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ORIGINAL RESEARCH ARTICLE

Development of Novel Prognostic Prediction Models including the Prognostic Nutritional Index for Patients with Colorectal Cancer after Curative Resection

Masaru Sasaki[1)], Norikatsu Miyoshi[1)2)], Shiki Fujino[1)], Satoshi Ishikawa[1)], Kazuhiro Saso[1)], Hidekazu Takahashi[1)], Naotsugu Haraguchi[1)], Taishi Hata[1)], Chu Matsuda[1)], Tsunekazu Mizushima[1)], Yuichiro Doki[1)] and Masaki Mori[1)]

1) Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Osaka, Japan
2) Department of Innovative Cancer Research and Translational Medicine, Osaka International Cancer Institute, Osaka, Japan

Abstract:

Objectives: It has been reported that there is an association between the nutritional condition and the prognosis of cancer. Here, we evaluated the relation between the prognostic nutritional index (PNI) and colorectal cancer (CRC). Methods: A total of 184 patients with CRC who underwent curative surgery from October 2011 to December 2012 at the Osaka University Hospital were investigated. According to the median PNI value of our data set, patients were classified into a high-PNI (≥46) group and a low-PNI (<46) group. The relationship between the PNI and the disease-free survival (DFS) and overall survival (OS) was analyzed by a Cox regression model. Results: A low PNI was significantly associated with poor DFS (P = 0.006) and OS (P < 0.001). A multivariate analysis showed that low PNI, venous invasion (present), and tumor location (rectum) were independent risk factors for recurrence. Low PNI, advanced age, and venous invasion were found to be independent risk factors for mortality. Using these clinicopathological factors, we developed nomograms to predict DFS and OS. The concordance index was 0.828 for DFS and 0.756 for OS. Conclusions: A low PNI is a prognostic indicator for recurrence and mortality in CRC. Nomograms constructed by clinicopathological factors including the PNI can provide individual prognostic outcomes.

Keywords:

prognostic nutritional index, PNI, colorectal cancer, prediction model, nomogram, prognosis

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Introduction

Colorectal cancer (CRC) is a frequent malignancy, the second most common cancer in women and the third most common in men, with an estimated 1.4 million cases and 693,900 deaths in 2012[1)]. Although the surgical procedures and chemotherapy for CRC have been developed in recent years[2-4)], some patients relapsed after curative resection, affecting the survival percentage. At present, the tumor-node-metastasis (TNM) staging system of the International Union Against Cancer (Union for International Cancer Control, UICC) is most commonly used to predict the prognosis for CRC of all stages[5)]. However, there are differences in prognosis among the same TNM stages[6)]. Therefore, it is necessary to develop a more accurate prognostic prediction model for individual outcomes, leading to personalized therapy. Recently, it has been considered that the progression and prognosis of cancer correlate with the inflammatory[7)] and nutritional status of patients[8,9)]. The prognostic nutritional index (PNI), calculated by serum albumin level and total lymphocyte count (TLC), has been reported to reflect the nutritional and immune condition of patients[10,11)]. PNI has also been reported to correlate with postoperative complications[12,13)] and is considered as a prognostic predictor for various can-

Corresponding author: Norikatsu Miyoshi, nmiyoshi@gesurg.med.osaka-u.ac.jp
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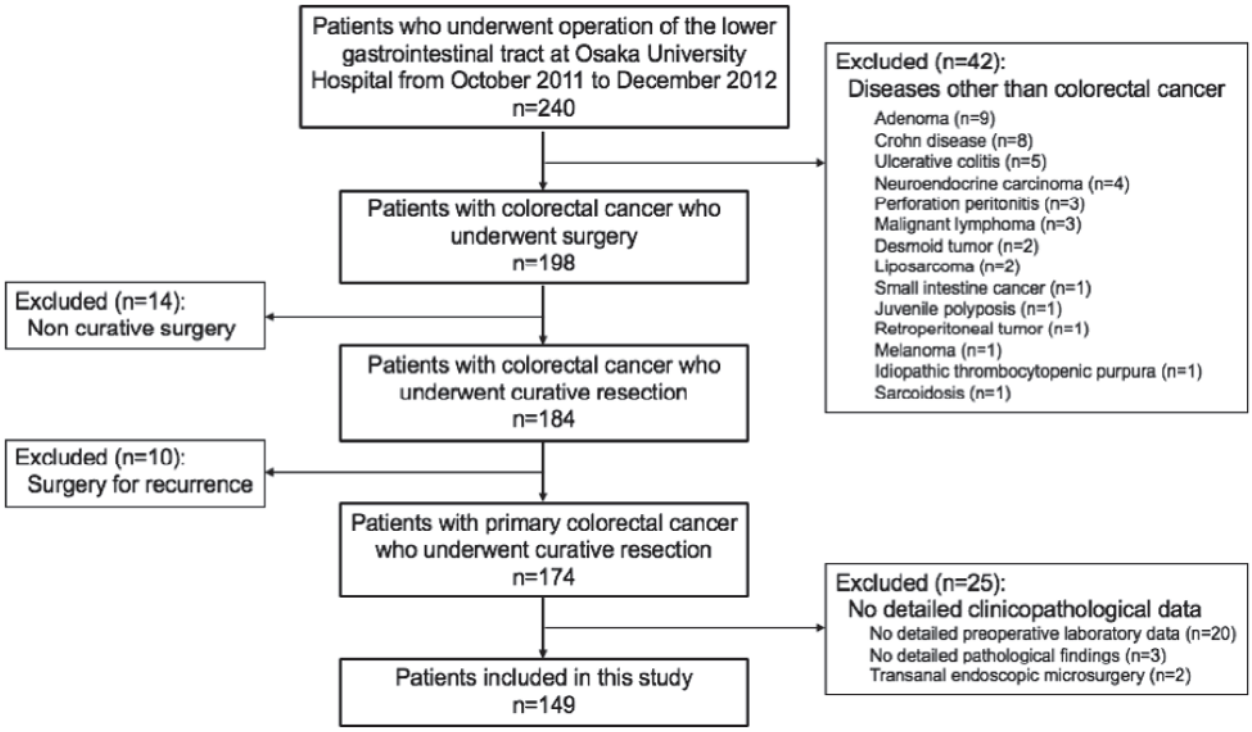

