The prognostic nutritional index as a predictor of long-term outcome in patients with resected esophageal squamous cell carcinoma

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Abstract

Background Preoperative nutritional and inflammation indexes have been shown to be associated with postoperative complications and the prognosis of patients with a malignant tumor. We evaluated several clinicopathological prognostic factors in patients with resected esophageal squamous cell carcinoma (ESCC).

Methods Seventy-eight patients who underwent curative resection for ESCC were included in this retrospective study. The associations of body mass index (BMI), the prognostic nutritional index (PNI), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and protein-albumin ratio (CAR) with various clinicopathological factors were evaluated.

Results In multivariate analyses, only low PNI (<46.8) independently and significantly predicted overall survival (OS) (P=0.002).

Conclusions The PNI is a simple, useful marker for predicting the long-term prognosis of patients with ESCC after esophagectomy. The PNI should be included in the routine assessment of patients with ESCC.

Introduction

Esophageal cancer is the eighth most common cancer worldwide, with an estimated 456,000 new cases and 400,000 deaths in 2012 [1]. Multidisciplinary treatments have improved, but surgical resection is still an alternative treatment. Additionally, its 5-year overall survival (OS) is poor because of the relatively advanced tumor stage at the time of diagnosis and rapid disease progression [2]. Thus, it is important to determine the preoperative risk factors and those that improve after operative treatment for esophageal cancer.

Recently, some studies reported that preoperative nutritional status is associated with postoperative complications and the long-term prognosis of malignant diseases [3]. Patients with esophageal cancer do not consume food well because of esophageal stenosis, causing them to have a lower nutritional state and cachexia compared to patients with organ cancers. Several studies described and evaluated benchmarks for nutritional-related prognostic factors, and some showed that the presence of a systematic inflammatory response could cause a high complication rate and poor survival in patients with malignant diseases [4] [5, 6]. Indicators of systemic nutrition and the inflammation index include body mass index (BMI), the prognostic nutrition index (PNI), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and C-reactive protein-albumin ratio (CAR), and those factors can be easily evaluated preoperatively [7-11] [12]. However, it remains unknown which indicator is the most valuable for predicting OS in patients with esophageal squamous cell carcinoma (ESCC).

This study aimed to determine preoperative prognostic factors for OS, such as patients' nutritional status, inflammation-based prognostic score, and combined indexes, in patients with resected ESCC.

Materials And Methods

Patients

Eighty-seven patients underwent curative resection for ESCC in the Surgical Division of Hitachi General Hospital between January 2006 and December 2015. We excluded 3 patients with in-hospital mortality and 6 patients with missing data. Therefore, 78 patients were included in this retrospective study.

Surgery

All patients underwent subtotal esophagectomy with D2 lymph node dissection through a right thoracotomy. Video-assisted thoracoscopic surgery was performed for 6 (7.1%) patients. The reconstructed organs were the stomach in 67 (85.9%) patients and colon in 11 (14.1%).

Clinical Data Collection

The following baseline characteristics were obtained from patients' electronic medical records: age, gender, weight, height, tumor stage, pretreatment laboratory data (within 4 weeks preoperatively) including counts of white blood cells, neutrophils, lymphocytes, platelets, C-reactive protein (CRP), albumin levels and OS.

BMI was calculated by dividing the weight in kilograms by height squared in accordance with its standardized definition. Onodera's PNI was calculated as follows: 10×albumin level+0.005×absolute lymphocyte count [13]. The NLR was calculated as the absolute neutrophil count (number of neutrophils/μL) divided by the absolute lymphocyte count (number of lymphocytes/μL), and PLR was calculated as the absolute platelet count (number of platelets/μL) divided by the absolute lymphocyte count. The CAR was calculated by dividing the serum CRP level by the albumin level. In the analysis of OS, receiver operating characteristic (ROC) curves were used to determine the following appropriate cutoff values for BMI, the PNI, NLR, PLR, CAR, operative time, and operative blood loss: 19.8, 46.8, 3.97, 153, 0.025, 522 minutes, and 297 ml, respectively. Postoperative complications were classified according to the Clavien-Dindo classification [14]. The total complications included those classified as more than as grade 3 or higher.

Follow-up

Patients were followed up in our outpatient clinic every 3–6 months postoperatively. Medical history taking, a physical examination, thoracoabdominal computed tomography, and blood tests including analysis of tumor markers were performed every 6 months.

Statistical Analysis

Data are expressed as a median (range). The Mann-Whitney U-test and chi-square test (or Fisher's exact test) were used to analyze differences between the two groups in univariate analyses of the continuous and categorical variables. Univariate and multivariate analyses of prognostic factors related to OS were calculated using the Cox proportional hazard model. OS was estimated using the Kaplan-Meier method and compared using the log-rank test. A P-value <0.05 was considered statistically significant. The statistical analysis was performed using SPSS 24 software (IBM Corp., Chicago, IL, USA).

