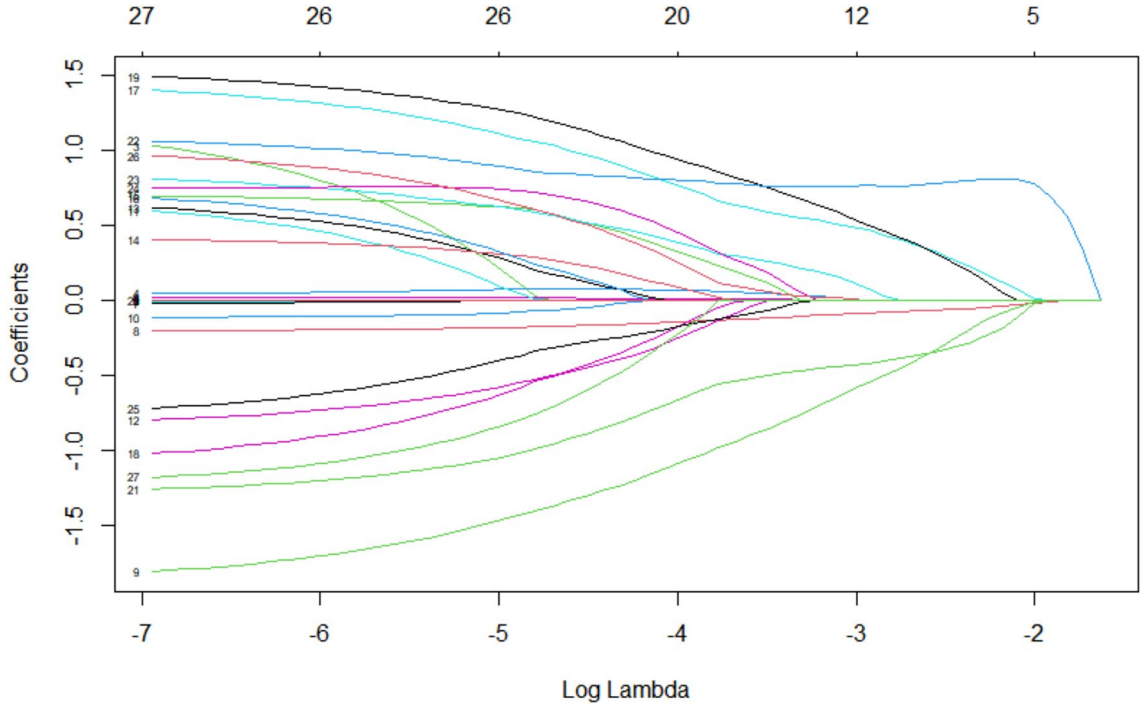

Fig. 1 Lasso coefficient path

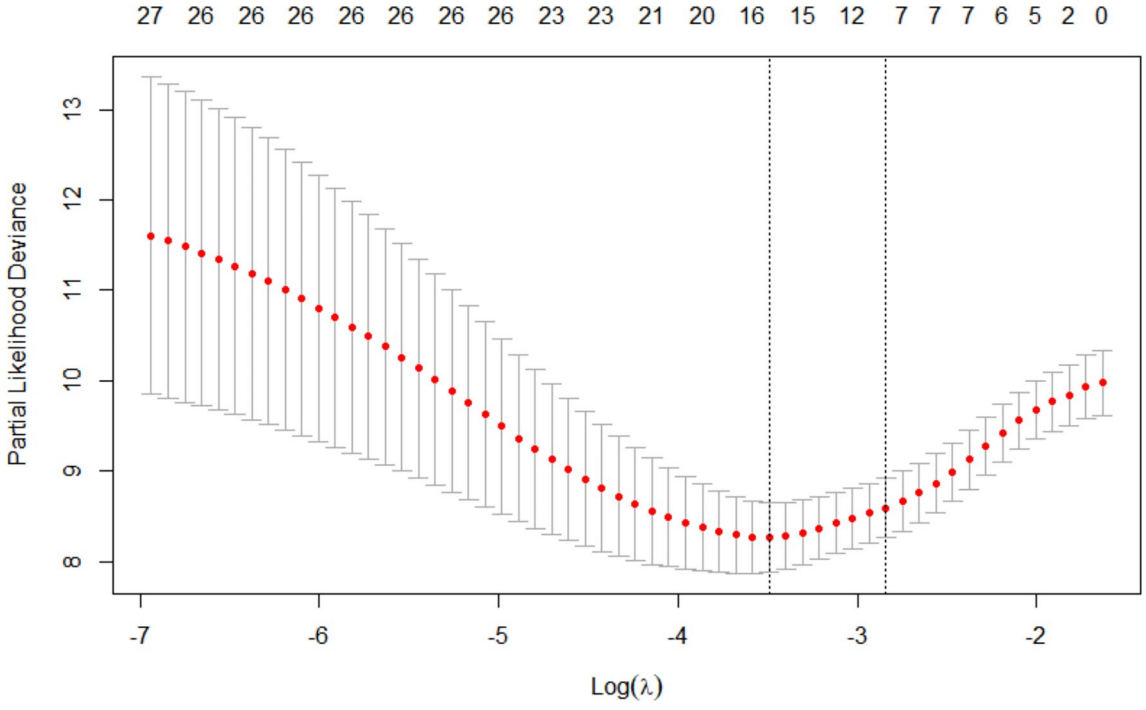

Fig. 2 FLasso cross-validation curve

predicted model are shown in Figs. 6 and 7, respectively. The AUC value and 95% CI of the training group were 0.913 (0.854–0.972) compared to 0.954 (0.899–1.000) in the validation group. These results suggested that the nomogram model was good for predicting the five-year survival in CRC patients. Finally, the correction curve was drawn, and revealed that the actual situation and prediction results were in high agreement, indicating that the predictive model was accurate (Figs. 8 and 9).

Table 2 Baseline characteristics of the training and validation sets

	Training set	Validation set	*P* value
	N = 159	*N* = 62	
Age > 60years(%)	76(47.8)	27(43.5)	0.675
Gender, male(%)	91(57.2)	39(62.9)	0.537
Hypertension(%)	45(28.3)	20(32.3)	0.678
Diabetes(%)	14(8.8)	5(8.1)	1.000
Obesity(%)	64(40.3)	29(46.8)	0.465