Figure 1. Flowchart of the patients included in this study.

cers[13,14], such as hepatocellular carcinoma[15], pancreatic carcinoma[16], gastric carcinoma[17], and CRC[18-20]. While several studies suggested that the PNI is related to the prognosis of CRC, the optimal cut-off values for the PNI to determine prognosis remain to be elucidated. In this study, we examined the clinicopathological risk factors including the PNI for recurrence and mortality in patients with CRC. The optimal cut-off values of the PNI for predicting prognosis were investigated. Moreover, we constructed a novel prediction model for disease-free survival (DFS) and overall survival (OS) using the PNI in patients with CRC. Developing this tool can provide beneficial information regarding selecting a personalized treatment for each patient.

Methods

Patients and data sets

240 patients with CRC who underwent curative resection for primary and metastatic lesions at Osaka University Hospital from October 2011 to December 2012 were enrolled in this study retrospectively. Patients with no detailed preoperative laboratory data and pathological findings were excluded. Patients who underwent transanal endoscopic microsurgeries were also excluded because of the lack of pathological findings. Finally, 149 patients were analyzed in this study (Figure 1). The median follow-up was 59 months (range: 1-73 months). Data on the age, sex, body mass index (BMI), American Society of Anesthesiologists Physical Status (ASA-PS), serum level of albumin, TLC, white blood cells (WBCs), C-reactive protein (CRP), carcinoembryonic antigen (CEA), primary tumor location (colon or rectum), distant metastases, and pathological findings (e.g., histological grade, tumor invasion, lymph node metastasis, lymphatic invasion, and venous invasion) were retrieved from the patients' medical records. The clinicopathological factors were classified according to the seventh edition of the UICC TNM classification[5]. Preoperative blood samples were obtained within a month before operation. The PNI was calculated as follows: 10 × serum albumin level (g/dL) + 0.005 × TLC (/mm^3)[10]. After surgery, all patients were followed up regularly, with blood examinations assessing CEA and carbohydrate antigen 19-9 and further screening by computed tomography every 3-6 months and colonoscopy every 1-2 years following the Japanese guidelines[21]. This study was approved by the Institutional Review Board of Osaka University.

Statistical analysis

Differences between the clinicopathological factors and the classified PNI groups were analyzed using the chi-squared test and Mann-Whitney *U* test. Univariate and multivariate analyses were performed using a Cox proportional hazards regression model to identify the independent prognostic factors for DFS and OS. Two-sided $P < 0.05$ was considered to denote statistical significance. Kaplan-Meier survival curves were plotted and compared with the generalized log-rank test. The predictive performance of the nomo-

Table 1. The Characteristics of the 149 Patients with CRC.

Variables	PNI	
	High (n = 82)	Low (n = 67)
Age (years) *	63 (26-87)	68 (42-85)
Sex		
Male/female	50/32	43/24
BMI (kg/m^2) *	22.2 (8.7-32.0)	21.8 (14.6-27.3)
ASA-PS		
1/2/3/4-6	42/37/3/0	23/35/9/0
Alb (g/dL) *	4.1 (3.6-4.9)	3.5 (1.9-4.2)
TLC (/μL) *	1,645 (881-3,734)	1,222 (463-3,018)
WBCs (/μL) *	5,415 (2,650-13,290)	5,660 (860-13,700)
CRP (mg/dL) *	0.06 (0.04-0.91)	0.32 (0.04-15.31)
Preoperative CEA (ng/mL) *	3 (1-19)	4 (0.1-174)
Tumor location		
Colon/rectum	50/32	45/22
Degree of differentiation		
tub1/tub2/por/pap/muc	38/37/2/2/3	35/26/3/0/3
Depth of tumor invasion		
Tis/T1/T2/T3/T4	4/33/17/27/1	5/9/11/32/10
Lymph node metastasis		
N0/N1/N2	60/15/7	46/17/4
Venous invasion		
Present/absent	16/66	16/51
Lymphatic vessel invasion		
Present/absent	37/45	42/25
Distant metastasis		
Present/absent	2/80	5/62
TNM stage		
0/I/II/III/IV	4/43/12/21/2	5/17/21/19/5

CRC: colorectal cancer; PNI: prognostic nutritional index; BMI: body mass index; ASA-PS: American Society of Anesthesiologists Physical Status; Alb: albumin; TLC: total lymphocyte count; WBC: white blood cell; CRP: C-reactive protein; CEA: carcinoembryonic antigen; tub1: well-differentiated adenocarcinoma; tub2: moderately differentiated adenocarcinoma; por: poorly differentiated adenocarcinoma; pap: papillary adenocarcinoma; muc: mucinous adenocarcinoma; TNM: tumor node metastasis. *Median (range).

gram was calculated by the concordance index (c-index)[22]. All statistical analyses were performed using JMP® software version 14 (SAS Institute Inc., Cary, NC, USA). The nomogram was structured using R 3.1.3 (CRAN; the R Foundation for Statistical Computing, Vienna, Austria)[23].

Results

Patient characteristics

The characteristics of all 149 patients are listed in Table 1. The median age was 64 years (range: 26-87 years). Seven patients (4.7%) were at stage IV. In the stage IV cases, which included liver metastasis (five cases), peritoneal dissemination (one case), and lymph node metastasis of extra region (one case), concurrent surgically curative resection of both primary and metastatic lesions was performed. There were 25 patients (16.8%) with recurrences after surgery, 8 with lung, 7 with liver, 5 with local site, 4 with lymph node, and 1 with ovary metastases.

