Prognostic value of nutrition and immune-related biomarkers in patients with locally advanced rectal cancer treated with chemoradiotherapy

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Received February 12, 2024; Accepted May 20, 2024

DOI: 10.3892/ol.2024.14580

Abstract. The ability of nutrition and immune-related biomarkers to predict outcomes in patients with locally advanced rectal cancer (LARC) treated with neoadjuvant therapy followed by surgery remains controversial due to the lack of evidence regarding the accuracy and reliability of these biomarkers in predicting outcomes for such patients. Therefore, the present study aimed to investigate the prognostic potential of nutrition and immune-related biomarkers in patients with LARC who underwent chemoradiotherapy followed by curative surgery. The clinical data of patients with LARC treated with neoadjuvant therapy followed by surgery between January 2010 and December 2019 were analyzed. In total, 214 consecutive patients were enrolled into the present study, who were then categorized into low and high prognostic nutritional index (PNI) groups. The X-tile 3.6.1 program was used to calculate and then determine the optimal cut-off values for PNI. Disease-free survival (DFS) and overall survival (OS) were compared between the low and high PNI groups. Cox regression analysis demonstrated that low PNI and high post-chemoradiotherapy carcinoembryonic antigen levels were significantly associated with reduced disease-free survival and overall survival. Specifically, a low PNI was associated with inferior 5-year DFS (P=0.025) and OS (P=0.018). These findings suggest that amongst the nutritional and immune-related biomarkers, PNI is a significant predictive factor for disease recurrence and mortality in patients with LARC treated with neoadjuvant therapy followed by surgery.

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Abbreviations: LARC, Locally Advanced Rectal Cancer; PNI, Prognostic Nutritional Index; pCR, Pathologic Complete Response; SII, Systemic Immune-Inflammation Index; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte ratio; LMR, Lymphocyte-to-Monocyte Ratio; LC, Lymphocyte Count; NC, Neutrophil Count; DFS, Disease-free Survival; OS, Overall Survival; HR, Hazard ratio

Key words: prognostic nutritional index, systematic inflammatory response, rectal cancer, chemoradiotherapy, immune-related biomarker

Introduction

Neoadjuvant chemoradiation therapy followed by surgery is the first-line therapeutic option for locally advanced rectal cancer (LARC) (1). Numerous studies have been performed to evaluate the risk factors for predicting outcomes in patients with rectal cancer following radical surgery (2,3). After neoadjuvant chemoradiation therapy, pathological lymph node status has been found to be one of the most effective risk factors for recurrence (4). In addition, achieving a pathological complete response (pCR) has been associated with superior outcomes following radical resection (5). The prognosis of LARC is associated with the physiological makeup of the patient pre-treatment, especially whether systemic inflammatory diseases were present and the immuno-nutritional status. The systemic inflammatory response serves a role in cancer development, progression, treatment response, and prognosis (6,7). This response can be measured using various indicators of hematological parameter changes, including the systemic immune-inflammation index (SII; neutrophil count X plated count/lymphocyte count), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and the lymphocyte-to-monocyte ratio (LMR) (8). Systemic inflammatory response markers, such as increased NLR and PLR, has been reported to ably predict an unfavorable prognosis in rectal cancer following neoadjuvant chemoradiotherapy (9,10). By contrast, increased LMR has been associated with superior survival outcomes in patients with LARC treated with neoadjuvant therapy followed by surgery (8). SII is a relatively novel marker compared with other inflammatory markers. It is calculated based on the neutrophil, platelet and lymphocyte counts (11). A previous meta-analysis reported its prognostic ability to predict poor

overall survival and progression-free survival in colorectal cancer (11).

The prognostic nutritional index (PNI; PNI=10 x albumin levels + 0.005 x total lymphocyte count) is a marker that can be used to reflect the nutritional and immunological status and is calculated based on a number inflammatory parameters and albumin levels (12). PNI has been reported to be accurate for predicting prognosis, with low PNI associated with worse overall survival and disease-free survival in patients with colorectal cancer (12,13). However, whilst a number of studies have previously explored the prognostic value of individual biomarkers such as NLR, PLR and SII in patients with LARC who have received neoadjuvant chemoradiotherapy, to the best of our knowledge studies that have collectively investigated and compared the prognostic value of these biomarkers remain scarce (14,15).

