

Combining Preoperative and Postoperative Prognostic Nutritional Index as an Improved Prognostic Factor for Overall Survival in Patients with Colorectal Cancer

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Purpose: While preoperative prognostic nutritional index (PNI) is a well-established prognostic marker in colorectal cancer (CRC), and postoperative PNI has gained attention, their combined prognostic value remains largely unexplored.

Patients and Methods: We analyzed patients who underwent curative surgery for stage I–III CRC between March 2004 and February 2014. The pre- and postoperative PNI, measured within 1 month before and 3–8 weeks after surgery, were combined to create “change-PNI”. The Cox proportional hazards model was used to assess the prognostic significance, and the C-index was compared across values.

Results: The optimal pre- and postoperative PNI cutoff values predicting 5-year overall survival (OS) were 48.05 and 43.65, respectively. The patients were categorized into four groups based on their pre- and postoperative values: pre-low + post-low (G1), pre-low + post-high (G2), pre-high + post-low (G3), and pre-high + post-high (G4). A multivariable Cox proportional hazards model demonstrated that patients in G2, G3, and G4 had significantly lower mortality risks than those in G1 (HR [95% CI] vs G1: G2, 0.341 [0.186–0.625]; G3, 0.457 [0.222–0.941]; G4, 0.222 [0.123–0.401]). The C-index of change-PNI (0.671, 95% CI 0.617–0.720) was superior to that of preoperative PNI (0.609, 95% CI 0.563–0.654) (bootstrap mean difference: 0.062, 95% CI 0.029–0.099) and postoperative PNI (0.622, 95% CI 0.581–0.664) (bootstrap mean difference: 0.049, 95% CI 0.014–0.085).

Conclusion: Change-PNI serves as a more effective independent immuno-nutritional marker than pre- or postoperative PNI in predicting OS in patients undergoing surgery for non-metastatic colorectal cancer.

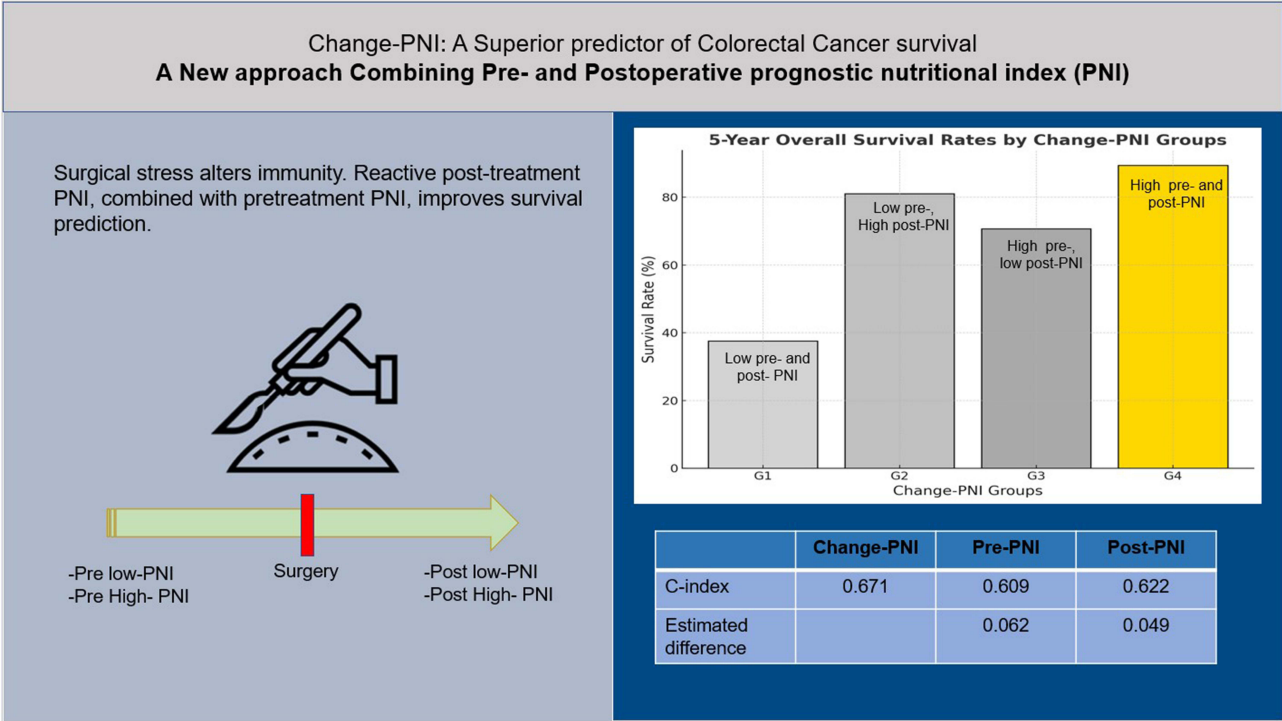
Keywords: colorectal cancer, prognostic nutritional index, postoperative outcomes, overall survival