Cut-off value of PNI

The median preoperative PNI was 46.7 (range: 23.6-63.0), and the PNI distribution was normal. According to the median PNI, we set 46 as the cut-off value for PNI and classified the patients into a high-PNI (≥46) group (82 patients, 55.0%) and a low-PNI (<46) group (67 patients, 45.0%). The relationship between the PNI status and clinicopathological factors in the patients is shown in Table 2. Between the high- and low-PNI groups, there were no significant differences in the sex, BMI, WBCs, tumor location, degree of differentiation, lymph node metastasis, venous invasion, and distant metastasis.

Table 2. The Relationship between the PNI Status and Clinicopathological Factors in 149 Patients with CRC.

Variables	Number (%)	PNI		
		High (%)	Low (%)	*P*-value
PNI	149 (100)	82 (55.0)	67 (45.0)	
Age (years)				<0.001*
Age < 65	77 (51.7)	53 (68.8)	24 (31.2)	
Age ≥ 65	72 (48.3)	29 (40.3)	43 (59.7)	
Sex				0.688
Male	93 (62.4)	50 (53.8)	43 (46.2)	
Female	56 (37.6)	32 (57.1)	24 (42.9)	
BMI (kg/m^2)				0.369
BMI ≥ 22	75 (50.3)	44 (58.7)	31 (41.3)	
BMI < 22	74 (49.7)	38 (51.3)	36 (48.7)	
ASA-PS				0.028*
1, 2	137 (91.9)	79 (57.7)	58 (42.3)	
3-6	12 (8.1)	3 (25.0)	9 (75.0)	
Alb (g/dL)				<0.001*
Alb ≥ 3.5	116 (77.9)	82 (70.7)	34 (29.3)	
Alb < 3.5	33 (22.1)	0 (0)	33 (100)	
TLC (/μL)				<0.001*
TLC ≥ 1,500	66 (44.3)	50 (75.8)	16 (24.2)	
TLC < 1,500	83 (55.7)	32 (38.6)	51 (61.4)	
WBCs (/μL)				0.076
WBCs ≥ 10,000	8 (5.4)	2 (25.0)	6 (75.0)	
WBCs < 10,000	141 (94.6)	80 (56.7)	61 (43.3)	
CRP (mg/dL)				<0.001*
CRP ≥ 1	18 (12.1)	0 (0)	18 (100)	
CRP < 1	131 (87.9)	82 (62.6)	49 (37.4)	
Preoperative CEA (ng/mL)				<0.001*
CEA ≥ 5	49 (32.9)	18 (36.7)	31 (63.3)	
CEA < 5	100 (67.1)	64 (64.0)	36 (36.0)	
Tumor location				0.434
Colon	95 (63.8)	50 (52.6)	45 (47.4)	
Rectum	54 (36.2)	32 (59.3)	22 (40.7)	
Degree of differentiation				0.928
tub1, tub2	136 (91.3)	75 (55.2)	61 (44.8)	
por, pap, muc	13 (8.7)	7 (53.9)	6 (46.1)	
Depth of tumor invasion				<0.001*
Tis, T1, T2	79 (53.0)	54 (68.3)	25 (31.7)	
T3, T4	70 (47.0)	28 (40.0)	42 (60.0)	
Lymph node metastasis				0.546
N0	106 (71.1)	60 (56.6)	46 (43.4)	
N1, N2	43 (28.9)	22 (51.2)	21 (48.8)	
Venous invasion				0.518
Present	32 (21.5)	16 (50.0)	16 (50.0)	
Absent	117 (78.5)	66 (56.4)	51 (43.6)	
Lymphatic vessel invasion				0.033*
Present	79 (53.0)	37 (46.8)	42 (53.2)	
Absent	70 (47.0)	45 (64.3)	25 (35.7)	
Distant metastasis				0.149
Present	7 (4.7)	2 (28.6)	5 (71.4)	
Absent	142 (95.3)	80 (56.3)	62 (43.7)	
TNM stage				0.003*
0-I	69 (46.3)	47 (68.1)	22 (31.9)	
II-IV	80 (53.7)	35 (43.8)	45 (56.2)	

CRC: colorectal cancer; PNI: prognostic nutritional index; BMI: body mass index; ASA-PS: American Society of Anesthesiologists Physical Status; Alb: albumin; TLC: total lymphocyte count; WBC: white blood cell; CRP: C-reactive protein; CEA: carcinoembryonic antigen; tub1: well-differentiated adenocarcinoma; tub2: moderately differentiated adenocarcinoma; por: poorly differentiated adenocarcinoma; pap: papillary adenocarcinoma; muc: mucinous adenocarcinoma; TNM: tumor node metastasis. Values with an asterisk indicate *P*-values of <0.05.

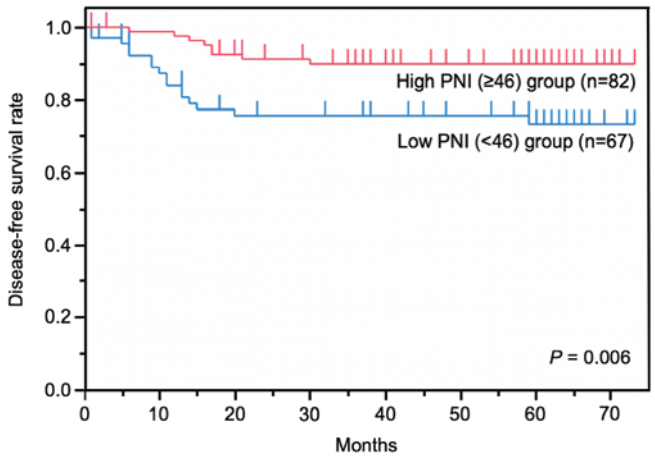

Figure 2. DFS curves according to the PNI. The Kaplan-Meier plots show the DFS based on the high-PNI (≥46) and the low-PNI (<46) group in 149 patients with CRC after curative resection. The DFS rate was significantly worse in the low-PNI group (P = 0.006).

