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The Clinical Impact of Prognostic Nutritional Index at Recurrence of Pancreatic Cancer

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Abstract

Background/Aim: Most patients with pancreatic cancer experience recurrence after curative surgical resection. Nutritional-related indicators have been evaluated to analyze prognosis in pancreatic cancer. However, it is unknown whether the cachexia index (CXI) or the prognostic nutritional index (PNI) is better for prediction of survival in patients with recurrence of pancreatic cancer. In this study, we compared the ability of the PNI to predict survival at 1 year after recurrence of pancreatic cancer with that of the CXI.

Patients and Methods: The study included 113 patients whom we retrospectively identified to have developed recurrence of pancreatic cancer as of September 2025 following pancreatectomy at our Institution between July 2005 and December 2022.

Results: The 5-year post-recurrence overall survival rate was 5.8% and the median survival time was 378 days. The 1-year survival curve was significantly better for the high PNI group than the low PNI group and for the high CXI group than the low CXI group ($p<0.001$ for both comparisons). Analysis of receiver-operating characteristic curves showed that the discriminatory ability of the PNI was higher than that of the CXI for prediction of 1-year post-recurrence survival [area under the curve: 0.711 for PNI ($p<0.001$) *vs.* 0.670 for CXI ($p=0.002$)]. Multivariate analysis identified the PNI as an independent prognostic factor for 1-year survival in patients with recurrence of pancreatic cancer ($p=0.006$).

Conclusion: Patients with a low PNI at the time of recurrence of pancreatic cancer have poorer prognostic outcomes than those with a high PNI. Improvement of nutritional status after curative surgery might improve prognosis after recurrence of pancreatic cancer.

Keywords: PNI, CXI, recurrent pancreatic cancer.

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Introduction

Pancreatic cancer remains one of the most lethal malignancies, with recurrence occurring in most patients after curative-intent resection (1-3). Survival after recurrence remains dismal for most of these patients. Patients with recurrent pancreatic cancer often die within a few months, before having the opportunity to benefit from systemic chemotherapy. Nutritional status is closely associated with both efficacy of treatment and survival in patients with various types of cancers at any stage (4-7). Therefore, it is important to know how nutritional status at the time of recurrence affects post-recurrence survival in patients with pancreatic cancer to optimize quality of life in their remaining lifetime.

There are several well-recognized serum albumin-based nutritional indices that are simple and convenient to use. The prognostic nutritional index (PNI), derived using serum albumin and the lymphocyte count, has been widely used in patients with various malignancies, including pancreatic cancer (8-13). In recent years, the cachexia index (CXI), which also reflects a patient's nutritional status and comprises the skeletal muscle index (SMI), serum albumin level, and neutrophil-to-lymphocyte ratio (NLR), has been reported to be a prognostic biomarker in patients who have undergone resection for pancreatic cancer (14, 15). Our research group has demonstrated the usefulness of the CXI as a predictor of survival after recurrence of pancreatic cancer (2). It is noteworthy that the PNI and CXI are similar prognostic nutritional indicators and both include albumin and inflammatory cells. However, to the best of our knowledge, the PNI and CXI have not yet been compared in terms of their ability to predict post-recurrence survival in patients with pancreatic cancer.

This study compared the prognostic significance of the PNI with that of the CXI with the aim of determining which index is the more reliable predictor of 1-year post-recurrence survival in patients with pancreatic cancer.

Patients and Methods

Study design and participant characteristics. Of 181 patients who underwent pancreatectomy for histologically confirmed pancreatic cancer at Tottori University Hospital between July 2005 and December 2022, 116 (64.1%) had developed postoperative recurrence by the cut-off date of September 2025. After exclusion of three patients with insufficient information available, data for 113 patients with recurrent pancreatic cancer were available for analysis.

The study was approved by the Tottori University Hospital Ethics Committee (approval number 21A125). The requirement for informed consent was waived in view of the retrospective observational nature of the research.

Postoperative recurrence was detected by radiological examinations, including computed tomography or magnetic resonance imaging and positron-emission tomography. The serum carbohydrate antigen 19-9 (CA19-9) level was also measured periodically.

The following patient demographic and clinical data at the time of recurrence were collected from the electronic medical records: Age, sex, body mass index, Eastern Cooperative Oncology Group performance status, initial site of recurrence, serum albumin level, CA19-9 level, NLR, SMI, and CXI and PNI scores. Information was also collected on time to recurrence after initial surgery, chemotherapy administered after recurrence, and pathological data for the primary tumor based on the Tumor–Node–Metastasis classification of the International Union Against Cancer (8th edition) (16).

