Annals of Gastroenterological Surgery

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Impact of Low Preoperative Prognostic Immune Nutritional Index on Survival and Postoperative Infectious Complications in Patients With Colorectal Cancer

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Received: 22 April 2025 | **Revised:** 13 July 2025 | **Accepted:** 12 August 2025

Funding: The authors received no specific funding for this work.

Keywords: colorectal cancer | postoperative infectious complications | prognostic immune nutritional index | propensity score matching analysis | surgical site infection

ABSTRACT

Aim: The prognostic immune nutritional index (PINI) is increasingly recognized for its potential clinical utility. However, multifaceted evaluations of its ability to predict oncological outcomes in colorectal cancer (CRC) and its association with postoperative infectious complications remain limited.

Methods: We analyzed the preoperative PINI in 487 patients with CRC who underwent surgical treatment between 2006 and 2015 to clarify its clinical relevance.

Results: A low preoperative PINI was significantly associated with several clinicopathological factors indicative of disease progression, including advanced pathological T category ($p < 0.001$) and lymph node metastasis ($p = 0.001$). It was an independent prognostic factor for disease-free survival (DFS) (hazard ratio [HR]: 1.91; 95% confidence interval [CI]: 1.22–3.00; $p = 0.005$) and overall survival (OS) (HR: 2.51; 95% CI: 1.50–4.18; $p < 0.001$). A low preoperative PINI was also an independent risk factor for total infection (odds ratio [OR]: 1.82; 95% CI: 1.11–3.00; $p = 0.02$), encompassing all postoperative infectious complications. In a subgroup analysis of patients with stage III and high-risk stage II CRC, a low preoperative PINI was an independent prognostic factor for both DFS (HR: 2.03; 95% CI: 1.24–3.32; $p = 0.005$) and OS (HR: 3.64; 95% CI: 1.61–8.19; $p = 0.002$). Additionally, propensity score matching analysis demonstrated that patients with a low preoperative PINI had significantly worse DFS ($p = 0.01$) and OS ($p = 0.02$).

Conclusion: The preoperative PINI is a valuable biomarker for both perioperative risk assessment and long-term oncological management in patients with CRC.

1 | Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide [1]. It is estimated that more than 900 000 deaths are caused by CRC annually, representing nearly 1 in 10 of all cancer deaths [1]. Despite advancements in screening and treatment, 60% of new cases in 2019 were diagnosed at an advanced stage, indicating a rising trend [2]. Moreover, an increase in incidence and mortality among younger populations has been observed, highlighting a concerning pattern that warrants further investigation and attention [1, 2].

Currently, the stratification of patients with CRC relies on Tumor-Node-Metastasis (TNM) staging, which forms the basis for constructing treatment algorithms. However, this classification is limited by its exclusive focus on tumor characteristics without incorporating host factors that may influence the prognosis, such as systemic inflammation and the nutritional status [3, 4]. In stratifying patients with CRC, biomarkers such as carcinoembryonic antigen and carbohydrate antigen 19-9 are used complementarily, although their clinical utility remains limited [5].

To improve outcomes for patients with CRC, there is an urgent need for reliable biomarkers that accurately reflect host factors and more precisely predict tumor behavior in clinical practice. Furthermore, recent studies have increasingly reported that postoperative infectious complications, such as surgical site infection (SSI), significantly impact oncological outcomes in CRC [6, 7]. This suggests that biomarkers capable of predicting not only the oncological prognosis but also postoperative infectious complications may offer greater clinical value and sophistication.

Systemic inflammation, driven by cytokines and immune cells, can be assessed using biochemical and hematological markers such as leukocytes, neutrophils, monocytes, and C-reactive protein—all of which are routinely measured through standard blood tests. Systemic inflammation plays a critical role in tumor formation, proliferation, progression, and metastasis in malignant diseases [8, 9]. Evaluating systemic inflammation provides valuable insights into disease activity and its underlying dynamics. The association between systemic inflammation markers and prognosis has been frequently reported across various cancers [10, 11]. Additionally, the preoperative nutritional status is widely recognized as an important factor in predicting oncological outcomes in patients with cancer [12, 13]. Composite indices that integrate both inflammation and nutrition have gained significant attention as useful tools for improving the accuracy of prognostic evaluations [14, 15].

In this context, a new biomarker called the prognostic immune nutritional index (PINI), which combines measures of systemic inflammation and the nutritional status, has been developed [16]. While several studies have demonstrated its utility in various cancers, comprehensive evaluations of its prognostic value in CRC remain limited [16, 17]. Furthermore, its relationship with postoperative infectious complications in CRC has yet to be clarified. Investigating these aspects may offer valuable insights to improve the management of patients with CRC. This study comprehensively evaluated the utility of the preoperative PINI as a prognostic biomarker for oncological outcomes in CRC from multiple perspectives. Additionally, we examined the potential of the preoperative PINI to predict the risk of postoperative infectious complications.

2 | Methods

2.1 | Patients and Methods

We initially identified 647 consecutive CRC patients who underwent surgery at our institution between January 2006 and December 2015. Of these, 160 were excluded due to incomplete blood test results, and the remaining 487 patients were included in this retrospective cohort study. This study was approved by the Review Board of Mie University Hospital (IRB number: H2025-062) and was carried out in accordance with the ethical principles of the Declaration of Helsinki. All patients were classified according to the Union for International Cancer Control (UICC) TNM Classification (8th edition). Patients who received neoadjuvant therapy before surgical resection were excluded from the study.

Surgical approaches included laparotomy and laparoscopy, with standard curative resection performed based on preoperative TNM staging. Resection of the primary tumor was carried out in all patients. Following surgery, 5-fluorouracil-based adjuvant chemotherapy was recommended for patients with stage IV disease, as well as for those with stage III or stage II disease with high-risk factors [18].

Patients were monitored every 3 months for the first 2 years after surgery, every 6 months for the subsequent 3 years, and annually thereafter. The median follow-up duration was 35.9 months. Follow-up protocols included tumor marker testing, computed tomography, endoscopic examinations, ultrasonography, and chest radiography.

Data collected from inpatient and outpatient records included demographic information (age and sex); body mass index (BMI), with obesity defined as BMI ≥ 25 [19]; comorbidities that could significantly affect PINI (collagen disease, liver cirrhosis, and chronic renal failure); preoperative tumor-related complications (bowel obstruction, perforation, and intra-abdominal abscess); factors potentially associated with postoperative infectious complications (diabetes mellitus and chronic corticosteroid therapy); tumor-specific characteristics (location, histology, T classification, venous and lymphatic invasion, lymph node metastasis, and distant metastasis); survival data, including disease-free survival (DFS) and overall survival (OS); and surgical details (surgical approach, operation time, and blood loss).