Therefore, the present study aimed to comprehensively analyze and compare the prognostic value of nutritional and immune-related biomarkers in patients with LARC treated with neoadjuvant therapy followed by surgery to devise strategies to optimize their individualized management protocols.

Patients and methods

Patients. A retrospective review of the medical records of patients with LARC who underwent radical resection at our Ajou University Hospital (Suwon, Korea) from January 2010 to June 2019. The present study included all patients diagnosed with LARC using endoscopy and radiological evidence (clinical stage II and III) who underwent surgery following neoadjuvant chemoradiotherapy. Histopathological staining is typically not necessary when the combination of endoscopic and radiological findings provides a clear and definitive diagnosis. This approach allows for prompt and appropriate treatment planning for patients. All patients were aged >18 years and had no history of other primary cancers. Patients diagnosed with distant metastases (to the liver, lung or peritoneum) during the initial operation (n=10) or those with whom no radical resection was performed following neoadjuvant chemoradiotherapy (n=1) were excluded (Fig. 1). The institutional review board of Ajou University Hospital (Suwon, Korea) approved the present study (approval no. AJOUIRB-MDB-2022-109). Informed consent was not required for the present study because the present study was a medical record review.

Tables I and II shows the demographic and clinical data collected. The present study included 214 patients (147 males and 67 females) with LARC treated with neoadjuvant therapy followed by surgery between 2010 and 2019. The median age of the patients was 59 years (range, 26-87 years). Staging was performed according to the tumor-node-metastasis classification of the American Joint Committee on Cancer (7th edition) (16). The distance from the anal verge to the lower margin of the tumor was measured preoperatively using rigid proctoscopy. Lower rectal cancer is characterized by lesions within 5 cm of the anal verge, whilst middle rectal cancer is characterized by tumors located 5-10 cm from the anal verge.

Hemoglobin, platelet count, lymphocyte count (LC), neutrophil count (NC), NLR, PLR, LMR, SII, PNI, carcinoembryonic antigen (CEA) and body mass index were all collected to develop a prognostic model. Baseline blood samples were collected 2 weeks before chemoradiotherapy, while preoperative samples were collected 2 weeks before surgery.

Table I. Clinicopathological characteristics (n=214).

Variables	N (%)
Sex	
Male	147 (68.7)
Female	67 (31.3)
Age, years	
<60	108 (50.5)
≥60	106 (49.5)
American Society of Anesthesiology score	
1	112 (52.3)
2	90 (42.1)
3	12 (5.6)
Body-mass index, kg/m^2	
≤25	155 (72.4)
>25	59 (27.6)
Radiotherapy interval, weeks	
≤8	124 (57.9)
>8	90 (42.1)
Location	
Mid	110 (51.4)
Low	104 (48.6)
Clinical T stage	
cT1-2	18 (8.4)
cT3-4	196 (91.6)
Clinical N stage	
cN0	21 (9.8)
cN1-2	193 (90.2)
Tumor circumference	
Non-encircling	175 (81.8)
Encircling	39 (18.2)

The cut-off values for platelet count, LC, NC, NLR, PLR, LMR, PNI and SII were calculated and determined using the X-tile 3.6.1 software (Fig. 2) (17). A brief overview of how the program was used to determine these values includes: Data input, statistical analysis, cut-off value selection and validation. A common method was applied within the program for all parameters. This means that the same approach for determining and validating the cut-off values was consistently used for platelet count, LC, NC, NLR, PLR, LMR, PNI and SII. Cut-off values for hemoglobin, CEA, albumin and body mass index were determined based on standard clinical values. Patients were classified into low and high groups based on the cut-off values of the parameters.