Calculation of PNI, NLR, and CXI. The PNI was calculated as follows: 10 × serum albumin level (g/dl) + 0.005 × total lymphocyte count (/mm^3). The NLR was obtained by dividing the peripheral neutrophil count by the peripheral lymphocyte count. The CXI was calculated using the following formula: CXI = serum albumin level (g/dl) × SMI/NLR. The SMI (cm^2/m^2) was determined by normalizing the cross-sectional area of skeletal muscle mass at the level of the third lumbar vertebra measured by a SYNAPSE VINCENT system (Fujifilm, Tokyo, Japan) to the patient's height (17).

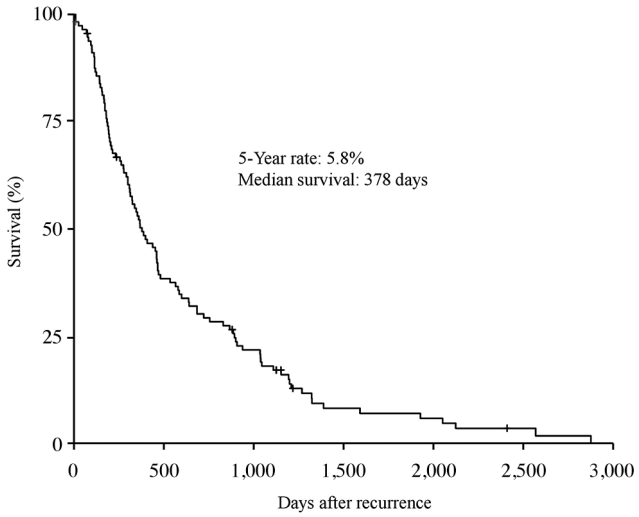

Figure 1. *Five-year post-recurrence overall survival curve for patients with pancreatic cancer (n=113).*

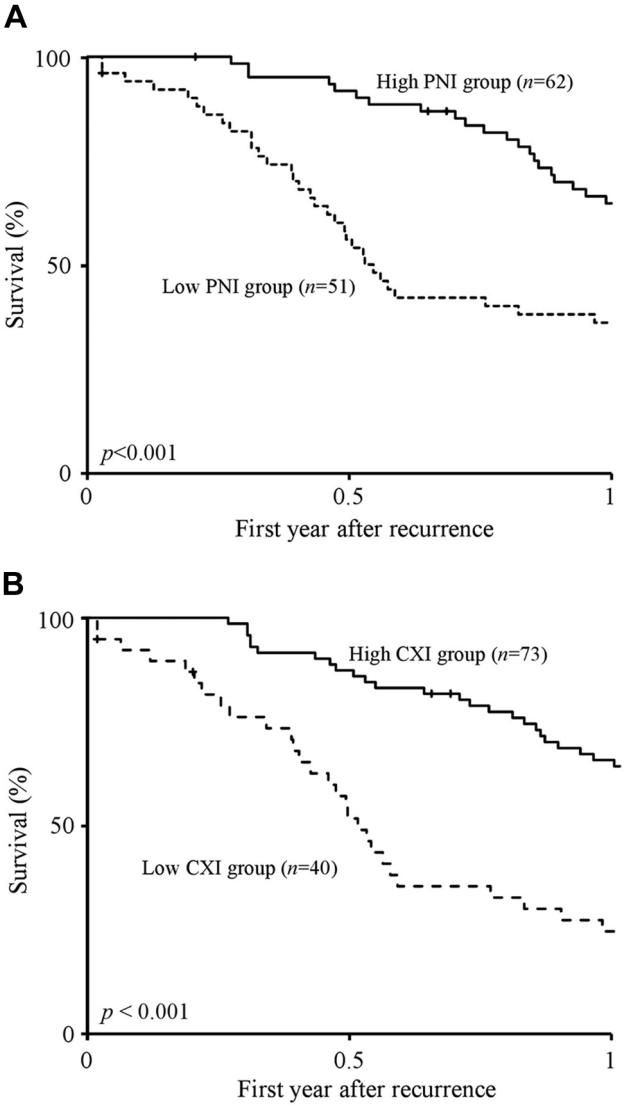

Figure 2. *One-year overall survival curves according to the prognostic nutritional index (PNI) (A) and the cachexia index (CXI) (B) in patients with recurrence of pancreatic cancer.*

