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Significance of the Prognostic Immune and Nutritional Index in Patients With Stage I-III Colorectal Cancer

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Abstract. *Background/Aim: Recently, the prognostic immune and nutritional index (PINI), which is calculated from the peripheral monocyte count and serum albumin level, has been reported to be useful as a prognostic marker in Korean and Chinese patients with colorectal cancer. The present study therefore examined the usefulness of the PINI as a marker for predicting the prognosis in Japanese colorectal cancer patients. Patients and Methods: A total of 529 patients who underwent curative surgery for stage I-III colorectal cancer between January 2015 and December 2019 were enrolled in this study. The PINI was calculated as [serum albumin concentration (g/dl)×0.9]–[peripheral monocyte count (mm^3)×0.0007]. Results: The median PINI was 3.242 (range=1.250-4.091). A receiver operating characteristic curve analysis revealed that the appropriate cut-off value of the PINI was 3.047. The low-PINI group had significantly lower relapse-free and overall survival rates than the high-PINI group (p<0.0001, p<0.0001, respectively). Conclusion: The PINI based on host factors is useful as a prognostic marker for Japanese patients with stage I-III colorectal cancer.*

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The prognosis of colorectal cancer is generally predicted by the TNM classification based on pathological findings (1). It is true that the TNM classification is closely related to the prognosis and is very useful in daily practice when determining treatment strategies, such as indications for adjuvant chemotherapy (2, 3). However, it is also true that there are differences in the prognosis even within the same TNM stage (4, 5). This may be because not only tumor factors, such as the tumor depth and lymph node metastasis, but also host factors, such as systemic inflammation and the nutritional status, are important factors affecting the prognosis of cancer patients.

Many prognostic markers related to host factors, such as the neutrophil-to-lymphocyte ratio (6), lymphocyte-to-monocyte ratio (7), modified Glasgow prognostic score (8), and C-reactive protein-to-albumin ratio (9), have been reported. All of these are excellent markers that correlate with the prognosis, but which marker has the best predictive value is unclear.

Recently, Sang-Hyuk Jung *et al*. reported that the prognostic immune and nutritional index (PINI), which is calculated from the peripheral monocyte count and serum albumin level, is useful as a prognostic marker in patients with colorectal cancer (10). Most of the known markers based on host factors that have been reported consist of either the number of immunocompetent cells in peripheral blood or serum protein concentration, but the PINI is a new indicator that combines both. A comparison of the predictive value of existing host-factor-based prognostic markers revealed that the PINI was the best prognostic marker (10). Following the large-scale study of Sang-Hyuk Jung *et al*. in Koreans, the large-scale study of Hailun Xie *et al*. in a Chinese population confirmed the usefulness of the PINI as a prognostic marker (11). In addition, a correlation between the PINI and postoperative complications was also found (11).

The present study therefore examined the usefulness of the PINI as a marker for predicting the prognosis and postoperative complications in Japanese colorectal cancer patients.

Patients and Methods

Patients. We retrospectively evaluated 529 consecutive patients who underwent curative surgery for stage I-III colorectal cancer at the Department of Gastroenterological Surgery of Osaka City University Hospital between January 2015 and December 2019. This retrospective study was approved by the Ethics Committee of Osaka City University (approval number: 4182) and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent for the treatment and data analyses.

Methods. Patients routinely received blood tests within a period of two weeks prior to the operation. The PINI was calculated as [serum albumin concentration (g/dl)×0.9]–[peripheral monocyte count (mm^3)×0.0007]. An appropriate cut-off value for the PINI was determined based on a receiver operating characteristic (ROC) curve analysis, and the patients were then classified into low-PINI and high-PINI groups.

Associations between the PINI and clinicopathological factors was analyzed using a chi-squared test and Fisher's exact test. The relapse-free survival was defined as the time from the date of operation until the date of diagnosis of first recurrence, death from any cause, or last follow-up. The overall survival was defined as the time from the date of operation until the date of death from any cause or last follow-up. Survival curves were estimated using the Kaplan-Meier method, and differences in the survival curves were assessed with a log-rank test. A multivariate Cox proportional hazard model was used to evaluate the prognostic factors associated with survival. Variables with a *p*-values of <0.1 in the univariate analysis were evaluated in the multivariate analysis. *p*-Values of <0.05 were considered to indicate statistical significance.

All analyses were conducted using the IBM SPSS Statistics software program for Windows (version 26; IBM Corp., Armonk, NY, USA).