Preoperative radiotherapy was administered to the pelvis of each patient 5 days weekly for 5 weeks, with each daily dose 1.8 Gy. In addition, a booster dose of 5.4 Gy was delivered to the tumor site. Concomitant chemotherapy was administered during radiotherapy. The chemotherapy regimen selected was 5-fluorouracil or capecitabine. For the 5-fluorouracil regimen, patients received 225 mg/m^2 intravenously over 24 h,

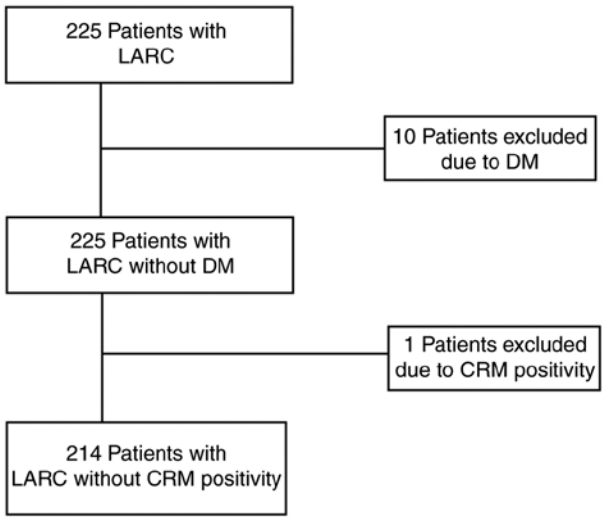

Figure 1. Flowchart of patient selection. LARC, locally advanced rectal cancer; DM, distant metastasis; CRM, circumferential resection margin.

daily. This administration occurred consecutively for 5 days each week, spanning a period of 5 weeks. Capecitabine was administered orally at a dose of 825 mg/m^2 twice daily on weekdays (Monday-Friday), spanning a period of 28-30 days. Surgery took place 6-8 weeks following chemoradiotherapy completion. Subsequently, patients were scheduled for outpatient follow-up visits every 3-6 months during the initial 2 years after surgery, which was set to every 6 months for the subsequent 3 years and then decreased to once-annual follow-ups thereafter. Physical examinations and serum CEA measurements were performed at each visit. Annually, chest radiography, chest and abdominopelvic CT and colonoscopy were performed if recurrence was suspected. PET would also be performed if recurrence was suspected. Cancer recurrence was identified using a combination of imaging data and CEA measurements, which were subsequently confirmed by pathological examination.

Patients were followed up until they succumbed or reached the designated cut-off date of December 31, 2021 (the last followed up date), whichever came first. The median follow-up time was 57.0 months (4.0-143.0 months). Disease-free survival (DFS) was defined as the time from irradiation initiation to disease recurrence or the last follow-up date. Overall survival (OS) was defined as the time from irradiation initiation to mortality.

Statistical analysis. Differences in the clinicopathological features were compared using χ^2 test. The data in Table II were evaluated for normality using the Kolmogorov-Smirnov test to determine whether they followed a normal distribution, which informed the decision to apply parametric or non-parametric statistical test for subsequent analysis. However, none of the data in the present study were found to be normally distributed. Therefore, Wilcoxon signed-rank test was used to analyze variables before and after chemoradiotherapy. Quantitative data that did not to the normal distribution are expressed as the median (interquartile range). Survival curves were evaluated using the Kaplan-Meier method and were compared using the log-rank test. Independent predictors were