Statistical analysis. Differences between groups were examined using the chi-squared test for categorical variables and the Mann–Whitney *U*-test for continuous variables with nonparametric distribution. The ability of the PNI and CXI to predict post-recurrence survival and the cut-off values for characteristics such as NLR, PNI, CXI, and CA19-9 were investigated by analysis of areas under the receiver-operating characteristic (ROC) curves. Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. A Cox proportional hazards model was used for univariate and multivariate analyses to identify factors that predicted survival at 1 year after recurrence. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 25; IBM Corp., Armonk, NY, USA). A value of $p<0.05$ was considered statistically significant.

Results

The median duration of follow-up after recurrence was 12.1 months (range=0.3-84.5 months). The curve of post-recurrence overall survival for the whole study cohort is shown in Figure 1. The 5-year overall survival rate after recurrence was 5.8% and the median survival was 378 days. By ROC curve analysis, the cut-off value at the time of recurrence was set at 56.1 for the PNI, and 51.2 in men and 69.5 in women for the CXI. Based on the PNI and CXI cut-off values, the patients were grouped into a high (n=62) or low (n=51) PNI group, and a high (n=73) or low (n = 40) CXI group. Figure 2 shows the 1-year post-recurrence overall survival curves for stratified by PNI and CXI group. The 1-year survival was significantly better

for the high PNI group than the low PNI group (p<0.001) and for the high CXI group than the low CXI group (p<0.001). The areas under the ROC curves revealed that the discriminatory ability of the PNI was higher than that of the CXI for prediction of 1-year post-recurrence survival (at 0.711 for the PNI, p<0.001; 0.670 for the CXI, p=0.002; Figure 3).

The clinicopathological characteristics of the high and low PNI groups are compared in Table I. There was no statistically significant between-group difference in age, sex, size of the primary tumor, lymph node metastasis, histological grade of the primary tumor, initial site of recurrence, or serum CA19-9 level at the time of recurrence. The rate of administration of chemotherapy after recurrence, body mass index, serum albumin level, and SMI and CXI at the time of recurrence were significantly higher for the high PNI group than for the low PNI group. Eastern Cooperative Oncology Group performance status was significantly better for the high PNI group. The incidence of recurrence within 12 months after surgery and the NLR were significantly higher for the low PNI group than the high PNI group.

Multivariate analysis identified independent prognostic risk factors for 1-year survival in patients with recurrence of pancreatic cancer to be a low PNI at the time of recurrence (p=0.010), a high CA19-9 level at the time of recurrence (p<0.001), early recurrence (within 12 months) after initial pancreatic surgery (p=0.020), and no chemotherapy after recurrence (p<0.001) (Table II).

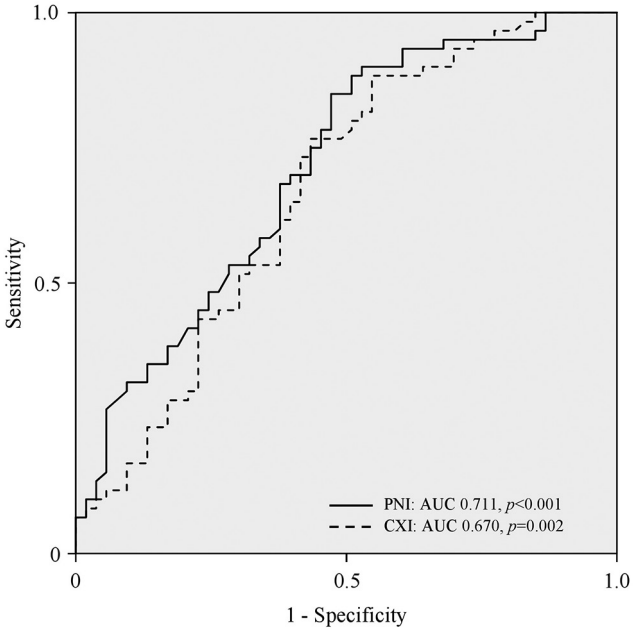

Figure 3. *Receiver-operating characteristic curves and areas under the curves (AUC) for the ability of the prognostic nutritional index (PNI) and the cachexia index (CXI) to predict survival after recurrence of pancreatic cancer.*

Discussion

Recurrence of cancer is considered incurable. The median duration of survival post-recurrence for patients with pancreatic cancer has been reported to be as short as 9-12 months, even if further treatment is provided (18, 19). In our study, we found that the survival rate decreased markedly during the first year following recurrence of pancreatic cancer and that the median survival after recurrence was about 1 year, which is consistent with the previous reports (18, 19).