Tumor position, rectum (%)	53(33.3)	21(33.9)	1.000
Surgical approach, knife(%)	67(42.1)	21(33.9)	0.330
CEA > 5ng/mL(%)	55(34.6)	21(33.9)	1.000
Diameter ≥ 5 cm((%)	71(44.7)	22(35.5)	0.276
Stage, III(%)	52(32.7)	21(33.9)	0.995
Transfer(%)	52(32.7)	21(33.9)	0.995
Pathological type, mid-to-high polarization(%)	111(69.8)	45(72.6)	0.809
Complications(%)	14(8.8)	7(11.3)	0.756
CA125>35U/mL(%)	26(16.4)	7(11.3)	0.460
CA199>37KU/L(%)	13(8.2)	8(12.9)	0.411
Anemic(%)	64(40.3)	31(50.0)	0.244
Bleeding > 100 ml(%)	55(34.6)	23(37.1)	0.847
Transfusion(%)	16(10.1)	1(1.6)	0.066
Neutrophil,10^9/L	5.58 ± 5.89	6.27 ± 8.49	0.492
Platelet,10^9/L	188.15 ± 71.06	184.61 ± 60.24	0.729
Monocyte,10^9/L	0.52 ± 0.51	0.67 ± 0.84	0.107
WBC,10^9/L	7.35 ± 2.91	7.71 ± 3.93	0.460
Pre-albumin, mg/L	187.26 ± 60.11	183.98 ± 59.29	0.715
Albumin, g/L	39.59 ± 5.06	39.38 ± 4.07	0.767
Lymphocyte,10^9/L	2.29 ± 1.74	2.44 ± 0.87	0.518
PNI	51.06 ± 10.04	51.60 ± 6.14	0.694
SII	562.95 ± 525.78	512.25 ± 455.03	0.505

