

## The Combination of Prognostic Nutritional Indicator and Serum Carcinoembryonic Antigen is Useful in Predicting Postoperative Recurrence in Stage II Colorectal Cancer

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### ABSTRACT

**Background** The efficacy of adjuvant chemotherapy in stage II colorectal cancer (CRC) patients has not been clearly demonstrated. Therefore, identification of robust prognostic factors is crucial for the assessment of recurrence risk in stage II CRC and appropriate adjuvant treatment, in clinical practice.

**Methods** We enrolled 135 colorectal adenocarcinoma patients who underwent proctocolectomies and had histologically diagnosed stage II CRC.

**Results** Receiver operating characteristic (ROC) analysis, to evaluate the predictive ability of certain serum factors for CRC recurrence, indicated that the prognostic nutritional indicator (PNI), followed by serum carcinoembryonic antigen (CEA) level, were the strongest predictive metrics. Based on cutoff values from ROC analyses, patients were divided as follows; CEA<sup>High</sup> ( $\geq 4.55$  ng/mL), CEA<sup>Low</sup> ( $< 4.55$  ng/mL), PNI<sup>High</sup> ( $\geq 47.72$ ), and PNI<sup>Low</sup> ( $< 47.72$ ). The recurrence rates of patients with CEA<sup>High</sup> and PNI<sup>Low</sup>, CEA<sup>High</sup> and PNI<sup>High</sup>, CEA<sup>Low</sup> and PNI<sup>Low</sup>, and CEA<sup>Low</sup> and PNI<sup>High</sup> were 34.3%, 0%, 6.8%, and 2.6%, respectively (a significant difference at  $P < 0.0001$ ). Logistic regression analysis revealed that the combination of serum CEA level and PNI was an independent predictive indicator of tumor recurrence after operation in stage II CRC patients. The 5-year disease specific survival rates of patients with CEA<sup>Low</sup>PNI<sup>High</sup>, CEA<sup>High</sup>PNI<sup>High</sup>, CEA<sup>Low</sup>PNI<sup>Low</sup>, CEA<sup>High</sup>PNI<sup>Low</sup> were 100%, 100%, 97.4%, and 77.5%, respectively ( $P < 0.0001$ ).

**Conclusion** The combination of CEA and PNI was useful in predicting postoperative recurrence in stage II CRC patients.

**Key words** carcinoembryonic antigen; colorectal cancer; prognostic nutritional indicator; prognosis

The efficacy of adjuvant chemotherapy in stage II colorectal cancer (CRC) patients has not been clearly demonstrated.<sup>1–3</sup> Therefore, adjuvant chemotherapy is

generally recommended only for patients with high-risk stage II CRC. The conventional factors to identify high-risk stage II CRC are; T stage, histology, the number of dissected lymph nodes, vascular or lymphatic invasion, and intestinal occlusion or perforation. However, these factors have often failed to show significant prognostic value in prospective clinical studies.<sup>4</sup> In this context, the identification of robust prognostic factors is crucial for appropriate assessment of recurrence risk in stage II CRC and appropriate adjuvant treatment in clinical practice.

Establishing non-invasive prognostic predictors from hematological and serologic markers for various cancers has garnered widespread interest. Serum markers that reflect inflammation, immune and nutritional states can be obtained from routine blood tests. Several indicators that use these markers, such as neutrophil to lymphocyte ratio, C-reactive protein (CRP) to albumin ratio and prognostic nutritional indicator (PNI), can help predict the prognosis of various cancer types, including CRC.<sup>5–7</sup> However, it remains unclear whether these indicators are useful in identifying high-risk stage II CRC patients. The aim of the current study was to determine the predictive ability of a panel of serum based-indicators in identifying high-risk stage II CRC patients.