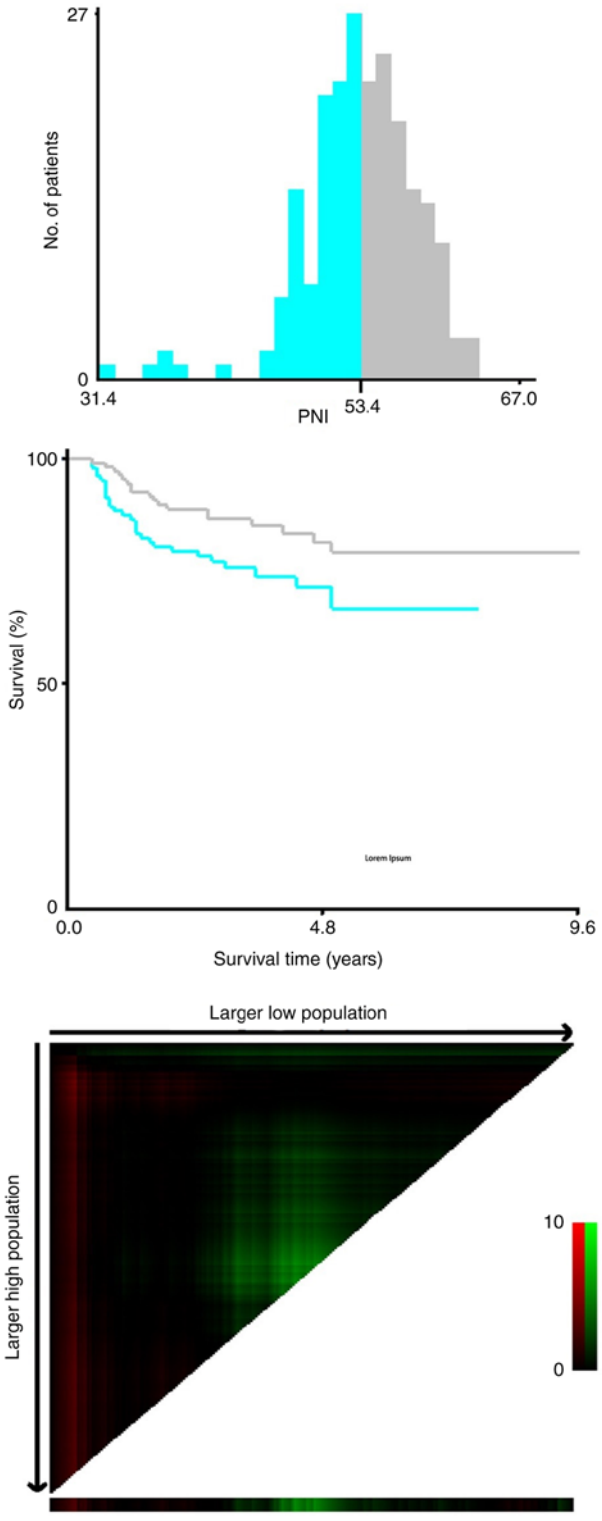

Figure 2. Using the X-tile 3.6.1 software, the cut-off value for the PNI of 53.4 was determined, which was identified from the minimum P-value according to the overall survival. PNI, prognostic nutritional index. The bottom heatmap panel visually represents the association between various cut-off values of a continuous variable and clinical outcome, aiding the identification of the most statistically significant cut-off points.

determined using multivariate Cox regression analyses of OS and DFS. Variables with P<0.05 in univariate analysis were included in the following multivariate analysis. P<0.05 was considered to indicate a statistically significant difference.

Table II. Tumor response data.

Variables	Initial	Post-CRT
Carcinoembryonic antigen, ng/ml		
≤5	106 (49.5)	178 (83.2)
>5	108 (50.5)	36 (16.8)
Serum albumin, g/l	4.4 (2.0-5.1)	4.4 (3.2-5.2)
Hemoglobin, g/dl	13.4 (5.4-17.2)	12.8 (5.9-16.5)
Lymphocyte count, 10^9/l	1,993 (1026-4014)	1,003.4 (280-3115)
Neutrophil count, 10^9/l	4,494 (1315-8904)	3,564 (1323-9298)
Platelet count, 10^9/l	274 (124-649)	243 (78-506)
Neutrophil-lymphocyte ratio	2.28 (0.62-5.60)	3.52 (0.89-22.07)
Platelet-lymphocyte ratio	140.4 (51.3-392.5)	240.8 (49.2-958.9)
Lymphocyte-monocyte ratio	4.1 (1.5-13.2)	2.2 (0.7-9.3)
Systemic immune-inflammatory index	598.4 (118.9-3191.2)	848.3 (119.3-5914.7)
Prognostic nutritional index	53.5 (31.4-67.0)	49.3 (37.7-61.1)

Table III. Univariate and multivariate analyses for factors predicting cancer recurrence.