Postoperative infectious complications were defined as those occurring within 30 days of surgery. Information on these complications was obtained from a prospectively maintained database and supplemented with patient medical records when necessary. Postoperative infectious complications included wound infection (superficial or deep infections requiring treatment with antibiotics or wound drainage), intra-abdominal abscess (fluid collection in the abdomen associated with fever or leukocytosis that either drained spontaneously or required surgical or radiologically guided drainage, with bacteria detected in blood or fluid cultures), respiratory tract infection (respiratory symptoms and signs, along with radiographic infiltration and fever or leukocytosis requiring antibiotic treatment), urinary tract infection, cholecystitis, and *Clostridium difficile*-associated enteritis. SSI was defined as wound infection or intra-abdominal abscess, while total infection referred to all postoperative infectious complications, including SSI.

2.2 | Laboratory Measurement of Preoperative PINI in Routine Blood Tests

Blood samples were obtained from each patient within 1 week prior to surgical resection of the primary tumor. The albumin concentration and monocyte count were measured as part

of routine preoperative blood tests, and the PINI was calculated using the following formula: (albumin × 0.9) − (monocytes × 0.0007) [16].

2.3 | Propensity Score Matching

To minimize the effects of selection bias, propensity score matching (PSM) was implemented. A high or low preoperative PINI in patients with CRC was designated as the objective factor. Seven covariates were used to build the propensity score: age (older or younger, divided at the median), BMI (high or low, divided at the median), pathological T category (T1/2 or T3/4), venous invasion (present or absent), lymphatic invasion (present or absent), lymph node metastasis (present or absent), and distant metastasis (present or absent). A one-to-one matching analysis between the two groups was performed based on the estimated propensity score for each patient using a logistic regression model. A caliper width of 0.2 of the standard deviation of the propensity score was used for the one-to-one matching analysis.

2.4 | Statistical Methods

Statistical analysis was performed using MedCalc version 22.023 (Mariakerke, Belgium). Results are expressed as median and interquartile range. Differences between groups were assessed using the Mann–Whitney U test or Kruskal–Wallis test. The median preoperative PINI in each analytical cohort was used as the cutoff value.

For time-to-event analyses, survival estimates were calculated using Kaplan–Meier analysis, and groups were compared with the log-rank test. DFS was measured from the date of curative surgery to the date of disease recurrence, death of any cause (i.e., cancer-unrelated deaths were not censored), or the last patient contact. OS was measured from the date of surgery to the date of death of any cause (i.e., cancer-unrelated deaths were not censored) or the last known follow-up for patients who remained alive.

Cox proportional hazards models were used to estimate hazard ratios (HRs) for recurrence or death. Variables with $p < 0.05$ in univariate analysis were included in the multivariate analysis using the Cox proportional hazards regression model. Multivariate logistic regression models were used to identify factors influencing postoperative infectious complications, with results expressed as odds ratios (ORs). All P values were two-sided, and $p < 0.05$ was considered statistically significant.

3 | Results

3.1 | Patient Characteristics

The patient population included 279 men (57.3%) and 208 women (42.7%), with a median age of 69 years (range: 31–94 years). The high-PINI and low-PINI groups consisted of 243 and 244 patients, respectively. The median BMI was 22.3 kg/m^2 (range: 13.5–34.3 kg/m^2). There were 50 patients (10.3%) with comorbidities that could significantly affect albumin or monocyte levels, and these comorbidities consisted of collagen disease, liver cirrhosis, and chronic renal failure. Additionally, there were 30 patients (6.2%) with preoperative tumor-related complications that could significantly affect the PINI, which consisted of bowel obstruction—defined as a condition requiring urgent decompression—, perforation, and abscess formation. As potential risk factors for postoperative infectious complications, 102 patients (20.9%) were classified as obese (BMI ≥ 25), 19 patients (3.9%) were receiving chronic corticosteroid therapy, and 102 patients (20.9%) had diabetes mellitus. The median operative time was 219 min (range: 52–1130 min), and the median intraoperative blood loss was 58 mL (range: 1–3125 mL).

3.2 | Decreased Preoperative PINI Was Significantly Associated With CRC Development

We evaluated the association between patient characteristics and the distribution of preoperative PINI values. As a result, a decreased preoperative PINI was significantly associated with older age (greater than the median, $p < 0.001$), lower BMI (less than the median, $p < 0.001$), presence of comorbidities affecting PINI ($p < 0.001$), and presence of preoperative tumor-related complications ($p < 0.001$), as well as several clinicopathological factors indicative of disease progression. These included undifferentiated histology ($p = 0.005$), advanced pathological T category ($p < 0.001$), presence of venous invasion ($p = 0.02$), presence of lymphatic invasion ($p = 0.002$), lymph node metastasis ($p = 0.001$), and distant metastasis ($p < 0.001$). Additionally, a significant association was observed between UICC stage and preoperative PINI, with lower PINI values observed in patients with advanced-stage ($p < 0.001$) (Table 1). On the other hand, the proportion of low PINI patients was comparable between Stage II (73 of 134 patients; 54.5%) and Stage III (67 of 131 patients; 51.1%), indicating that the relationship between UICC stage and PINI was not strictly linear (Figure 1A, Table S1).

3.3 | Low Preoperative PINI Was Significantly Associated With Poor Oncological Outcomes in CRC

We performed time-to-event analysis to evaluate the potential of the preoperative PINI as a prognostic biomarker. Patients with a decreased preoperative PINI had significantly poorer DFS (log-rank test, $p < 0.001$) (Figure 1B) and OS (log-rank test, $p < 0.001$) (Figure 1C). According to Cox univariate proportional hazards analysis, male sex, rectal tumor location, advanced T classification (pT3/T4), venous invasion, lymphatic invasion, lymph node metastasis, and a low preoperative PINI were all significantly associated with poor DFS. Multivariate Cox regression analysis confirmed that a low preoperative PINI was an independent prognostic factor for poor DFS (HR: 1.91, 95% CI: 1.22–3.00, $p = 0.005$) (Table 2) in patients with CRC. Similarly, low BMI, undifferentiated histology, advanced T classification (pT3/T4), venous invasion, lymphatic invasion, lymph node metastasis, distant metastasis, and a low preoperative PINI were significantly associated with poor OS. In the multivariate analysis, a low preoperative PINI was identified as an independent prognostic factor for OS (HR: 2.51, 95% CI: 1.50–4.18, $p < 0.001$) (Table 3).

TABLE 1 | Clinicopathological variables and preoperative PINI in patients with CRC.

