Preoperative prognostic nutritional index level is associated with tumour-infiltrating lymphocyte status in patients with surgically resected lung squamous cell carcinoma

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Abstract

OBJECTIVES: The prognostic nutritional index (PNI) is an indicator of systemic immune-nutritional condition and is a well-known prognostic biomarker in lung cancer patients. Tumour-infiltrating lymphocytes (TILs) is a specific histological feature of cancers, influencing an individual's immunological tumour responses. However, whether PNI can reflect lung cancer patients' prognosis through local immunity such as TIL is unclear.
METHODS: We selected 64 lung squamous cell carcinoma patients who underwent curative operations. We investigated the significance of preoperative PNI level and evaluated the relationship between PNI and immune cells surrounding the lung cancer tissue using immunohistochemical analysis of a cluster of differentiation (CD)3, CD4, CD8 and CD68.

RESULTS: A low-PNI level was significantly associated with a worse postoperative prognosis (P = 0.042). The PNI (hazard ratio 2.768, 95% confidence interval 1.320–5.957; P = 0.007) was an independent prognostic factor. The low-PNI group had a significantly shorter recurrence-free survival and overall survival (P = 0.013 and P = 0.002, log-rank test) compared with the high-PNI group. A significant positive correlation between PNI components including preoperative peripheral blood lymphocyte count and serum albumin concentration, and TILs, was observed. Absolute numbers of TILs in the preoperative high-PNI group were significantly increased compared with those in the preoperative low-PNI group (CD3+ cells; P = 0.002, CD4+ cells; P = 0.049 and CD8+ cells; P = 0.024).

CONCLUSIONS: The preoperative PNI level was strongly associated with the postoperative outcome in lung cancer patients. Considering the positive relationship between preoperative PNI level and TIL status, preoperative immune-nutritional condition may influence lung cancer patients’ postoperative prognosis through local immunity as well as systemic immune response.

Keywords: Lung squamous cell carcinoma • Preoperative prognostic nutritional index • Tumour-infiltrating lymphocytes • Prognostic factor

ABBREVIATIONS

AUC Area under the curve
BVI Intratumoural blood vessel invasion
CD Cluster of differentiation
CI Confidence interval
HR Hazard ratio
LVI Lymphatic vessel invasion
NSCLC Non-small-cell lung cancer
OS Overall survival
PNI Prognostic nutritional index
RFS Recurrence-free survival
SqCC Squamous cell carcinoma
TAM Tumour-associated macrophages
TIL Tumour-infiltrating lymphocytes

INTRODUCTION

Adenocarcinoma and squamous cell carcinoma (SqCC) are the most frequent histological subtypes of non-small-cell lung cancer (NSCLC) [1]. Recently, molecular targeted therapy has greatly improved the survival of NSCLC patients with common driver mutations. However, limited progress has been made in the treatment of SqCC, in which driver mutations are less frequent and the response to molecular target therapy is not favourable. Thus, SqCC represents an important field in which new therapeutic options are warranted.

Recently, host systemic immune activity, host nutritional condition and the immune microenvironment of the tumour have been highlighted as having an association with the prognosis of lung cancer [2]. Preoperative immunonutritional status has gained attention as a prognostic biomarker and several studies have reported that preoperative immunonutritional status is associated with long-term outcomes of patients with malignant tumours including lung cancer [3–5]. In addition, recent studies in the field of lung cancer research have reported the clinical impact of preoperative immunonutritional status on cancer outcomes [6–9].