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Abbreviations: 5-FU, 5-fluorouracil; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CONUT, controlling nutrition status; CRC, colorectal cancer; CRP, C-reactive protein; FOLFIRI, 5-FU and leucovorin with irinotecan; FOLFOX, 5-FU and leucovorin with oxaliplatin; LC, lymphocyte count; PNI, prognostic nutritional indicator; ROC, Receiver operating characteristic

## MATERIALS AND METHODS

### Patients

This study was based on retrospective analysis of 135 colorectal adenocarcinoma patients who underwent proctocolectomies at Tottori University Hospital and were histologically diagnosed with stage II CRC between January 2006 and December 2013. Patients who received preoperative chemotherapy or radiation therapy were excluded from this study. The clinicopathologic findings were determined according to the Japanese Classification of Colonic Carcinoma.<sup>8</sup>

Adjuvant chemotherapy was principally performed in patients with high risk of recurrence, such as T4 (depth of invasion), presence of intestinal occlusion and perforation, presence of vascular or lymphatic invasion, and undifferentiated histology. Among the 135 patients included in the current study, 34 patients underwent adjuvant chemotherapy with 5-fluorouracil (5-FU) based regimens, such as S-1, tegafur-uracil, 5-FU and leucovorin with oxaliplatin (FOLFOX) or with irinotecan (FOLFIRI), and tegafur-uracil with leucovorin.

Patients were periodically checked for recurrence by diagnostic imaging (using chest X-ray, colonoscopy, ultrasonography, computed tomography and magnetic resonance imaging). The causes of death and patterns of recurrence were determined by reviewing medical records (including laboratory data, ultrasonography, computed tomography, scintigrams, peritoneal punctures, and laparotomies) or by questioning family members. Recurrence was observed in 16 patients. At the time of analysis, the median follow-up period of the 88 surviving patients was 76.1 months. Of 47 patient deaths, 9 were related to recurrence of CRC and 38 to an unrelated malignancy, disease or accident.

Clinicopathological data including; age, sex, tumor localization, tumor size, depth of invasion, lymph node metastasis, distant metastasis, lymphatic invasion, and vascular invasion, were obtained from the hospital database. We also collected data for the absolute numbers of certain circulating blood cells (peripheral lymphocyte count (LC), monocyte count, neutrophil count, platelet count) and the serum levels of albumin, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and CRP from patients' preoperative blood test results (within one month before surgery). The neutrophil lymphocyte ratio, platelet lymphocyte ratio, and monocyte lymphocyte ratio were defined by dividing the neutrophil count, platelet count, and monocyte count by the LC, respectively. PNI was calculated using the formula:  $10 \times \text{serum albumin level (g/dL)} + 0.005 \times \text{total peripheral LC (/mm}^3\text{)}$ .<sup>9</sup> CRP to albumin ratio was defined by dividing the serum CRP level

by the serum albumin level. The controlling nutrition status (CONUT) score was calculated based on serum albumin, total cholesterol, and total LC: these factors were scored according to cut-off values, and the sum of the scores was used as the CONUT score.<sup>10</sup> Our study was approved by the institutional review board (18A052) and the informed consent requirement was waived for this retrospective study.

### Statistical analysis

The recurrence rates were compared using  $\chi^2$  tests. The correlation between serum CEA level and PNI was analyzed by calculating the Spearman rank correlation coefficient. The area under the curve (AUC) values calculated by receiver operating characteristic (ROC) analysis was used to compare the predictive ability of serum biomarkers for tumor recurrence. The Youden index was calculated by ROC analysis to determine optimal cutoff values for serum CEA level and PNI. Survival curves were calculated according to the Kaplan–Meier method. For disease-specific survival, patients who died from causes other than CRC were considered lost to follow-up at the time of death. Significance testing between survival curves was performed with log rank tests. We used logistic regression analysis to determine predictive factors associated with CRC recurrence after operation.  $P \leq 0.05$  was considered significant in all tests. GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, CA) and StatView 5.0 (Abacus Concepts, Inc., Berkeley, CA) software were used for the statistical analyses.