Introduction

The accurate prediction of cancer patient prognosis plays a crucial role in developing treatment strategies, evaluating responses, and conducting consultations with patients and their families.¹ For colorectal cancer (CRC), tumor-node-metastasis (TNM) staging based on clinical and pathological evaluations is widely used as the standard for prognostic assessment.² However, this tumor-based prediction method has limitations in accurately predicting disease progression. For example, a survival paradox can occur in which some early stage III patients may exhibit better survival outcomes than those with advanced stage II disease.³ To overcome these limitations, efforts are underway to modify the existing prediction models and identify new prognostic factors.⁴

Many investigators have identified the prognostic value of nutritional and inflammatory host-related biomarkers in patients with CRC, including the Glasgow Prognostic Score (GPS), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and prognostic nutritional index (PNI).^{5,6} The PNI, calculated from the lymphocyte count and serum albumin level, reflects a patient’s nutritional and immune status. These immuno-nutritional markers are

Graphical Abstract



considered important preoperative prognostic factors associated with delayed wound healing, muscle weakness, and immune dysfunction. Furthermore, they are linked to cancer progression, and several studies have identified the molecular pathways involved in cancer-related inflammation.^{7,8}

Significant immunological changes were observed in these patients during the perioperative period. An immunosuppressive state in response to acute inflammation and surgical stress can promote micrometastases and negatively affect oncological outcomes.⁹ The postoperative immune-nutritional status, such as PNI levels, has gained attention as a key determinant of prognosis in patients with cancer,^{10,11} raising the question of whether postoperative status affects survival independently or merely reflects preoperative conditions.

However, few studies have compared the importance of pre- versus postoperative immune-nutritional status, as most have focused on the preoperative period alone.^{11,12} This study investigated the prognostic impact of a combined pre- and postoperative PNI and compared its predictive efficacy with either one alone.

Materials and Methods

Study Patients

This retrospective cohort study examined patients who underwent curative resection for stage I–III colorectal adenocarcinoma and had available records of both pre- and postoperative PNI at Gangnam Severance Hospital, Yonsei University College of Medicine, between March 2004 and February 2014. We initially selected 1697 patients who underwent surgical resection of colorectal tumors during this period. Patients were excluded if they had histologically defined neuroendocrine or gastrointestinal stromal tumors (n = 112); appendiceal or anal cancers (n = 19); CRC tumors stage 0, IV, or missing stage information (n = 223); hereditary nonpolyposis CRC or familial adenomatous polyposis-associated cancers (n = 6); preoperative treatment (n = 112); emergent surgery (n = 4); inflammatory bowel disease-associated cancers (n = 2); of double primary or synchronous cancers (n = 20). Additionally, patients without available