Results

Patients' Characteristics

Of 78 patients, the median follow-up duration was 40 months (range 4–64 months), and 28 patients (35.9%) had tumor recurrence. The clinicopathological characteristics of patients are shown in Table 1. Sixty-nine were men and 9 were women. The median patient age was 65 years (range 44–84 years). Regarding the Union for International Cancer Control (UICC) tumor classification, 30 patients had stage I, 20 had stage II, and 28 had stage III. Patients in the low PNI and high CAR groups were older than those in the high PNI (P<0.001) and low CAR groups (P=0.005). Values of the PNI (P=0.049) was significantly different according to the lesion site. Patients with a low BMI, low PNI, and high CAR had deeper tumor invasion than those with a high BMI (P=0.004), high PNI (P=0.009), and low CAR (P=0.001). Only the CAR was identified as having a relationship with the UICC pathological stage (P=0.016), and the PNI was identified as having a relationship with SCC (P=0.001).

Risk Factors for OS

Univariate analyses showed that gender (0.024), BMI (P=0.032), the PNI (P<0.001), NLR (P=0.003), CAR (P=0.012), operative time (P=0.029), blood loss (P=0.008), and UICC pathological stage (P<0.001) were significantly associated with a shorter OS in patients with ESCC, whereas the PLR did not predict OS (Table 2). In the multivariate analyses, the PNI (hazard ratio [HR] 3.365; 95% confidence interval [CI] 1.590–7.122; P=0.002) was independent predictors of OS (Table 3).

The results of the calculated PNI are shown in Figure 1. We divided patients into two groups using the PNI cutoff value of 46.8. The respective 3-year and 5-year OS rates for patients with a high PNI were 78.0% and 67.4%, whereas those for patients with a low PNI were 21.6% and 13.0%. Patients with a low PNI had a significantly shorter OS than those with a high PNI (P<0.001).

Discussion

Onodera et al. first described the PNI in 1984 and calculated it by using the serum albumin concentration and total lymphocyte count from peripheral blood samples. It has been used as a nutritional and immunological indicator, and it was originally defined as a predictor of postoperative complications in patients with gastrointestinal cancers [13]. Only the serum albumin value and lymphocyte count were correlated with the preoperative nutritional evaluation index and incidence of postoperative complications, which led to the use of the functional equation in stepwise discriminant analysis.

The PNI is easy to measure on a daily basis because it is inexpensive and very convenient compared to tumor markers. The PNI may also have a higher applicability for evaluating patients' systemic inflammatory response. Therefore, it is a simple, reliable, inexpensive, and reproducible method whose interpretation is relatively easy in the context of non-septic neoplasia. Recently, the PNI has been widely using to evaluate preoperative prognostic factors for many malignant diseases [15]. Some studies reported use of the PNI in patients with ESCC. However, there is controversy over the optimal cutoff point of the PNI to predict cancer survival. The cutoff value is normally set to 45 [13]; however, the optimal cutoff value of the PNI for predicting the long-term prognosis of ESCC remains unknown.

Tables 4a and 4b summarize recent studies about the relationship between the preoperative PNI and long-term outcome in patients with esophageal cancer. Table 4a shows studies with significant differences[16-18], and Table 4b shows studies with no significant differences[5, 7, 19-21]. A significant difference was not found between the cutoff values near 45 and 50, but a significant difference was often found for cutoff values from 46 to 49.

In recent studies of long-term results for other organ cancer, significant differences were seen for cutoff values close to or lower than 45; for example, in Hirahara et al. and Nozoe et al.'s studies, the cutoff values were 44.3 for gastric cancer [22] and 40 for colon cancer 40, respectively [8]. Since esophageal cancer has a poor prognosis, a cutoff value slightly higher than 45 would be needed. In our study, the cutoff value derived by ROC curves was 46.8.

The mechanism of the independent correlation between the PNI and postoperative survival in patients with ESCC is unclear. Previous studies have suggested that albumin and lymphocyte levels are closely related to the presence of an inflammatory response in patients with cancer [23]. There is a strong connection between inflammation and cancer [24]. Therefore, it is logical that the PNI reflects systemic inflammation, considering its relationship with prognosis. It has been suggested that markers based on inflammation may reflect tumor burden and a positive treatment response. Inflammation promotes cancer cell proliferation, tumor angiogenesis, and metastasis. Systemic inflammation can increase the number of neutrophils and decrease the number of lymphocytes. Lymphocytes play a central role in antitumor immunity, and lymphocytopenia reflects impaired cellular immunity against cancer cells [24] [25]. Furthermore, pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha, have been shown to lower serum albumin levels by reducing the production of serum albumin by hepatocytes [26]. Thus, a low PNI is indicative of a tumor with greater malignant potential.

An accurate assessment of the postoperative risk of recurrence is important in planning customized risk-adaptive treatment strategies for each patient. In particular, identifying prognostic factors preoperatively is important for determining optimal preoperative treatment, and improving postoperative short-term and long-term outcomes [27]. Previous studies have shown that perioperative immuno-nutritional support improves the nutritional and immunological statuses of patients undergoing elective surgery [28]. However, it is still unclear whether such nutritional intervention will help improve the surgical outcome of patients with a low PNI. A larger randomized, multicenter, prospective study is needed to help clarify this.