## RESULTS

### Clinicopathological features of the patients included in the current study

The clinicopathological features of the study population are shown in Table 1. Tumor sites were most common in the rectum, followed by the sigmoid colon and ascending colon. Thirty-four patients received postoperative adjuvant therapy. With regard to conventional predictive factors for cancer recurrence in stage II CRC; undifferentiated adenocarcinoma including poorly differentiated adenocarcinoma was observed in 16 patients, T4 lesion in 12 patients, the number of lymph nodes removed in surgery  $< 12$  in 30 patients, intestinal occlusion in 16 patients, and intestinal perforations in one patient. Lymphatic and vascular invasion metrics were as follows; ly1 and ly2 were observed in 88 and 47 patients, respectively, while v1, v2 and v3 were observed in 84 patients, 38 patients, and 9 patients, respectively.<sup>10</sup>

**Table 1. Patient overview (n = 135)**

Variables	Mean ± SD	Number (%)
Age (years)	71.0 ± 9.9	
Gender		
Male		76 (56.3)
Female		59 (43.7)
Tumor location		
Cecum		9 (6.7)
Ascending colon		28 (20.7)
Transverse colon		17 (12.6)
Descending colon		3 (2.2)
Sigmoid colon		28 (20.8)
Rectum		50 (37.0)
Histology*		
Differentiated		119 (88.1)
Undifferentiated		16 (11.9)
Depth of invasion†		
T3		123 (91.1)
T4		12 (8.9)
Lymphatic invasion‡		
ly0		0 (0)
ly1		88 (65.2)
ly2		47 (34.8)
ly3		0 (0)
Venous invasion§		
v0		4 (3)
v1		84 (62.2)
v2		38 (28.1)
v3		9 (6.7)
Operation		
Open		85 (63)
Laparoscopy		50 (37)
Adjuvant chemotherapy		
Absent		101 (74.8)
Present		34 (25.2)
Number of dissected lymph nodes		
< 12		30 (22.2)
≥ 12		105 (77.8)
Intestinal occlusion		
Absent		119 (88.1)
Present		16 (11.9)
Intestinal perforation		
Absent		134 (99.3)
Present		1 (0.7)

\*Differentiated, papillary, or tubular adenocarcinoma; undifferentiated, poorly differentiated, mucinous adenocarcinoma, and signet-ring cell carcinoma. †Depth of invasion: T3, tumor invasion of the subserosa or within adventitia; T4, tumor penetration of the serosa or tumor invasion of adjacent organs. ‡Lymphatic invasion: ly0–ly3, grade of lymphatic invasion. §Venous invasion: v0–v3, grade of venous invasion. ||Colorectal obstruction due to colorectal cancer based on the findings of abdominal computed tomography and colonoscopy.