PNI data or blood test results within one month prior to surgery ($n = 52$) and those without PNI data collected between 3 and 8 weeks after surgery ($n = 482$) were excluded. Finally, 665 patients were included in this study. Postoperative PNI was assessed between 3 and 8 weeks after surgery based on our institution's standard protocol. Most patients are discharged within 7 days and return for follow-up at 3 weeks for pathology review and treatment planning. Adjuvant chemotherapy typically begins between 6 and 8 weeks postoperatively. To minimize the influence of surgery and chemotherapy, we set 8 weeks as the upper limit for postoperative PNI measurement. Details of the inclusion process are presented in [Supplementary Figure S1](#). The study protocol followed the ethical standards of the institutional and national research committees as well as the 1964 Helsinki Declaration and its later amendments.

Follow-Up

All patients underwent surgical resection and were followed up every 3–6 months to monitor for tumor recurrence. Blood tests were conducted at each visit and chest and abdominopelvic computed tomography scans were performed every 6–12 months. Adjuvant chemotherapy was primarily recommended for patients with high-risk stage II or stage III CRC, in accordance with the National Comprehensive Cancer Network guidelines.¹³ Colonoscopies were generally scheduled for patients at 1, 3, and 5 years postoperatively.

Determination of Cutoff Values for Pre- and Postoperative PNI, and Grouping Based on Combined PNI

The PNI value was calculated using the following formula: $10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{total peripheral lymphocyte count (cells/mm}^3\text{)}$. To establish optimal cutoff values for both pre- and postoperative PNI, we employed the X-tile program, an open-source tool specifically designed for cutoff selection in biomarker studies. Overall survival (OS) was used as the primary outcome to determine the cutoff values. The X-tile software evaluates various ways to divide the data into two groups (low vs high PNI) by analyzing their relationship with survival outcomes. Log rank tests were used to compare the survival curves between the groups and identify significant differences in survival. Additionally, chi-squared (χ^2) statistics were used to assess how effectively each cutoff separated patients into distinct prognostic groups, determining the division with the strongest correlation to survival differences. This dual analysis yielded the most accurate high and low PNI cutoff values for both the pre- and postoperative periods, ensuring precise prognostic stratification. The patients were then categorized into four groups (change-PNI) based on their preoperative (pre-PNI) and postoperative PNI (post-PNI) values: G1: pre-low + post-low; G2: pre-low + post-high; G3: pre-high + post-low; and G4: pre-high + post-high.

Statistical Analyses

All statistical analyses were performed using R version 4.1.0 (R-project, Institute for Statistics and Mathematics, Vienna, Austria). Categorical variables were compared using a chi-squared test or Fisher's exact test for two groups, and ANOVA was used for comparisons between multiple groups. A Mann–Whitney *U*-test was used for continuous variables for the two groups, while a Kruskal–Wallis test was used for comparisons across multiple groups. OS was defined as the time from the date of surgery to death from any cause. Patients with OS periods longer than 5 years were censored.

Multivariate Cox regression analysis was conducted to identify independent risk factors for OS. Owing to the potential multicollinearity between pre-, post-, and change-PNI, we excluded pre- and post-PNI from the multivariable model and retained change-PNI as the representative variable. Additionally, stages I and II were grouped and compared against stage III due to the relatively small number of stage I patients and the low number of events (deaths) in that subgroup, which limited statistical power for separate analysis. The Kaplan–Meier method with the Log rank test was used to compare OS between the patient groups. The concordance index (C-index) of pre-, post-, and change-PNI for OS prediction was compared using bootstrapped differences to evaluate the relative predictive performance of each variable. Statistical significance was defined as $P < 0.05$. However, for pairwise comparisons, the Bonferroni correction was applied, adjusting the significance threshold to $P < 0.0083$ ($0.05/6$) to account for multiple testing.

Results

The cutoff values for pre- and post-PNI were determined to be 48.05 and 43.65, respectively ([Supplementary Figure S2](#)). Based on these values, 665 patients were categorized into the following change-PNI groups: 37 (5.6%) in G1, 159 (23.9%) in G2, 41 (6.2%) in G3, and 428 (64.3%) in G4.

