

Prognostic impact of prognostic nutritional index in advanced (stage IIIB/IV) non-small cell lung cancer patients

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Prognostic nutritional index (PNI) is a parameter reflecting prognosis for various cancers, including resected lung cancer. However, there were few reports to study the relationship between the PNI and overall survival (OS) in patients with advanced (stage IIIB/IV) non-small lung cancer (NSCLC). In this study, we collected the clinical data of 315 patients with advanced (stage IIIB/IV) NSCLC who had received chemotherapy or epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) between January 2010 and June 2011. Survival curves were plotted using the Kaplan-Meier method. Multivariate analyses were used to evaluate prognostic significance of PNI in patients with advanced (stage IIIB/IV) NSCLC. In our analysis, we found that PNI ($p=0.001$) was significantly associated with OS in patients with advanced (stage IIIB/IV) NSCLC, so was smoking ($p<0.001$) and disease stage ($p=0.005$). We demonstrated that PNI could be utilized to predict survival outcomes in patients with advanced (stage IIIB/IV) NSCLC. Patients with a lower PNI may have worse prognosis.

Key words: non-small cell lung cancer, prognostic nutritional index, prognosis

Lung cancer remains the leading malignancy in terms of morbidity (11.6%) and mortality (18.4%) in the world, according to authoritative statistics from “Global cancer statistics 2018” [1]. By 2017, the incidence of lung cancer in China has risen to 800,000 and the death toll has reached 700,000, accounting for a quarter of all cancer deaths. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers [2].

Surgical treatment is the preferred treatment for NSCLC, but most lung cancer patients are stage IIIB and IV when diagnosed and lost the opportunity of radical resection. Thus, it is important for early detection of lung cancer. Currently, TNM staging is regarded as a crucial tool for clinical prognosis and outcome in lung cancer. Besides, it is reported that some biomarkers that indicate systemic inflammatory responses, simple and measurable, have been used to predict prognosis across multiple malignancies, including neutrophil lymphocyte ratio (NLR) [3, 4] and platelet lymphocyte ratio (PLR) [5, 6].

In recent years, prognostic nutritional index (PNI) which was used to assess immune-nutritional status of patients receiving gastrointestinal surgery [7, 8] has been identified to be a prognostic factor of cancers, such as liver, gastric and

esophageal cancer and pleural mesothelioma [9–13]. Many studies have suggested the prognostic value of PNI in patients with resectable lung cancer [14]. However, PNI in patients with advanced NSCLC has not previously been elucidated.

In the present study, we investigated the prognostic value of the PNI among patients with advanced (IIIB/IV) NSCLC who had no chance to receive surgery.

Patients and methods

Patients characteristics. The patients’ characteristics are presented in Table 1. This study comprised 333 patients with primary NSCLC who had received chemotherapy or epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) in Shandong Provincial Hospital between 2010 and 2011. All the patients included in the analysis were diagnosed with stage IIIB or IV lung cancer who had no chance to receive surgery. All laboratory data was collected before treatment. Patients with autoimmune diseases, previous or coexisting cancers other than NSCLC or hematological disorders were excluded. Of these, 18 patients were excluded. All patients provided informed consent prior to this study. This study was conducted with the approval of

Table 1. Clinicopathological characteristics of patients with NSCLC cancer (n=315).

Factor	Number (%)
Age (years)	
<58	130 (41.3%)
≥58	185 (58.7%)
Gender	
Female	102 (32.4%)
Male	213 (67.6%)
Smoking	
No smoking	205 (65.1%)
Smoking	110 (34.9%)
Disease stage	
IIIB	143 (45.4%)
IV	172 (54.6%)
Treatment	
Chemotherapy	240 (76.2%)
EGFR-TKIs	75 (23.8%)
PNI	
<50	179 (56.8%)
≥50	136 (43.2%)
Pathology	
SQ	110 (34.9%)
AD	162 (51.4%)
Others	43 (13.7%)

AD, adenocarcinoma; PNI, prognostic nutritional index; SQ, squamous cell carcinoma; EGFR-TKIs, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors.

Table 2. Relationship between PNI and clinicopathological features.

