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ORIGINAL RESEARCH

Preoperative Prognostic Nutritional Index Predicts Postoperative Outcomes in Colorectal Cancer: A Propensity Score-Matched Cohort Study

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Background: The Prognostic Nutritional Index (PNI) is a numerical score used to assess the nutritional and immunological status, derived from serum albumin concentration and lymphocyte count. While malnutrition and systemic inflammation are known to influence surgical outcomes and cancer prognosis, the predictive value of PNI in colorectal cancer (CRC) is underexplored. This study aimed to evaluate whether preoperative PNI predicts postoperative complications and long-term survival in patients with CRC undergoing curative-intent surgery.

Methods: The records of 2,026 patients who underwent curative-intent surgery for CRC between 2011 and 2023 at a tertiary center in Taiwan were retrospectively reviewed. Propensity score matching (PSM) was used and patients were stratified into high and low PNI groups based on the median value. Outcomes included in-hospital complications, 5-year overall survival (OS), and disease-free survival (DFS) in the subgroup of patients with stage I–III disease. Multivariable logistic regression and Cox proportional hazards models were used as well as restricted cubic spline (RCS) analysis.

Results: High PNI was independently associated with lower rates of overall complications (adjusted odds ratio [aOR] = 0.22, 95% confidence interval [CI]: 0.17–0.28), ileus (aOR = 0.23), anastomotic leakage (aOR = 0.16), and lung-related complications (aOR = 0.38). High PNI was also significantly associated with improved 5-year OS (aHR = 0.45, 95% CI: 0.38–0.55), but not DFS. In additional competing-risk and comorbidity-stratified analyses, high PNI remained protective for both cancer-related ($p = 0.0005$) and non–cancer-related mortality ($p < 0.0001$), with consistent effects across CCI strata and attenuation for cancer-related death in CCI ≥ 3 ($p = 0.1024$). Additionally, PNI demonstrated superior predictive performance over the neutrophil-to-lymphocyte ratio (NLR) for all complication types based on receiver operating characteristic (ROC) analysis.

Conclusion: Preoperative PNI was independently associated with postoperative complications and OS in patients with CRC undergoing curative surgery. Routine assessment of PNI may help refine risk stratification and guide perioperative management to improve surgical outcomes.

Keywords: colorectal cancer, prognostic nutritional index, postoperative complication, surgery, survival

Introduction

Cancer remains a leading cause of death globally.[1] Among malignancies, colorectal cancer (CRC) imposes a substantial burden, underscoring the need for simple preoperative markers to refine surgical risk stratification. CRC is the third most commonly diagnosed malignancy and the second leading cause of cancer-related death worldwide, with an estimated 1.9 million new cases and 930,000 deaths reported in 2020.[2] The global burden of CRC continues to rise across both developed and developing regions, driven by aging populations and changing lifestyles.[3] In Taiwan, CRC has become the

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most frequently diagnosed cancer, posing a significant public health challenge and contributing to a substantial economic burden on the healthcare system.[4] Surgical resection remains the cornerstone of curative treatment for patients with localized or locally advanced disease.[5] However, the risk of postoperative complications such as ileus, anastomotic leakage, and pulmonary infections remains considerable and can adversely affect recovery, prolong hospitalization, and compromise long-term oncologic outcomes.[6,7] This underscores the need for simple and reliable preoperative predictors to guide clinical decision-making and optimize patient outcomes.

Malnutrition and systemic inflammation are recognized determinants of surgical risk and cancer prognosis.[8] Current guidelines, including those from the European Society for Clinical Nutrition and Metabolism (ESPEN) and the Enhanced Recovery After Surgery (ERAS) Society, recommend routine preoperative nutritional assessment for patients with CRC to identify those at risk before surgery.[9,10] The Prognostic Nutritional Index (PNI), calculated from serum albumin concentration and peripheral lymphocyte count, has been shown to be a convenient and integrative marker of both nutritional and immune status.[11] Albumin concentration reflects protein reserves, systemic inflammation, and liver function, while lymphocyte count serves as a surrogate for host immunity and stress response.[12,13]

Other inflammation- and nutrition-based indices, such as the neutrophil-to-lymphocyte ratio (NLR) and the Controlling Nutritional Status (CONUT) score, have also been investigated as prognostic markers in CRC.[14,15] However, compared with these indices, the Prognostic Nutritional Index (PNI) offers a simpler and more integrative assessment by combining albumin and lymphocyte counts, capturing both nutritional and immune aspects of the host condition. Together, these parameters offer valuable insights into the physiological resilience of CRC patients prior to surgery.

While prior studies have linked low PNI with adverse outcomes in several gastrointestinal malignancies, such as gastric cancer, pancreatic cancer, and hepatocellular carcinoma (HCC), studies of the usefulness of the PNI in patients with CRC are limited and have provided inconsistent results.[16–18] Furthermore, few studies have simultaneously evaluated the relationship between PNI and perioperative complications, as well as long-term survival, in the same group of patients. Therefore, this study aimed to comprehensively evaluate the prognostic value of preoperative PNI in CRC by examining its association with both perioperative complications and long-term survival. By integrating nutritional and immune dimensions within a single index, this study sought to determine whether PNI could serve as a practical and reliable biomarker for preoperative risk stratification in patients undergoing curative-intent surgery. We hypothesized that patients with a higher preoperative PNI would experience fewer postoperative complications and improved long-term survival.

Methods

Study Design and Data Source

This retrospective observational study was conducted at Changhua Christian Hospital, a tertiary care center in central Taiwan. The records of patients diagnosed with CRC who underwent curative-intent surgical resection between January 2011 and December 2023 were retrospectively reviewed. The inclusion period was determined based on the availability of complete perioperative and follow-up data in our institutional database; more recent cases were excluded because long-term outcomes were not yet available at the time of data collection. Clinical and laboratory data were obtained from the electronic medical records system of the hospital, which contains comprehensive patient information including demographic characteristics, comorbidities, laboratory test results, treatment details, and follow-up records.

Data Collection

Patients were included if they had a diagnosis of primary colorectal adenocarcinoma and underwent elective surgical resection during the study period, and their records contained preoperative serum albumin concentration and lymphocyte count. Patients were excluded if they met any of the following criteria: aged <18 or ≥100; no primary colorectal tumor identified on surgical pathology; or missing/incomplete key clinical or biochemical data. All included patients underwent elective colorectal surgery. Those with emergency operations or preoperative active infections were not included, thereby

minimizing potential confounding from infection-related inflammation. The initial search identified 4,564 patients, and after applying the exclusion criteria 2,026 patients remained and were included in the analysis.

Ethics Statement

This study complies with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Changhua Christian Hospital. As this was a retrospective study that used de-identified data, the requirement of informed consent was waived.

Outcomes

The primary outcomes were in-hospital complications which were recorded as binary outcomes and long-term oncologic outcomes. In-hospital complications included the overall complication rate, postoperative ileus, anastomotic leakage, lung-related complications such as pneumonia and atelectasis, and cardiovascular events. Postoperative complications were primarily diagnosed based on clinical assessment and confirmed by attending surgeons. Imaging studies and laboratory findings were used as supportive evidence when applicable.

Long-term outcomes included 5-year OS, defined as the time from surgery to death from any cause, and 5-year DFS for the subgroup of stage I–III patients (n = 1695), defined as the time from surgery to cancer recurrence or death.

PNI

The exposure variable was the PNI, which was calculated using the formula: PNI = 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (/mm^3). Based on the median PNI value of 44 in the study population, patients were categorized into high and low PNI groups.

