# PNI, As a Nutritional and Inflammatory Index, Was Able to Predict Prognosis of Patients With Pancreatic Neuroendocrine Carcinoma

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# Abstract

**Background:** Recent studies have indicated that there is a strong link between the prognosis of cancer and the nutritional status. The purpose of this study is to investigate whether an indicator of nutritional status- the prognostic nutritional index (PNI), could affect overall survival in patients with pancreatic neuroendocrine carcinoma (p-NEC).

**Methods:** A total of 147 patients with p-NEC, who had successfully undergone biopsy by surgical operation in Shandong Provincial Hospital Affiliated to Shandong University from October 2010 to February 2019, were investigated. The serum albumin concentration and absolute lymphocyte count were used to calculate the PNI: serum albumin concentration (g/L) +5×total lymphocyte count ($\times 10^9$/L).

**Results:** Mean pretreatment PNI was 47.6. Weight loss (P = 0.003), lymphatic metastasis (P=0.006) and tumor ENETS (European Neuroendocrine Tumor Society) stage (P = 0.024), were significantly associated with PNI. Univariate analysis showed that the following factors caused decreased overall survival (OS): age (≧60years, p=0.006, vs. <60years), abdominal pain (p=0.038, vs absence of abdominal pain), weight loss (p=0.025, vs. absence of weight loss), lymphatic metastasis (p=0.0000 vs. absence of lymphatic metastasis) and tumor ENETS stage (I–II□p=0.0000, vs. III–IV). Following the multivariate analysis, PNI remained an independent prognostic factor in p-NEC. Patients with lower PNIs (PNI < 47.6) had higher risk of death than those with higher PNIs (PNI ≧ 47.6; hazard ratio: 4.508; 95 % confidence interval: 1.903–10.678; P = 0.001).

**Conclusions:** Our present study indicated that pretreatment PNI may be a novel independent prognostic factor in patients with p-NEC.


# Introduction

Pancreatic neuroendocrine carcinoma (p-NEC) is relatively uncommon and typically occurs in adults without a significant gender predilection [1]. A Japanese nationwide survey which was carried out in 2010 indicated that the estimated annual incidence for pancreatic NET was 1.27/100,000 population, and it was reported that P-NEC accounted for 7.5% of all P-NETs [2]. The symptoms related to the secretion of endocrine hormones from tumor cells could be used for identifying patients with p-NET. However, up to 40% of p-NETs do not secrete measurable levels of hormones and are nonfunctioning tumors, which make them difficult to diagnose [3, 4]. Recently, with approved drugs such as sunitinib and everolimus, the current level of treatment for p-NEC has improved, but these drugs primarily stabilize rather than cure the disease [5]. Evaluation of patient prognosis is essential to the choice of clinical diagnosis and treatment. Accordingly, to develop an accurate prognostic prediction model for individual outcomes is necessary. Nowadays, there are promising prognostic markers for survival in some adult cancers, but no useful prognostic markers for p-NEC has been reported [6].

Recent studies have indicated that the progression and prognosis of cancer are related to the nutritional status and inflammatory of patients [7–9]. PNI is calculated by combining total peripheral blood lymphocyte count with the serum albumin concentration, and has been reported to reflect the nutritional and immune condition of patients [10, 11]. It has been reported that lower PNI is a poor prognostic marker in patients with several cancers, such as liver, esophageal, pancreas, colorectal and stomach cancers [12–15]. Recent studies have indicated that PNI could predict prognosis of cancer regardless of the site of origin [16]. However, to our knowledge, little is known about prognostic and predictive factors in p-NEC, and no report about PNI in p-NEC has been published. Therefore, we retrospectively studied the relationship between PNI and clinic pathological characteristics and OS in p-NEC patients.