	Univariate			Multivariate		
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Sex, female vs. male	1.134	0.612-2.103	0.689			
Age, >60 vs. ≤60 years	1.238	0.693-2.213	0.471			
American Society of Anesthesiology score, 1 vs. 2-3	1.358	0.755-2.443	0.307			
Body mass index, <25 vs. ≥25 kg/m^2	2.653	1.125-6.259	0.026			
Radiotherapy interval, ≤8 vs. >8 weeks	1.048	0.571-1.925	0.879			
Location, low vs. high	1.019	0.566-1.837	0.949			
Clinical stage, III vs. II	2.696	0.653-11.131	0.171			
Tumor circumference, non-encircling vs. encircling	1.003	0.467-2.153	0.993			
Initial CEA, >5 vs. ≤5 ng/ml	1.785	0.986-3.231	0.056			
Post-chemoradiotherapy CEA, >5 vs. ≤5 ng/ml	2.966	1.579-5.570	0.001	3.003	1.596-5.649	0.001
Tumor response, non-complete response vs. complete response	3.517	1.090-11.348	0.035			
Prognostic nutritional index, <53.4 vs. ≥53.4	1.968	1.087-3.563	0.025	1.993	1.099-3.614	0.023
Neutrophil-lymphocyte ratio, >2.2 vs. ≤2.2	1.603	0.881-2.917	0.123			
Platelet-lymphocyte ratio, >126.7 vs. ≤126.7	1.319	0.718-2.421	0.372			
Lymphocyte-monocyte ratio, >2.8 vs. ≤2.8	1.502	0.594-3.803	0.390			
Systemic immune-inflammatory index, >508.8 vs. ≤508.8	1.750	0.888-3.449	0.106			

CEA, carcinoembryonic antigen; HR, hazard ratio.

Statistical analyses were performed using SPSS version 25.0 (IBM Corp.) and GraphPad Prism 9 (Dotmatics).

Results

Clinicopathological characteristics. For the present study, the X-tile program was used to compare the survival outcomes between groups categorized as low and high based on the parameters' cut-off values. The X-tile program identifies cut-off points that can maximize predefined criteria including maximizing the difference in survival between groups, maximizing the statistical significance of the difference (log-rank test), minimizing the P-value, maximizing the hazard ratio, balancing group sizes and optimizing clinical relevance. The criterion chosen for generating the cut-off point for the present study was maximizing the statistical significance of the difference. This criterion was selected because it ensures that the identified cut-off points are statistically robust, providing a more reliable basis for comparing the survival outcomes between the low and high groups. The optimal cut-off values

Table IV. Univariate and multivariate analyses for factors predicting mortality.

	Univariate			Multivariate		
Variables	HR	95% CI	P-value	HR	95% CI	P-value
Sex, female vs. male	1.413	0.727-2.746	0.308			
Age, >60 vs. ≤60 years	1.997	1.017-3.923	0.045			
American Society of Anesthesiology score, 2-3 vs. 1	1.181	0.620-2.251	0.612			
Body mass index, vs. ≥25 kg/m^2	1.588	0.698-3.616	0.270			
Radiotherapy interval, ≤8 vs. >8 weeks	1.103	0.560-2.175	0.776			
Location, low vs. high	1.039	0.544-1.985	0.907			
Clinical stage, III vs. II	1.010	0.358-2.855	0.984			
Tumor circumference, non-encircling vs. complete response	1.149	0.479-2.755	0.755			
Initial CEA, >5 vs. ≤5 ng/ml	1.551	0.804-2.992	0.190			
Post-chemoradiotherapy CEA, >5 vs. ≤5 ng/ml	3.738	1.920-7.277	<0.001	3.052	1.560-5.971	0.001
Tumor response, non-complete response vs. complete response	8.639	1.184-63.031	0.033			
Prognostic nutritional index, <54.3 vs. ≥53.4	2.204	1.122-4.329	0.022	2.030	1.032-3.992	0.040
Neutrophil-lymphocyte ratio, >2.2 vs. ≤2.2	1.174	0.612-2.250	0.629			
Platelet-lymphocyte ratio, >126.7 vs. ≤126.7	0.867	0.452-1.662	0.668			
Lymphocyte-monocyte ratio, >2.8 vs. ≤2.8	2.228	0.684-7.255	0.184			
Systemic immune-inflammatory index, >508.8 vs. ≤508.8	1.076	0.541-2.143	0.834			

HR, hazard ratio; CEA, carcinoembryonic antigen.

for LC, NC, platelet count, NLR, PLR, LMR, PNI and SII before neoadjuvant chemoradiotherapy were 1,530.0, 5,072.0, 326.0, 2.2, 126.7, 2.8, 53.4, and 508.8, respectively. The optimal cut-off values for LC, NC, platelet count, NLR, PLR, LMR, PNI and SII after neoadjuvant chemoradiotherapy were 776.0, 4,012.8, 278.0, 1.8, 213.9, 1.2, 46.4 and 722.9, respectively.

