Preoperative prognostic nutritional index associated with anastomotic leakage in colorectal cancer patients after surgery

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Abstract

Background. Anastomotic leakage (AL) is a severe complication of colorectal cancer (CRC) surgery and is associated with the immune and nutritional status.

Objectives. This study aimed to investigate the role of the prognostic nutritional index (PNI) in AL in CRC patients after surgery.

Materials and methods. A retrospective case–control study was designed in a single center. The clinicopathological features and preoperative laboratory data of 124 CRC patients and 120 non-cancer patients who underwent surgery were collected and examined. Among the CRC patients, 24 had AL.

Results. Nutritional indicators were lower in CRC patients than in non-cancer patients ($p < 0.05$), but the clinical parameters analysis showed that only metastasis (M) stage, albumin, carcinoembryonic antigen (CEA), CA153, and PNI were associated with AL in CRC after surgery ($p < 0.05$). Prognostic nutritional index had a moderate predictive value for AL, with an area under the curve (AUC) of 0.625. Using the median value as a cutoff point, a high PNI was associated with a longer survival time in CRC patients ($p = 0.033$), and AL showed marginal significance ($p = 0.048$). The nomogram showed that PNI has a better prognostic value than tumor–node–metastasis (TNM) staging in CRC patients who underwent surgery.

Conclusions. Prognostic nutritional index is a useful supplement for predicting AL in CRC patients after colorectal surgery. It also helps predict the prognosis of CRC patients.

Key words: colorectal cancer, anastomotic leakage, prognostic nutritional index

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Background

Surgery is a major treatment approach for colorectal cancer (CRC), and anastomotic leakage (AL) is one of the most severe early complications of colorectal surgery, with an incidence rate of 1–30%, depending on the site of anastomosis (rectum > colon).[1] Anastomotic leakage causes abdominal infections, sepsis and prolonged hospital stays, and is associated with a high reoperation rate, increased short- and long-term morbidity and mortality rates,[2,3] as well as reduced quality of life. Thus, identifying the risk factors associated with AL after colorectal surgery remains a critical need for doctors.[4]

The exact etiology of AL remains unclear. Current evidence indicates that AL is a result of multiple factors, including operation time,[5] steroidal anti-inflammatory drug use[6] and surgical experience.[7] In addition, nutritional status,[8] inflammation status[9] and immune system status[10] contribute to the occurrence of AL after colorectal surgery. Several indicators, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR), have reportedly been associated with AL.[11] In addition, some novel indicators, including the systemic immune-inflammation index (SII),[12] prognostic nutritional index (PNI), pan-immune-inflammation value (PIV),[13] as well as systemic inflammation response index (SIRI),[14] have been reported to be associated with the survival of various cancers.

Given that AL is associated with nutrition, inflammation and immune status, finding indicators that can be incorporated into routine blood examination to predict AL in CRC patients after colorectal surgery can help prevent the occurrence of AL, thus improving treatment efficacy.

Objectives

This study aimed to determine the association of NLR, LMR, PLR, PNI, SII, PIV, SIRI, and PNI with AL in CRC patients after colorectal surgery to identify reliable indicators that predict AL, and explore their association with the survival of CRC patients.

Materials and methods

Data collection

This study has a case–control design. The data were retrospectively collected from CRC patients who underwent surgery between March 2013 and July 2022 at Third Affiliated Hospital of Guangxi Medical University (Nanning, China). The inclusion criteria were as follows: 1) histopathologically validated CRC diagnosis; 2) surgical resection of the primary CRC tumor; and 3) complete clinicopathological and postoperative follow-up data. The exclusion criteria included 1) complications with other primary tumors; 2) complications with severe autoimmune diseases, infectious diseases, blood diseases, or injury; and 3) complications with severe liver or kidney malfunction. We also collected data from 120 non-cancer control patients who underwent abdominal surgery.

Clinical data collection and definitions

Clinicopathological features and preoperative laboratory data were collected from the patient's electronic medical records, and laboratory data used were collected within 3 days of surgery. As part of the clinicopathological analysis of CRC, data on patient's age, sex, body mass index (BMI), tumor–node–metastasis (TNM) stage, routine blood tests, liver function tests, and tumor biomarkers were collected. A summary of the surgical information included data on the surgical approach (laparoscopic or open), the operation time and the volume of bleeding that occurred during the surgery. The NLR, LMR, PLR, PNI, SII, PIV, SIRI, and PNI were calculated as previously described.[14–17] Anastomotic leakage was defined based on the statement of the International Study Group of Rectal Cancer,[18] in which the integrity of the intestinal wall fails at the anastomosis site, and the communication between the intraintestinal and extraintestinal compartments is established.