Other Variables

Other variables collected included age, sex, body mass index (BMI), Charlson Comorbidity Index (CCI), smoking, alcohol and betel nut use, tumor size and stage, neoadjuvant radiotherapy and chemotherapy, and baseline laboratory values such as hemoglobin, platelet count, creatinine, white blood cell (WBC) count, neutrophils, red cell distribution width (RDW), estimated glomerular filtration rate (eGFR), and carcinoembryonic antigen (CEA) level. Data on medication use, including antihypertensive drugs, statins, oral antidiabetic agents, and insulin were also obtained.

Statistical Analysis

All analyses were conducted using complete case data, as patients with missing laboratory or clinical covariates were excluded during initial data cleaning. Categorical variables were presented as count and percentage, and compared with the chi-squared test. Continuous variables with a normal distribution were expressed as mean ± standard deviation (SD) and compared with Student's test; data not normally distributed were presented as median (IQR: [interquartile range] 25th to 75th percentile). Associations between PNI and the risk of outcomes were examined using a restricted cubic spline (RCS) regression model with 3 knots (25th, 50^{th,} and 75th percentiles) in the total population. Kaplan–Meier curves were drawn and compared with the Log rank test for OS and DFS in relation to a high or low PNI (median cutoff of 44).

To account for confounders in the PNI group, a non-parsimonious multivariable logistic regression model was used to calculate the propensity score for each patient based on their demographic characteristics and covariates listed in Table 1, except for 1ymphocyte count, albumin, PNI, and NLR. A 1:1 propensity score matched (PSM) analysis was conducted using the nearest-neighbor method with a caliper of 0.1 SD units to create matched pairs.

Logistic regression was used to calculate the effect of high or low PNI on in-hospital complications, and results were presented as odds ratio (OR) and 95% confidence interval (CI). Cox proportional hazards regression was used to calculate the risk of high and low PNI for 5-year OS and DFS, and results were presented as hazard ratio (HR) and 95% CI. Multivariable logistic regression models were constructed using a stepwise selection method with significance levels for entry (SLE) and stay (SLS) both set at 0.05. To evaluate the robustness of the model selection, sensitivity analyses were performed using alternative approaches, including backward elimination (SLS = 0.05) and LASSO regression with cross-validation for penalty selection (Supplementary Table S1).

Table 1 Patient Characteristics

Characteristics	Before PSM				After PSM		
	Total	Low PNI (< 44)	High PNI (≥ 44)	p-value	Low PNI (< 44)	High PNI (≥ 44)	p-value
Number of patients	2,026	1012	1014		437	437	
Sex							
Female	882 (44)	452 (45)	430 (42)	0.305	192 (44)	198 (45)	0.683
Male	1,144 (56)	560 (55)	584 (58)		245 (56)	239 (55)	
Age, years	65.7±13.4	69.2±13.3	62.2±12.5	**<0.001**	65.9±13.5	65.2±13.3	0.452
BMI, kg/m^2	23.8 (21.2, 26.4)	23.0 (20.4, 25.7)	24.5 (22.1, 26.9)	**<0.001**	23.0 (20.4, 25.6)	24.3 (21.8, 27.0)	**<0.001**
Tumor size, mm	45.0 (31.0, 60.0)	55.0 (40.0, 70.0)	40.0 (26.4, 50.0)	**<0.001**	47.0 (33.0, 60.0)	45.0 (33.0, 58.0)	0.170
Stage							
I	339 (17)	105 (11)	234 (24)	**<0.001**	59 (14)	61 (15)	0.535
II	548 (27)	306 (31)	242 (24)		124 (29)	107 (26)	
III	733 (37)	358 (36)	375 (38)		152 (35)	163 (39)	
IV	367 (19)	228 (23)	139 (14)		94 (22)	82 (20)	
RT, neoadjuvant	201 (10)	128 (13)	73 (7)	**<0.001**	69 (16)	80 (18)	0.322
CT, neoadjuvant	303 (15)	182 (18)	121 (12)	**<0.001**	49 (11)	54 (12)	0.600
Smoking status							
Non-smoker	1,460 (72)	756 (75)	704 (69)	0.030	319 (73)	315 (72)	0.435
Former smoker	139 (7)	62 (6)	77 (8)		30 (7)	40 (9)	
Current smoker	427 (21)	194 (19)	233 (23)		88 (20)	82 (19)	
Alcohol consumption							
Non-drinker	1,781 (88)	900 (89)	881 (87)	0.366	392 (90)	389 (89)	0.662
Former drinker	54 (3)	25 (2)	29 (3)		8 (2)	12 (3)	
Current drinker	191 (9)	87 (9)	104 (10)		37 (8)	36 (8)	
Betel nut consumption							
Non-consumer	1,944 (96)	970 (96)	974 (96)	0.958	423 (97)	420 (96)	0.820
Former consumer	32 (2)	16 (2)	16 (2)		5 (1)	7 (2)	
Current consumer	50 (2)	26 (3)	24 (2)		9 (2)	10 (2)	
CCI	3 (2, 5)	3 (2, 7)	2 (2, 4)	**<0.001**	3 (2, 6)	3 (2, 6)	0.222
CCI category							
< 3	927 (46)	398 (39)	529 (52)	**<0.001**	199 (46)	195 (45)	0.786
> 3	1099 (54)	614 (61)	485 (48)		238 (54)	242 (55)	
Preoperative laboratory data							
Hemoglobin, g/dL	12.0 (10.3, 13.5)	10.8 (9.6, 12.3)	13.1 (11.8, 14.3)	**<0.001**	11.8 (10.6, 13.1)	12.0 (10.5, 13.1)	0.844
Platelet count, $10^9/L$	24.5 (19.1, 31.1)	24.6 (18.2, 33.0)	24.3 (19.8, 30.0)	0.726	24.4 (18.0, 31.1)	24.2 (19.3, 31.2)	0.441
Creatinine, mg/dL	0.8 (0.7, 1.0)	0.9 (0.7, 1.1)	0.8 (0.7, 1.0)	**0.002**	0.8 (0.7, 1.1)	0.8 (0.7, 1.0)	0.832
WBC, $10^9/L$	6.7 (5.4, 8.7)	6.8 (5.1, 9.4)	6.6 (5.5, 8.0)	**0.036**	6.5 (5.0, 8.8)	6.5 (5.3, 8.2)	0.808
Hematocrit, %	36.2 (31.2, 40.4)	32.9 (29.2, 36.9)	39.4 (35.6, 42.6)	**<0.001**	35.8 (32.3, 39.3)	36.2 (32.1, 39.6)	0.681
RDW, %	14.9 (13.6, 18.3)	16.4 (14.4, 20.8)	14.0 (13.3, 15.8)	**<0.001**	15.4 (14.0, 18.7)	15.0 (13.7, 18.5)	0.219
CEA, ng/mL	3.9 (2.0, 9.3)	5.0 (2.6, 15.6)	3.1 (1.8, 6.1)	**<0.001**	4.3 (2.2, 11.0)	3.7 (2.0, 7.8)	0.069
Lymphocyte count, $10^9/L$	1.3 (0.8, 1.8)	0.9 (0.5, 1.3)	1.7 (1.3, 2.1)	**<0.001**	1.0 (0.6, 1.4)	1.5 (1.1, 2.0)	**<0.001**
Neutrophil count, $10^9/L$	4.4 (3.2, 6.2)	4.9 (3.4, 7.4)	4.1 (3.2, 5.3)	**<0.001**	4.4 (2.9, 6.8)	4.2 (3.2, 5.6)	0.149
Albumin, g/dL	3.8 (3.2, 4.1)	3.2 (2.7, 3.6)	4.1 (3.9, 4.3)	**<0.001**	3.4 (2.9, 3.7)	4.1 (3.8, 4.2)	**<0.001**
PNI	43.9 (37.4, 49.2)	37.4 (31.4, 41.2)	49.2 (46.4, 52.3)	**<0.001**	39.1 (34.7, 42.0)	47.5 (45.6, 50.4)	**<0.001**
NLR	3.4 (2.2, 6.3)	5.4 (3.3, 10.4)	2.5 (1.8, 3.6)	**<0.001**	4.6 (2.9, 8.5)	2.8 (2.0, 4.1)	**<0.001**
Medication use before surgery							
Immunosuppressants	12 (1)	6 (1)	6 (1)	0.997	4 (1)	2 (1)	0.413
Antihypertensives	385 (19)	236 (23)	149 (15)	**<0.001**	90 (21)	90 (21)	>0.999
Statins	185 (9)	108 (11)	77 (8)	**0.016**	45 (10)	48 (11)	0.742
Anti-diabetic	175 (9)	102 (10)	73 (7)	**0.021**	37 (9)	44 (10)	0.414
Insulin	146 (7)	92 (9)	54 (5)	**0.001**	28 (6)	31 (7)	0.686

(*Continued*)

Table 1 (Continued).