Patient Characteristics According to Change-PNI Group

Patient characteristics were compared between the four change-PNI groups ([Table 1](#), [Supplementary Table S1](#)). The mean age varied significantly between the groups, with patients in G1 being the oldest (71.9 years) and those in G4 being the youngest (60.0 years). G1 had the highest percentage of American Society of Anesthesiologists Physical Status Classification (ASA) III and IV patients (13.5%), whereas G4 had the lowest percentage (5.1%). Regarding tumor location, G3 had the highest proportion of rectal cancer cases (70.7%), whereas G1 (83.8%) and G2 (87.4%) were predominantly colon cancer cases. Tumor size was significantly larger in G2 (66.7% of tumors being ≥ 5 cm) than in G3 (43.9%) and G4 (34.3%). Complications were less frequent in patients in the G2 (18.2%) and G4 (18.0%) groups than in

Table 1 Patient Characteristics According to Change-PNI Groups

Variables	Categorization	G1 Group (n = 37)	G2 Group (n = 159)	G3 Group (n = 41)	G4 Group (n = 428)	P
		n (%)	n (%)	n (%)	n (%)	
Sex	Female	8 (21.6)	72 (45.3)	14 (34.1)	169 (39.5)	0.054
	Male	29 (78.4)	87 (54.7)	27 (65.9)	259 (60.5)	
Age (years)	Mean (SD)	71.9 (10.1)	62.6 (11.3)	65.5 (11.6)	60.0 (10.2)	<0.001
BMI (kg/m ²)	Mean (SD)	22.7 (4.1)	22.8 (2.7)	23.9 (3.5)	23.7 (2.9)	0.106
ASA grade	I	8 (21.6)	69 (43.4)	18 (43.9)	207 (48.4)	0.068
	II	14 (37.8)	47 (29.6)	12 (29.3)	137 (32.0)	
	III & IV	5 (13.5)	11 (6.9)	4 (9.8)	22 (5.1)	
	Unknown	10 (27.0)	32 (20.1)	7 (17.1)	62 (14.5)	
CEA (ng/mL)	< 5	17 (45.9)	98 (61.6)	27 (65.9)	289 (67.5)	0.146
	≥ 5	19 (51.4)	57 (35.8)	13 (31.7)	124 (29.0)	
	Unknown	1 (2.7)	4 (2.5)	1 (2.4)	15 (3.5)	
Tumor location	Colon	31 (83.8)	139 (87.4)	12 (29.3)	283 (66.1)	<0.001
	Rectum	6 (16.2)	20 (12.6)	29 (70.7)	145 (33.9)	
Tumor size (cm)	< 5	14 (37.8)	53 (33.3)	23 (56.1)	281 (65.7)	<0.001
	≥ 5	23 (62.2)	106 (66.7)	18 (43.9)	147 (34.3)	
Histologic grade	G1 & G2	31 (83.8)	139 (87.4)	12 (29.3)	283 (66.1)	<0.001
	G3 & MC & SRC	6 (16.2)	20 (12.6)	29 (70.7)	145 (33.9)	
LVI	Absent	20 (54.1)	108 (67.9)	27 (65.9)	276 (64.5)	0.692
	Present	11 (29.7)	38 (23.9)	11 (26.8)	105 (24.5)	
	Unknown	6 (16.2)	13 (8.2)	3 (7.3)	47 (11.0)	
Stage	I&II	14 (37.8)	78 (49.1)	22 (53.7)	186 (43.5)	0.324
	III	23 (62.2)	81 (50.9)	19 (46.3)	242 (56.5)	
Complications	No	15 (40.5)	130 (81.8)	13 (31.7)	351 (82.0)	<0.001
	Yes	22 (59.5)	29 (18.2)	28 (68.3)	77 (18.0)	
Chemotherapy	No	22 (59.5)	21 (13.2)	19 (46.3)	48 (11.2)	<0.001
	Yes	15 (40.5)	138 (86.8)	22 (53.7)	380 (88.8)	
Pre- PNI	Mean (SD)	41.0 (5.0)	43.9 (3.7)	53.1 (4.7)	54.2 (4.1)	<0.001
Post- PNI	Mean (SD)	38.4 (4.4)	51.0 (4.1)	38.3 (4.5)	54.0 (4.5)	<0.001