# Materials And Methods

### Patient's selection and Follow-up

162 consecutive patients undergoing biopsy by surgical operation in Shandong Provincial Hospital Affiliated to Shandong First Medical University from October 2010 to February 2019, who were diagnosed with p-NEC, were enlisted in this study. The histopathological confirmed diagnosis of NEC (Ki-67>20%) with a pancreatic primary was the inclusion criteria. This study excluded patients with insufficient laboratory data and those with previous or coexisting cancers other than p-NEC, leaving a total of 147 patients. Histological diagnosis was based on 2017 World Health Organization (WHO) classification criteria [17] for pancreatic neuroendocrine neoplasms. P-NEC staging was based on the European Neuroendocrine Tumor Society (ENETS) classification criteria [18]. Prior to this study, all patients signed informed consent forms, and this study was approved by the Ethics Committee of Shandong First Medical University. All patients were followed up via outpatient visit, clinic visit or telephone until October 1, 2019, or death.

### Tumor characteristics

We collected the clinical characteristics of patients retrospectively from their medical records and evaluated as prognostic factors, including the patient's age, gender, drinking habits, weight loss, and abdominal pain, primary site of tumor, Ki-67 staining index, tumor size, postoperative systemic chemotherapy, lymphatic metastasis and ENETS stage. A clinical abdomen computed tomography examination (CT) or magnetic resonance imaging (MRI) before surgery was needed in each patient. Up to October 1, 2019, 129 patients (87.7%) had died. A total of 30 patients (20.4%) received platinum-based systemic chemotherapy for at least two cycles after surgery. The rest of the patients were treated with general nutritional support care.

### Immunological and nutritional assessment

All the data were obtained from pretreatment blood tests from the patients' medical records. The PNI was calculated based on the following formula: serum albumin concentration (g/L) +5×total lymphocyte

count ($\times 10^9$/L), according to a previous study [19].

### Statistical analysis

Time from the date of the biopsy through surgical operation to that of death or last follow-up was chosen to calculate the OS. At final follow-up, patients who were lost to follow-up were censored. Survival estimates were constructed using the Kaplan-Meier estimator method and survival curves were compared using the log-rank test. Univariate and multivariate Cox proportional hazards models were used to investigate the effects of several prognostic factors. SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Statistical significance was assessed by comparing mean values (± SD) using the student's t-test. P <0.05 was considered significant. Confidence intervals (CI) were calculated at 95 %.

## Results

### Characteristics of the patients

The clinic pathological data of all patients are summarized in Table 1. Patients comprised 81 males (55.1 %) and 66 females (44.9 %; male/female ratio: 1.23/1). The mean age was 55 years. A total of 138 patients (93.8%) presented with a non-functioning tumor, whereas 9 patients (6.2%) presented with a functioning tumor. A total of 48 patients (32.6%) drinked. Main symptoms were weight loss (53.1%) and abdominal pain (63.3 %). Among these patients, 55.1% (81/147) patients had a primary tumor site in pancreatic head, and 44.9% in pancreatic body and tail. All patients with locoregional (81, 55.1%) or metastatic disease (66, 44.9%) received surgical treatment, and 59.2% of the patients' tumor size was equal or greater than 4 centimeters. A total of 30 patients (20.4 %) received systemic chemotherapy after surgery. By the 2006 ENETS classification criteria for gastroenteropancreatic NETs, 54 patients (36.7%) were classified as stages I–II and 93 patients (63.3%) as stages III–IV. The percentage of patients with a Ki-67 index of <55% was 67.3 % ( 99/147).

### Relationship between the clinicopathologial characteristics and the PNI

Before surgery, the mean PNI was 47.6 (SD = 6.6). PNI was significantly related with weight loss, tumor distant metastasis and ENETS stage (Table 1). Mean PNI in patients with lymphatic metastasis was significantly lower than in patients with no metastasis (44.6 vs. 50.9, P =0.006). Mean PNI was lower in patients with stage III–IV than those with stage I–II (45.8 vs. 50.1, P =0.024). Meanwhile, mean PNI significantly differed in weight-loss group compared with weight-holding group (44.6 vs. 50.6, P = 0.003). There was no relation between PNI and age, gender, abdominal pain, drinking habits, tumor size, systemic chemotherapy, primary site of tumor or Ki-67 staining index (P >0.05).