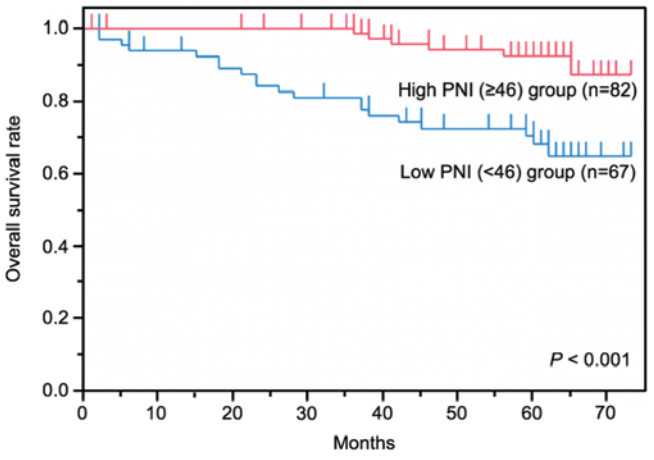

Figure 3. OS curves according to the PNI. The Kaplan-Meier plots show the OS based on the high-PNI (≥46) and the low-PNI (<46) group in 149 patients with CRC after curative resection. The OS rate was significantly worse in the low-PNI group (P < 0.001).

Survival analysis according to the PNI groups

The median patient follow-up time was 59 months. The DFS rate was significantly worse in the low-PNI group compared to the high-PNI group (P = 0.006) (Figure 2). The five-year DFS rate was 89.8% in the high-PNI group and 73.2% in the low-PNI group. The OS rate was also significantly worse in the low-PNI group compared to the high-PNI group (P < 0.001) (Figure 3). The five-year OS rate was 92.4% in the high-PNI group and 68.1% in the low-PNI group.

Risk factors for recurrence and mortality

Univariate and multivariate analyses of clinicopathological factors for DFS are shown in Table 3. According to the univariate analysis, a high preoperative serum CEA level (P = 0.010), tumor location at the rectum (P = 0.023), depth of tumor invasion (P = 0.002), lymph node metastasis (P = 0.001), venous invasion (P < 0.001), lymphatic vessel invasion (P = 0.003), distant metastasis (P < 0.001), and low PNI (P = 0.009) were significantly correlated with DFS. Furthermore, the multivariate analysis showed that tumor location at the rectum (P = 0.028), venous invasion (P = 0.009), and low PNI (P = 0.008) were independent recurrence risk factors. The univariate and multivariate analyses of clinicopathological factors for OS are shown in Table 4. According to the univariate analysis, advanced age (P = 0.045), preoperative low serum albumin level (P < 0.001), high CRP (P = 0.030), high preoperative CEA (P = 0.012), depth of tumor invasion (P = 0.007), venous invasion (P = 0.005), lymphatic vessel invasion (P = 0.022), distant metastasis (P = 0.026), and low PNI (P < 0.001) were significantly correlated with OS. Furthermore, the multivariate analysis showed that advanced age (P = 0.022), venous invasion (P = 0.027), and low PNI (P = 0.029) were independent prognostic risk factors. Moreover, we also performed univariate and multivariate analyses including the TNM stage instead of T, N, and M factors for DFS and OS (Supplementary Tables S1 and S2). The multivariate analysis showed that tumor location at the rectum (P = 0.010), venous invasion (P = 0.013), advanced TNM stage (P = 0.012), and low PNI (P = 0.038) were independent recurrence risk factors and that advanced age (P = 0.040), venous invasion (P = 0.018), and low PNI (P = 0.013) were independent prognostic risk factors.

Nomograms to predict prognosis

Nomograms to predict DFS and OS for patients with CRC who underwent curative surgery including stage IV were constructed. Since the TNM stage is the combination of primary tumor (T), regional lymph nodes (N), and distant metastasis (M), we developed nomograms using each independent clinicopathological risk factor shown in Table 3, 4. Preoperative PNI, tumor location, and venous invasion were included in the nomogram to predict the DFS (Figure 4). Preoperative PNI, age, and venous invasion were included in the nomogram to predict the OS (Figure 5). The concordance index (c-index) of the nomogram was 0.828 for DFS and 0.756 for OS.

Discussion

About 20-45% of patients with CRC who underwent curative resection had recurrence[24], and one-third of the patients died within 5 years after surgery[25]. It is important to prevent relapse in patients with CRC, even if they underwent curative resection. Recently, preoperative immune nu-

Table 3. Univariate and Multivariate Analyses of DFS in Patients with CRC.