Among several objective immunonutritional parameters, the prognostic nutritional index (PNI) is the most attractive immunonutritional biomarker. The PNI is calculated based on serum albumin concentrations and the total lymphocyte count in peripheral blood, and was originally proposed to assess perioperative immunonutritional status [10]. Serum albumin is the simplest and most valuable parameter for assessing nutritional status, while lymphocytes play a fundamentally important role in host immune responses [11–13]. Thus, the PNI is a measure of both the nutritional and systemic immunological condition of a patient. Recently, the PNI was shown to be a prognostic marker for various malignancies [14–16]. Furthermore, some studies have reported that the preoperative PNI level was an independent postoperative prognostic factor even in lung cancer patients [6, 17, 18]. Although the mechanism by which the preoperative PNI level affects the host systemic immunonutritional condition has been widely studied, whether it can regulate local immunity in lung cancer is unclear. Recently, the impact of local immunity including tumour-infiltrating lymphocytes (TILs) and tumour-associated macrophages (TAMs) has been highlighted in various malignancies and some studies have analysed TILs in NSCLC [19]. Those data showed that decreasing TILs and TAM in NSCLC correlated with a high risk of postoperative recurrence and poor prognosis; therefore, TILs and TAM are considered as local immune regulators in NSCLC.

We hypothesized the preoperative systemic immunonutritional condition of lung cancer patients might affect postoperative prognosis through local immunity. Nevertheless, few studies have objectively evaluated the relationship between the preoperative PNI level and local immunity, including TILs and TAM, in lung cancer patients.

To test this hypothesis, this study aimed to retrospectively analyse the association between the preoperative PNI status and TILs and TAM in lung cancer patients undergoing curative lung resections.

MATERIALS AND METHODS

Patients

This retrospective study was conducted at the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University. This study was approved by the ethics committee of Kyushu University Hospital (approval number, 29-402; approval date, 29 November 2017). The need for consent was waived because of the retrospective nature of this study.

From August 2005 to September 2018, 1255 consecutive patients with primary lung cancer underwent complete surgical
resection. We selected consecutive 64 of those patients with pulmonary SqCC for this study. The results were determined in follow-up examinations occurring over a median period of 25 months (range 0–154 months) after surgical resection. Postoperative follow-ups were performed as previously described [6]. The study group included 5 women and 59 men, with a mean age at their surgeries of 69 years (range 45–88 years). Eleven (17.2%) patients had never smoked and the remaining 53 patients were former or current smokers. Three (4.7%) patients underwent bi-lobectomies with systemic lymphadenectomies, 40 (62.5%) patients underwent lobectomies with systemic lymphadenectomies and 21 patients underwent limited resections, including segmentectomies or wedge resections in those with peripheral lesions or poor pulmonary function. Postoperative recurrence occurred in 18 patients (28.1%). During the follow-up period, 32 (50.0%) patients were alive.

Preoperative calculation of the PNI and the cut-off value of the PNI

The preoperative PNI was calculated using the following formula: 10 × serum albumin levels (g/dl) + 0.005 × total lymphocyte count in peripheral blood (per mm<sup>3</sup>) [8]. We decided that the best cut-off value for preoperative PNI levels was 49.08 (sensitivity: 52.83%; specificity: 78.57%; area under the receiver operating characteristics curve (AUC): 0.672) (Supplementary Material, Fig. S1). Thirty-eight (59.4%) patients had preoperative PNI levels >49.08 (high PNI) and the remaining 26 (40.6%) patients had a lower preoperative PNI (low PNI).

Histopathological evaluation

We retrospectively collected formalin-fixed and paraffin-embedded SqCC surgical specimens and reviewed them as haematoxylin–eosin-stained sections. Elastic and connective tissues were stained to determine pleural invasion, and intratumoural blood vascular invasion (BVI) and intratumoural lymphatic invasion (LVI). BVI and LVI were distinguished by Elastica van Gieson staining. A specimen was considered positive for intratumoural vessel invasion when cancer cells were observed in the intratumoural vessel lumen. Twenty-three (35.9%) patients were found to have a visceral pleural invasion, 29 (45.3%) had BVI and 12 (18.7%) had LVI.

Patients’ pathological stages were based on the 8th tumour, node and metastasis classification of the International Union Against Cancer [20]. Of the 64 patients, 33 (51.6%) had pathological stage I, 24 (37.5%) had pathological stage II and 7 (10.9%) had pathological stage III.