Variables		*N*	Preoperative PINI	
			Median (IQR)	*p*
Sex	Male	279	3.32 (2.98–3.70)	0.12[a]
	Female	208	3.43 (3.07–3.76)	
Median age (year)	> 69	240	3.23 (2.86–3.58)	< 0.001*[a]
	≤ 69	247	3.53 (3.12–3.82)	
Median BMI (kg/m^2)	> 22.3	243	3.49 (3.08–3.76)	< 0.001*[a]
	≤ 22.3	244	3.26 (2.94–3.66)	
Comorbidities affecting PINI[b]	Present	50	3.04 (2.76–3.34)	< 0.001*[a]
	Absent	437	3.43 (3.06–3.74)	
Preoperative tumor-related complications[c]	Present	30	2.77 (2.47–3.23)	< 0.001*[a]
	Absent	457	3.42 (3.06–3.73)	
Histological type	Differentiated	442	3.41 (3.06–3.72)	0.005*[a]
	Undifferentiated	45	3.02 (2.56–3.67)	
Location	Colon	327	3.34 (3.00–3.71)	0.15[a]
	Rectum	160	3.43 (3.04–3.75)	
Pathological T category	pT1/T2	168	3.57 (3.26–3.83)	< 0.001*[a]
	pT3/T4	319	3.23 (2.91–3.64)	
Venous invasion	Present	231	3.28 (2.97–3.68)	0.02*[a]
	Absent	256	3.44 (3.08–3.74)	
Lymphatic invasion	Present	322	3.31 (2.94–3.68)	0.002*[a]
	Absent	165	3.48 (3.14–3.76)	
Lymph node metastasis	Present	190	3.25 (2.90–3.64)	0.001*[a]
	Absent	297	3.45 (3.08–3.75)	
Distant metastasis	Present	77	3.10 (2.77–3.43)	< 0.001*[a]
	Absent	410	3.43 (3.07–3.75)	
UICC stage classification	Stage I	145	3.54 (3.24–3.84)	< 0.001*[d]
	Stage II	134	3.30 (2.98–3.68)	
	Stage III	131	3.38 (3.01–3.71)	
	Stage IV	77	3.10 (2.77–3.43)	

Abbreviations: BMI, body mass index; CRC, colorectal cancer; IQR, interquartile range; PINI, prognostic immune nutritional index.
[a]Mann–Whitney *U* test.
[b]The comorbidities affecting PINI consisted of collagen diseases, chronic renal failure, and liver cirrhosis.
[c]The preoperative tumor-related acute complications consisted of bowel obstruction, perforation, and intra-abdominal abscess.
[d]Kruskal–Wallis test.
*$p < 0.05$.

3.4 | Diminished Preoperative PINI Was Significantly Associated With Postoperative Infectious Complications

To determine the clinical impact of the preoperative PINI as a predictive biomarker for postoperative infectious complications in patients with CRC, we evaluated the correlation between the preoperative PINI and postoperative infectious complications (Table S2A). The preoperative PINI was not associated with postoperative anastomotic leakage ($p = 0.29$) (Figure 1D). However, patients with SSI had a significantly lower preoperative PINI than those without such infectious complications ($p = 0.001$) (Figure 1E). The preoperative PINI was also correlated with total infection, which included all postoperative infectious complications ($p < 0.001$) (Figure 1F). When total infection were subdivided, significant associations were observed between

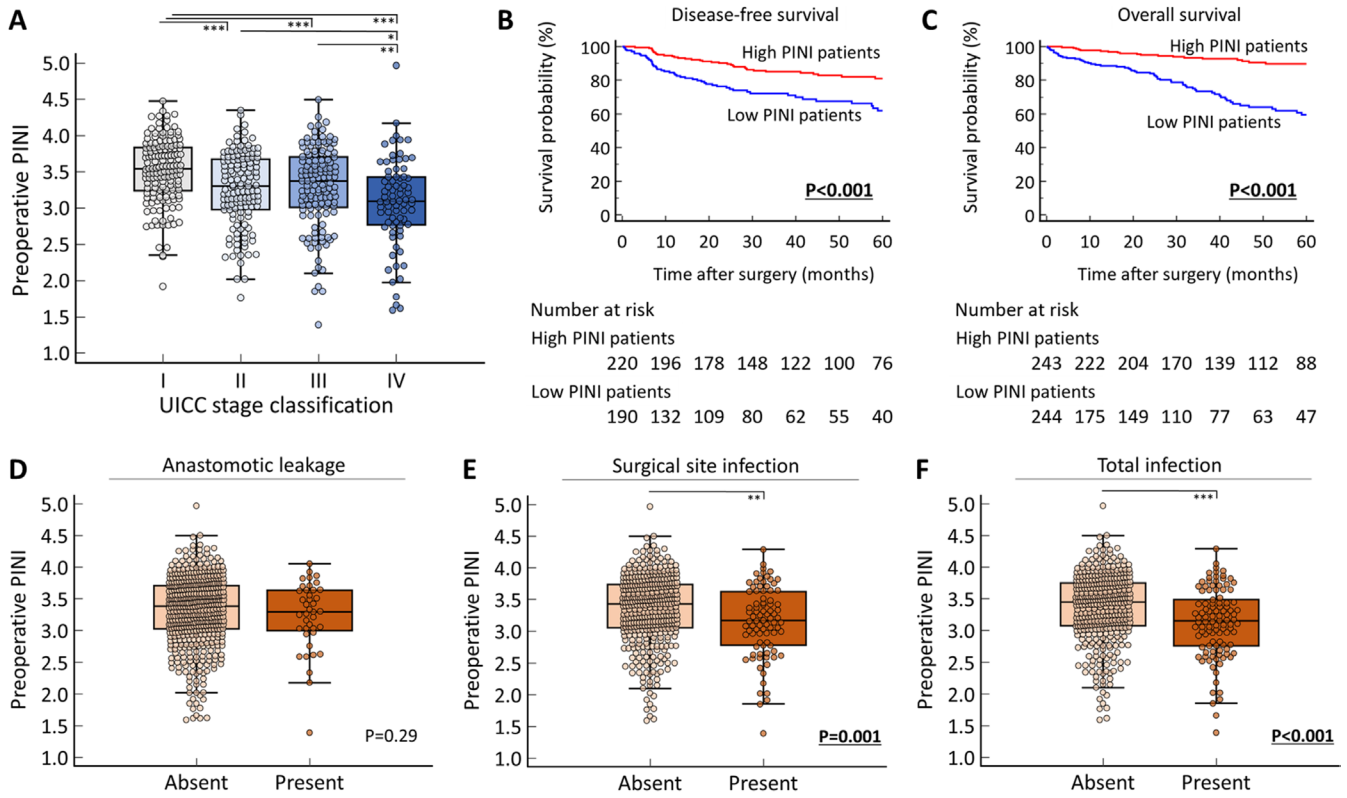

FIGURE 1 | (A) Scattergrams of preoperative PINI according to pathological stage in patients with CRC. A correlation was observed between a lower preoperative PINI and more advanced stages. (B, C) Kaplan–Meier analysis of DFS and OS in patients with CRC stratified by preoperative PINI. Patients with a low preoperative PINI had significantly lower (B) DFS and (C) OS than those with a high preoperative PINI ($p < 0.001$ for both, log-rank test). (D–F) Box plots showing the correlation between postoperative complications and preoperative PINI. Anastomotic leakage occurred in 32 of 487 patients (6.6%), SSI in 86 (17.7%), and TI in 106 (21.8%). (D) No correlation was observed between the preoperative PINI and anastomotic leakage ($p = 0.29$). However, significant correlations were found with (E) SSI ($p = 0.001$) and (F) TI ($p < 0.001$). CRC, colorectal cancer; DFS, disease-free survival; OS, overall survival; PINI, prognostic immune nutritional index; SSI, surgical site infection; TI, total infection. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