Variables	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (<65/≥65 years)	2.227	0.961-5.759	0.062			
Sex (male/female)	1.008	0.449-2.401	0.984			
BMI (<25/≥25)	1.677	0.578-7.104	0.372			
ASA-PS (<3/≥3)	1.363	0.287-24.389	0.750			
Alb (<3.5/≥3.5)	1.493	0.541-3.563	0.412			
TLC (<1,500/≥1,500)	1.744	0.767-4.303	0.199			
WBCs (≥10,000/<10,000)	1.033	0.058-4.906	0.975			
CRP (≥1/<1)	1.376	0.325-3.993	0.620			
Preoperative CEA (≥5/<5)	2.865	1.281-6.528	0.010*	1.393	0.564-3.554	0.474
Tumor location (rectum/colon)	2.557	1.144-5.933	0.023*	2.591	1.111-6.256	0.028*
Degree of differentiation (por, pap, muc/tub1, tub2)	2.097	0.610-5.543	0.214			
Depth of tumor invasion (T3, T4/Tis, T1, T2)	4.178	1.750-11.529	0.002*	1.096	0.296-3.904	0.888
Lymph node metastasis (present/absent)	3.951	1.765-9.177	0.001*	2.550	0.955-7.640	0.062
Venous invasion (present/absent)	6.850	3.053-15.948	<0.001*	3.714	1.384-11.030	0.009*
Lymphatic vessel invasion (present/absent)	5.000	1.890-17.192	0.003*	1.174	0.282-5.198	0.825
Distant metastasis (present/absent)	7.797	2.555-19.753	<0.001*	3.029	0.921-8.747	0.067
PNI (<46/≥46)	2.972	1.306-7.335	0.009*	3.446	1.376-9.290	0.008*

CRC: colorectal cancer; DFS: disease-free survival; HR: hazard ratio; CI: confidence interval; BMI: body mass index; ASA-PS: American Society of Anesthesiologists Physical Status; Alb: albumin; TLC: total lymphocyte count; WBC: white blood cell; CRP: C-reactive protein; CEA: carcinoembryonic antigen; por: poorly differentiated adenocarcinoma; pap: papillary adenocarcinoma; muc: mucinous adenocarcinoma; tub1: well-differentiated adenocarcinoma; tub2: moderately differentiated adenocarcinoma; PNI: prognostic nutritional index. Values with an asterisk indicate *P*-values of <0.05.

Table 4. Univariate and Multivariate Analyses of OS in Patients with CRC.

Variables	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age (≥65/<65 years)	2.232	1.017-5.242	0.045*	2.969	1.168-8.290	0.022*
Sex (male/female)	1.453	0.652-3.544	0.369			
BMI (<25/≥25)	3.034	0.900-18.882	0.078			
ASA-PS (≥3/<3)	3.283	0.959-8.599	0.057			
Alb (<3.5/≥3.5)	5.775	2.661-12.726	<0.001*			
TLC (<1,500/≥1,500)	1.309	0.601-2.991	0.502			
WBCs (≥10,000/<10,000)	3.770	0.891-10.895	0.068			
CRP (≥1/<1)	3.108	1.134-7.321	0.030*	1.215	0.400-3.285	0.716
Preoperative CEA (≥5/<5)	2.697	1.243-5.943	0.012*	1.164	0.461-2.976	0.749
Tumor location (rectum/colon)	1.459	0.663-3.161	0.340			
Degree of differentiation (por, pap, muc/tub1, tub2)	2.152	0.629-5.633	0.198			
Depth of tumor invasion (T3, T4/Tis, T1, T2)	2.970	1.333-7.244	0.007*	1.242	0.400-3.863	0.706
Lymph node metastasis (present/absent)	1.422	0.606-3.120	0.403			
Venous invasion (present/absent)	3.249	1.451-7.054	0.005*	3.002	1.136-8.150	0.027*
Lymphatic vessel invasion (present/absent)	2.609	1.146-6.684	0.022*	1.334	0.483-3.963	0.585
Distant metastasis (present/absent)	4.173	1.218-10.945	0.026*	2.861	0.723-9.502	0.125
PNI (<46/≥46)	4.670	1.988-12.776	<0.001*	2.889	1.109-8.422	0.029*

CRC: colorectal cancer; OS: overall survival; HR: hazard ratio; CI: confidence interval; BMI: body mass index; ASA-PS: American Society of Anesthesiologists Physical Status; Alb: albumin; TLC: total lymphocyte count; WBC: white blood cell; CRP: C-reactive protein; CEA: carcinoembryonic antigen; por: poorly differentiated adenocarcinoma; pap: papillary adenocarcinoma; muc: mucinous adenocarcinoma; tub1: well-differentiated adenocarcinoma; tub2: moderately differentiated adenocarcinoma; PNI: prognostic nutritional index. Values with an asterisk indicate *P*-values of <0.05.