Notes: Statistically significant pairwise differences ($P < 0.0083$) were observed among change-PNI groups in age, tumor location, tumor size, histologic grade, complications, chemotherapy, and pre-/ post-PNI values. Detailed results of intergroup comparisons are provided in [Supplementary Table S1](#).

Abbreviations: SD, Standard Deviation; BMI, Body Mass Index; ASA, American Society of Anesthesiologists Physical Status Classification; CEA, Carcinoembryonic Antigen; MC, Mucinous Adenocarcinoma; SRC, Signet-Ring Cell; LVI, Lymphovascular Invasion.

the G1 and G3 groups, while chemotherapy treatment was more common in G2 (86.8%) and G4 (88.8%) group patients. The pre- and post-PNI values varied significantly between the groups according to the definition of each group.

Predictive Factors Associated with OS

Age ≥ 70 years, CEA ≥ 5 ng/mL, tumor size ≥ 5 cm, postoperative complications, lymphovascular invasion (LVI), stage III, adjuvant chemotherapy, pre-PNI, post-PNI, and change-PNI were significant predictors of OS in a univariable analysis (Table 2). A multivariable Cox regression model adjusted for age, CEA, tumor size, postoperative complications, LVI, tumor stage, and adjuvant chemotherapy demonstrated that patients in groups G2, G3, and G4 had

Table 2 Univariable Analysis of Factors Associated with Overall Survival

Variables	Categorization	HR (95% CI)	P
Sex	Female	I	0.229
	Male	1.273 (0.859–1.885)	
Age (years)	< 70	I	<0.001
	≥ 70	2.739 (1.881–3.986)	
BMI (kg/m ²)	< 25	I	0.066
	≥ 25	0.649 (0.410–1.029)	
ASA grade	I	I	0.828
	II	1.051 (0.670–1.647)	
	III & IV	1.147 (0.517–2.543)	
	Unknown	1.600 (0.981–2.609)	
CEA (ng/mL)	< 5	I	0.001
	≥ 5	1.827 (1.248–2.672)	
	Unknown	1.070 (0.335–3.416)	
Tumor location	Colon	I	0.849
	Rectum	1.040 (0.694–1.558)	
Tumor size (cm)	< 5	I	0.014
	≥ 5	1.595 (1.096–2.322)	
Complications	No	I	<0.001
	Yes	2.386 (1.627–3.500)	
Histologic grade	G1 & G2	I	0.235
	G3 & MC & SRC	1.420 (0.796–2.534)	
LVI	Absent	I	0.001
	Present	1.884 (1.268–2.801)	
	Unknown	0.838 (0.401–1.753)	
Stage	I & II	I	0.007
	III	1.714 (1.154–2.545)	
Chemotherapy	No	I	<0.001
	Yes	0.377 (0.252–0.566)	
Pre-PNI	Low	I	<0.001
	High	0.397 (0.273–0.577)	
Post-PNI	Low	I	<0.001
	High	0.200 (0.134–0.299)	
Change PNI	G1	I	<0.001
	G2	0.173 (0.100–0.298)	
	G3	0.306 (0.152–0.616)	
	G4	0.091 (0.054–0.151)	

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; BMI, Body mass index, ASA, American society of anesthesiologists Physical Status Classification, CEA, Carcinoembryonic antigen, MC, Mucinous adenocarcinoma, SRC, Signet-ring cell, LVI, Lymphovascular invasion.