Results

There were 313 men and 216 women and the median age of the overall population was 71 years (range=21-100 years). The median PINI was 3.242 (range=1.250-4.091). The median duration of follow-up was 50.3 months. One hundred and five patients (19.8%) relapsed, and 77 patients (14.6%) died during the follow-up period.

Classification according to the PINI. The PINI, as a continuous variable, was used as the test variable, and the five-year survival was used as the state variable. A ROC curve analysis revealed that the appropriate cut-off value of the PINI was 3.047 (sensitivity: 71.2%, specificity: 59.0%) (Figure 1). We therefore set 3.047 as the cut-off value and classified patients into the low-PINI (n=176) and high-PINI (n=353) groups.

Associations between the PINI and clinicopathological factors. The associations between the PINI and clinicopathological factors are shown in Table I. A low PINI was significantly associated with a larger tumor diameter, higher T stage, undifferentiated histological type, and higher carcinoembryonic antigen (CEA) level than a high PINI.

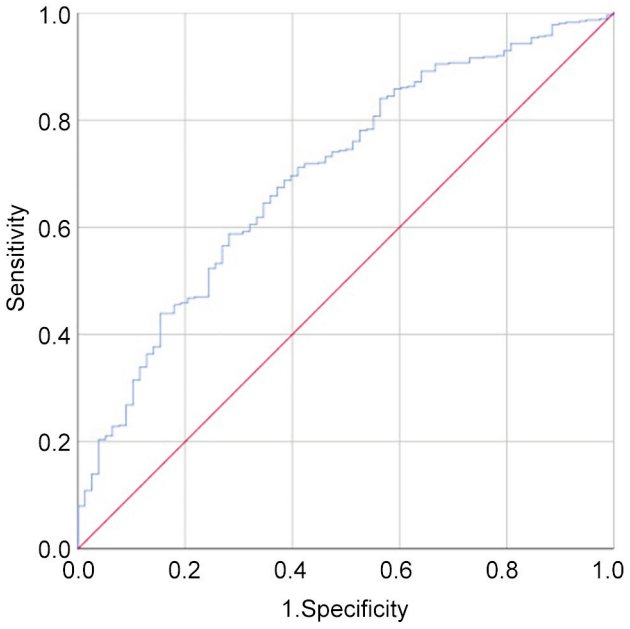

Figure 1. *A receiver operating characteristic curve analysis of the prognostic immune and nutritional index. Area under the curve (AUC): 0.699; 95% confidence interval=0.637-0.761; p<0.001.*

Results of a survival analysis according to the PINI. The low-PINI group had significantly lower relapse-free and overall survival rates than the high-PINI group ($p<0.0001$, $p<0.0001$, respectively) (Figure 2).

Prognostic factors for the relapse-free/overall survival identified by univariate and multivariate analyses. The associations between the relapse-free survival and various clinicopathological factors are shown in Table II. According to the univariate analysis, the relapse-free survival was significantly associated with the tumor diameter, tumor depth, lymph node metastasis, and PINI. The multivariate analysis indicated that a higher T stage (T4), the presence of lymph node metastasis, and a low PINI were independent prognostic factors for a poor relapse-free survival.

The associations between the overall survival and various clinicopathological factors are shown in Table III. According to the univariate analysis, the overall survival was significantly associated with the tumor depth, histological type, lymph node metastasis, and PINI. The multivariate analysis indicated that a higher T stage (T4) and low PINI were independent prognostic factors for a poor overall survival.

Associations between the PINI and postoperative complications. The PINI was not associated with the

Table I. *The associations between the prognostic immune and nutritional index (PINI) and clinicopathological factors.*

Factors		Low-PINI group (n=176)	High-PINI group (n=353)	*p*-Value
Location of the tumor, n	Right side	65	109	
	Left side	111	244	0.170
Histological type, n	Well-/moderately differentiated	165	345	
	Poorly differentiated, Mucinous, Signet	11	8	0.026
Tumor diameter (cm), n	<5	115	311	
	≥5	61	42	<0.001
Depth of tumor, n	T1-3	152	325	
	T4	24	28	0.044
The number of harvested lymph nodes, n	<12	46	101	
	≥12	130	252	0.607
Lymph node metastasis, n	Negative	126	263	
	Positive	50	90	0.530
Serum CEA level (ng/ml), n	≤5.0	103	264	
	>5.0	73	89	<0.001

CEA: Carcinoembryonic antigen.