Univariate and multivariate analyses for DFS and OS. Upon evaluation of the levels of nutrition and immune-related biomarkers calculated before and after neoadjuvant chemoradiotherapy, no significant difference was observed in DFS and OS between the high and low groups of each parameter tested, except for between the high and low PNI groups (Tables III and IV). Low PNI was found to be significantly associated with decreased 5-year DFS and OS rates (72.9 vs. 87.0%; P=0.018) compared with high PNI (65.6 vs. 79.7%; P=0.025; Fig. 3). In addition, high post-chemoradiotherapy CEA levels were significantly associated with decreased 5-year OS (61.1 vs. 87.1%; P<0.001) and DFS (61.1 vs. 82.0%; P<0.001) (Fig. 3). Non-complete response status was also significantly associated with decreased 5-year OS (79.8 vs. 97.2%; P=0.010) and DFS (75.8 vs. 91.7%; P=0.025; Fig. 3). Multivariate analysis for cancer recurrence demonstrated that PNI [hazard ratio (HR), 1.993; 95% CI, 1.099-3.614; P=0.023] and post-chemoradiotherapy CEA level (HR, 3.003; 95% CI, 1.596-5.649; P=0.001) were significant predictors of 5-year cancer recurrence (Table III). Multivariate analysis of mortality demonstrated that PNI (HR, 2.030; 95% CI, 1.032-3.992; P=0.040) and post-chemoradiotherapy CEA level (HR, 3.052; 95% CI, 1.560-5.971; P=0.001) were significant predictors of the 5-year mortality (Table IV).

Comparison of clinicopathological characteristics between low PNI and high PNI. No significant associations could be observed between any of the clinicopathological features and PNI, except for age and body mass index (Table V).

Discussion

The present study investigated the prognostic impact of nutrition and immune-related biomarkers combined with various clinicopathological features in patients with LARC treated with neoadjuvant therapy followed by surgery. Although it was found that the calculated cut-off values for SII, PLR, LMR and NLR were similar compared with those in previous studies (11,18), when the prognostic value of these biomarkers was assessed, none emerged as an independent predictor in the present cohort. Only the initial PNI strongly predicted disease recurrence and survival in patients with LARC treated with neoadjuvant therapy followed by surgery.

Previous studies have demonstrated that malnutrition and the immunological status serve a role in cancer development (19,20). Therefore, several scoring systems such as PNI, SII and NLR based on the nutritional and immunological status have been established to predict colorectal cancer prognosis. Among those, PNI appears to be the most accessible, since it can be readily calculated from albumin levels and total LC. In addition, PNI has been documented to be an independent predictor of colorectal cancer outcomes (21,22).

The present study focused on the prognostic value of nutrition and immune-related biomarkers in patients with LARC treated with neoadjuvant therapy followed by surgery. Notably,