Table 3 Multivariable Analysis of Factors Associated with Overall Survival

Variables	Categorization	HR (95% CI)	P
Change-PNI	G1	1	
	G2	0.341 (0.186–0.625)	<0.001
	G3	0.457 (0.222–0.941)	0.03
	G4	0.222 (0.123–0.401)	<0.001

Note: Covariates: age, carcinoembryonic antigen, tumor size, complications, lymphovascular invasion, stage, and chemotherapy.

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval.

significantly lower mortality risks than those in group G1 (Table 3). The hazard ratios (HRs) and 95% confidence intervals (CIs) were as follows (vs G1): G2, 0.341 (0.186–0.625); G3, 0.457 (0.222–0.941); and G4, 0.222 (0.123–0.401).

Survival Probability According to Change-PNI Groups

Kaplan–Meier survival analysis revealed significant differences in OS among the change-PNI groups (Figure 1). The patients in G4 (89.4%) had a significantly better OS than those in all other groups (G1: 37.6%, $P < 0.001$; G2: 81.0%, $P = 0.005$; G3: 70.7%, $P < 0.001$). Patients in the G1 group had the worst survival outcomes compared with patients in the other groups (G2, $P < 0.001$; G3, $P = 0.005$; G4, $P < 0.001$). However, the outcomes in patients in the G2 and G3 groups were not significantly different ($P = 0.09$).

C-Index Comparison between Change-PNI, Pre-PNI, and Post-PNI

The C-index of change-PNI (0.671, 95% CI 0.617–0.720) was superior to that of pre-PNI (0.609, 95% CI 0.563–0.654), with a bootstrap mean difference of 0.062 (95% CI 0.029–0.099). In addition, the C-index of change-PNI was superior to post-PNI (0.622, 95% CI 0.581–0.664), with a bootstrap mean difference of 0.049 (95% CI 0.014–0.085) (Table 4).

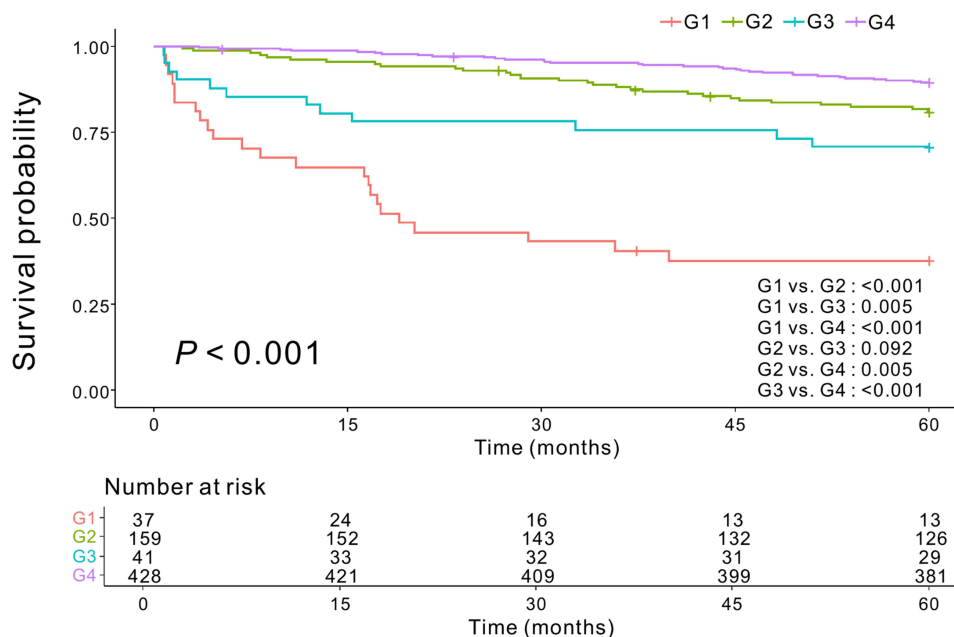


Figure 1 Survival probability according to change-PNI groups. Significant differences in 5-year overall survival were observed between the groups (G1: 37.6%; G2: 81.0%; G3: 70.7%; and G4: 89.4%). However, the comparison between G2 and G3 showed only a non-significant trend ($P = 0.092$).