low preoperative PINI and the occurrence of organ/space SSI ($p = 0.04$) and respiratory tract infection ($p = 0.03$) (Table S2B).

To further assess the clinical relevance of the preoperative PINI for short-term outcomes, we evaluated its predictive value using multivariate logistic regression analysis, applying the same cut-off value used in the survival analyses. This analysis showed that a decreased preoperative PINI tended to be associated with a higher risk of SSI (OR: 1.63, 95% CI: 0.96–2.78, $p = 0.07$) (Table 4). Furthermore, a decreased preoperative PINI was identified as an independent risk factor for total infection (OR: 1.82, 95% CI: 1.11–3.00, $p = 0.02$) (Table 5).

3.5 | Decreased Preoperative PINI Was Significantly Associated With CRC Development in Stage III and High-Risk Stage II

To further evaluate the potential of the preoperative PINI as a prognostic biomarker, we conducted an analysis focusing on patients with CRC classified as stage III and high-risk stage II. In this study, stage II patients were considered high-risk if they met any of the following criteria extracted from the NCCN guidelines [18]: fewer than 12 assessed lymph nodes, T4 tumors, obstruction or perforation at diagnosis, vascular or lymphatic invasion, poor histological differentiation, or positive resection margins. Based on these criteria, we identified 131 patients with stage III CRC and, together with 109 patients with high-risk stage II CRC, analyzed a total cohort of 240 patients.

Adjuvant chemotherapy was administered to 113 patients (47.1%), while the remaining patients did not receive it because of factors such as advanced age, comorbidities, or personal preference. Within this group, analysis of the association between clinicopathological factors and the preoperative PINI showed that a decreased preoperative PINI was significantly associated with older age ($p = 0.002$), presence of comorbidities affecting PINI ($p = 0.01$), presence of preoperative tumor-related complications ($p < 0.001$), advanced T classification ($p = 0.008$), and non-implementation of adjuvant chemotherapy ($p = 0.001$). However, no significant association was observed with lymph node metastasis, a decisive factor in staging (Table S3).

3.6 | Low Preoperative PINI Was Significantly Associated With Poor Oncological Outcomes in Stage III and High-Risk Stage II CRC

We performed a time-to-event analysis in this group as well, using the median preoperative PINI as the cutoff value. Patients

TABLE 2 | Multivariate analysis for predictors of disease-free survival in patients with CRC.

	Univariate			Multivariate		
Variables	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Sex (male)	1.57	1.00–2.45	**0.05***	1.40	0.89–2.20	0.14
Age (> 69 year[a])	1.19	0.78–1.82	0.41			
BMI (≤ 22.3 kg/m^2)[b]	1.46	0.95–2.23	0.08			
Comorbidities affecting PINI[c] (present)	1.20	0.63–2.27	0.58			
Preoperative tumor-related complications[d] (present)	1.38	0.60–3.16	0.45			
Histological type (undifferentiated)	1.45	0.73–2.89	0.31			
Location (rectum)	2.09	1.36–3.20	< 0.001*	2.40	1.54–3.74	< 0.001*
T classification (pT3/4)	2.95	1.76–4.96	< 0.001*	1.55	0.85–2.81	0.15
Venous invasion (present)	3.22	2.06–5.02	< 0.001*	1.89	1.17–3.06	0.009*
Lymphatic invasion (present)	2.95	1.74–5.01	< 0.001*	1.70	0.95–3.02	0.07
Lymph node metastasis (present)	2.52	1.65–3.85	< 0.001*	1.72	1.09–2.71	0.02*
Preoperative PINI (≤ 3.376)[e]	2.19	1.43–3.37	< 0.001*	1.91	1.22–3.00	0.005*

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; PINI, prognostic immune nutritional index.
[a]The median age at surgery was 69 years in this cohort.
[b]The median BMI at surgery was 22.3 kg/m^2 in this cohort.
[c]The comorbidities affecting PINI consisted of collagen diseases, chronic renal failure, and liver cirrhosis.
[d]The preoperative tumor-related acute complications consisted of bowel obstruction, perforation, and intra-abdominal abscess.
[e]The cutoff for preoperative PINI was set at the median value of this cohort.
*$p < 0.05$.

TABLE 3 | Multivariate analysis for predictors of overall survival in patients with CRC.

	Univariate			Multivariate		
Variables	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Sex (male)	1.41	0.90–2.18	0.13			
Age (> 69 year)[a]	1.27	0.84–1.94	0.26			
BMI (≤ 22.3 kg/m^2)[b]	1.83	1.18–2.82	0.007*	1.38	0.88–2.15	0.16
Comorbidities affecting PINI[c] (present)	1.65	0.93–2.96	0.09			
Preoperative tumor-related complications[d] (present)	1.72	0.83–3.57	0.14			
Histological type (undifferentiated)	3.07	1.80–5.23	< 0.001*	2.82	1.63–4.87	< 0.001*
Location (rectum)	1.43	0.92–2.22	0.11			
T classification (pT3/4)	4.34	2.30–8.17	< 0.001*	1.10	0.51–2.39	0.80
Venous invasion (present)	3.04	1.94–4.79	< 0.001*	1.51	0.90–2.52	0.12
Lymphatic invasion (present)	3.67	1.99–6.74	< 0.001*	1.60	0.78–3.26	0.20
Lymph node metastasis (present)	2.94	1.90–4.55	< 0.001*	1.12	0.69–1.83	0.65
Distant metastasis (present)	8.49	5.52–12.94	< 0.001*	5.66	3.49–9.19	< 0.001*
Preoperative PINI (≤ 3.376)[e]	3.92	2.43–6.33	< 0.001*	2.51	1.50–4.18	< 0.001*

Abbreviations: BMI, Body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; PINI, prognostic immune nutritional index.
[a]The median age at surgery was 69 years in this cohort.
[b]The median BMI at surgery was 22.3 kg/m^2 in this cohort.
[c]The comorbidities affecting PINI consisted of collagen diseases, chronic renal failure, and liver cirrhosis.
[d]The preoperative tumor-related acute complications consisted of bowel obstruction, perforation, and intra-abdominal abscess.
[e]The cutoff for preoperative PINI was set at the median value of this cohort.
*$p < 0.05$.