### Patient survival and PNI

Patients were divided into the PNI-low group (72 patients [49%] with PNI < 47.6) and the PNI-high group (75 patients [51%] with PNI ≧47.6) according to the mean PNI (47.6) in our study. By the end of the follow-up, 129 patients had died. Median OS of all patients was 6 months (range: 0.5–76 months). The log-rank test and Kaplan-Meier method identified that the lower PNI value was associated with shorter OS (P = 0.000; Fig. 1). Median OS of patients in the PNI-high and PNI-low group was 12 and 4 months, respectively (Table 2). 1-year OS rates were 44% and 8.3% in PNI-high group and PNI-low group, respectively, and the 2-year OS rate was 30.8 % for PNI-high group and 0% for PNI-low group (Fig. 1).

In univariate analysis of OS, advanced age ≧ 60 (p=0.006), low PNI (P = 0.000), weight loss (P = 0.025), distant metastasis (p=0.000), ENETS stage III–IV (p=0.000), and the presence of abdominal pain (P = 0.038) were associated with poorer prognosis (Table 2).

The multivariate analysis showed PNI to be an independent prognostic factor in p-NEC. Patients with lower PNIs had a higher risk of death than those with higher PNIs (HR: 4.508; 95 % CI: 1.903–10.678; P = 0.001; Table 3). These analyses were adjusted for patient age, gender, drinking habits, abdominal pain, primary tumor site, weight loss, systemic chemotherapy and ENETS stage.

# Discussion

Recent studies have indicated that systemic immune-inflammation and a poor nutritional status correlate with a poor prognosis in a lot of malignant tumors [20]. Malnutrition was very common in cancer patients whether surgical treatment or not. Onodera et al. first introduced PNI and they evaluated patients with gastric cancers undergoing surgeries with different catabolic state [21]. Two simple laboratory parameters-albumin and absolute lymphocyte count which were previously reported that these two parameters were associated with the prognosis of cancer, were used to evaluate the PNI [22]. Mounting evidence has indicated that low PNI is associated with poor prognosis in various types of malignancies. Meanwhile, it is stated by Proctor et al. that PNI can forecast the prognosis of malignancy regardless of the site of origin [23].

P-NEC is frequently associated with malnutrition, probably because of tumor growth and decreased oral intake due to abdominal pain. However, as far as we know there has been no relevant study on PNI in p-NEC. So far, in our study, we assessed the association of the nutrition-inflammation-based PNI with prognosis in p-NEC patients. Based on the results of the present study, we found that PNI could serve as independent predictors for p-NEC better than other parameters.

Our Kaplan-Meier analyses showed a positive correlation between PNI and p-NEC patients' OS. In PNI-high group, the mean OS was longer than that in PNI-low group (P = 0.003). These results are consistent with several previous studies which evaluated the predictive role of PNI in a variety of malignancies [24–26].

In our cohort study, the most frequent symptoms of patients with p-NEC were weight loss and abdominal pain. Interestingly, in our present study, we found a close correlation between PNI and weight loss, and mean PNI in patients with weight loss was significantly lower than patients who has maintained their weight (P = 0.003). However, we found no significant relationship between PNI and abdominal pain.

Based on the results of current study, five prognostic factors, including age, abdomimal pain, weight loss, lymphatic metastasis and ENETs stage, predicted a poor prognosis following our univariate analysis. Next, these five parameters were used in multivariate analysis, and our results showed that PNI was an independent prognosticator in patients with P-NEC.

According to the WHO 2010 grade classification system, Ki-67 staining index was described as an independent predictor of clinical outcomes. Nevertheless, Bettini et al. published the opposite conclusion, in which the Ki-67 index was not demonstrated to have predictive value. GI-NEC patients with ki-67 < 55% were insensitive to platinum-based chemotherapy, but had a longer survival than patients with a higher Ki-67 staining index. A recent study on NEC reported that the survival time was somewhat more favorable in patients with a Ki-67 index of < 55% (median:14months) than in those with a Ki-67 index of ≧ 55% (median:10months). Based on these observations, we chose 55% as the Ki-67 cut-off value in this study. We found that the median surrival for p-NEC patients with Ki-67 staining index ≧ 55% was 3.5 months, while patients with Ki-67 staining index < 55% was 7months. Disappointingly, however, our study showed the OS between these two groups had no significant relationship (P = 0.105).