Immunohistochemical staining and analysis

We used 4-μm thick FFPE tumour tissue sections to conduct immunohistochemistry of cluster of differentiation (CD)3, CD4, CD8 and CD68 in 64 surgically resected SqCC patients with available surgical specimens. Immunohistochemical staining was performed as previously described [21]. The immunohistochemical analysis was conducted using commercially available antibodies as follows: anti-CD3 antibody (prediluted; mouse monoclonal, clone PS1, Nichirei Biosciences, Tokyo, Japan), anti-CD4 antibody at 1:100 dilution (mouse monoclonal, clone 4B12, DakoCytomation, Carpinteria, CA, USA), anti-CD8 antibody at 1:100 dilution (prediluted; mouse monoclonal, clone 1A5, BioGenex, Fremont, CA, USA) and anti-CD68 antibody (mouse monoclonal, clone PG-M1, DakoCytomation). Cytoplasmic or membrane expression on cells was defined as positive.

All immunohistochemical data were evaluated by 2 observers (T.A. and F.S.), who were blinded to the clinical status of the patients. Sections were scanned using a NanoZoomer digital pathology microscope (Hamamatsu Photonics K.K., systems division, Hamamatsu, Japan), and the number of CD3+, CD4+, CD8+ and CD68+ cells in each case was counted and averaged over 5 high-power fields for each case and average numbers of CD3+, CD4+, CD8+ and CD68+ cells were calculated (Supplementary Material, Fig. S2A and B).

Statistical analysis

Categorical variables were analysed using Fisher’s exact test. Continuous variables were expressed as mean and standard deviation and compared using the Student’s t-test. The receiver operating characteristics curve of preoperative PNI levels was analysed, and postoperative overall survival (OS) during the follow-up period was predicted by comparing the AUC and using the Youden index. Recurrence-free survival (RFS) was defined as the interval between resection and the first recurrence event. The OS was calculated from the time of resection to the date of death from any cause. We analysed patients’ survival using the Kaplan–Meier method and compared groups using the log-rank test. We used the Cox proportional hazards model to identify independent prognostic factors among 9 clinicopathological characteristics: patients’ age, sex, smoking history, preoperative PNI level, tumour pathological stage, surgical procedures, pleural invasion, intratumoural blood vessel invasion and intratumoural lymphatic invasion. The proportional hazard assumption was checked using plots of Schoenfeld residuals. Linear regression was performed to calculate the Pearson correlation coefficient of determination (R<sup>2</sup>). P < 0.05 was considered significant and no correction for multiple testing was performed. All statistical analyses were performed using the JMP software programme, version 14.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Association between patients’ characteristics and preoperative PNI level

A low-PNI level was significantly associated with a worse postoperative prognosis (P = 0.042), but not other factors (Table 1).

Prognostic factors in surgically resected SqCC patients

We compared OS in patients who were older than 75 years versus younger than 75 years, male versus female, past or current smokers versus never-smokers, by preoperative PNI level (low vs high), pathological stage (II–III vs I), and in patients who underwent limited resection versus lobectomies, patients with pleural invasion versus those without pleural invasion, patients with BVI versus those without BVI, and patients with LVI versus those without LVI (Table 2). Univariable analyses showed that preoperative PNI levels (P = 0.003) and smoking status (P = 0.023) significantly affected OS. The hazard ratio (HR) for patients with low preoperative PNI levels were 3.129 versus patients with high
preoperative PNI levels [95% confidence interval (95% CI) 1.492–6.728] and 3.960 for patients with smoking history versus patients without smoking history (95% CI 1.320–5.957; P = 0.007) was only an independent prognostic factor (Table 2).

Preoperative PNI levels and RFS and OS in surgically resected SqCC patients

In the Kaplan–Meier analysis of RFS and OS by PNI level for 64 surgically resected SqCC patients

PNI group had a significantly shorter RFS and OS than the high-PNI group (RFS; P = 0.013, log-rank test, Fig. 1A and OS; P = 0.002, log-rank test, Fig. 1B).