Characteristics	Before PSM				After PSM		
	Total	Low PNI (< 44)	High PNI (≥ 44)	p-value	Low PNI (< 44)	High PNI (≥ 44)	p-value
Outcomes							
Complication[a]							
Ileus	583 (29)	444 (44)	139 (14)	**<0.001**	189 (43)	70 (16)	**<0.001**
Leakage	130 (6)	115 (11)	15 (2)	**<0.001**	40 (9)	9 (2)	**<0.001**
Lung-related complication	540 (27)	397 (39)	143 (14)	**<0.001**	155 (36)	75 (17)	**<0.001**
Heart-related complications	15 (1)	9 (1)	6 (1)	0.435	2 (1)	4 (1)	0.413
Recurrence	1367 (68)	601 (59)	766 (76)	**<0.001**	192 (44)	95 (22)	**<0.001**
Death	785 (39)	579 (57)	206 (20)	**<0.001**	211 (48)	283 (65)	**<0.001**
Propensity score	0.5 (0.2, 0.8)	0.2 (0.1, 0.5)	0.8 (0.6, 0.9)	**<0.001**	0.5 (0.3, 0.7)	0.5 (0.3, 0.7)	0.952

Notes: [a]Overall complications that occurred during hospitalization, including ileus, anastomotic leakage, lung-related complication (acute respiratory failure, pneumonia, lower respiratory tract infection), heart-related complication (infective endocarditis, acute myocardial infarction, cardiopulmonary resuscitation), acute venous thromboembolism, and colitis. Continuous data with normal distribution are presented as mean ± standard deviation; other data are presented as median (25^{th} to 75^{th} percentile). Categorical variables are presented as counts (percentages). Values in **bold** indicate statistically significant differences between groups ($p < 0.05$).
Abbreviations: PSM, propensity-score matching; DM, diabetes mellitus; WBC, white blood cell; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; RDW, red cell distribution width; CEA, Carcinoembryonic antigen; CCI, Charlson comorbidity index; RT, radiotherapy; CT, chemotherapy.

Candidate variables for the outcome analysis included demographic characteristics (age, sex), tumor-related factors (tumor size, disease stage, neoadjuvant radiotherapy, neoadjuvant chemotherapy), clinical and lifestyle factors (BMI, CCI], smoking, alcohol use, and betel nut use), laboratory parameters (hemoglobin, platelet count, creatinine, white blood cell count, RDW, eGFR, and neutrophil count), and medication use (antihypertensives, statins, anti-diabetic drugs, and insulin).

To further explore the association between PNI and survival outcomes, we conducted a competing risk analysis using the Fine and Gray model for subdistribution hazard ratio (SHR), distinguishing cancer-related and non-cancer-related mortality. Subgroup analyses were also performed according to comorbidity burden (Charlson Comorbidity Index [CCI] < 3 and ≥ 3) to examine effect modification by baseline health status (Supplementary Table S2).

All statistical analyses were performed using the SAS version 9.4 software. Visualization plots were created using R software version 4.1.0 (The Comprehensive R Archive Network: http://cran.r-project.org). A 2-sided p-value of < 0.05 was considered statistically significant.

Results

Study Population Selection

A flow diagram of patient inclusion is shown in Figure 1. After applying the exclusion criteria, 2,026 patients were left to be included in the analysis. After PSM, there were 437 patients in the high PNI group and 437 in the low PNI group.

Patient Characteristics

A total of 2,026 patients were included in the analysis, and were divided into a low PNI group and a high PNI group based on a median PNI of 44 (< 44, ≥ 44). The mean age of all patients was 65.7 years (Table 1). After PSM, there were 437 patients in each group, and the median PNI in the low group was 39 and the median PNI in the high group was 48. Patients in the high PNI group had a significantly higher mean BMI compared to those in the low PNI group (24.3 kg/m^2 vs 23.0 kg/m^2, $p < 0.001$). Additionally, patients in the high PNI group had a higher lymphocyte count ($1.53 \times 10^3/\mu L$ vs $0.99,10^3/\mu L$, $p < 0.001$) and albumin concentration (4.1 g/dL vs 3.4 g/dL, $p < 0.001$), and had a lower NLR (2.84 vs 4.55, $p < 0.001$) compared to those with a low PNI.

In terms of clinical outcomes, the high PNI group had a lower percentage of complications, including ileus (16.0% vs 43.2%, $p < 0.001$), leakage (2.1% vs 9.2%, $p < 0.001$), and lung-related complication (17.2% vs 35.5%, $p < 0.001$), recurrence (21.7% vs 43.9%, $p < 0.001$) and death (64.8% vs 48.3%, $p < 0.001$).

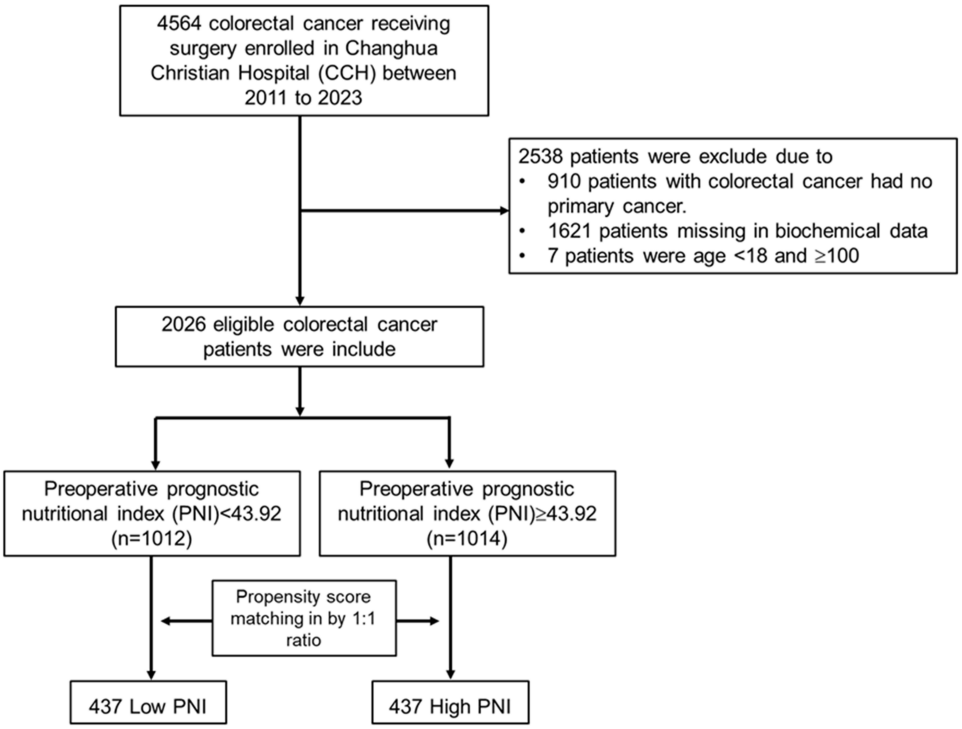

Figure 1 Flow diagram of patient selection.