### Prognostic indicator in stage II CRC

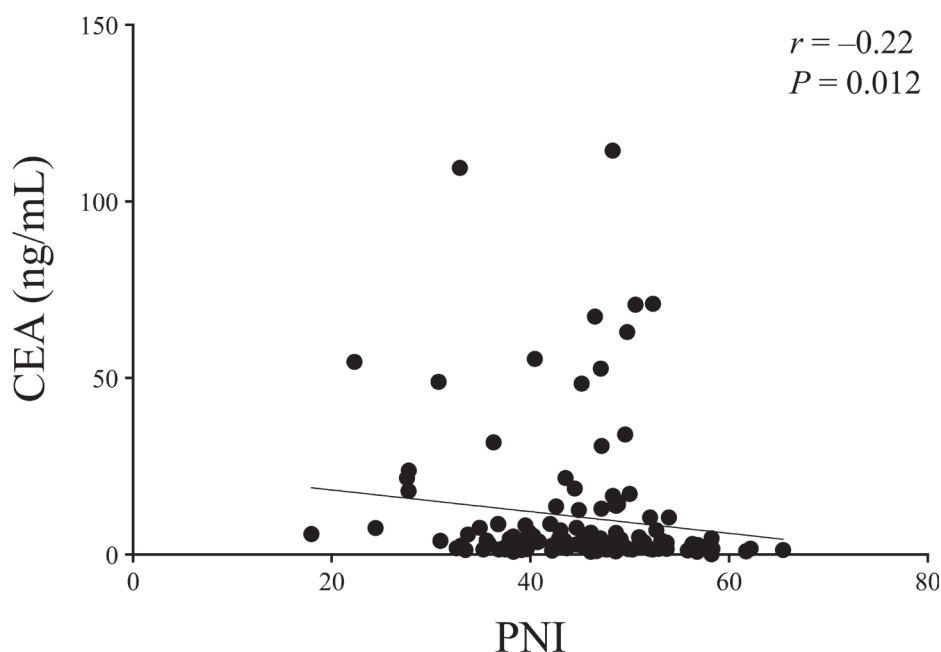
ROC curves were constructed, and the AUC values were compared to assess the ability of serum-based indicators (Table 2) to predict CRC recurrence. The AUC of PNI was the highest, followed by serum CEA level, indicating that they are most useful in identifying high-risk stage II CRC patients, among the indicators included in this study. Although there was a statistically significant correlation between CEA and PNI, the relative coefficient was low ( $r = -0.22$ ,  $P = 0.012$ , Fig. 1). This indicates that the combination of CEA and PNI might be more useful than either CEA or PNI alone, in identifying high-risk stage II CRC patients. ROC analysis indicated that optimal cutoff values of CEA and PNI were 4.55 ng/mL and 47.72, respectively. Based on these cutoff values, patients were divided as follows; CEA<sup>High</sup> ( $\geq 4.55$  ng/mL), CEA<sup>Low</sup> ( $< 4.55$  ng/mL), PNI<sup>High</sup> ( $\geq 47.72$ ), and PNI<sup>Low</sup> ( $< 47.72$ ). The number of patients with CEA<sup>High</sup> and PNI<sup>Low</sup>, CEA<sup>High</sup> and PNI<sup>High</sup>, CEA<sup>Low</sup> and PNI<sup>Low</sup>, and CEA<sup>Low</sup> and PNI<sup>High</sup> were 35, 17, 44, and 39. The recurrence rates of patients with CEA<sup>High</sup> and PNI<sup>Low</sup>, CEA<sup>High</sup> and PNI<sup>High</sup>, CEA<sup>Low</sup> and PNI<sup>Low</sup>, and CEA<sup>Low</sup> and PNI<sup>High</sup> were 34.3%, 0%, 6.8%, and 2.6%, respectively, and this difference was statistically significant ( $P < 0.0001$ ; Fig. 2). Logistic regression analysis revealed that the combination of serum CEA level and PNI was an independent predictive indicator for recurrence after operation in stage II CRC patients (Table 3). The five year disease-specific survival rates of patients with CEA<sup>Low</sup>PNI<sup>High</sup>, CEA<sup>High</sup>PNI<sup>High</sup>, CEA<sup>Low</sup>PNI<sup>Low</sup>, and CEA<sup>High</sup>PNI<sup>Low</sup> and were 100%, 100%, 97.4%, and 77.5%, respectively ( $P < 0.0001$ , Fig. 3), indicating that the combination of serum CEA level and PNI was also useful in predicting disease-specific survival in stage II CRC patients.

Finally, we determined the usefulness of the combination of CEA and PNI as a predictive indicator for recurrence in either stage II CRC patients who underwent adjuvant chemotherapy or those who did not undergo adjuvant chemotherapy. Among stage II CRC patients who underwent adjuvant chemotherapy, the number of patients with CEA<sup>High</sup> and PNI<sup>Low</sup>, CEA<sup>High</sup> and PNI<sup>High</sup>, CEA<sup>Low</sup> and PNI<sup>Low</sup>, and CEA<sup>Low</sup> and PNI<sup>High</sup> were 8, 6, 8, and 11, respectively. Among stage II CRC patients who did not undergo adjuvant chemotherapy, the number of patients with CEA<sup>High</sup> and PNI<sup>Low</sup>, CEA<sup>High</sup> and PNI<sup>High</sup>, CEA<sup>Low</sup> and PNI<sup>Low</sup>, and CEA<sup>Low</sup> and PNI<sup>High</sup> were 27, 11, 35, and 28, respectively. In stage II CRC patients who underwent adjuvant chemotherapy, the recurrence rates were 62.5% and 4.0% in patients with CEA<sup>High</sup> and PNI<sup>Low</sup> and other patients, respectively ( $P = 0.0013$ ; Fig. 4a). Furthermore, the