Conclusions

The PNI is a simple, useful marker for predicting the long-term prognosis of patients with ESCC postoperatively. The survival rate of ESCC can be classified into two groups according to the PNI (≥46.8 and <46.8). Therefore, the PNI should be included in the daily assessment of patients with ESCC. For patients with a lower PNI preoperatively, nutritional intervention by total parenteral nutrition or enteral nutrition are necessary. It may also be difficult, but it is necessary to find a way to management for inflammation.

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Tables

Due to technical limitations, tables are only available as a download in the supplemental files section.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of the Hitachi General Hospital (acceptance number 2017 - 99) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As this was a retrospective, non-interventional study, the committee waived the need for written informed consent from the patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used or analyzed 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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Authors' contributions

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

Conception and design of study: TM, MS, SS. Acquisition of data: TM, AS, HH, KU. Analysis and interpretation of data: TM, MS, SS. Drafting the manuscript: TM, MS. Revising the manuscript critically for important intellectual content: SS. Approval of the version of the manuscript to be published: TM, MS, AS, HH, KU, SS.

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Not applicable.

Figures

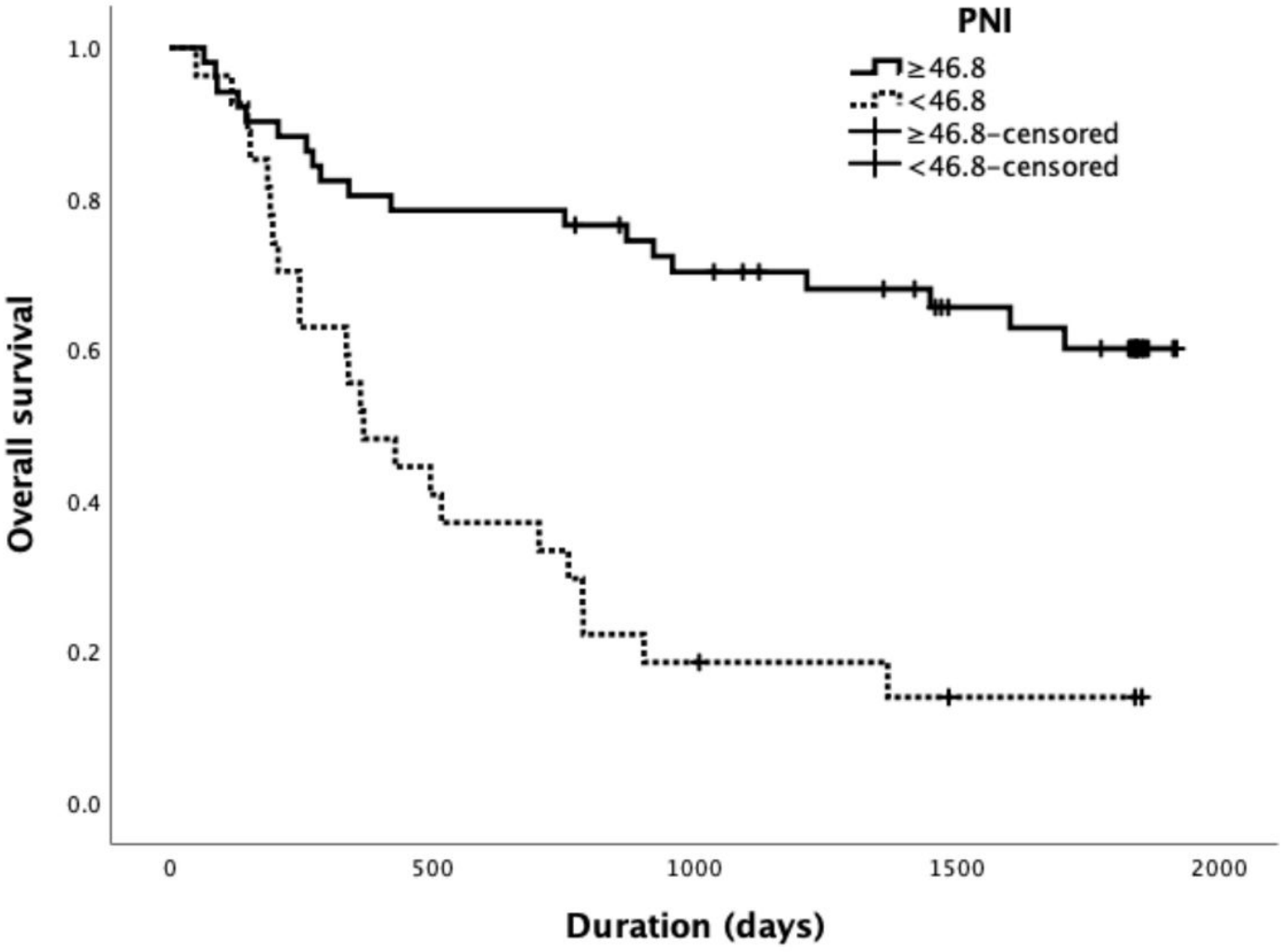

Figure 2

The results of the calculated PNI are shown in Figure 1.

Supplementary Files

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