Associations of PNI and Overall Complication, Ileus, Anastomotic Leakage, and Lung-Related Complication

RCS was used with three knots at the 25th, 50^{th,} and 75th percentiles to flexibly model the association between PNI and overall complication, ileus, leakage, and lung-related complication. RCS indicated that the relationship between PNI and overall complication, ileus, leakage, and lung-related complication was linear (p for linearity < 0.001), as illustrated separately in Figures 2A–D. In addition, it also suggested non-linear correlations between PNI and ileus (p for non-linearity < 0.001) and lung-related complications (p for non-linearity = 0.032).

Association Between PNI and OS and DFS

RCS indicated the association between PNI with OS (Figure 3A) and with recurrence or death event for stage I–III (Figure 3B) was linear (p value for linearity < 0.001), whereas the non-linearity only showed in OS (p for non-linearity < 0.001).

The Difference in OS and DFS Between Low and High PNI Groups

The OS (Figure 4A) and DFS (Figure 4B) for stage I–III had significant differences between the low and high PNI groups. Patients in the high PNI group had higher overall survival (p < 0.001) and disease-free survival for stage I–III (p = 0.020). In sensitivity analyses, high PNI remained associated with a lower risk of both cancer-related (p = 0.0005) and non–cancer-related mortality (p < 0.0001), with generally consistent effects across CCI subgroups. Although the association with cancer-related death was attenuated in patients with higher comorbidity (CCI ≥ 3, p = 0.1024), the overall direction of effect remained protective (Supplementary Table S2).

Associations Between PNI and in-Hospital Complications

The univariate, multivariable, and PSM analyses of the associations between PNI and in-hospital complications are shown in Table 2. In univariate analysis, patients in the high PNI group had lower overall complications (crude OR = 0.17, 95% CI: 0.14–0.21), ileus (crude OR = 0.20, 95% CI: 0.16–0.25), anastomotic leakage (crude OR = 0.12, 95% CI: 0.07–0.20), and lung-related complication (crude OR = 0.25, 95% CI: 0.20–0.32).

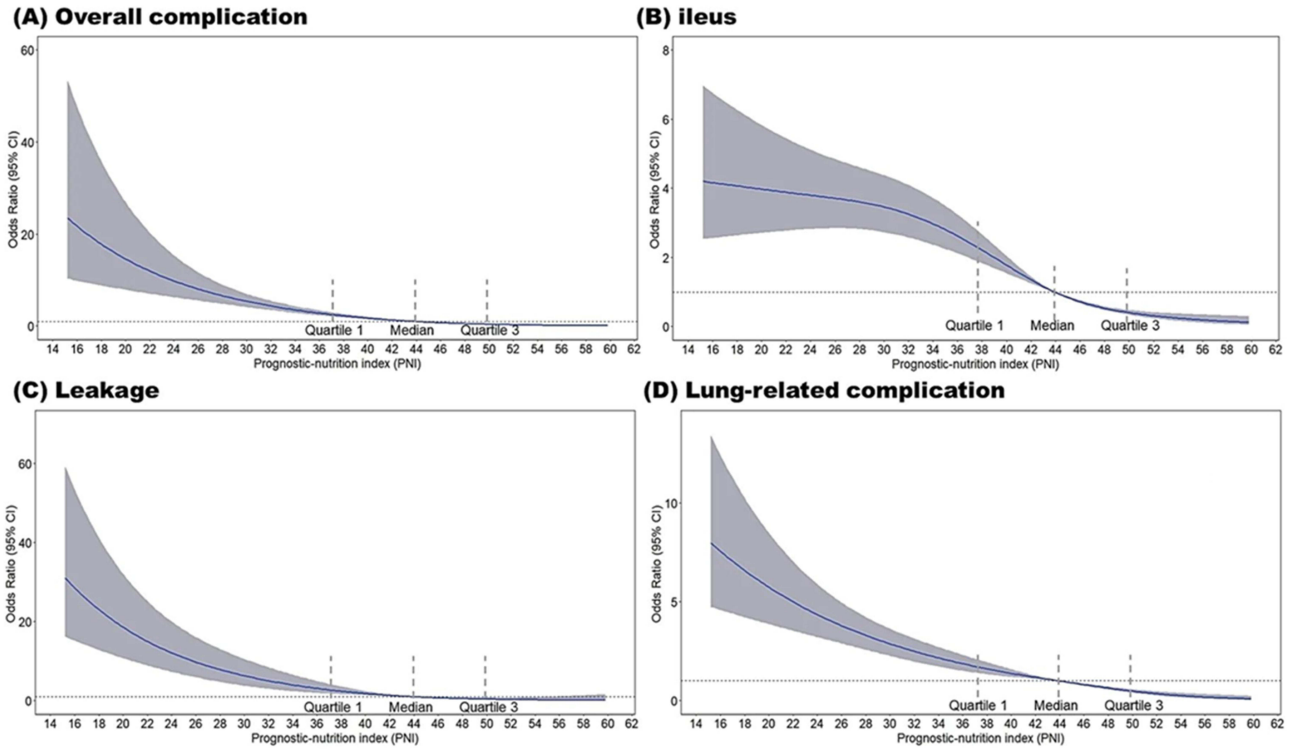

Figure 2 Restricted cubic spline regression analysis of associations of PNI levels with in-hospital (**A**) overall complications, (**B**) ileus, (**C**) anastomotic leakage, and (**D**) lung-related complications. The blue line represents the estimated odds ratio (OR) for each outcome across the continuous spectrum of PNI values, while the shaded gray area indicates the corresponding 95% confidence interval (CI). Dashed vertical lines denote the first quartile, median, and third quartile of PNI distribution. The dotted line indicates no association between the PNI and the odds of the in-hospital complication. A linear relationship between PNI and complication risk was observed for overall complications, ileus, leakage, and lung-related complications (all *p* for linearity < 0.001). Non-linear associations were noted for ileus (*p* for non-linearity < 0.001) and lung-related complications (*p* for non-linearity = 0.032).

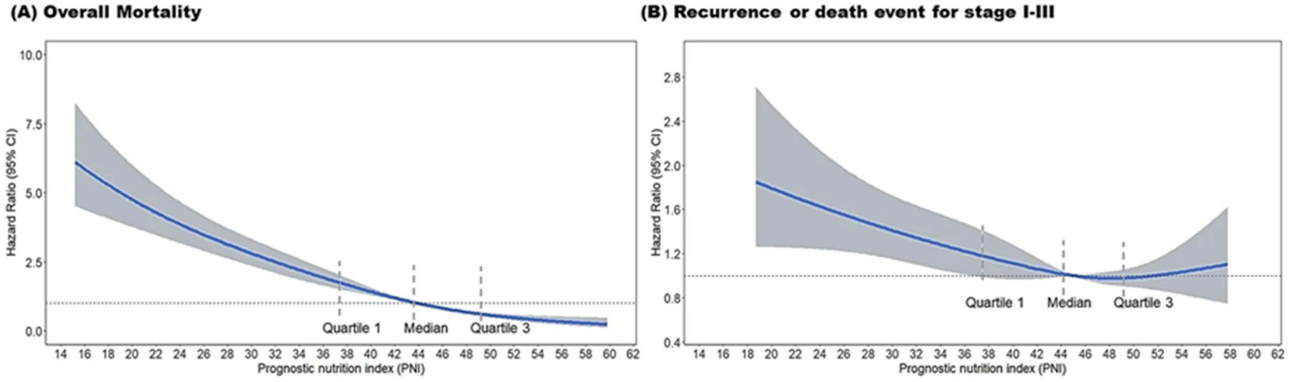

Figure 3 Association between PNI and (**A**) overall survival and (**B**) disease-free survival using a restricted cubic spline regression model in the total population. The blue line represents the estimated hazard ratio (HR) derived from the Cox proportional hazards model across PNI levels, and the shaded gray area represents the 95% confidence interval (CI). The dotted line (HR = 1.0) marks the reference level, and the dashed vertical lines indicate the first quartile, median, and third quartile of PNI distribution. The association between PNI and OS was significant (*p* for linearity < 0.001; *p* for non-linearity < 0.001), while the association with recurrence or death for stage I–III disease showed a linear pattern (*p* for linearity < 0.001).