TABLE 4 | Multivariate analysis for predictors of surgical site infection in patients with CRC.

	Univariate			Multivariate		
Variables	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Sex (male)	0.98	0.62–1.58	0.95			
Age (> 69 year)[a]	1.10	0.69–1.75	0.70			
Obesity[b] (present)	0.92	0.51–1.64	0.77			
Chronic corticosteroid therapy (yes)	0.87	0.25–3.05	0.83			
Diabetes mellitus (present)	0.92	0.51–1.64	0.77			
Comorbidities affecting PINI[c] (present)	1.03	0.48–2.20	0.95			
Preoperative tumor-related complications[d] (present)	2.95	1.35–6.45	0.007*	1.82	0.79–4.21	0.16
Histological type (undifferentiated)	0.85	0.36–1.96	0.70			
Location (rectum)	0.98	0.60–1.62	0.95			
T classification (pT3/4)	1.93	1.13–3.31	0.02*	1.31	0.72–2.39	0.37
Venous invasion (present)	1.34	0.84–2.14	0.22			
Lymphatic invasion (present)	1.40	0.84–2.34	0.20			
Lymph node metastasis (present)	1.09	0.68–1.75	0.72			
Distant metastasis (present)	0.84	0.43–1.63	0.60			
Preoperative PINI (≤ 3.376)[e]	2.25	1.38–3.67	0.001*	1.63	0.96–2.78	0.07
Open versus laparoscopic surgery (open)	2.27	1.40–3.67	< 0.001*	1.13	0.60–2.15	0.70
Operation time (> median)	1.68	1.05–2.70	0.03*	1.52	0.90–2.55	0.11
Blood loss (> median)	3.14	1.88–5.23	< 0.001*	2.16	1.14–4.01	0.02*

Abbreviations: CI, confidence interval; CRC, colorectal cancer; OR, odds ratio; PINI, prognostic immune nutritional index.
[a]The median age at surgery was 69 years in this cohort.
[b]Obesity was defined as a Body Mass Index of ≥ 25 kg/m^2.
[c]The comorbidities affecting PINI consisted of collagen diseases, chronic renal failure, and liver cirrhosis.
[d]The preoperative tumor-related acute complications consisted of bowel obstruction, perforation, and intra-abdominal abscess.
[e]The cutoff for preoperative PINI was set at the median value of this cohort.
*$p < 0.05$.

with a decreased preoperative PINI had significantly poorer DFS (log-rank test, $p = 0.01$) (Figure 2A) and OS (log-rank test, $p < 0.001$) (Figure 2B).

Based on Cox univariate analysis, a low preoperative PINI status was significantly associated with poor DFS. Multivariate analysis confirmed a low preoperative PINI as an independent prognostic factor for DFS (HR: 2.03, 95% CI: 1.24–3.32, $p = 0.005$) (Table 6). The analysis also showed that a low preoperative PINI was significantly associated with poor OS. Multivariate analysis identified a high preoperative PINI as an independent prognostic factor for OS (HR: 3.64, 95% CI: 1.61–8.19, $p = 0.002$) (Table 7).

Furthermore, when patients were stratified by receipt of adjuvant chemotherapy, time-to-event analyses in each subgroup revealed that a low preoperative PINI was consistently associated with a trend toward poorer DFS (Figure S1A,B). In addition, OS was significantly worse in patients with a low PINI, regardless of adjuvant chemotherapy status (Figure S1C,D).

3.7 | PSM Analysis Validated the Impact of Decreased Preoperative PINI on Prognosis of CRC

PSM analysis is a widely recognized statistical method used to address selection bias and differences in patient characteristics, thereby enhancing the validity of nonrandomized observational studies [20]. To evaluate the robustness of preoperative PINI as a prognostic biomarker in patients with colorectal cancer, we performed a PSM analysis. A total of 298 patients were matched, with 149 patients each in the high and low preoperative PINI groups (Figure S2). The matched cohort consisted of 178 men (59.7%) and 120 women (40.3%), with a median age of 70 years (range: 31–90 years) and a median BMI of 22.6 kg/m^2 (range: 14.7–34.3 kg/m^2). The differences in patient characteristics between the high and low preoperative PINI groups observed before PSM analysis were no longer present after matching (Tables S4A and S4B). Kaplan–Meier survival curve analysis in the PSM cohort demonstrated that patients with a low preoperative PINI had significantly worse DFS (log-rank test, $p = 0.01$)

TABLE 5 | Multivariate analysis for predictors of total infection in patients with CRC.

	Univariate			Multivariate		
Variables	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Sex (male)	1.18	0.76–1.82	0.47			
Age (> 69 year)[a]	1.14	0.74–1.76	0.54			
Obesity[b] (present)	0.72	0.41–1.27	0.26			
Chronic corticosteroid therapy (yes)	0.96	0.31–2.95	0.94			
Diabetes mellitus (present)	0.99	0.58–1.67	0.96			
Comorbidities affecting PINI[c] (present)	1.30	0.66–2.55	0.44			
Preoperative tumor-related complications[d] (present)	3.47	1.64–7.37	0.001*	1.80	0.81–4.01	0.15
Histological type (undifferentiated)	0.89	0.41–1.91	0.76			
Location (rectum)	1.01	0.64–1.60	0.97			
T classification (pT3/4)	2.22	1.34–3.68	0.002*	1.38	0.79–2.41	0.27
Venous invasion (present)	1.45	0.94–2.24	0.09			
Lymphatic invasion (present)	1.47	0.92–2.37	0.11			
Lymph node metastasis (present)	1.14	0.74–1.77	0.55			
Distant metastasis (present)	1.02	0.57–1.84	0.94			
Preoperative PINI (≤ 3.376)[e]	2.72	1.72–4.29	< 0.001*	1.82	1.11–3.00	0.02*
Open versus laparoscopic surgery (open)	2.99	1.90–4.71	< 0.001*	1.33	0.74–2.38	0.33
Operation time (> median)	1.34	0.87–2.07	0.18			
Blood loss (> median)	3.44	2.14–5.52	< 0.001*	2.34	1.33–4.09	0.003*

Abbreviations: CI, confidence interval; CRC, colorectal cancer; OR, odds ratio; PINI, prognostic immune nutritional index.
[a]The median age at surgery was 69 years in this cohort.
[b]Obesity was defined as a Body Mass Index of ≥ 25 kg/m^2.
[c]The comorbidities affecting PINI consisted of collagen diseases, chronic renal failure, and liver cirrhosis.
[d]The preoperative tumor-related acute complications consisted of bowel obstruction, perforation, and intra-abdominal abscess.
[e]The cutoff for preoperative PINI was set at the median value of this cohort.
*$p < 0.05$.