Because of properties of NEC of rapid progression, chemotherapy is usually given to patients with metastatic NEC. Based on two first-line chemotherapy studies published, the combination of cisplatin and etoposide is recommended as first-line therapy for metastatic NEC. In our study, only 30 patients (20.4 %) received postoperative adjuvant chemotherapy, the median survival of these patients was 7 months, while the median survival of patients with no chemotherapy was 6 months (p = 0.577).

However, this study still has some shortcomings. As a retrospective, single medical center study, it had its own drawback because of sample limitations. In future, a larger, prospective, randomized controlled research is needed to validate our results.

Taken together, our present study indicated that the PNI was an independent prognostic predictor of OS for p-NEC. A low PNI was associated with poor prognosis in p-NEC.

# Declarations

### Ethics approval and consent to participate

*Prior to this study, all patients signed informed consent forms, and this study was approved by the Ethics Committee of* Shandong First Medical University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research

committee. All methods were performed in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Consent for publication

Not applicable

### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.


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Not applicable


### Authors' contributions

JL and XGT contributed equally to the design and drafting of this manuscript. All authors meet the ICMJE criteria for authorship, revised the manuscript and approved it for publication.


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# Tables

**Table 1.** Relationship between the clinicopathological characteristics and the PNI

| Variables | *N*(%) | PNI | *P* value |
|---|---|---|---|
| Age(years) | | | |
| <60 | 93(63.2%) | 48.8±1.27 | |
| ≧60 | 54(36.8%) | 45.1±1.34 | 0.108 |
| Gender | | | |
| Male | 81(55.1%) | 46.5±1.28 | |
| Female | 66(44.9%) | 48.6±1.47 | 0.644 |
| Abdominal pain | | | |
| Yes | 93(63.2%) | 46.9±1.11 | |
| No | 54(36.8%) | 48.4±1.83 | 0.628 |
| Drinking habits | | | |
| Yes | 48(32.6%) | 46.4±1.71 | |
| No | 99(67.4%) | 47.9±1.18 | 0.921 |
| Weight loss | | | |
| Yes | 78(53.1%) | 44.6±1.28 | |
| No | 69(46.9%) | 50.6±1.18 | 0.003 |
| Primary site of tumor | | | |
| Caput pancreatis | 81(55.1%) | 46.1±1.33 | |
| Pancreatic body and tail | 66(44.9%) | 49.0±1.37 | 0.308 |
| Tumor size(centimeter) | | | |
| ≧4 | 87(59.2%) | 46.4±1.26 | |
| <4 | 60(40.8%) | 48.9±1.47 | 0.296 |
| Lymphatic metastasis | | | |
| Yes | 81（55.1%） | 44.6±1.00 | |
| No | 66（44.9%） | 50.9±1.49 | 0.006 |
| ENETS stage | | | |
| Ⅰ-Ⅱ | 54（36.7%） | 50.1±1.87 | |
| Ⅲ-Ⅳ | 93（63.3%） | 45.8±0.99 | 0.024 |
| Systemic hemotherapy | | | |

| | | | |
|---|---|---|---|
| Yes | 30(20.4%) | 45.6±2.29 | |
| No | 117(79.6)) | 47.8±1.06 | 0.942 |
| Ki67 | | | |
| <55% | 99(67.3%) | 48.5±1.16 | |
| ≧55% | 48(32.7%) | 45.1±1.65 | 0.054 |

**Table 2.** Univariate analysis of prognostic factors of overall survival

| Variables | | MOS(months) | *P* value |
|---|---|---|---|
| Age(years) | ≧60 | 5 | |
| | <60 | 8 | 0.006 |
| Gender | Male | 5 | |
| | Female | 8 | 0.096 |
| Abdominal pain | Yes | 5 | |
| | No | 7.5 | 0.038 |
| Drinking habits | Yes | 5.5 | |
| | No | 7 | 0.449 |
| Weight loss | Yes | 4 | |
| | No | 9 | 0.025 |
| Primary site of tumor | Caput pancreatis | 5 | |
| | Pancreatic body and tail | 7.5 | 0.245 |
| ENETS stage | □-□ | 14.5 | |
| | □-□ | 5 | 0.000 |
| Lymphatic metastasis | Yes | 4 | |
| | No | 12 | 0.000 |
| Tumor size(centimeter) | ≧4 | 5 | |
| | <4 | 8.5 | 0.164 |
| Systemic hemotherapy | Yes | 7 | |
| | No | 6 | 0.577 |
| Ki67 | ≧55% | 3.5 | |
| | <55% | 7 | 0.105 |
| PNI | PNI-high | 12 | |
| | PNI-low | 4 | 0.000 |