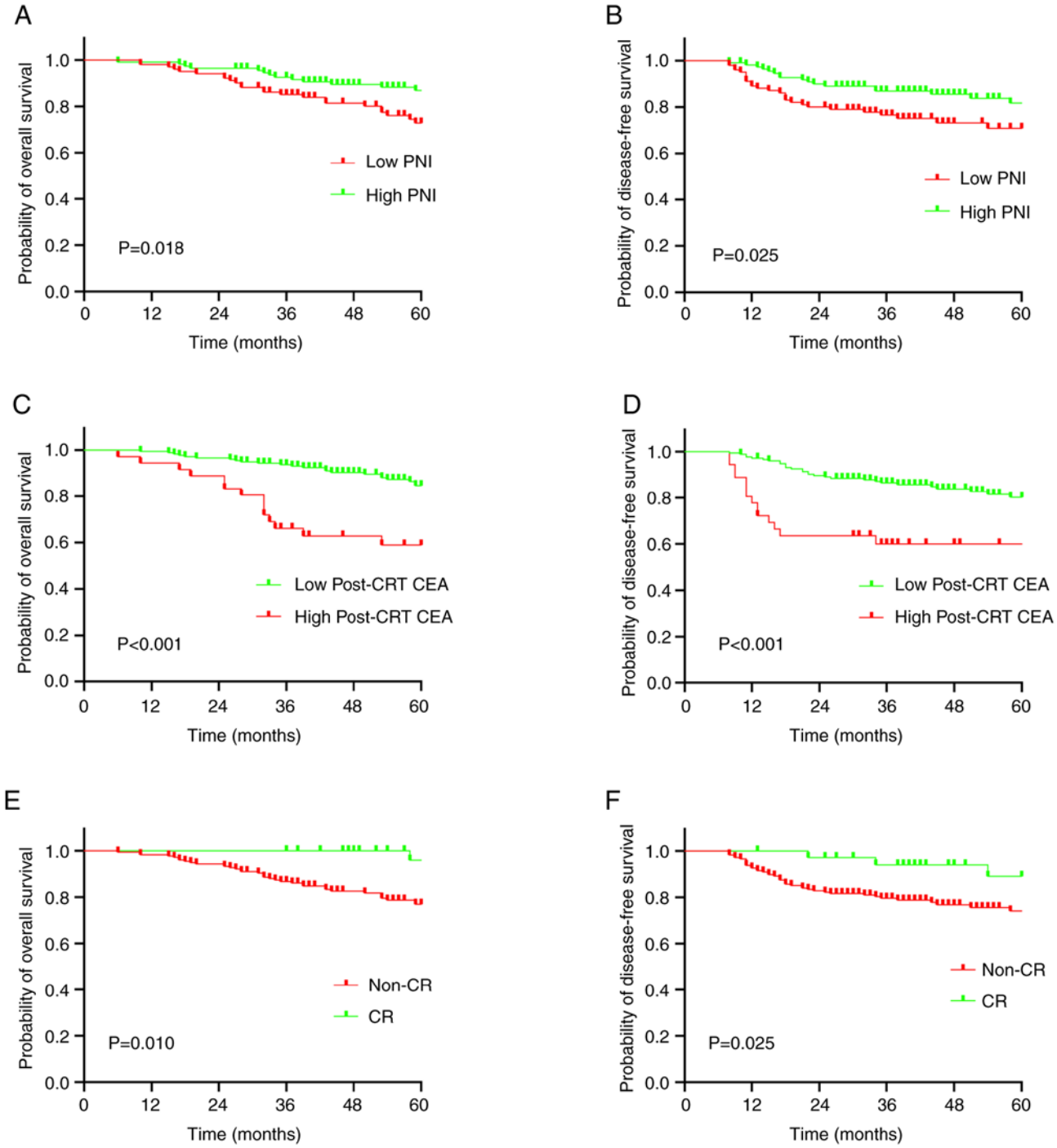

Figure 3. Comparison of (A) 5-year overall survival and (B) 5-year disease-free survival according to PNI. Comparison of (C) 5-year overall survival and (D) 5-year disease-free survival according to post-CRT CEA levels. Comparison of (E) 5-year overall survival and (F) 5-year disease-free survival according to complete response occurrence. PNI, prognostic nutritional index; CRT, chemoradiotherapy; CEA, carcinoembryonic antigen; CR, complete response.

two previous studies have reported the prognostic ability of PNI in patients with LARC (13,23). Okugawa *et al* (13) attempted to use the patient nutritional status to predict long-term oncological outcomes, which was reflected by applying the PNI. It was found that a low pre-chemoradiotherapy PNI was significantly associated with shorter DFS and OS in 114 patients with LARC (13). Similarly, Wang *et al* (23) previously measured various systemic inflammatory response markers, nutrition and immune-related biomarkers to examine the chemoradiotherapy response and long-term oncological outcomes in 273 patients with LARC. This previous study reported that PLR and PNI independently predicted responses to chemoradiotherapy, where PNI was also an independent predictor of DFS and OS in patients with LARC (23). The present study explored the utility of various systemic inflammatory response markers, including SII and nutrition and immune-related biomarkers, to examine the response to chemoradiotherapy and long-term oncological outcomes in 214 patients with LARC. However, an association between the tested biomarkers and pathological response could not be found, though PNI and

Table V. Association between each of the clinicopathological characteristics and PNI.