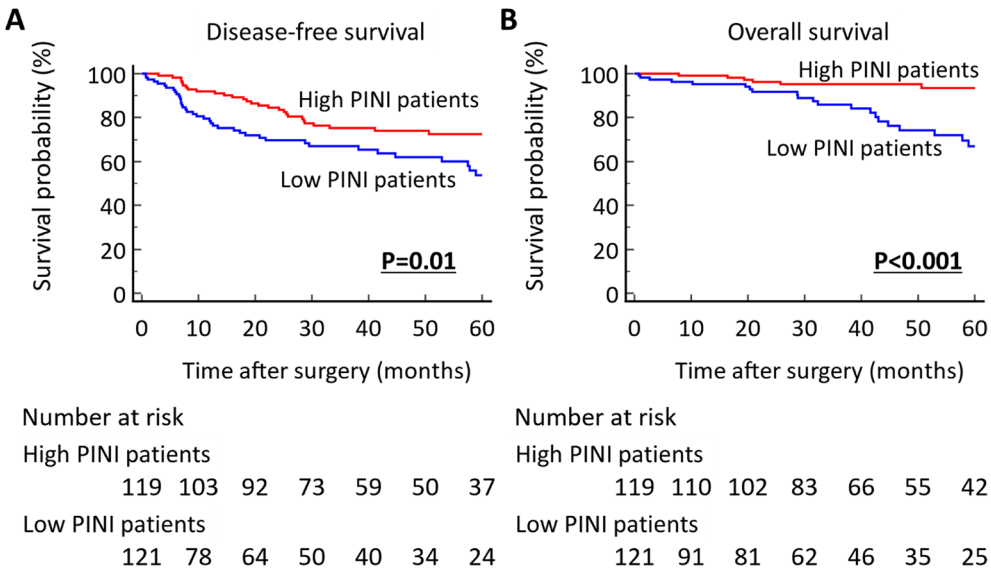

FIGURE 2 | Kaplan–Meier analysis of DFS and OS in patients with stage III and high-risk stage II colorectal cancer stratified by preoperative PINI. Patients with a low preoperative PINI had significantly lower (A) DFS and (B) OS than those with a high preoperative PINI ($p = 0.01$ and $p < 0.001$, respectively; log-rank test). DFS, disease-free survival; OS, overall survival; PINI, prognostic immune nutritional index.

TABLE 6 | Multivariate analysis for predictors of disease-free survival in patients with stage III and high-risk stage II CRC.

	Univariate			Multivariate		
Variables	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Sex (male)	1.21	0.74–1.97	0.45			
Age (> 69 year)[a]	1.03	0.64–1.67	0.89			
BMI (≤ 22.1 kg/m^2)[b]	1.40	0.86–2.27	0.17			
Comorbidities affecting PINI[c] (present)	1.27	0.69–2.65	0.53			
Preoperative tumor-related complications[d] (present)	1.0	0.43–2.31	1.0			
Histological type (undifferentiated)	1.12	0.56–2.27	0.74			
Location (rectum)	2.11	1.29–3.44	0.003*	2.07	1.26–3.41	0.004*
T classification (pT3/4)	3.78	0.93–5.46	0.06			
Venous invasion (present)	2.40	1.38–4.17	0.002*	2.15	1.23–3.76	0.007*
Lymphatic invasion (present)	1.40	0.64–3.06	0.40			
Lymph node metastasis (present)	1.68	1.01–2.78	0.05*	1.87	1.12–3.11	0.02*
Adjuvant chemotherapy (yes)	1.09	0.67–1.76	0.73			
Preoperative PINI (≤ 3.307)[e]	1.86	1.14–3.02	0.01*	2.03	1.24–3.32	0.005*

Abbreviations: BMI, Body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; PINI, prognostic immune nutritional index.
[a]The median age at surgery was 69 years in this cohort.
[b]The median BMI at surgery was 22.1 kg/m^2 in this cohort.
[c]The comorbidities affecting PINI consisted of collagen diseases, chronic renal failure, and liver cirrhosis.
[d]The preoperative tumor-related acute complications consisted of bowel obstruction, perforation, and intra-abdominal abscess.
[e]The cutoff for preoperative PINI was set at the median value of this cohort.
*$p < 0.05$.

TABLE 7 | Multivariate analysis for predictors of overall survival in patients with stage III and high-risk stage II CRC.

	Univariate			Multivariate		
Variables	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Sex (male)	1.19	0.57–2.49	0.63			
Age (> 69 year)[a]	1.37	0.67–2.80	0.39			
BMI (≤ 22.1 kg/m^2)[b]	1.55	0.74–3.24	0.25			
Comorbidities affecting PINI[c] (present)	1.74	0.66–4.60	0.26			
Preoperative tumor-related complications[d] (present)	1.14	0.34–3.77	0.83			
Histological type (undifferentiated)	2.39	1.02–5.59	0.05*	2.16	0.92–5.07	0.08
Location (rectum)	1.22	0.56–2.69	0.62			
T classification (pT3/4)	—	—	0.96			
Venous invasion (present)	2.12	0.96–4.64	0.06			
Lymphatic invasion (present)	1.16	0.35–3.84	0.81			
Lymph node metastasis (present)	1.41	0.66–2.98	0.37			
Adjuvant chemotherapy (yes)	0.62	0.30–1.29	0.20			
Preoperative PINI (≤ 3.307)[e]	3.76	1.67–8.47	0.001*	3.64	1.61–8.19	0.002*

Abbreviations: BMI, Body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; PINI, prognostic immune nutritional index.
[a]The median age at surgery was 69 years in this cohort.
[b]The median BMI at surgery was 22.1 kg/m^2 in this cohort.
[c]The comorbidities affecting PINI consisted of collagen diseases, chronic renal failure, and liver cirrhosis.
[d]The preoperative tumor-related acute complications consisted of bowel obstruction, perforation, and intra-abdominal abscess.
[e]The cutoff for preoperative PINI was set at the median value of this cohort.
*$p < 0.05$.

(Figure S3A). Similarly, OS was also significantly worse in this group (log-rank test, $p = 0.02$) (Figure S3B).