Table II. *Univariate and multivariate Cox regression analyses for overall survival in the whole patient cohort.*

	Univariate			Multivariate		
	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Tumor location (Right *vs*. Left side)	1.000	0.666-1.501	>0.999			
Tumor diameter (>5 *vs*. ≤5 cm)	1.573	1.014-2.438	0.043	1.057	0.671-1.667	0.811
Histological type (Poorly, Mucinous *vs*. Well, Moderately)	1.619	0.658-3.980	0.294			
Tumor depth (T4 *vs*. T1-3)	3.347	2.087-5.368	<0.001	2.413	1.478-3.938	<0.001
The number of harvested lymph nodes (<12 *vs*. ≥12)	0.911	0.596-1.392	0.666			
Lymph node metastasis (Positive *vs*. Negative)	2.753	1.877-4.040	<0.001	2.329	1.563-3.470	<0.001
Serum CEA level (>5 *vs*. ≤5 ng/ml)	1.372	0.919-2.048	0.122			
PINI (<3.047 *vs*. ≥3.047)	2.564	1.747-3.764	<0.001	2.424	1.629-3.609	<0.001

CI: Confidence interval; CEA: carcinoembryonic antigen; PINI: prognostic immune and nutritional index.

presence of anastomotic leakage or any surgical site infection (Table IV).

Discussion

In this study, the new prognostic marker, PINI, was shown to be associated with the long-term survival after curative surgery in Japanese patients with stage I-III colorectal cancer, similar to findings in Chinese and Korean patients with colorectal cancer. Furthermore, the PINI was a prognostic factor independent of TNM classification.

Since the prognosis of cancer patients is strongly correlated with the components of TNM classification, such as the tumor depth and lymph node metastasis, treatment strategies, such as the indication for adjuvant chemotherapy, are often determined based on TNM classification in daily practice. However, many studies have reported that the prognosis is greatly influenced by not only the TNM classification but also host factors (4, 5). One reason for this is that systemic inflammation and an increase or decrease in immunocompetent cells provide an environment in which the growth of micrometastasis is facilitated (12). The serum albumin level reflects not only the nutritional status but also systemic inflammation. In the presence of inflammation, cancer cells are activated by cytokines, thus facilitating the growth of micrometastasis (13-16). In contrast, monocytes in peripheral blood are recruited to the cancer microenvironment and transformed into macrophages (17, 18). Most macrophages in the cancer microenvironment exist as the M2-like phenotype type and are involved in cancer progression