The same results were found after using the stepwise selection method to adjust for related covariates in the multivariable analysis (overall complications, aOR = 0.22, 95% CI: 0.17–0.28; ileus, aOR = 0.23, 95% CI: 0.18–0.29; anastomotic leakage, aOR = 0.16, 95% CI: 0.09–0.28; lung-related complications, aOR = 0.38, 95% CI: 0.29–0.48) and in the PSM analysis (overall complications, PSM OR = 0.27, 95% CI: 0.20–0.37; ileus, PSM OR = 0.29, 95% CI: 0.21–

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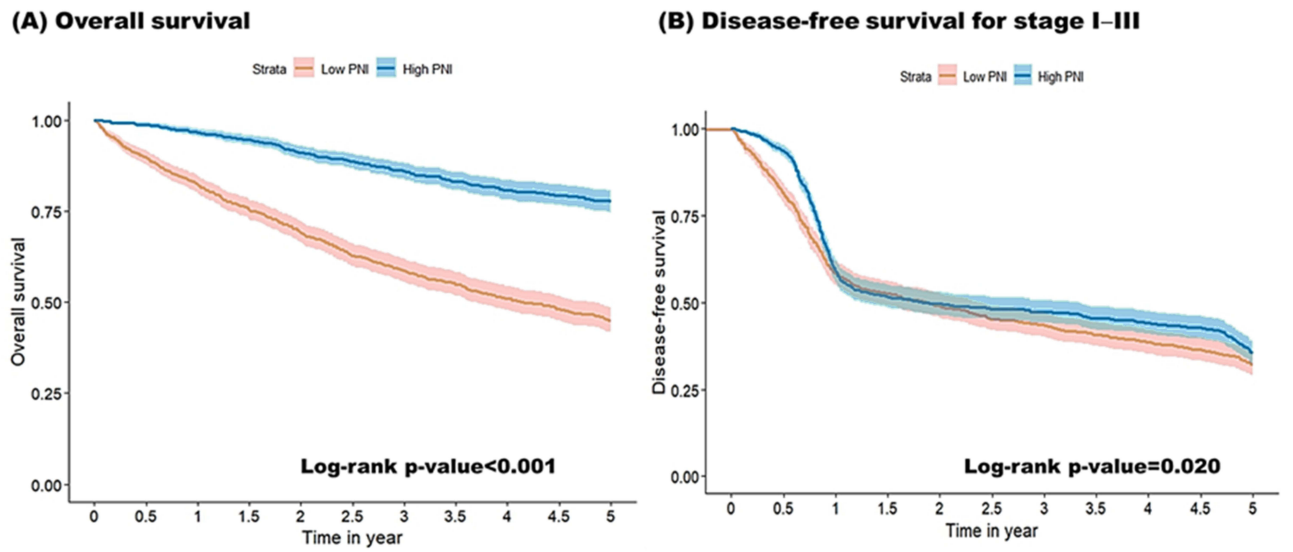

Figure 4 Kaplan–Meier curve for 5-year (**A**) overall survival and (**B**) disease-free survival by PNI group. The survival curve is represented by the solid line, and the 95% confidence interval (CI) by the shaded area. Patients with a high PNI showed significantly better OS ($p < 0.001$) and improved DFS ($p = 0.020$, Log rank test).

0.41; anastomotic leakage, PSM OR = 0.26, 95% CI: 0.12–0.56; lung-related complication, PSM OR = 0.42, 95% CI: 0.30–0.59). However, there was no difference in heart-related complications between low and high PNI groups.

Additionally, in the multivariable analysis several other risk factors for in-hospital complications were identified (Figure 5A–D). Overall complications were significantly associated with age, male sex, disease stage, WBC count, antihypertensive drug use, and insulin use. Being male, disease stage, platelet count, and insulin use were risk factors for ileus. Anastomotic leakage was associated with tumor size, disease stage, smoking, and neutrophil count. Age, disease

Table 2 Associations Between High and Low PNI and in-Hospital Complications

Complication	Univariate Analysis		Multivariable Analysis [a]		PSM Analysis [b]	
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	PSM OR (95% CI)	p-value
Overall complication						
Low PNI	1 (reference)		1 (reference)		1 (reference)	
High PNI	0.17 (0.14, 0.21)	**<0.001**	0.22 (0.17, 0.28)	**<0.001**	0.27 (0.20, 0.37)	**<0.001**
Ileus						
Low PNI	1 (reference)		1 (reference)		1 (reference)	
High PNI	0.20 (0.16, 0.25)	**<0.001**	0.23 (0.18, 0.29)	**<0.001**	0.29 (0.21, 0.41)	**<0.001**
Leakage						
Low PNI	1 (reference)		1 (reference)		1 (reference)	
High PNI	0.12 (0.07, 0.20)	**<0.001**	0.16 (0.09, 0.28)	**<0.001**	0.26 (0.12, 0.56)	**<0.001**
Lung-related complication						
Low PNI	1 (reference)		1 (reference)		1 (reference)	
High PNI	0.25 (0.20, 0.32)	**<0.001**	0.38 (0.29, 0.48)	**<0.001**	0.42 (0.30, 0.59)	**<0.001**
Heart-related complications						
Low PNI	1 (reference)		1 (reference)		1 (reference)	
High PNI	0.66 (0.24, 1.87)	0.438	0.96 (0.33, 2.85)	0.947	4.41 (0.48, 40.21)	0.188

Notes: [a]Multivariable logistic regression using stepwise selection and the candidates for outcomes presented in Table 1, including age, sex, tumor size, stage, neoadjuvant radiotherapy, neoadjuvant chemotherapy, BMI, CCI score, smoking, alcohol use, betel nut consumption, laboratory data (hemoglobin, platelet count, creatinine level, white blood cell count, red cell distribution width, estimated glomerular filtration rate, neutrophil count), and medication use (antihypertensives, statins, antidiabetic, insulin).[b]PSM logistic regression was adjusted for variables including propensity score and BMI.Values in **bold** indicate statistically significant differences between groups ($p < 0.05$).
Abbreviations: PSM, propensity score matching; OR, odds ratio; CI, confidence interval; PNI, prognostic nutrition index.