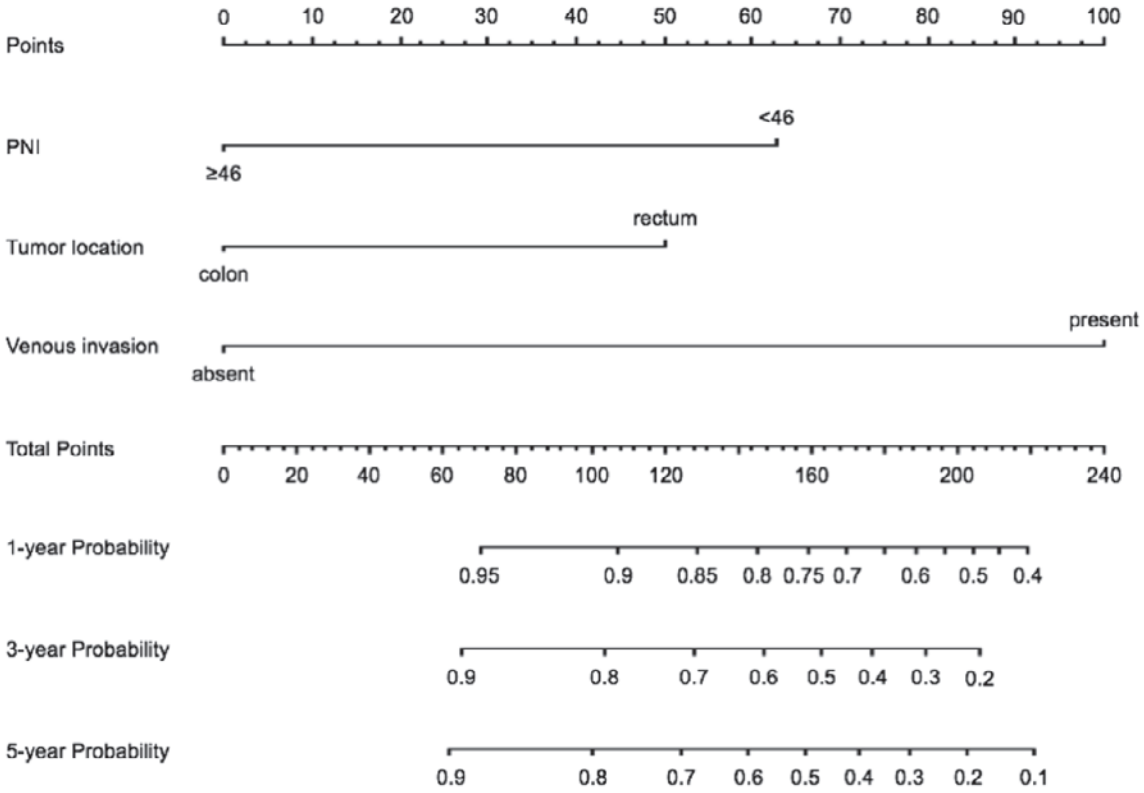

Figure 4. Nomogram to predict DFS for CRC after curative surgical resection. The model was constructed using the Cox regression model. The clinicopathological factors used were the PNI, tumor location, and venous invasion. The prediction model can provide the probabilities of one-year, three-year, and five-year DFS after curative resection for individual patients by comparing the sum of the points identified on the points scale with the prediction scale.

tritional status has been considered to be an indicator of prognosis for patients with CRC. Various methods such as PNI, Glasgow Prognostic Score[26], subjective global assessment[27], and controlling nutritional status[28] have been reported to evaluate the immune nutritional status. In this study, the Kaplan-Meier survival analysis showed that the PNI was significantly associated with prognosis in CRC. It was also revealed that low PNI, tumor location (rectum), and venous invasion were independent risk factors for DFS and that low PNI, advanced age, and venous invasion were independent risk factors for OS. In addition, we examined the relationship between the PNI and TNM stage (Supplementary Figure. S1). Even though the PNI tended to be low as the TNM stage went up, no dominant correlation among them was found. Therefore, we considered that the PNI was an independent prognostic factor that did not depend on the TNM stage. We also examined the survival analysis of DFS and OS according to the TNM stage. The DFS rate did not exhibit a significant difference in all stages (Supplementary Figure. S2). The OS rate was significantly worse in the low-PNI group compared with the high-PNI group in stage I and II patients (Supplementary Figure. S3). However, the number of patients was too small to analyze every stage.

It was previously reported that serum albumin level and number of lymphocytes are associated with the prognosis of cancer[29-31]. Lymphocytes are considered to be essential for the elimination of cancer cells[32], and malnutrition[33,34] and low number of lymphocytes[31,35] have been reported to correlate with an immunosuppressed condition. Inadequate antitumor immunological reaction was caused by the patient's immunosuppressed condition[31,35], which led to the establishment of a favorable microenvironment for recurrence due to interplay among soluble factors such as cytokines, chemokines, surface receptors and adhesion molecules[36]. However, the mechanism still remains to be elucidated.

Several cut-off values of PNI were reported according to the many situations. Various PNI values are used for each purpose. In patients with terminal cancer at 42 days before death, the value of 30 was reported to associate with survival time[37]. The value of 45 was used to predict the postoperative complications for patients with CRC[13], and the value of 45-50 has been reported to be associated with recurrence and mortality in patients with CRC[38-40]. The cut-off value was also 46 in our study. Our method guaranteed satisfactory accuracy as shown in the Kaplan-Meier survival analysis with *P*-value and the nomograms with c-index.