3.8 | Prognostic Utility of Preoperative PINI Was Demonstrated Using ROC-Derived Cut-Off Values

Receiver operating characteristic (ROC) curve analyses using Youden's index were performed to identify optimal cut-off values of the PINI for various clinical outcomes, such as survival and postoperative infectious complications. For DFS, the optimal PINI cut-off was determined to be 3.160, which allowed discrimination between patients with poor and favorable prognosis (AUC: 0.627, sensitivity: 50.0%, specificity: 71.4%). Similarly, the cut-off value for OS was 3.140 (AUC: 0.688, sensitivity: 59.8%, specificity: 70.3%). For short-term outcomes, the optimal cut-offs were 3.370 for SSI (AUC: 0.610, sensitivity: 66.3%, specificity: 54.6%) and 3.431 for total infection (AUC: 0.635, sensitivity: 51.2%, specificity: 73.6%) (Figure S4).

Using these cut-off values, we performed multivariate analyses to assess the prognostic significance of preoperative PINI. A low preoperative PINI was identified as an independent predictor of both poor DFS (HR: 2.74, 95% CI: 1.75–4.29, $p < 0.001$) and OS (HR: 2.36, 95% CI: 1.48–3.78, $p < 0.001$) (Tables S5A and S5B). Furthermore, a low PINI showed a trend toward increased risk of SSI (HR: 1.69, 95% CI: 0.99–2.89, $p = 0.06$) and was significantly associated with total infection (HR: 1.95, 95% CI: 1.16–3.26, $p = 0.01$) (Tables S6A and S6B). These findings were largely consistent with those obtained using the median PINI value as the cut-off.

4 | Discussion

Systemic inflammation is a well-recognized hallmark of cancer, closely linked to both its etiology and progression. Various inflammatory biomarkers, such as the C-reactive protein concentration [21] and monocyte count [22], have been extensively studied, with several reports highlighting their strong prognostic value in patients with cancer. Additionally, novel prognostic indices that incorporate multiple inflammatory markers have been developed, offering further insight into patient outcomes [11, 23]. Preoperative malnutrition is also a critically important concern in cancer care. Patients with CRC, in particular, exhibit the highest prevalence of malnutrition among cancer types, largely because of localized effects on intestinal function resulting from obstruction or malabsorption [24]. Beyond these structural causes, metabolic abnormalities driven by systemic inflammation can lead to anorexia, weight loss, and ultimately cachexia syndrome, further worsening the prognosis [9]. Therefore, in patients with CRC, inflammation and nutrition are key factors of clinical significance. In response, indices such as the modified Glasgow prognostic score, which reflect both the inflammatory and nutritional status, have gained attention as potential biomarkers for predicting CRC outcomes [25]. Moreover, therapeutic strategies aimed at improving body composition and managing inflammation in patients with gastrointestinal cancers are also receiving increasing recognition [26].

The PINI is a recently reported novel indicator composed of albumin and monocytes [16]. Albumin, produced in the liver, accounts for approximately 60% of serum proteins [27]. It has long been used by clinicians as a reliable marker for assessing the nutritional status. However, recent studies suggest that albumin levels are also significantly influenced by inflammation [15]. Inflammatory processes are believed to increase capillary permeability, causing albumin to redistribute and resulting in hypoalbuminemia [28]. In patients with cancer, hypoalbuminemia is therefore thought to reflect both malnutrition and heightened inflammatory activity. It is also associated with declines in muscle mass and cognitive and immune function, reduced quality of life, and ultimately, shortened OS [29, 30]. Monocytes, a subset of circulating blood cells derived from bone marrow progenitor cells, play a pivotal role in the tumor microenvironment by influencing cancer progression and modulating immune responses [31]. Attracted to tumor sites by tumor-derived signals, they differentiate into tumor-associated macrophages, which can adopt dual phenotypes: antitumor M1 and protumor M2. In many malignancies, tumor-associated macrophages are predominantly of the M2 phenotype, known to promote angiogenesis, immune suppression, and tumor progression [22]. Recently, the monocyte count has also been identified as significantly associated with the oncological prognosis in solid tumors [22]. By incorporating both albumin and monocytes, the PINI reflects the host's condition with respect to inflammation and nutrition.

Several studies have verified the prognostic predictive ability of the PINI in various types of cancer, including CRC [16, 17]. However, to the best of our knowledge, detailed investigations into the prognostic value of the preoperative PINI in CRC and its association with postoperative infectious complications have been lacking. Therefore, this study explored the prognostic value of the preoperative PINI in predicting oncological outcomes in patients with CRC from multiple perspectives and conducted a detailed analysis of its association with postoperative infectious complications. Our results demonstrated that a low preoperative PINI was significantly associated with clinicopathological factors indicative of disease progression and that patients with CRC and a low preoperative PINI had poorer DFS and OS than those with a high preoperative PINI. Furthermore, a low preoperative PINI was identified as an independent prognostic factor for both DFS and OS. These findings are largely consistent with previous studies [16].

Our study also highlighted several new insights. First, we identified a relationship between the preoperative PINI and postoperative infectious complications, revealing that the preoperative PINI is a potential predictor of SSI and total infection, encompassing all types of postoperative infectious complications. Second, despite the minimal difference in PINI values between stage II and stage III patients, subgroup analysis of patients with stage III and high-risk stage II CRC showed that those with a low preoperative PINI had poorer DFS and OS than those with a high preoperative PINI. This trend remained consistent even when stratified by the receipt of adjuvant therapy. Furthermore, a low preoperative PINI was confirmed as an independent prognostic factor for both DFS and OS in this group. Third, we performed a PSM analysis to address potential selection bias due to patient characteristics. Even within this matched cohort,

patients with CRC and a low preoperative PINI exhibited significantly worse DFS and OS than those with a high preoperative PINI.

Recently, increasing attention has been directed toward the association between postoperative infectious complications and oncological outcomes in gastrointestinal cancers. Matsuda et al. [7] conducted a retrospective analysis of 1817 patients with stage I–III CRC, demonstrating a link between postoperative infections and worse oncological outcomes. Similarly, a meta-analysis by Lawler et al. [32], which included 43 studies and 154 981 patients with CRC, identified a significant association between SSI and adverse oncological outcomes. These findings underscore the growing importance of vigilant management of postoperative infectious complications, including SSI, as a means to potentially improve the prognosis of patients with CRC. Our study demonstrated that the preoperative PINI serves as a valuable biomarker for predicting oncological outcomes in CRC and is significantly associated with the occurrence of postoperative infectious complications. Given the critical impact of these complications in CRC, stratifying patients based on the preoperative PINI measurements offers the potential to improve oncological outcomes beyond the capabilities of traditional prognostic markers.