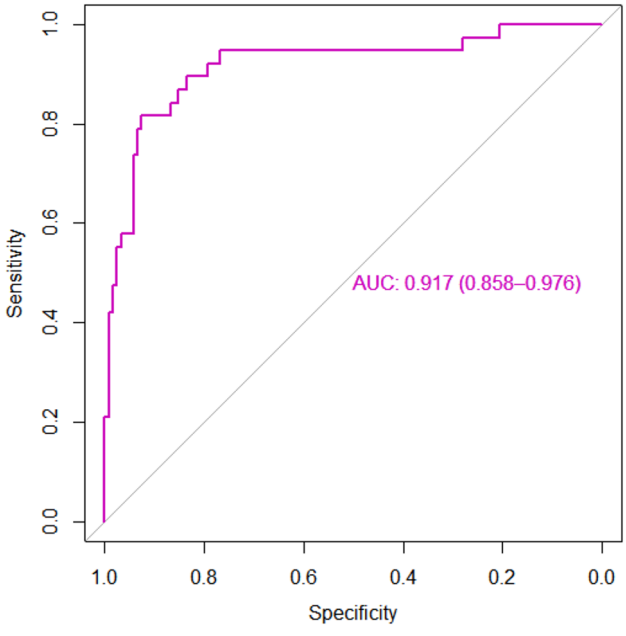

Fig. 3 ROC curve for variable selection in the training group

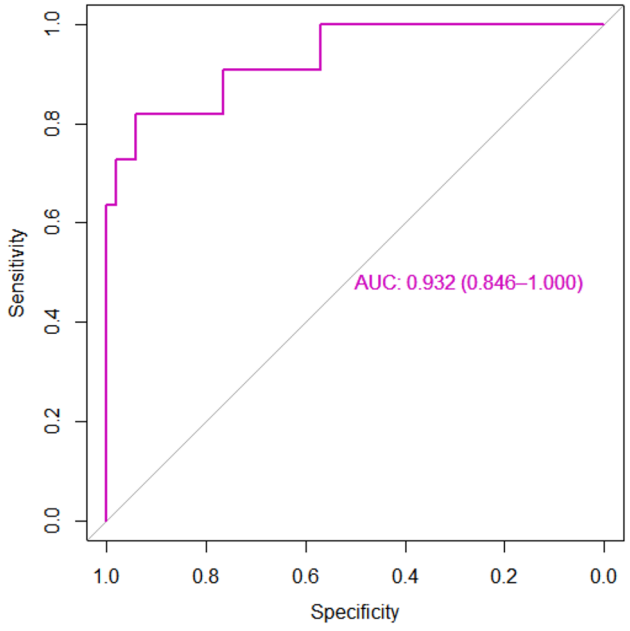

Fig. 4 ROC curve for variable selection in the validation group

Table 3 Multivariate analysis of risk factors for postoperative complications in CRC patients

	OR	95%CI	*P* value
Diabetes	7.207	(0.907–55.995)	0.057
Surgical approach	1.914	(0.677–5.692)	0.228
CEA	5.060	(2.021–13.584)	0.001
Complications	2.929	(0.653–13.67)	0.161
Danhe	2.262	(0.341–21.282)	0.492
WBC	1.217	(0.934–1.585)	0.142
Pre-albumin	0.998	(0.99–1.007)	0.722
Albumin	1.415	(1.111–1.867)	0.009
PNI	0.614	(0.474–0.758)	0.000
SII	1.000	(0.999–1.002)	0.938

Discussion

There is growing evidence that the SII and PNI, which reflect systemic inflammation and nutritional status, can reflect the relationship between host inflammation and immune status, and accurately predict the prognosis of cancer patients [32]. However, the relationship between the PNI, SII and clinical outcomes in CRC patients remains unclear. The primary objective of this study was to assess the prognostic value of the SII and PNI in CRC patients undergoing surgical removal. Our results show that among the risk factors associated with five-year survival or death in CRC patients, the PIN and SII are closely associated with mortality in CRC patients. Survival analysis revealed that CEA, tumor stage, pathological type, postoperative complications and PNI were significant risk factors for CRC patients, with PNI showing the highest significance.