Follow-up

The follow-up for patients with CRC after surgery was performed every 3 months for the first 2 years, followed by a 6-month follow-up frequency for the next 2 years. The last follow-up date was July 12, 2022. In this study, overall survival (OS) was defined as the number of years between the date of surgery and the date of death or last follow-up of the patient.

Statistical analyses

The distribution of data was tested using the Shapiro–Wilk test, with a p-value <0.05 indicating a normal distribution. The results are listed in Supplementary Table 1. Student's t-tests with Welch's correction were used to compare normally distributed continuous data. Median and interquartile range (IQR) as well as the Mann–Whitney U test were used to compare data that were non-normally distributed. Data from categorical variables are presented as absolute numbers (percentages) and compared using the χ^2 test or Fisher's exact test if the sample size was small (when the expected frequency count in any cell of the table was less than 5). The survival analysis was conducted using the Kaplan–Meier plots and log-rank tests. The predictive advantage was distinguished using the receiver operating characteristic (ROC) and area under the curve (AUC). A value of $p < 0.05$ was considered statistically significant.

Table 1. Clinical characteristics of the included participants

Clinical variables		CRC (n = 124)	Non-cancer (n = 120)	χ^2/t/Z-value	p-value
Gender	male	61 (49.2%)	64 (53.3%)	–	–
	female	63 (50.8%)	56 (46.7%)	–	–
Age		63.5 ±13.3	61.4 ±8.45	1.4617	0.145*
BMI		22.1 (19.7–24.7)	22.8 (20.4–24.8)	4684.5	0.328
WBC		6.80 (5.80–8.43)	6.70 (5.50–8.03)	6871	0.302
Hemoglobin		116 (99.8–130)	138 (122–148)	10886	<0.001
Platelet		288 (224–361)	244 (222–279)	5536	0.001
Neutrophil		4.29 (3.29–5.87)	3.53 (2.79–4.70)	5709.5	0.002
Lymphocyte		1.58 (1.06–1.90)	2.01 (1.59–2.45)	10323	<0.001
Monocyte		0.55 (0.43–0.80)	0.60 (0.50–0.75)	7966.5	0.339
Fibrinogen		4.09 (3.45–4.69)	2.95 (2.58–3.40)	2732.5	<0.001
Albumin		36.7 ±4.26	40.5 ±3.80	7.433	<0.001*
Globulin		27.0 (24.9–29.9)	26.0 (23.8–28.2)	6097	0.015
AGR		1.36 (1.21–1.48)	1.52 (1.41–1.74)	10963.5	<0.001
Total protein		63.6 (60.1–68.3)	66.9 (62.9–69.8)	9216	0.001
Prealbumin		182 ±52.5	255 ±62.3	9.860	<0.001*
Ferritin		120 (34.2–258)	171 (69.1–295)	8653.5	0.028
CEA		4.60 (2.29–13.7)	1.75 (1.10–2.82)	3149.5	<0.001
AFP		2.40 (1.80–3.10)	2.25 (1.70–3.00)	6975	0.399
CA125		10.3 (7.50–19.0)	8.62 (6.82–12.6)	5805.5	0.003
CA153		10.4 (6.84–16.2)	10.2 (7.20–14.6)	6910	0.456
CA199		11.9 (6.85–24.8)	8.60 (4.62–12.7)	5561	0.001
PLR		184 (130–270)	126 (95.4–162)	4094	<0.001
NLR		3.02 (1.76–4.71)	1.69 (1.32–2.42)	4632	<0.001
LMR		2.53 (1.82–3.65)	3.32 (2.48–4.35)	9192	0.001
SII		1672 (1098–3001)	1717 (1086–2826)	7252	0.733
PIV		997 (540–2122)	1021 (589–2210)	7767	0.553
SIRI		1.54 (0.94–3.27)	1.05 (0.73–1.96)	5680	0.001
PNI		43.8 (41.5–47.3)	51.5 (47.2–54.3)	11961.5	<0.001

CRC – colorectal cancer; BMI – body mass index; CEA – carcinoembryonic antigen; WBC – white blood cells; NLR – neutrophil-to-lymphocyte ratio; LMR – lymphocyte-to-monocyte ratio; PLR – platelet-to-lymphocyte ratio; SII – systemic immune-inflammation index; PNI – prognostic nutritional index; PIV – pan-immune-inflammation value; SIRI – systemic inflammation response index; * data were compared using Student's t-test; # data were compared using the χ^2 test; the other parameters were compared using the Mann–Whitney U test. AGR – albumin-to-globulin ratio.