Currently, adjuvant chemotherapy is recommended after surgery for patients diagnosed with pathological stage III or high-risk stage II CRC, with the goal of minimizing the risk of local or metastatic recurrence [33]. However, studies report that only approximately 20% of patients with stage III CRC derive a benefit from adjuvant chemotherapy, indicating that a considerable number of patients undergo unnecessary treatment and are exposed to the risk of adverse effects [34]. This highlights the urgent need for more accurate methods to identify patients at high risk of recurrence, which continues to drive extensive research in the field. Our study demonstrated that preoperative PINI values showed no substantial difference between patients with stage II and those with stage III colorectal cancer. Nevertheless, when the analysis was limited to patients with stage III and high-risk stage II CRC, a low preoperative PINI was significantly associated with poor oncological outcomes. This unfavorable prognostic trend for the low PINI group persisted even after stratifying patients according to whether they received adjuvant chemotherapy. Taken together, these findings suggest that preoperative PINI may serve as a stage-independent prognostic marker, as it captures host-related factors not adequately reflected by conventional staging systems. While the necessity of perioperative interventions for such subgroups remains under debate, the preoperative PINI may serve as a valuable tool to pinpoint patients who would truly benefit from intensified therapeutic strategies. Furthermore, we believe that integrating host-related biomarkers—such as the preoperative PINI, which reflects systemic inflammation and the nutritional status—with tumor-derived biomarkers, such as liquid biopsy for the detection of minimal residual disease (which has recently gained considerable attention), may support the development of a more reliable and comprehensive prognostic stratification system [35].

There were several limitations to the present study. First, it was a retrospective observational study and may be subject to bias. Second, all patients were from a single institution in Japan, so the results may not be universally generalizable. Third, some of the individual infections included in the definition of total infection had very low incidence rates, leaving uncertainty regarding their true clinical relevance. Fourth, the optimal cutoff threshold for the preoperative PINI remains unclear. In this study, we used the median value as the cutoff and suggested the predictive utility of the preoperative PINI for oncological outcomes and postoperative infectious complications. We also conducted additional analyses using outcome-specific cutoff values derived from ROC curve analyses, which yielded largely consistent results. Nevertheless, variability was observed between the median value and the ROC-derived cutoff values for each outcome, and it remains uncertain which threshold is most appropriate or whether any of them can be reliably applied to broader populations. Moreover, as ROC-derived thresholds are inherently optimized for the dataset from which they are generated, they are susceptible to overfitting. Although this study was conducted at a single institution, such thresholds ideally require validation in independent external cohorts. To address these limitations, larger, multicenter prospective controlled trials should be conducted across various countries and regions.

In conclusion, our study highlights the clinical utility of the preoperative PINI as a predictive biomarker for both postoperative infectious risk and oncological outcomes in patients with CRC. Evaluating the preoperative PINI may assist physicians in designing more effective perioperative management plans and enhancing postoperative oncological follow-up strategies for patients with CRC.

Author Contributions

Shinji Yamashita: conceptualization, methodology, software, data curation, investigation, validation, formal analysis, visualization, writing – original draft, resources. **Yoshinaga Okugawa:** writing – review and editing, project administration, supervision, validation, formal analysis, visualization, methodology. **Hiroki Imaoka:** data curation, investigation. **Tadanobu Shimura:** data curation, investigation. **Takahito Kitajima:** investigation, data curation. **Mikio Kawamura:** investigation, data curation. **Yoshiki Okita:** investigation, data curation. **Masaki Ohi:** investigation, data curation. **Minako Kobayashi:** investigation, data curation. **Yuji Toiyama:** writing – review and editing, project administration, supervision.

Acknowledgments

The authors thank the medical and co-medical staff at Mie University Hospital for their cooperation. The authors also thank Angela Morben, DVM, ELS, from Edanz (https://jp.edanz.com/ac), for editing a draft of this manuscript.

Ethics Statement

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. This retrospective study was approved by the Review Board of Mie University Hospital (IRB number: H2025-062).

Consent

All patients provided written informed consent.

Conflicts of Interest

Yuji Toiyama is an editorial board member of *Annals of Gastroenterological Surgery*. The other authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Kaplan–Meier analysis of DFS and OS stratified by preoperative PINI, with patients categorized according to receipt of adjuvant chemotherapy. (A, B) Regardless of adjuvant chemotherapy status, patients with a low preoperative PINI showed a trend toward lower DFS ($p = 0.08$ and $p = 0.05$, respectively; log-rank test). (C, D) In addition, OS was significantly lower in patients with a low preoperative PINI ($p = 0.05$ and $p = 0.01$, respectively; log-rank test). DFS, disease-free survival; OS, overall survival; PINI, prognostic immune nutritional index. **Figure S2:** Flow diagram of patient selection and PSM. A total of 647 patients with colorectal cancer who underwent primary tumor resection between January 2006 and December 2015 were initially identified. After excluding 160 patients with incomplete laboratory data, 487 patients were enrolled and stratified into high PINI ($n = 243$) and low PINI ($n = 244$) groups. PSM was then performed, resulting in 149 matched patients in each group. PINI, prognostic immune nutritional index; PSM, propensity score matching. **Figure S3:** Kaplan–Meier analysis of DFS and OS in the post-PSM cohort stratified by preoperative PINI. Patients with a low preoperative PINI had significantly lower (A) DFS and (B) OS than those with a high preoperative PINI ($p = 0.01$ and $p = 0.02$, respectively; log-rank test). DFS, disease-free survival; OS, overall survival; PINI, prognostic immune nutritional index. **Figure S4:** ROC curve analyses for the prognostic value of preoperative PINI. ROC curves were generated to identify optimal cut-off values of preoperative PINI for each outcome. The optimal cut-off was 3.160 for disease-free survival (AUC = 0.627), 3.140 for overall survival (AUC = 0.688), 3.370 for surgical site infection (AUC = 0.610), and 3.431 for total infection (AUC = 0.635). PINI, prognostic immune nutritional index; ROC, receiver operating characteristic. **Table S1:** Association between preoperative PINI and UICC Stage Classification. **Table S2A:** Infectious complications after surgery and preoperative PINI in patients with CRC. **Table S2B:** Subcategorized total Infections and preoperative PINI in patients with CRC. **Table S3:** Clinicopathological variables and preoperative PINI in patients with stage III and high-risk stage II CRC. **Table S4A:** Clinicopathological variables by level of preoperative PINI in patients with CRC. **Table S4B:** Clinicopathological variables by level of preoperative PINI in patients with CRC using propensity score matching analysis for survival. **Table S5A:** Multivariate analysis for predictors of disease-free survival in patients with CRC using PINI cut-off determined by ROC curve analysis. **Table S5B:** Multivariate analysis for predictors of overall survival in patients with CRC using PINI cut-off determined by ROC curve analysis. **Table S6A:** Multivariate analysis for predictors of surgical site infection in patients with CRC using PINI cut-off determined by ROC curve analysis. **Table S6B:** Multivariate analysis for predictors of total infection in patients with CRC using PINI cut-off determined by ROC curve analysis.