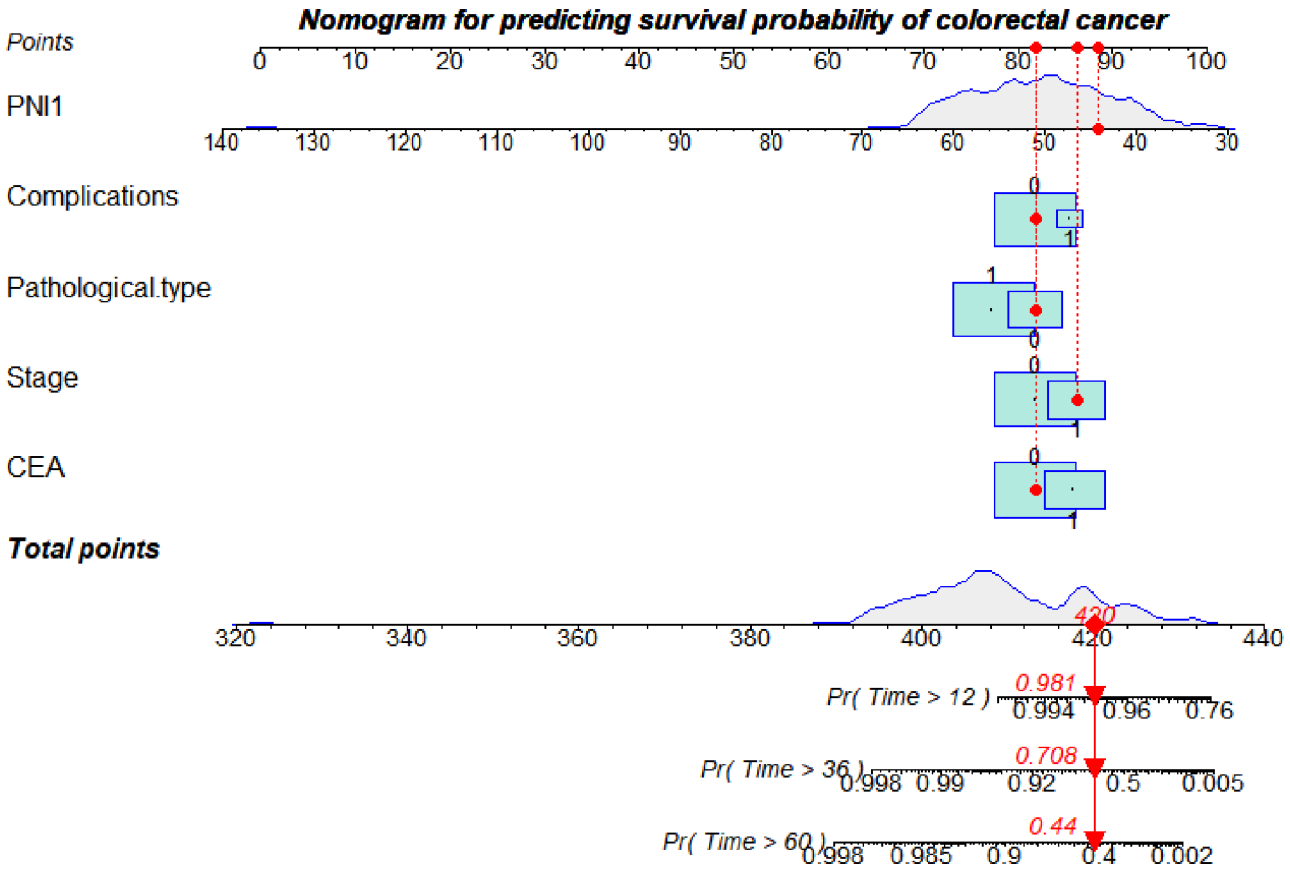

Fig. 5 Prediction of OS nomogram after laparoscopic radical resection of CRC

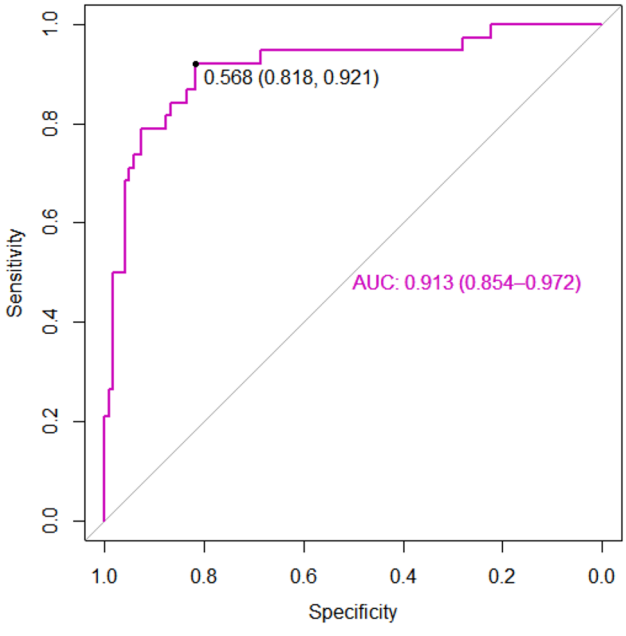

Fig. 6 ROC curve for predictive model in the training group

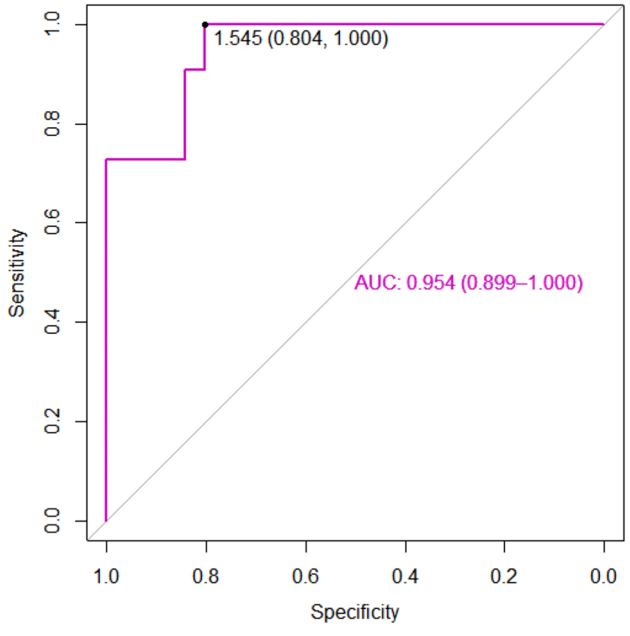

Fig. 7 ROC curve for predictive model in the validation group

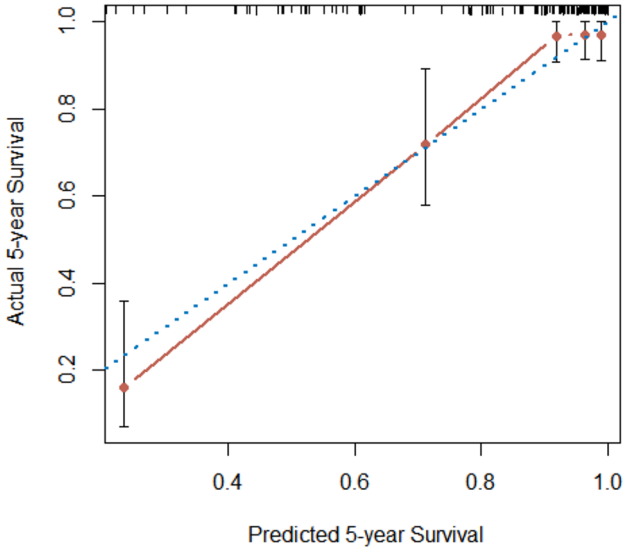

Fig. 8 Calibration curve for predictive model in the training group

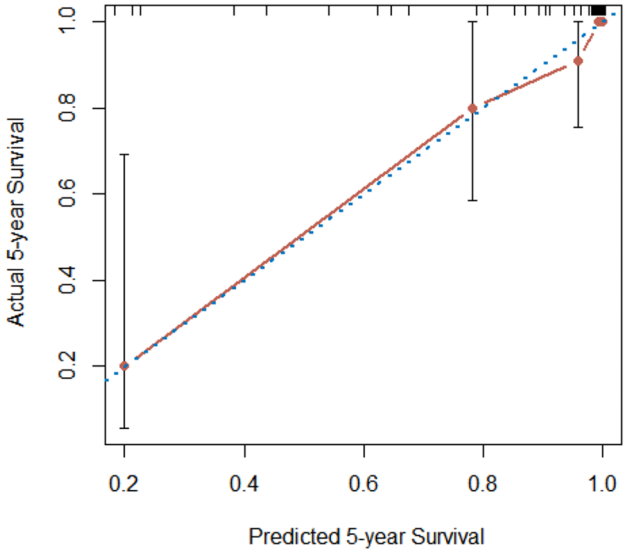

Fig. 9 Calibration curve for predictive model in the validation group

The nutritional and inflammatory status of the body has been shown to play an important role in the occurrence, development and prognosis of tumors. Previous studies have confirmed that preoperative hypoalbuminemia is closely related to postoperative morbidity and mortality, as well as a poor survival rate after tumor surgery [33]. Serum albumin levels are important independent biomarkers for a wide range of human diseases, including cancer [34]. Interestingly, albumin has been shown to display active tumor targeting effects through its interactions with GP60 and secreted protein acidic and rich in cysteine in tumor-associated endothelial cells and the tumor microenvironment [35].