**Table 2. Receiver operating characteristic analysis of possible recurrence indicators**

	AUC	95% CI	P value
CEA	0.665	0.508–0.823	0.032
CA19-9	0.567	0.387–0.748	0.38
NLR	0.522	0.364–0.680	0.78
PLR	0.616	0.474–0.757	0.13
MLR	0.655	0.514–0.796	0.044
PNI	0.693	0.574–0.812	0.012
CRP / ALB	0.559	0.390–0.727	0.45
CONUT score	0.650	0.524–0.777	0.052

ALB, albumin; AUC, area under curve; CI, confidence interval; MLR, monocyte lymphocyte ratio; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio



**Fig. 1.** The correlation between serum CEA concentration and PNI.

five-year disease-specific survival rates were 72.9% and 95.5% in patients with CEA<sup>High</sup> and PNI<sup>Low</sup> and other patients, respectively ( $P = 0.0097$ ; Fig. 4c). In stage II CRC patients without adjuvant chemotherapy, the recurrence rates were 25.9% and 4.1% in patients with CEA<sup>High</sup> and PNI<sup>Low</sup> and other patients, respectively ( $P = 0.0033$ ; Fig. 4b). Furthermore, the five-year disease-specific survival rates were 78.3% and 100% in patients with CEA<sup>High</sup> and PNI<sup>Low</sup> and other patients, respectively ( $P < 0.0001$ ; Fig. 4d).

## DISCUSSION

For CRC, radical resection (R0 resection) offers the best chance of cure. However, a substantial number of

patients experience recurrence even after R0 resection because of micrometastases that cannot be detected by ordinary diagnostics, such as ultrasonography, computed tomography, and positron emission tomography. Therefore, adjuvant chemotherapy has been recommended for clearing these microscopic tumors: the principle being that the circulation of anticancer drugs through the entire body can control micrometastases and prevent cancer recurrence. The efficacy of postoperative adjuvant chemotherapy in preventing recurrence has been shown in CRC patients who underwent curative operations<sup>3, 11</sup>; however, its efficacy remains unclear in stage II CRC patients. In fact, a recent study failed to demonstrate the effectiveness of adjuvant chemotherapy

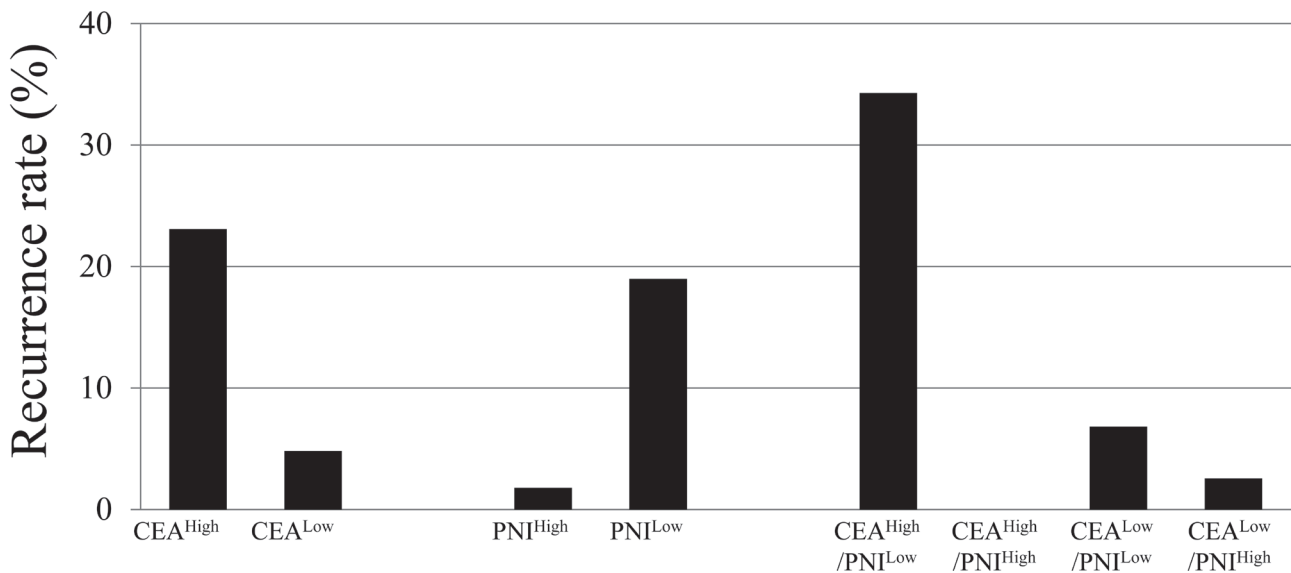


Fig. 2. Recurrence rates of stage II CRC patients according to serum CEA concentration and PNI.