All studies were performed with the use of R language (v. 4.1.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics of the included participants

A total of 124 CRC patients and 120 non-cancer patients who underwent abdominal surgery were included in the study. Adenocarcinoma was the histological type of all CRCs. The results of variance homogeneity t-tests for patients with and without CRC are listed in Supplementary Table 2. A comparison of clinicopathological and preoperative laboratory data between CRC and non-cancer patients is listed in Table 1. Age, gender and BMI of CRC patients showed little significance between cancer and non-cancer patients ($p > 0.05$). Blood nutritional indicators, including hemoglobin, albumin, globulin, total protein, and prealbumin levels, were lower in CRC patients than in non-cancer patients ($p < 0.05$). The levels of tumor biomarkers, including carcinoembryonic antigen (CEA), CA125 and CA199, were significantly higher in CRC patients than in non-cancer patients. Other blood indicators, including PLR, NLR, albumin-to-globulin ratio (AGR), and PNI, were substantially elevated in CRC patients compared to non-cancer patients ($p < 0.05$).

Patients who exhibited risk factors related to AL underwent surgeries for CRC

The results of the variance homogeneity t-tests between patients with and without AL are presented in Supplementary Table 3. As listed in Table 2, M0 stage and laparoscopic surgery were associated with AL in patients who underwent surgeries for CRC. Patients complicated with AL exhibited low levels of albumin, CEA, CA153, and PNI as compared to patients without AL ($p < 0.05$). Age, sex, tumor type,

Table 2. Risk factors related to anastomotic leakage (AL) for patients who underwent colorectal cancer (CRC) surgery

Clinical variables		Non-AL (n = 100)	AL (n = 24)	χ^2/t/Z-value	p-value
Sex	male	53 (53.0%)	8 (33.3%)	2.260	0.133#
	female	47 (47.0%)	16 (66.7%)		
Age		64.7 ±12.9	58.5 ±13.7	2.031	0.050*
Cancer type	colon cancer	67 (67.0%)	11 (45.8%)	2.864	0.091#
	rectal cancer	33 (33.0%)	13 (54.2%)		
Tumor location	right side	31 (31.0%)	3 (12.5%)	4.508	0.105#
	left side	35 (35.0%)	8 (33.3%)		
	rectal	34 (34.0%)	13 (54.2%)		
Tumor grade	high	8 (8%)	3 (12.5%)	0.790	0.674#
	middle	79 (79%)	19 (79.2%)		
	low	13 (13%)	2 (8.3%)		
Surgery type	laparoscope	77 (77.0%)	13 (54.2%)	3.988	0.046#
	open	23 (23.0%)	11 (45.8%)		
Operation time		180 (159–235)	235 (175–286)	911.5	0.068
Intraoperative bleeding		50.0 (20.0–100)	50.0 (20.0–200)	954.0	0.113
T stage	T1	3 (3.00%)	0 (0.00%)	3.341	0.359#
	T2	12 (12.0%)	4 (16.7%)		
	T3	31 (31.0%)	11 (45.8%)		
	T4	54 (54.0%)	9 (37.5%)		
N stage	N0	45 (45.0%)	12 (50.0%)	0.947	0.977#
	N1	32 (32.0%)	8 (33.3%)		
	N2	20 (20.0%)	4 (16.7%)		
	NX	3 (3.00%)	0 (0.00%)		
M stage	M0	68 (68.0%)	22 (91.7%)	6.117	0.038#
	M1	16 (16.0%)	2 (8.33%)		
	MX	16 (16.0%)	0 (0.00%)		
Tumor stage	I	13 (13.0%)	2 (8.33%)	2.356	0.607#
	II	30 (30.0%)	11 (45.8%)		
	III	44 (44.0%)	9 (37.5%)		
	IV	13 (13.0%)	2 (8.33%)		
BMI		21.8 (19.6–24.0)	24.4 (20.6–26.4)	1579.5	0.057
WBC		7.10 (5.97–8.53)	6.10 (5.02–6.85)	1243.5	0.016
Hemoglobin		113 ±24.6	114 ±32.6	0.150	0.882*
Platelet		282 (220–348)	290 (259–374)	1546	0.333
Neutrophil		4.50 (3.53–6.12)	3.34 (2.50–4.90)	1296	0.029
Lymphocyte		1.60 (1.05–1.95)	1.50 (1.24–1.80)	1402.5	0.544
Monocyte		0.57 (0.44–0.80)	0.50 (0.40–0.64)	1166.5	0.199
Fibrinogen		4.12 (3.45–4.65)	4.02 (3.50–5.17)	1570.5	0.832
Albumin		**37.1 (33.9–39.7)**	**35.9 (33.2–37.1)**	995.5	**0.019**
Globulin		26.7 (24.7–29.5)	28.4 (25.4–32.1)	1379.5	0.196
AGR		1.36 (1.24–1.50)	1.31 (1.16–1.45)	1072.5	0.256