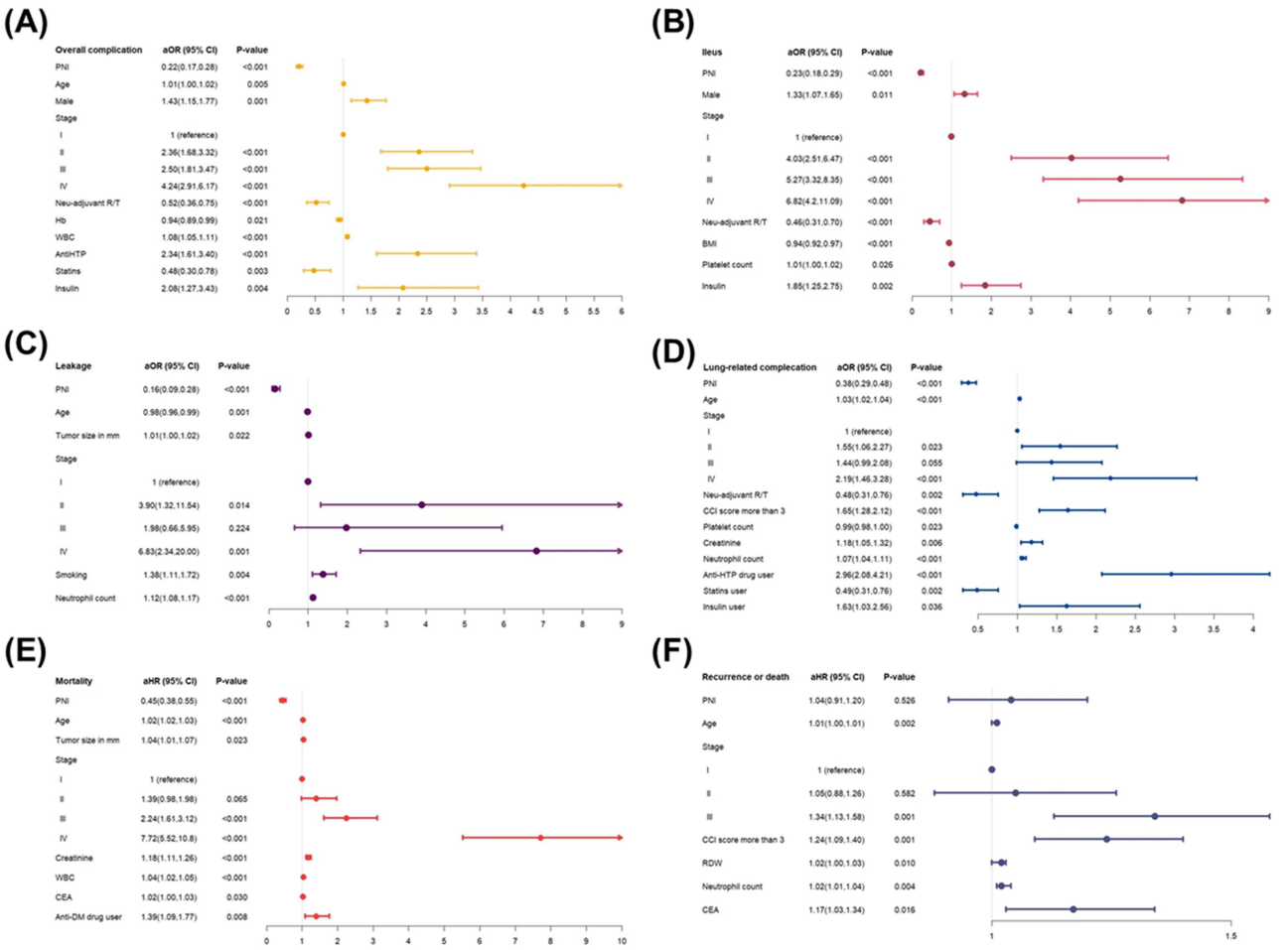

Figure 5 Significant risk factors for (**A**) overall complications, (**B**) ileus, (**C**) anastomotic leakage, (**D**) lung-related complication, (**E**) 5-year overall survival, and (**F**) 5-year recurrence and death. Panels A–D are based on multivariable analyses from Table 2, and panels E–F from Table 3.

stage, CCI > 3, creatinine level, neutrophil count, and the use of antihypertensive drugs and insulin were risk factors for lung-related complications.

Associations Between PNI and 5-Year OS and Recurrence or Death in the Subgroup of Patients with Stage I–III Diseases

The associations between PNI and 5-year OS and recurrence or death in stage I–III patients are shown in Table 3. A high PNI was associated with a lower mortality risk (crude HR = 0.30, 95% CI: 0.25–0.35). This finding remained consistent in both multivariable analysis (aHR = 0.45, 95% CI: 0.38–0.55) and PSM analysis (HR = 0.59, 95% CI: 0.45–0.76) after adjusting for related covariates. However, there was no difference in death or recurrence for stage I–III between the 2 groups.

Results of the multivariable analysis (Figures 5E and F) indicated that age, tumor size, disease stage, creatinine level, WBC count, CEA, and antidiabetic drug use were associated with increased mortality risk. Age, disease stage, CCI > 3, RDW, neutrophil count, and CEA level were significant risk factors for recurrence or death. Sensitivity analyses using backward elimination (SLS = 0.05) and LASSO regression with cross-validation for penalty selection yielded consistent results, confirming the robustness of the identified predictors (Supplementary Table S1).

Table 3 Cox Proportional Hazards Regression Analyses of the Associations Between PNI, 5-Year Overall Survival, and Recurrence or Death

	Univariate Analysis		Multivariable Analysis[a]		PSM Analysis[b]	
	Crude HR (95% CI)	**P-value**	**Adjusted HR (95% CI)**	**P-value**	**PSM HR (95% CI)**	**P-value**
Overall survival						
Low PNI	1 (reference)		1 (reference)		1 (reference)	
High PNI	0.30 (0.25,0.35)	**<0.001**	0.45 (0.38,0.55)	**<0.001**	0.59 (0.45,0.76)	**<0.001**
Recurrence or death in stage I–III (n = 1,695)						
Low PNI	1 (reference)		1 (reference)		1 (reference)	
High PNI	0.88 (0.78,0.99)	**0.029**	1.04 (0.91,1.20)	0.526	1.12 (0.79,1.59)	0.446

Notes: [a]Multivariable Cox proportional hazards regression using stepwise selection and the candidates for outcomes adjusted for variables presented in Table 1, including age, sex, tumor size, stage, neoadjuvant radiotherapy, neoadjuvant chemotherapy, BMI, CCI score, smoking, alcohol use, betel nut consumption, laboratory data (hemoglobin, platelet count, creatinine level, white blood cell count, red cell distribution width, estimated glomerular filtration rate, neutrophil count), medication use (antihypertensives, statins, antidiabetic drugs, insulin).[b]PSM Cox proportional hazards regression was adjusted for variables including propensity score and BMI.Values in **bold** indicate statistically significant differences between groups ($p < 0.05$).

Abbreviations: PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; PNI, prognostic nutrition index.

Comparison Between the Performance of PNI and NLR in Predicting Outcomes

To compare the predictive performance of PNI and the NLR for overall complications, ileus, anastomotic leakage, and lung-related complications, the area under the receiver operating characteristic (ROC) curve (AUC) was calculated for each parameter. As shown in Figures 6A–D, PNI consistently demonstrated superior discriminative ability compared to NLR, with higher AUC values for overall complications (0.77 vs 0.66), ileus (0.74 vs 0.64), anastomotic leakage (0.82 vs 0.75), and lung-related complications (0.72 vs 0.63).

Discussion

This study demonstrated that the preoperative PNI, an integrative marker reflecting nutritional and immunological status, is significantly associated with both perioperative complications and long-term survival outcomes in patients undergoing curative surgery for CRC. In a large cohort of patients from a high-volume tertiary care center in Taiwan, those with higher PNI values experienced substantially lower rates of in-hospital complications including postoperative ileus, anastomotic leakage, and lung-related complications. In addition, the RCS analysis confirmed a linear relation between PNI and overall complications, with evidence of non-linear associations with ileus and lung-related complications. Multivariable logistic regression and PSM analyses further supported that a high PNI is independently associated with reduced odds of perioperative morbidity. Furthermore, patients in the high PNI group exhibited significantly better 5-year OS than those in the low PNI group. While the association between PNI and DFS for stage I–III CRC patients did not reach statistical significance after adjustment, a high PNI still trended toward better oncologic outcomes. When compared to NLR, PNI consistently demonstrated superior predictive performance for major complications, as reflected by higher AUC values in the ROC analyses. Collectively, these findings suggest that preoperative PNI may be a practical prognostic tool for risk stratification and surgical outcome prediction in CRC patients, with potential to inform perioperative management and follow-up strategies.