Table 3. Logistic regression analysis of predictive factors associated with recurrence

Variables	<i>P</i> value	Odds ratio	95% CI
Age (years) ( $\geq 75$ vs. $< 75$ )	0.42	0.520	0.104–2.590
Gender (male vs. female)	0.17	0.345	0.075–1.590
Location (rectum vs. colon)	0.38	2.030	0.415–9.900
Depth of invasion (T4 vs. T3)	0.64	1.610	0.211–12.30
Approach (laparoscopy vs. open)	0.39	1.970	0.414–9.360
Histology (undifferentiated vs. differentiated)	0.09	5.800	0.749–44.80
Intestinal occlusion (present vs. absent)	0.54	1.840	0.258–13.10
Lymphatic invasion (ly2/3 vs. ly 0/1)	0.87	1.120	0.272–4.640
Vascular invasion (v2/3 vs. v0/1)	0.37	1.830	0.484–6.940
Number of dissected lymph nodes ( $< 12$ vs. $\geq 12$ )	0.76	0.753	0.125–4.540
Adjuvant chemotherapy (present vs. absent)	0.46	1.740	0.402–7.500
CEA and PNI (CEA <sup>High</sup> PNI <sup>Low</sup> vs. others)	0.0005	14.50	3.200–65.80

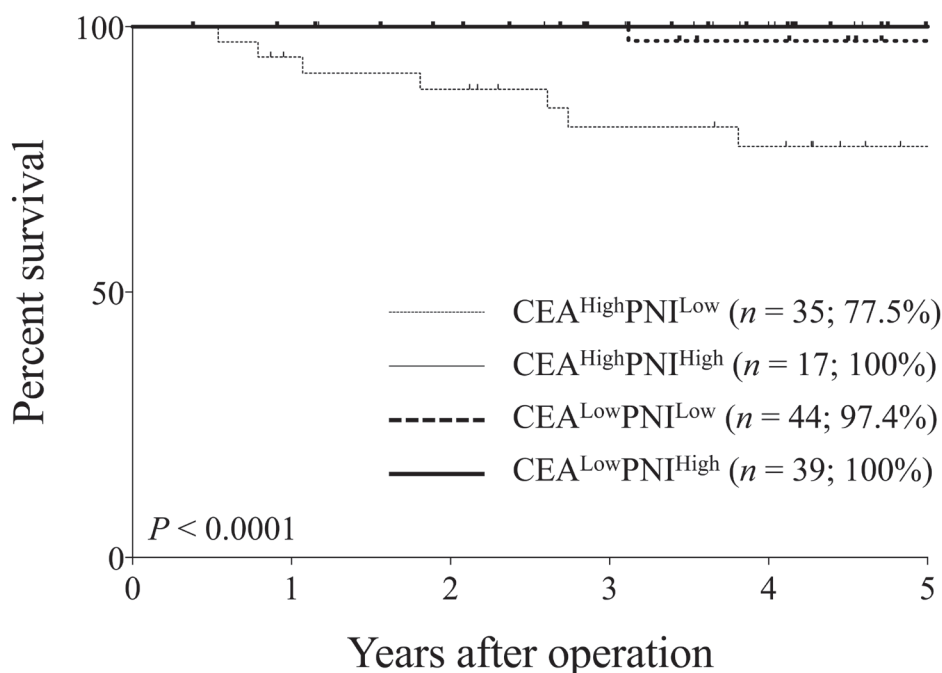
CI, confidence interval. See table 1 for the detail of depth of invasion and lymphatic or vascular invasion.

with oral tegafur-uracil in stage II CRC patients.<sup>12</sup> As such, most treatment guidelines recommend adjuvant chemotherapy only for stage II CRC patients with a high possibility of recurrence.