Table 2. Risk factors related to anastomotic leakage (AL) for patients who underwent colorectal cancer (CRC) surgery – cont

Clinical variables	Non-AL (n = 100)	AL (n = 24)	χ^2/t/Z-value	p-value
Total protein	63.5 (60.0–68.2)	65.6 (60.2–68.6)	1328.5	0.420
Prealbumin	185 ±51.8	171 ±55.1	1.081	0.287*
Ferritin	144 (35.6–277)	70.6 (16.9–193)	1316	0.124
CEA	4.93 (2.30–12.3)	3.40 (2.00–16.7)	1496.5	0.463
AFP	2.50 (1.83–3.11)	2.01 (1.58–2.52)	1269	0.061
CA125	10.8 (7.59–18.7)	9.13 (6.91–27.8)	1551	0.663
CA153	**11.4 (7.28–17.0)**	**8.36 (4.74–12.9)**	1320.5	**0.026**
CA199	12.0 (6.92–26.6)	9.75 (6.70–15.9)	1250	0.446
PLR	179 (128–271)	198 (146–268)	1043	0.321
NLR	3.12 (1.79–4.53)	2.03 (1.58–4.74)	1356	0.324
LMR	2.46 (1.61–3.70)	2.84 (2.31–3.60)	1077.5	0.438
SII	1944 (1121–3097)	1432 (1080–1957)	1404	0.197
PIV	1077 (546–2383)	710 (481–1058)	1446	0.120
SIRI	1.69 (0.97–3.27)	1.12 (0.76–2.07)	1463	0.096
PNI	**43.9 (41.7–48.6)**	**41.4 (40.8–44.5)**	1491	**0.007**

BMI – body mass index; WBC – white blood cells; CEA – carcinoembryonic antigen; NLR – neutrophil-to-lymphocyte ratio; LMR – lymphocyte-to-monocyte ratio; PLR – platelet-to-lymphocyte ratio; SII – systemic immune-inflammation index; PNI – prognostic nutritional index; PIV – pan-immune-inflammation value; SIRI – systemic inflammation response index; * data were compared using Student's t-test; # data were compared using the χ^2 test; other parameters were compared using the Mann–Whitney U test. The values in bold indicated statistically significant change.

tumor location, TNM stage, and other blood indicators were not significantly associated with AL ($p > 0.05$). Using a ROC curve analysis, we found that albumin, CA153 and PNI had a moderate predictive value for AL, with AUC values of 0.662 (95% confidence interval (95% CI): 0.55–0.76), 0.648 (95% CI: 0.52–0.78) and 0.625 (95% CI: 0.52–0.73), respectively, whereas the predictive value of CEA was low, with an AUC of 0.535 (95% CI: 0.42–0.68) (Fig. 1).

Survival analysis of the blood biomarkers and anastomotic leakage in CRC patients

Previous studies have indicated that SII,[19] PIV,[20] SIRI,[21] and PNI[22] were associated with the survival of patients with CRC who underwent surgery. In this study, we determined the association of the 4 biomarkers and AL with the survival of patients with CRC. Using the median value as a cutoff point, we found that high PNI was associated with a longer survival time in CRC patients ($p = 0.033$), and AL was marginally associated with the survival of CRC patients ($p = 0.048$), while SII, PIV and SIRI did not show an obvious association with the patients' survival ($p > 0.05$) (Fig. 2).

Association of PNI with clinicopathological features in CRC

Next, we explored the association of PNI with clinicopathological features in CRC patients. As illustrated in Fig. 3, PNI was significantly associated with T stage ($p = 0.044$), but was not associated with sex, cancer type, N stage, M stage, and tumor stage ($p > 0.05$).