Variables	Total (n=214)	PNI <53.4 (n=102)	PNI >53.4 (n=112)	P-value
Sex				0.542
Male	147	68	79	
Female	67	34	33	
Age, years				<0.001
<60	108	37	71	
≥60	106	65	41	
ASA score				0.080
1	112	47	65	
2-3	102	55	47	
Body-mass index, kg/m^2				0.013
≤25	155	82	73	
>25	59	20	39	
Radiotherapy interval, weeks				0.977
≤8	124	59	65	
>8	90	43	47	
Location				0.348
Mid	110	49	61	
Low	104	53	51	
Clinical T stage				0.484
cT1-2	18	10	8	
cT3-4	196	92	104	
Clinical N stage				0.997
cN0	21	10	11	
cN1-2	193	92	101	
Tumor circumference				0.617
Non-encircling	175	82	93	
Encircling	39	20	19	
Initial CEA, ng/ml				0.677
≤5	106	49	57	
>5	108	53	55	
Post-chemoradiotherapy CEA, ng/ml				0.501
≤5	178	83	95	
>5	36	19	17	
Tumor response				0.430
CR	36	15	21	
Non-CR	178	87	91	

CEA, carcinoembryonic antigen; CR, complete response; PNI, prognostic nutritional index.

pCR were found to be independent predictors of DFS and OS. This is consistent with previous observations that LARC with pCR results in highly favorable oncological outcomes (5,24).

Hu *et al* (25) previously described SII based on NC, LC and platelet counts. A subsequent study demonstrated the prognostic value of SII in colorectal cancer (26). SII was previously revealed to be an independent predictive factor for pCR in patients with LARC receiving chemoradiotherapy (14). To the best of our knowledge, SII has not yet been reported to be associated with cancer recurrence and mortality in patients with LARC. Therefore, SII was included in the present analysis to determine whether it was associated with oncologic outcomes. However, no association could be found between SII and cancer recurrence or mortality.

CEA is produced and secreted by colorectal cancer cells (27). Serum CEA is a representative tumor marker for colorectal cancer and has been widely used for surveillance after colorectal cancer surgery (28). Previously, serum CEA levels in rectal cancer before and after neoadjuvant chemoradiotherapy have been reported to be associated with treatment response

and survival (29,30). The multivariate analysis performed in the present study revealed that post-chemoradiotherapy CEA levels were strongly associated with DFS and OS in patients with LARC treated with preoperative chemoradiotherapy.

The present study has a number of limitations. Potential selection bias may persist, due to its retrospective design and the inclusion of a small cohort from a single institution. Therefore, there needs to be more prospective validation. Nevertheless, these data were systematically collected from an electronic database that were regularly updated. Therefore, the data used for the present analysis were reflective of current clinical practices, thereby providing a solid foundation for the findings. The present study was conducted using a single cohort, focusing on patients with LARC treated with neoadjuvant therapy followed by surgery. Therefore, in the inclusion and exclusion criteria mainly pertained to clinical stage. Other inclusion and exclusion criteria such as performance status, biomarkers status, nutritional status and comorbidities, should be considered for future studies. Preoperative PNI in patients undergoing curative surgery for rectal cancer served as a simple and cost-effective method to identify individuals with a potentially unfavorable prognosis. Early detection of recurrence may enable the resection of metastatic lesions in patients with rectal cancer, and understanding the risk factors that can predict recurrence would be beneficial for managing LARC. However, the optimal PNI threshold for predicting recurrence remains to be determined. Therefore, further assessment in lager, multi-center studies is required to evaluate the robustness of prediction models.

In conclusion, results from the present study suggest that PNI is a robust predictive factor for disease recurrence and survival in patients with LARC treated with neoadjuvant therapy followed by surgery. These findings may facilitate the risk stratification of patients and the selection of optimal personalized treatment plans for patients with LARC.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SYO and GP contributed to the design of this paper, data analysis and revising this paper. Both authors read and approved the final version of the manuscript. SYO and GP confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study received full ethical approval from the Institutional Review Board of Ajou University School of Medicine (approval no. AJOUIRB-MDB-2022-109; Suwon, Korea).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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