Malnutrition has been long recognized as a factor adversely affecting overall health, outcomes of the treatment of medical conditions, and peri- and post-operative surgical outcomes.[19,20] Malnutrition is associated with decreased quality of life, increased mortality and length of hospital stays, and increased health care spending.[15] Notably, recent research has suggested that poor nutrition contributes to a chronic inflammatory state associated with aging, given the name "inflammaging".[21] Yet despite these findings, nutritional assessment is rarely incorporated into preoperative or medical protocols.[19,20]

The PNI is derived from 2 common biochemical tests, serum albumin level and lymphocyte count, and thus reflects nutritional and immune system status.[11–13] The PNI has been studied as a prognostic marker in many conditions, and studies have shown that a low PNI is associated with adverse outcomes of medical conditions like coronary artery disease, postoperative outcomes after spine surgery, and malignancies ranging from lung cancer to renal cell

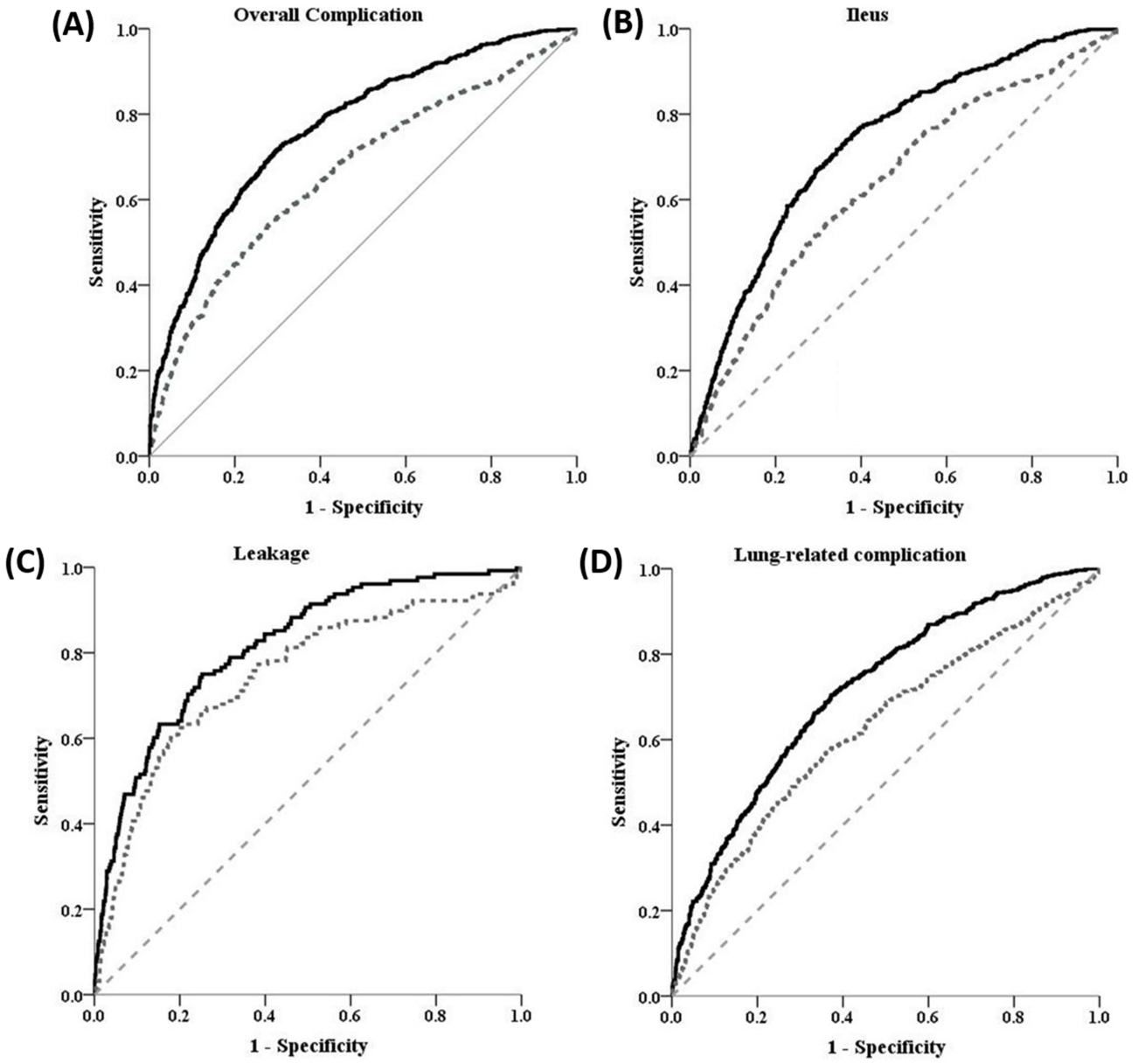

Figure 6 Receiver operating characteristics curves (ROC) of the PNI (solid line) and NLR (dashed line) for prediction of (**A**) overall complications, (**B**) ileus, (**C**) anastomotic leakage, and (**D**) lung-related complication. The dashed line is the reference line, which represents the ROC at 0.5. PNI demonstrated higher discriminatory power than NLR for all outcomes (AUCs for overall complications 0.77 vs 0.66; ileus 0.74 vs 0.64; leakage 0.82 vs 0.75; lung-related complications 0.72 vs 0.63, all within the corresponding 95% confidence intervals (CIs)).

carcinoma.[22–26] From a pathophysiological perspective, hypoalbuminemia may impair collagen synthesis and wound healing.[27] Meanwhile, lymphopenia reflects immune suppression that compromises host defense, increasing susceptibility to postoperative infections.[28] The results of this study add to a large list of medical and surgical conditions for which the PNI is a reliable prognostic indicator.

Our study evaluated both short- and long-term outcomes, and although few prior studies have examined the value of the PNI in patients with CRC, our results are consistent with those of prior studies. For example, Xie et al studied 1,014 patients undergoing surgical treatment of CRC.[29] A low PNI was associated with high tumor burden and invasive pathological features, and a higher incidence of complications and longer hospital stay. A low PNI was also an independent risk factor for postoperative complications, as well as OS and PFS. Another prospective study of patients undergoing curative intent surgery for CRC reported that the was a significant predictor of overall complications (relative

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risk [RR] = 0.279; 95% CI: 0.141–0.552), severe complications (RR = 0.355; 95% CI: 0.130–0.965), infectious complications (RR = 0.220; 95% CI: 0.099–0.489), and anastomotic leakage (RR = 0.151; 95% CI: 0.036–0.640).[30] Keskinkilic et al studied the value of the PNI in patients with metastatic CRC, and reported that a high PNI value (≥ 46.6) was associated with significantly longer OS than a value < 46.6 (53 months vs 39 months, P = 0.039).[11] The analysis of PFS between groups did not reach statistical significance. Collectively, these findings across independent cohorts support the consistency and external validity of our results.

Although our study primarily focused on PNI, it is important to contextualize its performance relative to other commonly used biomarkers. Among inflammatory indices, the NLR and C-reactive protein (CRP) are well-established markers that primarily reflect systemic inflammation. However, they do not capture the patient's nutritional or immune reserve, which are key determinants of surgical recovery. In contrast, the PNI combines serum albumin and lymphocyte count, integrating both nutritional and inflammatory components into a single, easily accessible metric. In our analysis, the PNI demonstrated superior discriminative ability over NLR in predicting major postoperative complications, underscoring its broader prognostic relevance.

Beyond these single-domain indicators, several composite or integrative biomarkers have been developed to provide a more comprehensive assessment of host status, such as the Glasgow Prognostic Score (GPS), the albumin-to-globulin ratio (AGR), and the C-reactive protein–albumin–lymphocyte (CALLY) index. Notably, Li et al demonstrated that patients with a low AGR and a low PNI had the worst overall and progression-free survival among different biomarker combinations in CRC, highlighting the additive value of these integrative indices.[31] Moreover, both GPS and CALLY have also been investigated in relation to CRC prognosis in previous studies.[32,33] Collectively, these findings suggest that multi-dimensional indices provide a more holistic reflection of the complex interplay between inflammation, nutrition, and immunity that underlies surgical and oncologic outcomes in CRC.