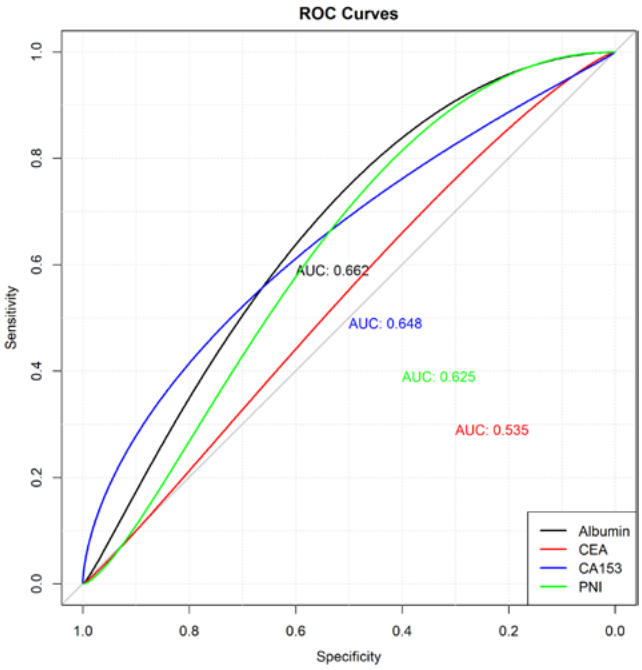

Fig. 1. Predictive value of albumin, carcinoembryonic antigen (CEA), CA153, and prognostic nutritional index (PNI) on anastomotic leakage (AL) in colorectal cancer (CRC) patients after surgery

ROC – receiver operating characteristic; AUC – area under the curve.

Comparison of the prognostic value of clinical parameters in CRC patients

To compare the prognostic value of clinical features in CRC patients who underwent surgery, the nomogram was prepared after analyzing age, TNM stage, tumor stage,