Relationship between preoperative peripheral blood lymphocyte count, serum albumin concentration or PNI level, and TILs or macrophage status

The immunohistochemical staining results for CD3, CD4, CD8 and CD68 cells are shown in Fig. 2. A significant positive relationship between preoperative peripheral blood lymphocyte count and CD3+ cells (P < 0.0001) and CD8+ cells (P < 0.008) was observed (Fig. 3A). Conversely, a significant-close association between preoperative serum albumin concentration and CD3+ cells (P = 0.012), CD4+ cells (P = 0.005) and CD8+ cells (P = 0.022) was also found (Fig. 3B). Numbers of CD3+ cells, CD4+ cells and CD8+ cells in the preoperative high-PNI group were significantly increased compared with the preoperative high-PNI group (CD3: high PNI vs low PNI = 67.1 ± 21.5 vs 51.9 ± 14.2, P = 0.002, Fig. 4A; CD4: high PNI vs low PNI = 45.3 ± 15.8 vs 37.7 ± 13.4, P = 0.049, Fig. 4B; CD8: high PNI vs low PNI = 37.0 ± 16.7 vs 28.0 ± 12.7, P = 0.024, Fig. 4C), although there was no significant difference between the number of CD68+ cells (high PNI vs low PNI = 18.2 ± 7.8 vs 16.4 ± 8.7, P = 0.385, Fig. 4D).

DISCUSSION

Lymphocytes have an important role in preventing the spread of cancer cells by initiating cytotoxic immune responses and inhibiting cancer cell proliferation, invasion and migration [11, 12]. The host immune response to cancer cells mainly depends on systemic lymphocytes; therefore, a low systemic lymphocyte count may lead to tumour progression. Conversely, serum albumin is commonly used as an important indicator of nutritional condition, with hypo-albuminaemia seen in malnutrition and cachexia. Nutrition is a crucial element of the immune response, thus, hypo-albuminaemia may correlate with an impaired immune response [13]. As a result, PNI levels can reflect both systemic immunological and nutritional conditions and may be an excellent immunonutritional marker. In this study, a low preoperative PNI level was significantly associated with a worse postoperative prognosis. In addition, a low preoperative PNI level was an
independent prognostic factor for postoperative outcomes in lung SqCC patients. These findings are similar to those of previous studies [6, 17, 18], indicating that the PNI can reflect systemic immunity.

Recently, the number of published studies investigating the prognostic impact of TILs in NSCLC has been rapidly increasing. Many studies have examined CD3+, CD4+ and CD8+ TILs, and, as a result, TILs have been shown to have an important role in tumour suppression with CD8+ cytotoxic T cells and CD4+ helper T cells in particular shown to have positive prognostic effects [22–24]. In addition, TAMs are believed to influence tumour progression and the prognosis of lung cancer patients, and the presence of CD68-positive TAMs is an independent prognostic factor for prolonged survival in NSCLC patients [25].

We hypothesized that the systemic immunonutritional status represented by preoperative PNI level also affects the local immunity in lung cancer. Therefore, we investigated the association between preoperative PNI level and TILs or TAMs status using a pathological approach. As a result, this study showed several novel findings. First, we constructed Kaplan–Meier curves for OS according to the TIL and TAM status of 64 SqCC patients by analysing the number of CD3+ TILs and CD68+ TAMs to predict postoperative OS and comparing the AUC (CD3 cut-off 59.2, AUC 0.625; CD68 cut-off 24.2, AUC 0.513). This revealed that the low-TIL group had a significantly shorter OS, although there was no significant difference between the TAM groups (Supplementary Material, Fig. S3 and Fig. 4).

The absolute number of TILs positive for CD3, CD4 and CD8 in the preoperative high-PNI group was significantly increased compared with the preoperative low-PNI group. This result indicates that the preoperative systemic immunonutritional status also reflects the local immunity surrounding lung cancer tissue.