*MOS* median overall survival, *ENETS* European Neuroendocrine Tumor Society, *PNI* prognostic nutritional index

**Table 3.** Multivariate survival analysis for various potential prognostic factors of overall survival

| Variables | HR | 95%CI | *P* value |
|---|---|---|---|
| Age | 1.713 | 0.856-3.429 | 0.128 |
| Abdominal pain | 1.871 | 0.865-4.047 | 0.112 |
| Weight loss | 1.032 | 0.488-2.179 | 0.935 |
| PNI | 4.508 | 1.903-10.678 | 0.001 |
| Lymphatic metastasis | 3.474 | 0.966-12.490 | 0.056 |
| ENETS stage | 0.717 | 0.177-2.894 | 0.640 |

Multivariate analysis was assessed using time-dependent Cox model

*HR* hazard ratio, *CI* confidence interval, *PNI* prognostic nutritional index, *ENETS* European Neuroendocrine Tumor Society

# Figures

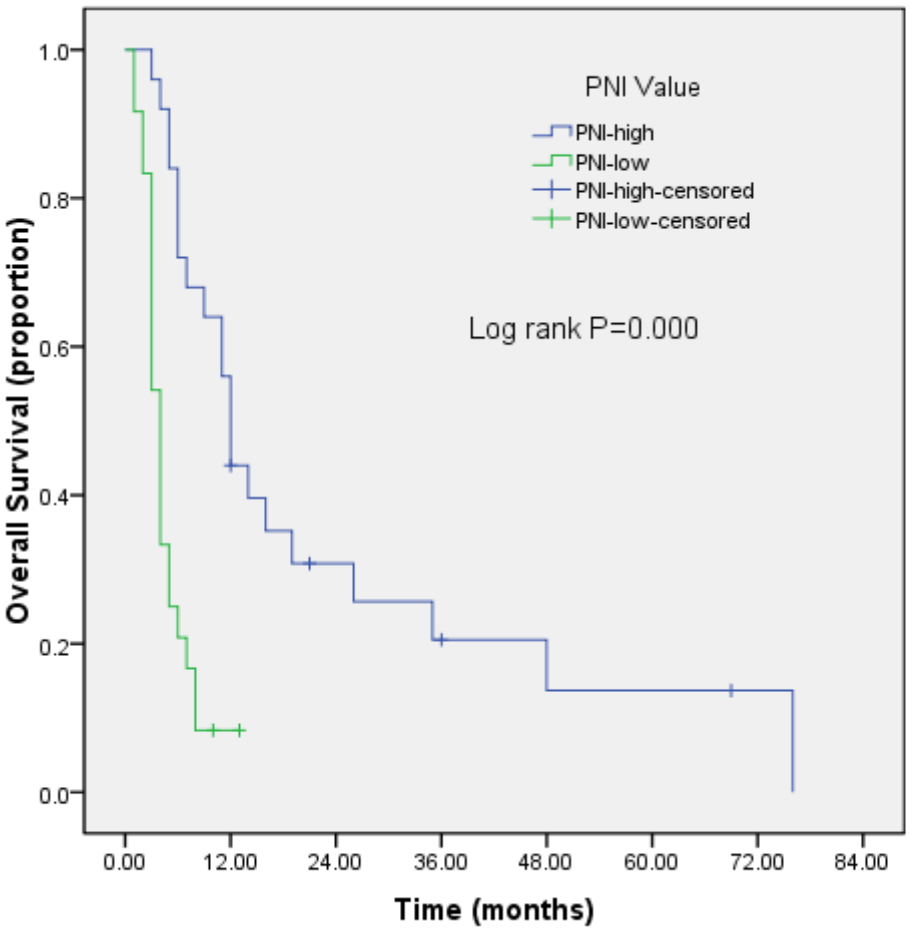


**Figure 1**

Kaplan-Meier survival curves evaluate the overall survival (OS) according