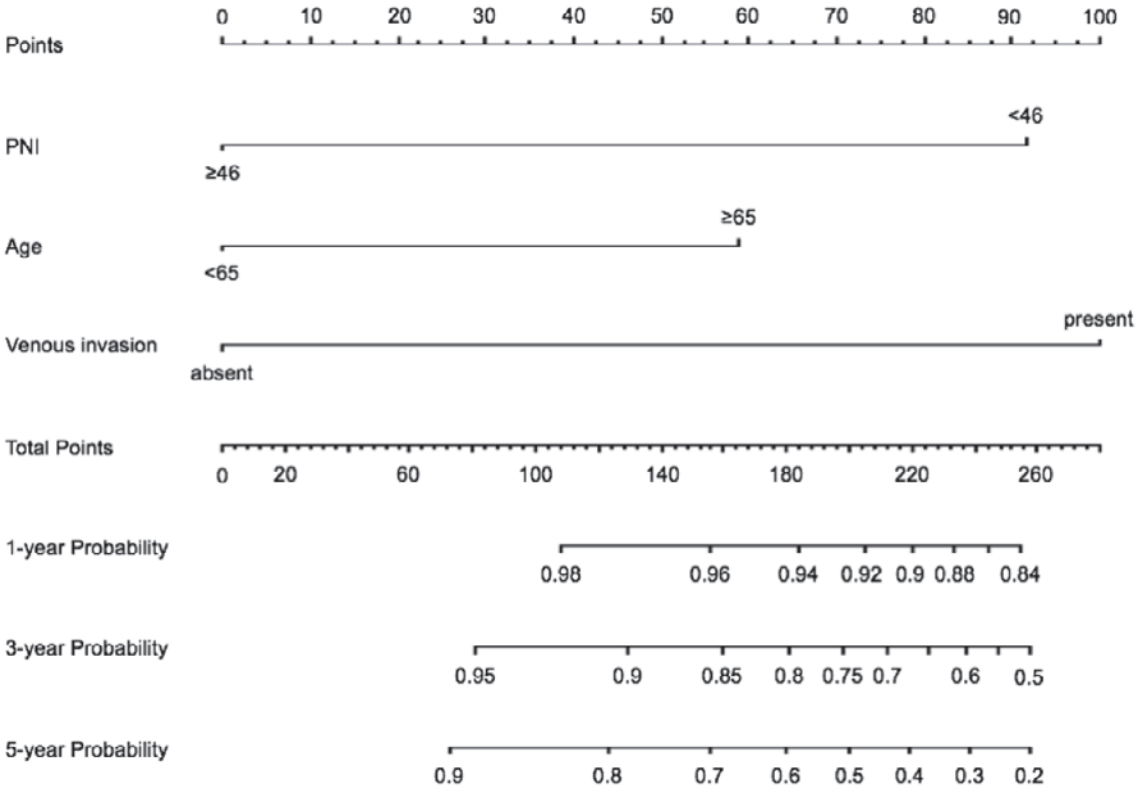

Figure 5. Nomogram to predict OS for CRC after curative surgical resection. The model was constructed using the Cox regression model. The clinicopathological factors used were the PNI, age, and venous invasion. The prediction model can provide the probabilities of one-year, three-year, and five-year OS after curative resection for individual patients by comparing the sum of the points identified on the points scale with the prediction scale.

In order to identify patients with poor survival, we developed novel and reliable personalized prognostic models using the PNI value, leading to the improvement of the strategies for cancer treatment. A nomogram is constructed by combining multiple prognostic variables. It provides more accurate prognostic prediction for individual patients than the classification by a single risk factor and might support the TNM staging system. Useful nomograms have been reported to predict survival for CRC previously. However, there was only one report of the nomogram using PNI, and it was for a patient with non-metastatic CRC to predict their survival[41]. Our study included stage IV patients after curative resection, so this is the first report of nomograms for patients with CRC at all stages. These models will contribute to identifying patients at a high risk of CRC who require careful follow-up and/or postoperative treatment even after curative resection.

There are some limitations in this study. First, this study was retrospective and had a single-center design. Second, we evaluated only a small number of patients. Therefore, a large number of prospective studies should be performed to examine the truly important risk factors and construct better predictive models. Third, we did not evaluate whether the improvement of the preoperative nutritional status led to a better prognosis. Some reports suggested that the enhanced recovery after the surgical protocol was associated with improved five-year cancer-specific survival[42] and was less likely to develop postoperative complications[43]. To clarify the relationship between preoperative PNI and the prognosis, it will be necessary to improve preoperative nutritional status and compare the outcomes.

In conclusion, low PNI was related to recurrence and mortality in patients with CRC who underwent curative surgical resection. We developed novel prognostic prediction models for patients with CRC using the PNI. These models may provide more accurate individual prognostic outcomes and help personalized treatments.

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Conflicts of Interest

There are no conflicts of interest.

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics. 2012. CA Cancer J Clin. 2015 Mar; 65(2): 87-108.

2. Wolpin BM, Mayer RJ. Systemic treatment of colorectal cancer. Gastroenterology. 2008 May; 134(5): 1296-310.

3. De Stefano A, Moretto R, Bucci L, et al. Adjuvant treatment for locally advanced rectal cancer patients after preoperative chemoradiotherapy: when, and for whom? Clin Colorectal Cancer. 2014 Sep; 13(3): 185-91.

4. Papamichael D, Audisio RA, Glimelius B, et al. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol. 2015 Mar; 26(3): 463-76.

5. Sobin LH, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors, 7th ed. Oxford: Wiley-Blackwell; 2009. pp 100-9.

6. Puppa G, Sonzogni A, Colombari R, et al. TNM staging system of colorectal carcinoma: a critical appraisal of challenging issues. Arch Pathol Lab Med. 2010 Jun; 134(6): 837-52.

7. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature. 2008 Jul; 454(7203): 436-44.

8. Compton CC. Colorectal carcinoma: diagnostic, prognostic, and molecular features. Mod Pathol. 2003 Apr; 16(4): 376-88.

9. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care. 2009 May; 12(3): 223-6.

10. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. Nihon Geka Gakkai Zasshi. 1984 Sep; 85(9): 1001-5.

11. Tabira Y, Okuma T, Kondo K, et al. Does neoadjuvant chemotherapy for carcinoma in the thoracic esophagus increase postoperative morbidity? Jpn J Thorac Cardiovasc Surg. 1999 Aug; 47(8): 361-7.

12. Nozoe T, Kimura Y, Ishida M, et al. Correlation of pre-operative nutritional condition with post-operative complications in surgical treatment for oesophageal carcinoma. Eur J Surg Oncol. 2002 Jun; 28(4): 396-400.

13. Mohri Y, Inoue Y, Tanaka K, et al. Prognostic nutritional index predicts postoperative outcome in colorectal cancer. World J Surg. 2013 Nov; 37(11): 2688-92.

14. Sun K, Chen S, Xu J, et al. The prognostic significance of the prognostic nutritional index in cancer: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2014 Sep; 140(9): 1537-49.

15. Chan AW, Chan SL, Wong GL, et al. Prognostic nutritional index (PNI) predicts tumor recurrence of very early/early stage hepatocellular carcinoma after surgical resection. Ann Surg Oncol. 2015 Dec; 22(13): 4138-48.

16. Kanda M, Fujii T, Kodera Y, et al. Nutritional predictors of postoperative outcome in pancreatic cancer. Br J Surg. 2011 Feb; 98 (2): 268-74.

17. Migita K, Takayama T, Saeki K, et al. The prognostic nutritional index predicts long- term outcomes of gastric cancer patients independent of tumor stage. Ann Surg Oncol. 2013 Aug; 20(8): 2647-54.