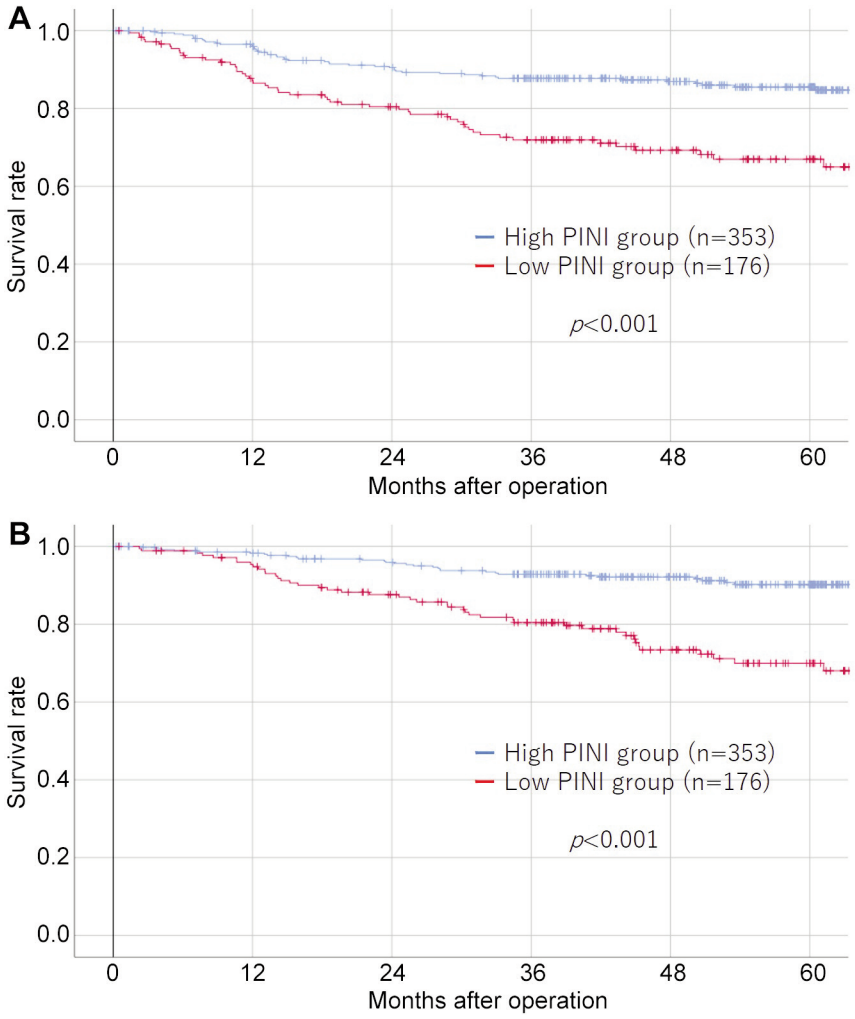

Figure 2. *Kaplan-Meier survival curves for the relapse-free and overall survival according to the prognostic immune and nutritional index (PINI). (A) The low-PINI group had a significantly worse relapse-free survival rate than the high-PINI group (p<0.0001). (B) The low-PINI group had a significantly worse overall survival rate than the high-PINI group (p<0.0001).*

Table III. *Associations between the overall survival and various clinicopathological factors.*

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Tumor location (Right *vs*. Left side)	1.032	0.644-1.656	0.895			
Tumor diameter (>5 *vs*. ≤5 cm)	1.160	0.668-2.013	0.598			
Histological type (Poorly, Mucinous *vs*. Well, Moderately)	2.848	1.235-6.566	0.014	1.626	0.687-3.851	0.269
Tumor depth (T4 *vs*. T1-3)	3.126	1.798-5.433	<0.001	2.696	1.507-4.823	0.001
The number of harvested lymph nodes (<12 *vs*. ≥12)	0.746	0.462-1.202	0.228			
Lymph node metastasis (Positive *vs*. Negative)	1.597	1.003-2.543	0.048	1.235	0.756-2.017	0.400
Serum CEA level (>5 *vs*. ≤5 ng/ml)	1.389	0.873-2.210	0.166			
PINI (<3.047 *vs*. ≥3.047)	3.317	2.106-5.225	<0.001	3.182	2.015-5.025	<0.001

CI: Confidence interval; CEA: carcinoembryonic antigen; PINI: prognostic immune and nutritional index.

Table IV. *Associations between the prognostic immune and nutritional index (PINI) and postoperative complications.*

Postoperative complications	Low-PINI group (n=176)	High-PINI group (n=353)	*p*-Value
Surgical site infection, n			
Absent	138	261	
Present	38	92	0.285
Anastomotic leakage, n			
Absent	158	318	
Present	18	35	>0.999

and metastasis *via* angiogenesis and immunosuppression (19). Therefore, hypoalbuminemia and an elevated monocyte count are associated with a poor prognosis.

Most of the known prognostic markers based on host factors consist of either the concentration of serum proteins or the number of immunocompetent cells in peripheral blood. In contrast, the PINI is an index composed of both of these factors. This may be why the prognostic accuracy of the PINI was superior to that of previously reported prognostic markers associated with host factors.

In the present study, the PINI was significantly correlated with the prognosis, as in previous reports, but no correlation was found between the PINI and postoperative complications. Indeed, hosts with a poor condition may be more prone to developing infection and suffering delayed wound healing, leading to postoperative complications (20). However, postoperative complications are influenced by not only host factors but also surgical factors. For example, excessive surgical stress, such as a longer operative time and increased blood loss, increase the risk of postoperative complications (21, 22). In addition, intraoperative factors, such as the blood supply at the anastomotic site, the location of the anastomotic site, and the number of stapler cartridges for rectal transection, may also contribute to the development of complications (23, 24). Because postoperative complications are caused by multiple factors and not just host factors, the present study may have found no significant correlation between the PINI and postoperative complications.

The present study is associated with several limitations. First, this was a retrospective study with a small cohort in a single center. Second, the cut-off value used in this study is a provisional value calculated from the data of patients registered in this study. Third, the level of serum albumin, a component of the PINI, is usually decreased in patients with nephrotic syndrome, who leak proteins, and liver cirrhosis, who have a decreased ability to synthesize protein, but these comorbidities have not been investigated. Fourth, the serum C-reactive protein level, which has been reported to be strongly correlated with the prognosis of cancer patients (25), has not been compared in terms of prognostic accuracy.

In conclusion, the PINI, which is based on host factors, is useful as a prognostic marker for patients with stage I-III colorectal cancer.

Conflicts of Interest

The Authors declare no conflicts of interest in association with the present study.

Authors' Contributions

MS designed the study, performed the statistical analysis, and drafted the manuscript. SK, TF, YI, HK, and KM designed the study and critically reviewed the manuscript. All Authors read and approved the final manuscript.

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