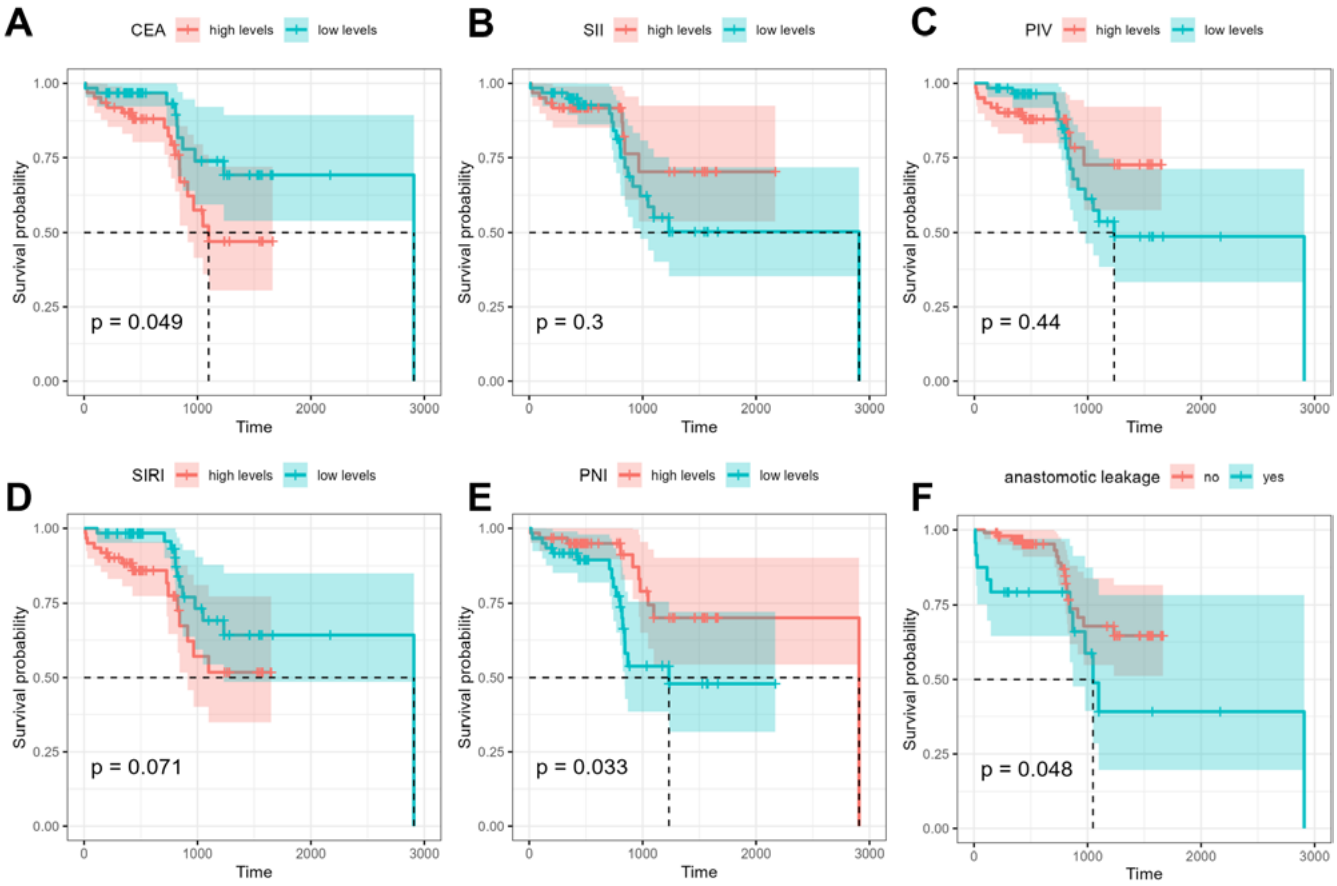

Fig. 2. Survival analysis of the blood biomarkers and anastomotic leakage (AL) in colorectal cancer (CRC) patients. A. Carcinoembryonic antigen (CEA); B. Systemic immune-inflammation index (SII); C. Pan-immune-inflammation value (PIV); D. Systemic inflammation response index (SIRI); E. Prognostic nutritional index (PNI); F. AL

AL, and PNI. As shown in Fig. 4, PNI showed a better prognostic value in CRC patients who underwent surgery for 1-, 3- and 5-year survival time as compared to other clinicopathological features such as age, TNM stage, tumor stage, and AL.

Discussion

Due to the high risk of AL in patients after colorectal surgery, this study explored the indicators that could serve as predictive biomarkers for AL. By comparing the data between CRC and non-cancer patients, we found that several blood cell count indicators were increased, while the nutritional status was decreased in CRC patients. Next, we compared the clinicopathological features of CRC patients with and without AL after colorectal surgery, and found that female sex, M stage, albumin, CEA, CA153 and PNI were associated with AL, and albumin, CA153 and PNI had a moderate predictive value for AL, suggesting that these indicators may help screen patients at high risk of AL after colorectal surgery. Subsequently, we explored the association between SII, PIV, SIRI and PNI, and found that high PNI was associated with longer survival time in CRC patients. Moreover, the nomogram showed that PNI had a better prognostic value for 1-, 3- and 5-year survival time compared with other clinicopathological features in CRC patients who underwent surgery. Taken together, these results demonstrate that CRC patients with AL present with lower nutritional status and that PNI could help predict AL. Prognostic nutritional index was associated with the survival of CRC patients and showed a better prognostic value in CRC patients who underwent surgery.

Prognostic nutritional index is calculated based on serum albumin levels and peripheral blood lymphocyte counts, and is an indicator that reflects both the nutritional and immune status of patients.[23,24] Our results showed that patients with AL had lower albumin levels than those without AL, although no significant difference was noted in lymphocyte counts. The role of PNI in predicting AL in gastrointestinal tumors had been reported before. A previous study[25] stated that preoperative PNI showed no significant prognostic value for short-term outcomes in patients with AL after cancerous esophagectomy. Another study[26] reported that PNI is useful for predicting the onset of postoperative complications (including AL) in patients with esophageal cancer after resection. Recently, a study[27] concluded that PNI was a predictor of AL (risk ratio (RR): 0.151; 95% CI: 0.036–0.640) in CRC