![Figure 1](image1.png)

**Figure 1:** (A) Kaplan–Meier curve analysis of recurrence-free survival for 64 surgically resected lung squamous cell carcinoma patients by preoperative PNI level. Blue line: high-PNI group; red line: low-PNI group. The 2 groups were significantly different (median survival time: 62.0 vs 32.9 months, \( P = 0.013 \)). (B) Kaplan–Meier curve analysis of overall survival for 64 surgically resected lung squamous cell carcinoma patients by pretreatment PNI level. Blue line: high-PNI group; red line: low-PNI group. The 2 groups were significantly different (median survival time: 75.9 vs 47.3 months, \( P = 0.002 \)). PNI: prognostic nutritional index.

![Figure 2](image2.png)

**Figure 2:** Immunohistochemical staining (high number and low number). (A and B) cluster of differentiation (CD)3+ tumour-infiltrating lymphocytes, (C and D) CD4+ tumour-infiltrating lymphocytes, (E and F) CD8+ tumour-infiltrating lymphocytes and (G and H) CD68+ cells.
Figure 3: (A) Correlation between the number of tumour-infiltrating lymphocytes (TILs) and CD68+ cells, and preoperative total lymphocyte count. (a) CD3+ TILs, (b) CD4+ TILs, (c) CD8+ TILs and (d) CD68+ cells. Positive correlation between CD3+ TILs and CD8+ TILs, and preoperative total lymphocyte count ($P < 0.0001$ and $P = 0.008$, respectively). (B) Correlation between the number of TILs and CD68+ cells, and preoperative serum albumin concentration. (a) CD3+ TILs, (b) CD4+ TILs, (c) CD8+ TILs and (d) CD68+ cells. Positive correlation between CD3+ TILs, CD4+ TILs and CD8+ TILs, and preoperative serum albumin concentration ($P = 0.012$, $P = 0.005$ and $P = 0.022$, respectively). CD: cluster of differentiation.
Moreover, we investigated the correlation between each component of the PNI, i.e. preoperative peripheral blood lymphocyte count and serum albumin level, and TILs or TAMs separately. As a result, preoperative peripheral blood lymphocyte count was shown to be significantly proportional to both CD3+ TILs and CD8+ TILs. This positive correlation indicates that systemic lymphocytes may also control TILs; thus, preoperative peripheral blood lymphocytopenia might correlate with the decreasing number of TILs resulting in local tumour immunosuppression. Remarkably, this study also revealed that preoperative serum albumin concentration was correlated with CD3+ TILs, CD4+ TILs and CD8+ TILs. This shows that preoperative nutritional status also affects the local immune system surrounding lung cancer tissue. Wang et al. [26] mentioned that the positive correlation between the number of TILs and preoperative serum albumin level was significant in colorectal cancer patients, supporting our data. From our findings, it is reasonable to suggest that the PNI level affects TIL status in lung cancer patients.

We recently studied the PNI and other nutritional indexes, such as the controlling nutritional score (CONUT) and the geriatric nutritional risk index, in preoperative lung cancer patients [7, 8]. The PNI is composed of the serum albumin concentration and the peripheral lymphocyte count, while the CONUT score is calculated according to the albumin, lymphocyte and total cholesterol concentrations. In general, the total cholesterol concentration is within an almost normal range in lung cancer patients compared with patients with other diseases such as hepatic disease. In addition, some patients are administered statins (which influences the patient’s total cholesterol status) prophylactically to prevent cardiovascular events. Thus, in many cases, the total cholesterol concentration itself cannot reflect the patient’s ‘true’ nutritional status. However, the geriatric nutritional risk index only comprises the serum albumin level and body mass index; therefore, the geriatric nutritional risk index mainly reflects the patient’s ‘nutritional status’. Thus, we considered that the PNI level is the most useful biomarker to reflect the preoperative ‘immune-nutritional condition’ of lung cancer patients.