Abbreviation: PNI, prognostic nutritional index.

Table 4 Comparison of Concordance Index Between Change-, Pre-, and Post-PNI

Variables	Change-PNI	Pre-PNI	Post-PNI
C-index (95% CI) (bootstrapped)	0.671 (0.617–0.720)	0.609 (0.563–0.654)	0.622 (0.581–0.664)
Estimated Difference		0.062 (0.029–0.099)	0.049 (0.014–0.085)

Abbreviations: Concordance index, C-index; CI: Confidence Interval.

Discussion

This study demonstrated that the integrated categorization of pre- and postoperative PNI offers a better prediction of OS than either pre- or post-PNI alone in patients with stage I–III CRC. Although a few studies have briefly described survival curves using similar groupings,^{13,14} to our knowledge, this is the first study demonstrating that combined pre- and post-PNI provides superior risk stratification for predicting OS compared to pre- and post-PNI alone.

There is evidence that systemic inflammatory markers are associated with mortality in various types of cancers.⁸ Markers such as LMR, NLR, and PLR are well-known indicators of inflammatory response; however, recent studies have suggested that controlling nutritional status score and PNI, incorporating both serum albumin and lymphocyte counts, could more accurately predict patient prognosis.^{15,16} The hypoalbuminemia in patients with CRC may result from increased metabolic demand, anorexia, or bowel obstruction. A poor nutritional status may lead to impaired immune surveillance and decreased responsiveness to cancer treatments.¹⁷ Lymphopenia may also affect the prognosis by suppressing adaptive immune responses, enhancing tumor immune evasion, and promoting a tumor-favoring, inflammatory, and immunosuppressive microenvironment.^{18,19} However, research on systemic markers has traditionally focused on baseline values prior to the initiation of cancer treatment.

Recently, the prognostic value of systemic inflammatory markers during the post-treatment period has gained attention.^{14,20–22} Tamai et al demonstrated that postoperative PNI, measured before adjuvant chemotherapy, was an independent predictor of OS in high-risk patients with stage II and III CRC. In their study, patients with a low PNI at recurrence had worse survival outcomes than those with a high PNI.¹⁴ C-reactive protein (CRP), another systemic inflammatory marker, has been shown to predict oncological outcomes, and several studies have reported that postoperative CRP levels significantly affect survival.^{20,22} Although the cutoff values for postoperative CRP differ between studies, elevated postoperative CRP has been consistently identified as an independent risk factor for recurrence in patients with CRC.

The relationship between pre- and postoperative inflammatory markers and their prognostic value remains unclear. The pre- and postoperative levels of systemic inflammatory markers are generally correlated, but significant changes are observed in a substantial proportion of patients following surgery. Interestingly, Guthrie et al observed in 206 patients undergoing CRC resection that among those with preoperative modified GPS of 2 (indicative of poor prognosis), 68% shifted to a score of 0 or 1 postoperatively, whereas only 32% remained at a score of 2.²³ This aligns with our findings, where 80.8% of patients initially classified as having a low pre-PNI shifted to the high post-PNI group.

Several studies have reported that postoperative inflammatory markers are strong predictors of cancer prognosis.^{24,25} In this study, the differences in OS based on post-PNI levels (low vs high: 55.0% vs 87.2%) were more pronounced than those based on pre-PNI levels (low vs high: 72.8% vs 87.8%) ([Supplementary Figure S3](#)). Notably, there was no significant difference ($P = 0.092$) in OS between patients with low post-PNI only (G3) and those with low pre-PNI (G2), suggesting that patients with low post-PNI may require additional attention compared with those with low pre-PNI ([Figure 1](#)).