Both nutritional status and the systemic inflammatory response play an important role in the onset and progression of cancer and directly affect the survival outcome (20-23). Therefore, objective assessment using nutritional markers composed of both albumin and inflammatory indicators has become a focus of attention in the context of survival outcomes in patients with cancer. Several nutritional markers have been reported to have prognostic value in patients with various types of cancer, including pancreatic cancer (24-28). However, as far as we are aware, there are no reports on the correlations of the values for these nutritional markers at the time of recurrence with survival 1 year later in patients with pancreatic cancer. In the present study, we confirmed correlations of two nutritional markers, the PNI and CXI, both of which include serum albumin, with death within 1 year after recurrence of pancreatic cancer. We found that the PNI was a more reliable marker than the CXI in terms of being able to predict 1-year survival after recurrence in these patients. Furthermore, a low PNI at the time of recurrence of pancreatic cancer was a significant

Table I. *Comparison of clinicopathological characteristics according to prognostic nutritional index (PNI) group at the time of recurrence of pancreatic cancer.*

Variable		High PNI group (n=62)	Low PNI group (n=51)	*p*-Value
Age[a], years	Median (range)	72.0 (40-86)	71.0 (48-89)	0.874
Sex, n (%)	Male	35 (56.5)	32 (62.7)	0.498
BMI[a], kg/m^2	Median (range)	20.7 (14.1-27.9)	19.2 (13.3-24.7)	**0.003**
ECOG PS[a], n (%)	1 or 2	17 (27.4)	24 (47.1)	**0.031**
Primary tumor location, n (%)	Pancreatic head	35 (56.5)	39 (76.5)	**0.026**
Size of primary tumor, mm	Median (range)	30.0 (10.0-85.0)	28.0 (5.0-70.0)	0.339
Lymph node metastasis, n (%)	Yes	43 (69.4)	37 (72.5)	0.710
Histological grade, n (%)	1[b]	31 (50.0)	22 (43.1)	0.467
Initial site of recurrence, n (%)	Distant recurrence	47 (75.8)	32 (62.7)	0.132
CA19-9[a], U/mL	Median (range)	112.6 (0.7-4,853.0)	213.4 (0.1-20,460.0)	0.078
Time to recurrence after pancreatectomy, n (%)	<12 Months	30 (48.4)	36 (76.0)	**0.017**
Chemotherapy after recurrence, n (%)	Yes	53 (85.5)	35 (68.6)	**0.032**
Albumin[a], g/dl	Median (range)	4.2 (3.3-5.0)	3.6 (1.5-4.3)	**<0.001**
NLR[a]	Median (range)	1.3 (0.3-8.0)	2.3 (0.4-18.6)	**<0.001**
SMIa, cm^2/m^2	Median (range)	38.9 (25.5-59.1)	35.7 (18.3-53.7)	**0.015**
CXI[a]	Median (range)	124.1 (30.3-555.9)	51.8 (2.7-267.9)	**<0.001**

BMI: Body mass index; CA19-9: carbohydrate antigen 19-9; CXI: cachexia index; ECOG PS: Eastern Cooperative Oncology Group performance status; NLR: neutrophil-to-lymphocyte ratio; SMI: skeletal muscle mass index. [a]At recurrence. [b]Well-differentiated. Statistically significant *p*-values are shown in bold.

Table II. *Results of univariate and multivariate analyses of prognostic factors for 1-year overall survival after recurrence in patients with pancreatic cancer.*