The prognostic value of a pretreatment PNI in patients with lung cancer was systematically evaluated in a 2018 meta-analysis. A low pretreatment PNI was found to be closely associated with poor OS in lung cancer patients, and a predictor of poor survival [36]. Similarly, Zhang et al. examined the relationship between the PNI and OS, disease free survival and progression free survival in breast cancer patients receiving clinical treatment. High PNI values were found to be a favorable independent predictor of prolonged OS and progression free survival in breast cancer patients after clinical treatment, and the PNI was significantly correlated with the prognosis of breast cancer patients [37].

A study evaluating the relationship between preoperative SII and the prognosis and clinicopathological features of bladder cancer in 7087 patients found that preoperative SII elevation was associated with poor tumor differentiation, high tumor stage, lymph node involvement, and tumor size ≥ 3 cm. Moreover, preoperative SII elevation was significantly associated with poor survival outcomes and adverse pathological features [38]. The SII, as an inflammatory indicator, has been identified as a prognostic biomarker in various diseases including acute kidney injury, fatty liver, hyperlipidemia, ischemic stroke, Alzheimer's disease and cerebral hemorrhage [39–42].

In recent years, increasing evidence has suggested that the interaction between tumor cells and platelets is a prerequisite for the successful transmission of blood metastasis [43]. Platelets stimulate the proliferation of cancer cells by releasing a variety of cytokines and chemokines, as well as accelerate tumor angiogenesis through various angiogenic regulatory factors, thereby playing a crucial role in the growth and metastasis of cancer cells. Zhang et al. demonstrated that cancer cells can be reprogrammed to a metastatic state by acquiring platelet mitochondria via the PINK1/Parkin-Mfn2 signaling pathway. In addition, platelet mitochondria regulate the GSH/GSSG ratio and reactive oxygen species of tumor cells, promoting lung metastasis of osteosarcoma [44]. Neutrophils are the most abundant myeloid cells in human blood and are important regulators of cancer [45]. External stimulation of the tumor microenvironment can trigger the accumulation of tumor-associated neutrophils in local areas and switch between anti-tumor and pro-tumor phenotypes [46]. Anti-tumor neutrophils kill tumor cells directly through cytotoxic effects, as well as indirectly through the activation of adaptive immune responses. In contrast, the pro-tumor phenotype of neutrophils may be related to cell proliferation, angiogenesis, and immunosuppression in the tumor microenvironment [47].