18. Yang Y, Gao P, Chen X, et al. Prognostic significance of preoperative prognostic nutritional index in colorectal cancer: results from a retrospective cohort study and a meta-analysis. Oncotarget. 2016 Sep; 7(36): 58543-52.

19. Nozoe T, Kohno M, Iguchi T, et al. The prognostic nutritional index can be a prognostic indicator in colorectal carcinoma. Surg Today. 2012 Jun; 42(6): 532-5.

20. Li MX, Liu XM, Zhang XF, et al. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Int J Cancer. 2014 May; 134(10): 2403-13.

21. Watanabe T, Itabashi M, Shimada Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. Int J Clin Oncol. 2012 Feb; 17(1): 1-29.

22. Harrell FE. Regression modeling strategies, with applications to linear models, survival analysis and logistic regression. New York: Springer; 2001. pp256-58.

23. Harrell FE. Package 'rms' - Regression Modeling Strategies. Vienna: The R Foundation for Statistical Computing, 2002.

24. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale-update based on new evidence. Gastroenterology. 2003 Feb; 124(2): 544-60.

25. Mcardle CS, Hole DJ. Outcome following surgery for colorectal cancer: analysis by hospital after adjustment for case-mix and deprivation. Br J Cancer. 2002 Feb; 86(3): 331-5.

26. Mauricio SF, da Silva JB, Bering T, et al. Relationship between nutritional status and the Glasgow Prognostic Score in patient with colorectal cancer. Nutrition. 2013 Apr; 29(4): 625-9.

27. Gupta D, Lammerfeld CA, Vashi PG, et al. Prognostic significance of Subjective Global Assessment (SGA) in advanced colorectal cancer. Eur J Clin Nutr. 2005 Jan; 59(1): 35-40.

28. Iseki Y, Shibutani M, Maeda K, et al. Impact of the preoperative controlling nutritional status (CONUT) score on the survival after curative surgery for colorectal cancer. PLoS One. 2015 Jul; 10(7): e0132488.

29. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J. 2010 Dec; 9(1): 69.

30. Liang L, Zhu J, Jia H, et al. Predictive value of pretreatment lymphocyte count in stage II colorectal cancer and in high-risk patients treated with adjuvant chemotherapy. Oncotarget. 2016 Jan; 7 (1): 1014-28.

31. Ray-Coquard I, Cropet C, Van Glabbeke M, et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. Cancer Res. 2009 Jul; 69(13): 5383-91.

32. Rosenberg SA. Progress in human tumour immunology and immunotherapy. Nature. 2001 May; 411(6835): 380-84.

33. Gao Y, Zhou S, Jiang W, et al. Effects of ganopoly (a Ganoderma lucidum polysaccharide extract) on the immune functions in advanced- stage cancer patients. Immunol Invest. 2003 Aug; 32(3): 201-15.

34. Mainous MR, Deitch EA. Nutrition and infection. Surg Clin North Am. 1994 Jun; 74(3): 659-76.

35. Mazur G, Bogunia-Kubik K, Wrobel T, et al. TGF-beta1 gene polymorphisms influence the course of the disease in non-Hodgkin's lymphoma patients. Cytokine. 2006 Feb; 33(3): 145-9.

36. Chu-Yuan H, Jing P, Yi-Sheng W, et al. The impact of chemotherapy-associated neutrophil/lymphocyte counts on prognosis of adjuvant chemotherapy in colorectal cancer. BMC Cancer. 2013 Apr; 13(1): 177.

37. Koyama N, Matsumura C, Morii H, et al. Investigation of optimal time for starting betamethasone using fatigue scores and prognostic nutritional index in terminally ill patients with cancer-related fatigue. Am J Hosp Palliat Care. 2017 Jun; 34(5): 449-55.

38. Tokunaga R, Sakamoto Y, Nakagawa S, et al. Prognostic nutri-

tional index predicts severe complications, recurrence, and poor prognosis in patients with colorectal cancer undergoing primary tumor resection. Dis Colon Rectum. 2015 Nov; 58(11): 1048-57.

39. Shibutani M, Maeda K, Nagahara H, et al. The prognostic significance of the postoperative prognostic nutritional index in patients with colorectal cancer. BMC Cancer. 2015 Jul; 15(1): 521.

40. Song Y, Yang Y, Gao P, et al. The preoperative neutrophil to lymphocyte ratio is a superior indicator of prognosis compared with other inflammatory biomarkers in resectable colorectal cancer. BMC Cancer. 2017 Nov; 17(1): 744.

41. Jiang H, Tang E, Xu D, et al. Development and validation of nomograms for predicting survival in patients with non-metastatic colorectal cancer. Oncotarget. 2017 May; 8(18): 29857-64.

42. Gustafsson UO, Oppelstrup H, Thorell A, et al. Adherence to the ERAS protocol is associated with 5-year survival after colorectal cancer surgery: a retrospective cohort study. World J Surg. 2016 July; 40(7): 1741-7.

43. Eskicioglu C, Forbes SS, Aarts MA, et al. Enhanced recovery after surgery (ERAS) programs for patients having colorectal surgery: a meta-analysis of randomized trials. J Gastrointest Surg. 2009 Dec; 13(12): 2321-9.

Supplementary Files

Supplementary Table S1. Univariate and multivariate analyses of DFS including the TNM stage in patients with CRC.

Supplementary Table S2. Univariate and multivariate analyses of OS including the TNM stage in patients with CRC.

Supplementary Figure S1. Relationship between the PNI and TNM stage.

Supplementary Figure S2. DFS curves according to the TNM stage by the PNI.

Supplementary Figure S3. OS curves according to the TNM stage by the PNI.

Please find supplementary file(s);
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