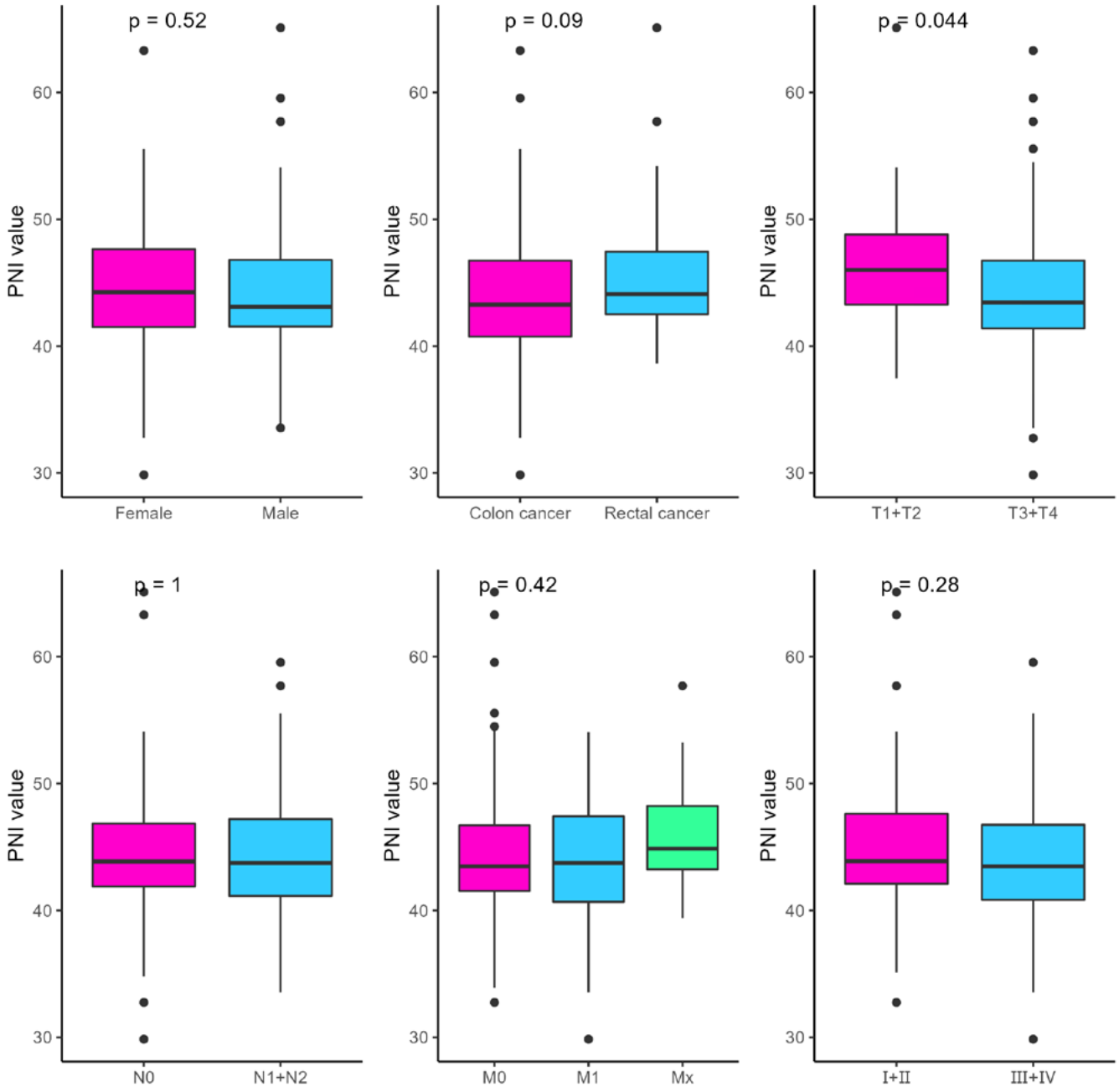

Fig. 3. Association of prognostic nutritional index (PNI) with clinicopathological features in colorectal cancer (CRC). Data were compared using the Mann–Whitney U test. The whiskers extend from the box to the minimum and maximum values of the dataset, excluding any outliers. Outliers are data points that fall more than 1.5 times of the interquartile range (IQR) beyond the nearest quartile. They are represented by individual points outside the whiskers

patients after curative surgery. In this study, we found that, similar to the result of CA153, PNI exhibited a moderate predictive value for AL, but was superior to CEA, suggesting that high PNI and CA153 could help screen patients at risk of AL, but CEA showed little significance in this aspect. However, the number was small, with only 11 patients having an AL; thus, the reliability of PNI in predicting AL needs to be further validated.