In the current study, we determined the prognostic value of serum-based indicators and demonstrated that the combination of CEA and PNI was useful in identifying high-risk stage II CRC patients. CEA, a glycoprotein, was the first human cancer-associated antigen to be identified, in colon carcinoma in 1965,<sup>13</sup> and is the most frequently used tumor marker for CRC prognosis. CEA is produced in gastrointestinal tissue during fetal

development, and production normally stops before birth, therefore the serum level of this protein becomes very low after birth, or is undetectable. Some tumors produce this protein and its subsequent elevation in the serum of those patients allows it to be used as a tumor marker in clinical tests. CEA is recommended by the NCCN guidelines as a prognostic and monitoring indicator.

The PNI, as described by Onodera et al.,<sup>9</sup> is a simple index calculated by the serum albumin concentration and total LC to evaluate a patient's nutritional status. The PNI was originally designed to assess perioperative



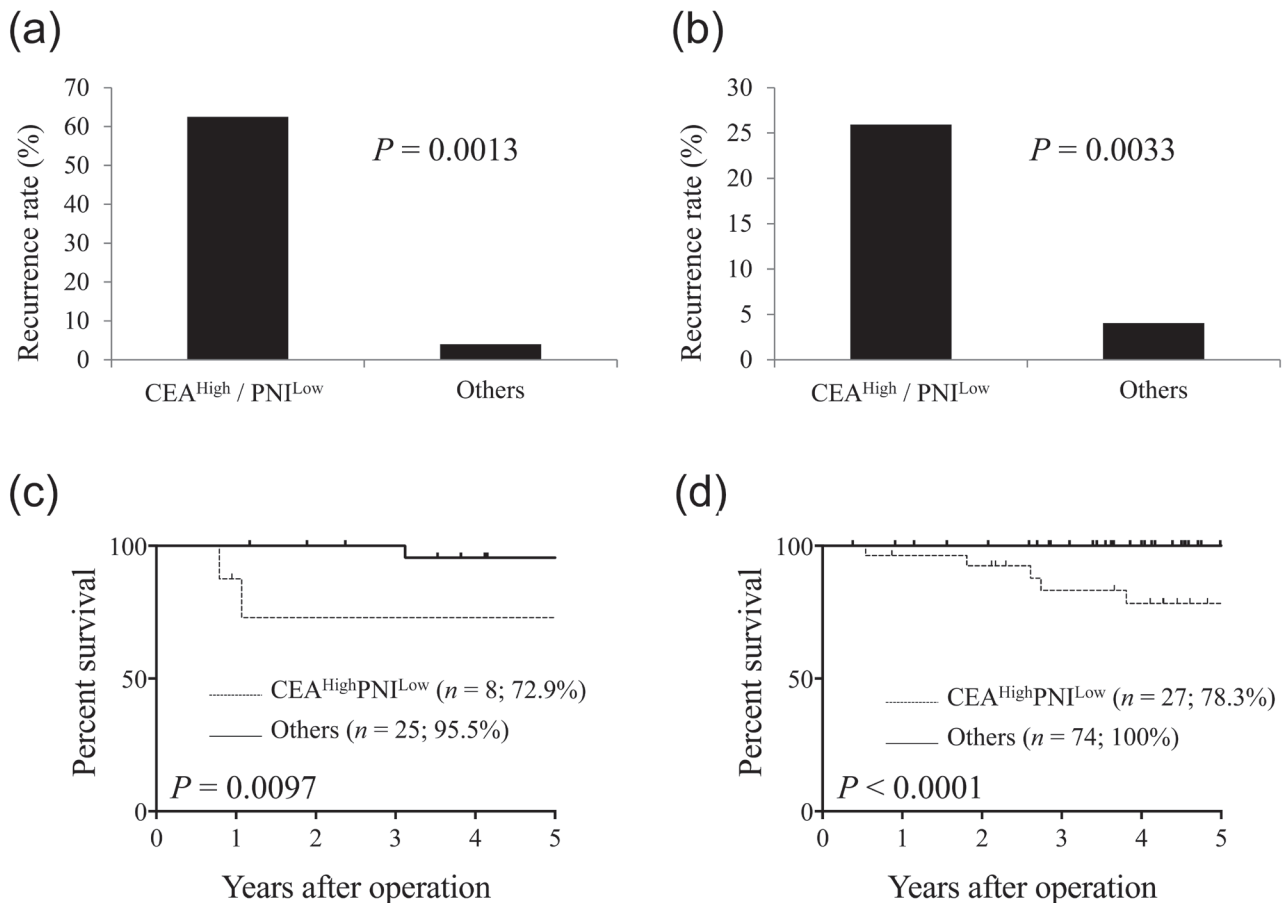
**Fig. 3.** Disease-specific survival rates of stage II CRC patients according to serum CEA concentration and PNI.