Cancer immunotherapy using immune checkpoint inhibitors including anti-programmed cell death-1 antibodies and anti-programmed cell death-ligand-1 antibodies has gained widespread acceptance for the treatment of various malignancies, including NSCLC. Programmed cell death-ligand-1 is an immune

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**Figure 4:** The absolute number of cells surrounding lung cancer tissue according to preoperative PNI level. (A) The number of CD3+ TILs in patients with a high-PNI level were significantly increased compared with that in patients with a low-PNI level ($P = 0.002$). (B) The number of CD4+ TILs in patients with a high-PNI level was significantly increased compared with that in patients with a low-PNI level ($P = 0.049$). (C) The number of CD8+ TILs in patients with a high-PNI level was significantly increased compared with patients with a low-PNI level ($P = 0.024$). (D) There was no difference in the number of CD68+ cells between patients with a high-PNI level and those with a low-PNI level ($P = 0.002$). CD: cluster of differentiation; PNI: prognostic nutritional index.
checkpoint protein expressed on both tumour cells and TILs. Both anti-programmed cell death-1 and anti-programmed cell death-ligand-1 antibodies enable T-cell activation and immune system recognition. We previously reported that the pretreatment PNI level was a predictive factor of immune checkpoint inhibitor response in NSCLC patients [27]. However, the mechanism was unclear. The pretreatment low-PNI level also means the absolute decreasing number of TILs obtained from this study might be a reason why lung cancer patients with low-PNI levels before treatment showed resistance to immune checkpoint inhibitor therapy.

In the clinic, we considered 4 treatment strategies for lung cancer patients with poor preoperative PNI levels: (i) immunonutritional support before thoracic surgery and radical resection; (ii) neoadjuvant and/or adjuvant therapy; (iii) limited resection; and (iv) avoidance of surgical resection and selection of alternative therapies such as radiotherapy, chemotherapy, or palliative care. To clarify which of these treatment strategies are correct, we perform or plan prospective studies. We undertook a prospective and single-arm pilot study to observe changes in patients’ immunonutritional condition following immunonutritional support during the preoperative period. This study revealed that short-term preoperative immunonutritional support can improve immunonutritional parameters immediately before surgery. In the future, we intend to perform a prospective study to evaluate whether preoperative immunonutritional support of elective lung cancer patients with low preoperative PNI levels might improve their prognosis and their risk of postoperative recurrence. In addition, this study revealed that the preoperative PNI level could reflect local immunity against cancer cells; therefore, we intend to evaluate the effect of neoadjuvant or adjuvant chemotherapy for lung cancer patients with preoperative poor PNI level.

Limitations

As this investigation was a retrospective study from a single institution, it lacked complete data. Furthermore, the sample size was too small to draw any meaningful conclusions. Therefore, a multicentric prospective study to evaluate the association between the preoperative PNI level and TIL status in a larger scale study, or in adenocarcinoma or other histological subtypes, is warranted. In addition, a prospective study is required to evaluate the survival benefit of multimodality therapies, such as induction or adjuvant chemotherapy, in NSCLC patients with a low preoperative PNI level.

CONCLUSION

In conclusion, preoperative PNI level is a reasonable and acceptable biomarker that can affect the postoperative outcome through systemic and local immunity. Preoperative systemic immunonutritional condition might influence postoperative prognosis in lung cancer patients through local immunity and systemic immune response.

SUPPLEMENTARY MATERIAL

Supplementary material is available at EJCTS online.

Conflict of interest: none declared.

Author contributions

Hirokazu Kitahara: Data curation; Investigation; Methodology; Validation; Writing—original draft. Fumihiro Shoji: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing—original draft. Takaki Akamine: Data curation; Formal analysis; Methodology; Validation. Fumihiko Kinoshita: Data curation; Investigation; Methodology; Validation. Naoki Haratake: Data curation; Investigation; Methodology; Validation. Tomoyoshi Takenaka: Resources; Validation. Tetuzo Tagawa: Data curation; Methodology; Validation. Takashi Sonoda: Investigation; Validation; Visualization. Mototsugu Shimokawa: Statistical analysis. Yoshihiko Maehara: Formal analysis; Investigation; Methodology; Supervision; Validation. Masaki Mori: Conceptualization; Investigation; Supervision; Writing—review & editing.

Reviewer information

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