		Univariate analysis			Multivariate analysis		
Variable		HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
Age at recurrence	≥75 *vs.* <75 Years	1.072	0.618-1.859	0.805			
Sex	Male *vs.* female	1.259	0.723-2.195	0.416			
BMI at recurrence	<20 *vs.* ≥20 kg/m^2	1.956	1.098-3.484	**0.023**	1.529	0.837-2.794	0.167
Primary tumor location	Head *vs.* body and tail	0.906	0.520-1.579	0.728			
Primary tumor size	≥20.0 *vs.* <20.0 mm	0.667	0.300-1.482	0.320			
Histological grade of primary tumor	1[a] *vs.* other	0.785	0.456-1.351	0.382			
Lymph node metastasis at initial surgery	Yes *vs.* no	2.373	1.192-4.727	**0.014**	1.986	0.964-4.092	0.101
CA19-9 at recurrence	≥197.8 *vs.* <197.8 U/ml	3.418	1.930-6.055	**<0.001**	3.149	1.698-5.842	**<0.001**
Time to recurrence after pancreatectomy	<12 (Early) *vs.* ≥12 (late) months	2.650	1.437-4.886	**0.002**	2.256	1.136-4.480	**0.020**
Chemotherapy after recurrence	Yes *vs.* no	0.328	0.183-0.587	**<0.001**	0.254	0.618-0.499	**<0.001**
Pattern of recurrence	Distant *vs.* local	0.739	0.395-1.381	0.343			
CXI at recurrence	Low *vs.* high	3.462	2.009-5.966	**<0.001**	1.183	0.618-2.262	0.376
PNI at recurrence	Low *vs.* high	2.837	1.631-4.935	**<0.001**	2.310	1.220-4.374	**0.010**

BMI: Body mass index; CA19-9: carbohydrate antigen 19-9; CI: confidence interval; CXI: cachexia index; HR: hazard ratio; PNI: prognostic nutritional index. [a]Well-differentiated.

independent risk factor for a poor prognosis. To our knowledge, this is the first study to identify the importance of assessing the PNI at the time of recurrence in patients with pancreatic cancer.

Cancer-related malnutrition reflects hypercatabolism, which is promoted by aggressive tumor behavior (29). Systemic inflammation also has a profound effect on the complex interactions between the tumor and host factors in

patients with advanced cancer, leading to reduced oral intake and a wasting syndrome characterized by muscle loss and poor performance status, known as cancer cachexia (30-32). Both malnutrition and systemic inflammation weaken a patient's ability to tolerate treatment for cancer, such as chemotherapy, while improvement of nutritional status enhances the antitumor immune response and prolongs patient survival by improving therapeutic responsiveness to immune checkpoint inhibitors (33, 34). Nutritional improvement also reduced the rate of invasive tumor formation and attenuated the immune-suppressive microenvironment: following ectopic tumor implantation in an immunocompetent host, nutritional supplements reduced tumor growth in association with attenuated recruitment of myeloid-derived suppressor cells and lower interleukin 6 expression (35).

The CXI was originally established to reflect the cachectic status resulting from long-term depletion of skeletal muscle, and its usefulness as a prognostic factor was first identified in non-small-cell lung cancer (17). Our previous study also found that the prognosis was poor after recurrence in patients with a low CXI and that there was a positive correlation between the CXI and tolerability of treatment in patients with recurrent pancreatic cancer (2). Our study demonstrated that the 1-year survival post recurrence was significantly better for the group with a high PNI or a high CXI, and that the discriminatory ability of the PNI was higher than that of the CXI for prediction of 1-year survival post-recurrence. The PNI consists of serum albumin and the peripheral total lymphocyte count. Albumin is a negative acute-phase marker, and hypoalbuminemia is associated with impaired cell-mediated immunity (36-38). The peripheral total lymphocyte count reflects inflammation and immunity. The PNI was also reported to be associated with 1-year survival after surgery in patients with periampullary/pancreatic cancer (39). Therefore, the PNI might reflect the immune status of patients with cancer more clearly than the CXI, which is affected by changes in skeletal muscle mass in patients with cancer for a long period.

Study limitations. Firstly, it had a retrospective design and included a small sample from a single institution. Secondly, it is unclear whether the cut-off values for the PNI and CXI determined in this study are adequate for prediction of prognosis after recurrence of pancreatic cancer. A larger prospective study is needed to confirm the true prognostic impact of the PNI in patients with recurrence of pancreatic cancer.

Conclusion

The PNI is useful for predicting the prognosis at 1 year in patients with a recurrence of pancreatic cancer. Patients with a low PNI at the time of recurrence have a poorer prognosis than those with a high PNI. Improvement of nutritional status after curative surgery might improve prognosis after recurrence of pancreatic cancer.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Study conception and design: TS. Data acquisition: KU, JY, MK and YM. Data analysis and interpretation: MM, KM, YS, and TM. Statistical analysis: TS, KK, and MY. Manuscript preparation: TS. Manuscript editing: TM. Manuscript review: YF. Final approval of the article: all Authors.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine-learning software, were used in the preparation, analysis, or presentation of this manuscript.

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