The cause of persistently low postoperative PNI levels following CRC resection remains unclear, but it may be related to the chronic dysregulation of immune and inflammatory responses triggered by micrometastatic disease or non-malignant tissue injury/necrosis.²³ Plausible mediators include pro-inflammatory cytokines, such as interleukin (IL)-6 and IL-8, which are known to be elevated in patients with CRC.²⁶ These cytokines, especially IL-6 and IL-8, are moderately associated with systemic inflammation markers and contribute to tumor survival, growth, and metastasis by promoting angiogenesis and chemotaxis of monocytes to the tumor site.^{27,28} In addition, postoperative nutritional

deterioration—such as sarcopenia induced by surgical stress or poor oral intake due to gastrointestinal dysfunction—may also contribute to sustained low PNI levels.^{29,30} These factors can impair immune recovery and delay return to homeostasis, thereby potentially worsening long-term oncologic outcomes.

Unsurprisingly, patients with consistently high (G4) or low (G1) PNI levels both pre- and postoperatively exhibited the best and worst survival outcomes, respectively. However, caution is warranted when comparing outcomes between patients with a low PNI at only one time point, either preoperatively (G2) or postoperatively (G3). Although G2 patients (low pre-PNI and high post-PNI) were more likely to have larger (>5 cm) colon tumors, they experienced fewer postoperative complications and received adjuvant chemotherapy more frequently than G3 patients (high pre-PNI and low post-PNI). Further studies are needed to elucidate the prognostic differences between these groups.

This study had some limitations. First, although the sample size was large, the retrospective nature of the study and its single-institution setting limited the generalizability of the findings. Second, the cutoff values for PNI are not standardized and vary across studies; in this study, we determined the cutoff values based on the characteristics of the included patients, which may have influenced the results and prevented the direct comparison with previous literature. Third, there was variability in the timing of PNI measurements among patients. Preoperative blood tests were performed within 8 weeks of surgery, following our institution's policy for preoperative anesthetic evaluation, and postoperative measurements were obtained 3–8 weeks after surgery. This variability may affect the accuracy of the prognostic assessments. Fourth, microsatellite instability status (MSI) was not routinely assessed during the study period and could not be incorporated into the survival analysis. Given the known prognostic relevance of MSI, particularly in stage II–III CRC, this omission may have limited the precision of our survival modeling. Finally, certain pathological predictors of prognosis (eg, surgical margins) and treatment-related factors such as chemotherapy regimens (eg, FOLFOX) or surgical techniques were not included in the analysis.

Conclusion

In conclusion, our results suggest that the combined pre- and postoperative PNI value serves as an independent prognostic factor for non-metastatic CRC and offers a more accurate prediction of OS compared to pre- or post-PNI alone. Therefore, postoperative PNI should be routinely assessed in the management of patients with CRC to guide personalized treatment and enhance patient outcomes.

Ethics Statements

The Gangnam Severance Hospital Institutional Review Board approved this study (approval number: 3-2024-0313) and waived the requirement for written informed consent owing to the retrospective nature of the study. All clinical data were fully anonymized before access and analysis. No personally identifiable information was collected or stored, and all patient records were handled in compliance with institutional data protection policies and the Declaration of Helsinki.

Acknowledgments

We would like to thank Editage (www.editage.co.kr) for the English language editing. The abstract of this paper was presented at the 2025 American Society of Colon and Rectal Surgeons Annual Scientific Meeting as a Quick Shot presentation (session: Quick Shot: Colorectal Cancer and Quality and Cost; presentation ID: QS200) on Monday, May 12, 2025. The abstract is available at: <https://ascrs25.eventscribe.net/fsPopup.asp?PresentationID=1555571&mode=presInfo>.

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.

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (No. 2022R1F1A1074811).

Disclosure

The authors report no conflicts of interest in this work.

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