This study introduces the PNI as a novel prognostic marker for CRC, addressing a gap in the current literature. We utilized LASSO regression for feature selection, followed by Cox regression analysis and ROC curve evaluation to validate the robustness of our findings.

Based on these analyses, we developed a nomogram that facilitates individualized survival predictions. Furthermore, the study investigates the potential role of PNI in CRC prognosis by linking it to underlying biological mechanisms. PNI offers several advantages, including cost-effectiveness and ease of measurement, making it a valuable tool for preoperative risk assessment and providing crucial support for postoperative follow-up care. However, there are several limitations associated with the analytical process of this retrospective study. First, subjectivity in the collection of CRC patient data may have contributed to biases in our findings. Secondly, the influencing factors included in our study are not comprehensive. Third, this retrospective study is a single-center study that includes a relatively small number of patients, which may affect the accuracy of our results. Future studies that incorporate more patients from multiple centers and a comprehensive risk factor analysis are the next step to carry out survival and related risk factor analyses of CRC patients to better serve clinicians and patients.

Recommendations and future perspectives

First, future studies should consider incorporating the PNI and SII into the routine preoperative assessment of CRC patients. These indices offer valuable insights into a patient's nutritional and inflammatory status, which are critical for predicting postoperative outcomes. Furthermore, SII, as a robust marker of systemic inflammation, provides essential information regarding the patient's overall inflammatory state, particularly in the context of the immune response within the tumor microenvironment. With the advancement of precision medicine, it is imperative to integrate genomic and molecular biology research with PNI and SII to elucidate their specific roles in tumorigenesis and cancer progression. Such interdisciplinary approaches could uncover novel mechanisms underlying CRC development and identify potential therapeutic targets.

In terms of therapeutic strategies, we recommend further investigation into the efficacy of immunomodulators and nutritional interventions in CRC patients. Given the well-documented immunomodulatory properties of vitamin D and certain repurposed drugs, future studies should explore their potential as adjunctive therapies in CRC treatment [48]. Additionally, the repurposing of existing pharmacological agents, such as anti-inflammatory or immunomodulatory drugs, as adjunctive treatments for CRC warrants further exploration. These approaches could offer cost-effective and readily available options to enhance current treatment regimens.

Conclusion

The PNI is a simple and feasible indicator for predicting CRC, and can therefore be used as an effective prognostic indicator for postoperative survival, which will benefit clinicians in their decision making processes regarding individual patient treatment strategies and medication plans.

Abbreviations

CRC	Colorectal Cancer
SII	Systemic Immune-Inflammation Index
PNI	Prognostic Nutritional Index
AUC	Area Under the Curve
ROC	Receiver Operating Characteristic Curves
CEA	Carcinoembryonic Antigen
CA19-9	Carbohydrate Antigen 19–9
TP53	Tumor Protein p53
BMI	Body Mass Index
OS	Overall Survival

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Author contributions

HGQ and QYZ conceived and designed the experiments and supervised the study. SFF collected the data. WS and JFW analysed and interpreted the data. BJ and SZ applied for approval of ethics. HFL wrote the manuscript and supervised the study. All authors read and approved the final manuscript for publication.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethical approval

This study involving human participants was approved by the Medical Ethics Committee of the Taizhou People's Hospital Affiliated to Nanjing Medical University (Taizhou, China)(No. KY 2024-030-01). The ethics committee waived the requirement for informed consent from patients.

Competing interests

The authors declare no competing interests.

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