nutritional conditions and postoperative complications in patients with CRC in Japan.<sup>9</sup> It is simple to calculate and easily implemented in clinical practice. Since PNI includes the peripheral LC, it is also believed to reflect a patient's immune status. Furthermore, prolonged inflammation impairs the production of albumin, which results in its low serum concentration.<sup>14</sup> Therefore, the PNI is also influenced by patients' inflammation status. During the past few years, the capacity of the described PNI to predict both morbidity and long-term outcomes of patients with various malignancies has been recognized. It also has been shown to be a useful prognostic indicator in CRC patients.<sup>7</sup> The close correlation between low PNI and high recurrence rate was observed in this study. In this regard, The LC, which is indicator used to determine the PNI, is believed to reflect patients' immune status. Lymphopenia is frequently observed in patients with advanced cancer, and several studies have shown that a low preoperative LC is related to a poor prognosis in patients with various types of cancer.<sup>15–18</sup> These findings suggest that the LC in peripheral blood reflects immune activity against cancer cells. Furthermore, peripheral lymphocytes also include natural killer cells, gamma-delta T cells, natural killer T cells, and B cells. A close correlation between decreased numbers of these immune cells and poor prognosis has also been demonstrated in both peripheral blood and cancer tissue in patients with some types of cancer.<sup>19–21</sup> Therefore, the peripheral LC might be

a good indicator of the cell-mediated immune status, including both acquired and adaptive immunity, and the humoral immune status against CRC. Overall, the PNI might be an effective indicator of immune status in CRC patients.

Our results here demonstrate that the combination of CEA and PNI measurements was more useful in identifying high-risk stage II CRC patients than either CEA or PNI values alone. Furthermore, multivariate analysis revealed that the combination of CEA and PNI values was an independent predictive indicator of recurrence in stage II CRC patients. Notably, the T stage, the number of dissected lymph nodes, vascular or lymphatic invasion, and intestinal occlusion, all of which were recommended in most guidelines to identify high-risk stage II CRC, were not identified as predictive indicators in this study. CEA is principally produced by the tumor cells, whereas PNI reflects the patient's immune, inflammation, and nutritional states. Our results indicate that it is important to consider both cancer-related factors and patient-related factors in identifying which stage II CRC cancer patients are high-risk, when used serum-based indicators. Furthermore, serum CEA level can be influenced by various nonmalignant conditions, including smoking status, renal function, and diabetes mellitus. The combination of CEA and PNI is likely to minimize such influences compared with the usage of CEA alone when predicting the recurrence.

There are some limitations with this study: As a



**Fig. 4.** Recurrence rates of stage II CRC patients with (a) or without (b) adjuvant chemotherapy according to serum CEA concentration and PNI. Recurrence-free survival rates of stage II CRC patients with (c) or without (d) adjuvant chemotherapy according to serum CEA concentration and PNI.

retrospective study, some bias was present. We also only measured eight indicators in this study, and other unmeasured serum-based indicators are possibly associated with recurrence in stage II CRC patients. In addition, the number of patients included in the current study was small and a large-scale trial is needed to confirm our results.

In conclusion, the combination of CEA and PNI measurements was useful in predicting high-risk stage II CRC. Treatment strategies guided by these indicators might improve the prognosis of CRC patients.

*The authors declare no conflict of interest.*

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