After confirming the association between PNI and AL in CRC patients after colorectal surgery, we investigated the prognostic value of PNI in CRC. Prognostic nutritional index has been reported to be associated with the treatment response and survival of various malignant tumors such as CRC,[28] breast cancer[17] and esophageal cancer,[29] suggesting that PNI could be a novel prognostic indicator for patients with cancer. Our results are in line with those of previous studies,[30] which confirmed the association of PNI and AL with the survival of CRC patients after colorectal surgery. More importantly, PNI-based nomograms showed better prognostic accuracy than TNM stage, tumor stage and AL, which has not been reported in previous studies, indicating that PNI could act as an auxiliary indicator to predict the prognosis of CRC patients. Moreover, the nomograms revealed that PNI showed a much better predictive accuracy; thus, it could serve as a reliable indicator to estimate the prognosis of CRC patients.

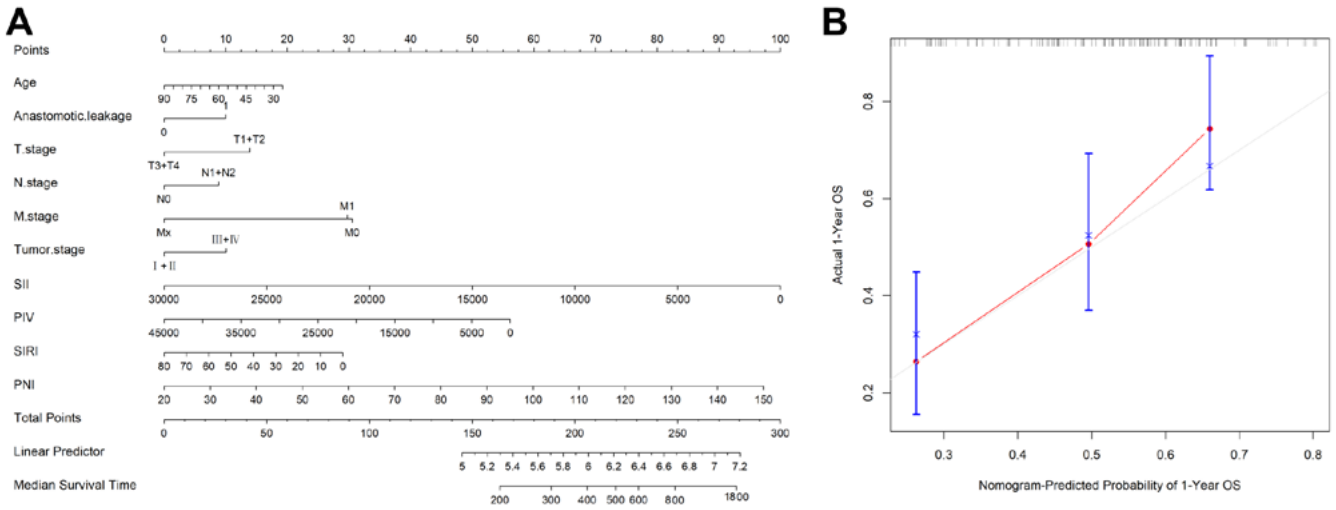

Fig. 4. Comparison of the prognostic value of clinicopathological features for colorectal cancer (CRC) patients. A. Nomogram; B. Calibration curve

SII – systemic immune-inflammation index; PNI – prognostic nutritional index; PIV – pan-immune-inflammation value; SIRI – systemic inflammation response index; OS – overall survival.

Limitations

The present study has some limitations. First, it had a retrospective design and was a single-center study, which inevitably led to selection bias. Second, even though we retrieved a long period of medical records, the number of ALs was relatively small, and the robustness of the results was undermined. Third, some factors that might affect nutritional status, such as genetics and intestinal microbiota, were not taken into consideration in this study; thus, the reliability of our results might be reduced. Fourth, molecular status, such as microsatellite instability (MSI), is an important prognostic and predictive factor in patients with CRC. However, due to the limited data of our study, we could not analyze the effect of molecular status on AL after surgery. Therefore, our results need to be validated in prospective, larger, multicenter cohorts.

Conclusions

This study demonstrated that preoperative PNI is a useful supplement for predicting AL in CRC patients after colorectal surgery and it also helps predict the prognosis of CRC patients. However, considering the limitations of this study, a larger study is required to validate these results.

Supplementary data

The supplementary materials are available at https://doi.org/10.5281/zenodo.8106981. The package contains the following files:

Supplementary Table 1. Continuous data distribution analysis with Shapiro–Wilk normality test.

Supplementary Table 2. Variance homogeneity t-test results between patients with or without CRC.

Supplementary Table 3. Variance homogeneity t-test results between patients with or without anastomotic leakage.

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