Notably, although our results showed a significant association between PNI and OS, we did not observe an association between PNI and DFS. Additional sensitivity analyses helped clarify this apparent discrepancy. In a Fine and Gray competing-risk model, high PNI was associated with a lower risk of both cancer-related and non–cancer-related mortality, and this protective effect was generally consistent across CCI strata, although the association with cancer-related death was attenuated in patients with higher comorbidity (CCI ≥ 3). This may be due to several factors such as comorbidities and variations in treatment response. These findings suggest that the discrepancy may be related to several factors, including comorbidities and variations in treatment response. It may also reflect competing risks, as patients with low PNI often have higher non–cancer mortality due to frailty or chronic comorbidities, which affects OS but not DFS.[34] Additionally, patients with better nutritional and immune status may tolerate adjuvant therapy more effectively after recurrence, thereby improving overall survival without altering recurrence risk.

Although we did not evaluate specific interventions, our findings provide important translational insights. Recent studies suggest that strategies aimed at improving nutritional status and reducing systemic inflammation may positively impact prognosis. Among these, preoperative immunonutrition has been shown to reduce wound infection rates and shorten hospital stays in patients undergoing elective colorectal surgery. Immunonutrition is a nutritional method that uses specific nutrients to support and enhance the immune system.[35] Diets are enriched with nutrients believed to have immune-modulating properties, which can improve immune function and modulate inflammatory responses. It is believed that immunonutrition can reduce the risk of surgical complications and improve outcomes in patients with critical illnesses.[35] Studies on the benefits of immunonutrition have been somewhat inconsistent. For example, a randomized controlled trial by Lee et al reported that immunonutrition did not reduce infectious complications or length of hospital stay in patients undergoing colon cancer surgery.[36] On the other hand, a recent meta-analysis by Wong et al reported that immunonutrition significantly reduced the risk of wound infection in patients undergoing open surgery for CRC.[37] It should be noted that standardization of immunotherapy is lacking, and thus comparing the results of different studies is difficult.[35]

Implications for Practice

The results of this study demonstrated that the PNI is a strong, independent predictor of postoperative complications and long-term survival in patients with CRC undergoing surgery. Incorporating routine preoperative assessment of PNI into

clinical practice help identify high-risk surgical candidates, inform surgical decision-making, and guide perioperative management. In current surgical workflows, the overall operative risk is typically evaluated using global indices, such as the American Society of Anesthesiologists (ASA) physical status classification and the Charlson Comorbidity Index (CCI), which primarily reflect the comorbidity burden and anesthetic fitness but do not capture nutritional or immune status. The PNI may serve as a complementary biomarker to help identify patients who appear clinically fit for surgery by ASA or CCI criteria but may remain physiologically vulnerable due to malnutrition or immunologic compromise.

For patients with a low PNI, preoperative nutritional support and postoperative early mobilization and respiratory therapy should be considered to improve physiological resilience. Closer postoperative monitoring and individualized care pathways based on PNI may help reduce complications and optimize outcomes, while also enabling more efficient resource allocation. Moreover, as PNI reflects both nutritional and immune status, it may represent a modifiable biomarker. Nutritional optimization, including immunonutrition strategies, could potentially enhance PNI values and improve postoperative recovery. It may be feasibly integrated into existing risk assessment frameworks and ERAS protocols to support individualized optimization before surgery. However, prospective interventional studies are warranted to determine whether improving PNI can directly translate into better surgical and oncologic outcomes.

Beyond perioperative management, PNI may also have broader clinical applications. A lower PNI has been associated with reduced chemotherapy tolerance and greater treatment-related toxicity, suggesting its potential use in tailoring adjuvant therapy intensity.[38] As an integrative measure of immune–nutritional status, PNI may also provide insight into immunotherapy responsiveness and help identify patients more likely to benefit from immune-checkpoint blockade.[39] Furthermore, postoperative monitoring of PNI could assist in guiding the timing and progression of rehabilitation programs.[40] These potential extensions of PNI underline its versatility as a biomarker, and they warrant validation in future prospective and interventional studies.

Strengths and Limitations

This study has several notable strengths. First, the inclusion of a large cohort of CRC patients who underwent curative-intent surgery over a 13-year period provides substantial statistical power and allows for more precise estimates of associations. The extended follow-up duration of up to 5 years also enables a comprehensive evaluation of both perioperative complications and long-term oncologic outcomes, including OS and DFS. Second is the richness and completeness of the dataset, which was derived from a high-volume tertiary care center with access to detailed clinical, laboratory, and treatment records. This allowed for extensive multivariable adjustment for a wide range of demographic, clinical, and biochemical variables, thereby enhancing the internal validity of the results. Third is the study design incorporated PSM, which helped minimize confounding by balancing baseline characteristics between the high and low PNI groups. In addition, we performed multiple sensitivity analyses, including alternative variable selection strategies (backward elimination and LASSO) and competing-risk models for cause-specific mortality, all of which yielded results consistent with the primary analyses, supporting the robustness of our findings. Furthermore, the study uniquely examined both surgical and oncologic outcomes within the same cohort, which is relatively uncommon in previous literature. Finally, the study directly compared PNI with another commonly used inflammatory biomarker, the NLR, demonstrating that PNI had superior predictive performance in relation to surgical complications. This adds practical clinical value by identifying a more informative and accessible marker for preoperative risk stratification.

Despite these strengths, several limitations must be acknowledged. The retrospective observational design is inherently susceptible to selection bias and residual confounding, despite the application of PSM and multivariable regression. Because this was a single-center study conducted in Taiwan, the findings may not be fully generalizable to other healthcare settings or ethnic populations. The number of recurrence events in our cohort was relatively limited, which may have reduced the statistical power to detect a significant association between PNI and DFS. Additionally, the low incidence of heart-related complications may have limited the statistical power to detect between-group differences.

Because complications were extracted retrospectively from medical records, they were recorded as binary outcomes rather than graded using standardized indices (eg, Clavien–Dindo or the Comprehensive Complication Index), which may limit the discrimination of severity. Although the study included a relatively long follow-up period, certain long-term complications or late recurrences may still have been missed, particularly in elderly patients or those lost to follow-up. Another limitation is that PNI was calculated from a single preoperative blood test, which may not fully capture fluctuations in nutritional and

immunologic status over time. Finally, although extensive covariate adjustment was performed, certain potentially influential factors such as sarcopenia, frailty, inflammatory markers (eg, C-reactive protein), differences in perioperative management, or surgeon experience and technique were not captured and thus could not be evaluated in the analysis. Moreover, while PNI was significantly associated with overall survival, it was not independently associated with disease-free survival after adjustment, and this null finding should be interpreted with caution.

Conclusions

In this large retrospective cohort study, a higher preoperative PNI was significantly associated with reduced rates of postoperative complications and improved long-term survival in patients undergoing curative surgery for CRC. PNI outperformed the NLR in predicting perioperative risk, supporting its clinical utility as a simple, cost-effective, and integrative biomarker reflecting both nutritional and immune status. Given the retrospective single-center design, further validation in diverse populations is needed to confirm generalizability. Future prospective and multicenter studies are warranted to validate these results and explore whether targeted interventions to improve PNI could translate into better surgical and oncologic outcomes in patients with CRC.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Institutional Review Board (IRB) of Changhua Christian Hospital. As this was a retrospective study that used de-identified data, the requirement of informed consent was waived.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Consent for Publication

All authors have reviewed the manuscript and consent to its publication.

Disclosure

The authors have declared that no competing interests exist in this work.

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