Factors	PNI ≥50	PNI <50	p-value
Age (years)			0.175
<58	62 (45.6%)	68 (38%)	
≥58	74 (54.4%)	111 (62%)	
Gender			0.335
Female	48 (35.3%)	54 (30.2%)	
Male	88 (64.7%)	125 (69.8%)	
Smoking			0.284
Smoking	43 (31.6%)	67 (37.4%)	
No smoking	93 (68.4%)	112 (62.6%)	
Disease stage			<0.001
IIIB	81 (60%)	62 (34.6%)	
IV	55 (40%)	117 (65.4%)	
Treatment			0.049
Chemotherapy	111 (81.6%)	129 (72.1%)	
EGFR-TKIs	25 (18.4%)	50 (27.9%)	
Pathology			0.49
AD	75 (55.2%)	87 (48.6%)	
SQ	43 (31.6%)	67 (37.4%)	
Others	18 (13.2%)	25 (14%)	

AD, adenocarcinoma; PNI, prognostic nutritional index; EGFR-TKIs, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors; SQ, squamous cell carcinoma.

the institutional Ethics Committee of Shandong Provincial Hospital Affiliated to Shandong University.

Data collection and definition. The clinical characteristics of patients in our study including age, sex, history of tobacco exposure, pathological type, TNM stage and the details of treatment were collected by electronic medical records. Computed tomography (CT) was carried out before treatment. A total of 240 (76.2%) patients received systemic chemotherapy for at least two cycles. The remaining 75 (23.8%) patients were treated with EGFR-TKIs. Blood sample collection was routinely performed before the initiation of any treatment, including serum albumin and lymphocyte count. Then, the PNI was calculated as $10 \times \text{serum albumin (g/dl)} + 0.005 \times \text{total lymphocyte count (per mm}^3\text{)}$ [10]. The PNI cut-off value for clinically significant malnutrition was set at below 50 in this approach.

Patient follow-up. Follow-up was performed for all patients every 3 months for the first 2 years, every 3–6 months for 2–5 years until September 1, 2016. The follow-up included reviewing the patient's medical history, blood routine, tumor markers, biochemical examination. In addition, chest x-ray films or CT scans were performed at least twice per year. The period from the therapy to the date of death was defined as the OS time.

Statistical analysis. Statistical analysis was performed using SPSS for Windows version 22.0 (SPSS, Chicago, IL, USA). The χ^2 test was used to compare categorical variables. OS was calculated from the date of therapy to the date of NSCLC-associated death. The Kaplan-Meier method was used to estimate the survival rates for different groups and the equivalences of the survival curves were tested by log-rank statistics. The proportional hazards assumption was explored using log-minus-log-plots. The Cox proportional hazards model was used for univariate and multivariate survival analysis (multivariate survival analysis consisted of variables with p-value <0.05 in univariate analysis). A p<0.05 was considered statistically significant.

Results

Patients characteristics. A total of 315 patients with NSCLC were eligible for analysis. The age of patients ranged from 26 to 79 years (mean, 58.53 years). Of these patients, 213 (67.6%) were males and 102 (32.4%) were females; 110 (34.9%) patients smoked. According to TNM classification, there were 143 patients (45.4%) in pathological stage IIIB and 172 patients (54.6%) in stage IV. A total of 240 (76.2%) patients received systemic chemotherapy and 75 (23.8%) patients EGFR-TKIs. There were 162 (51.4%) patients with adenocarcinoma, 110 (34.9%) with squamous cell carcinoma, and 43 (13.7%) with other histological types. The baseline characteristics of the 315 patients are shown (Table 1).

Association of PNI with clinicopathological characteristics. Table 2 shows the relationship between PNI and the clinicopathological features. Significant differences

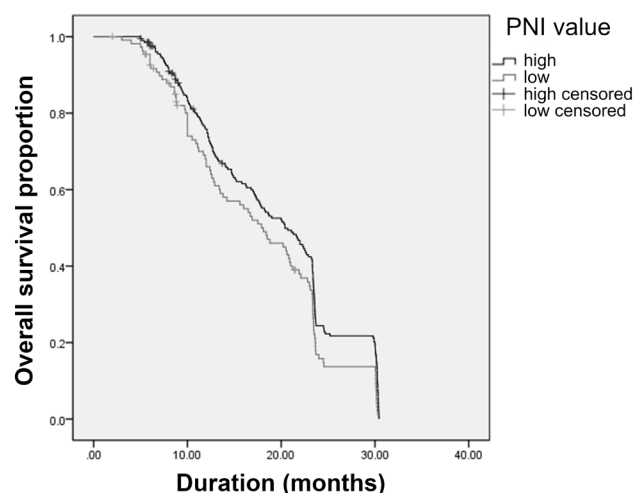


Figure 1. Kaplan-Meier survival curves according to the pretreatment PNI level.

were observed with respect to disease stage and treatment. Patients with a higher PNI (≥ 50) tended to be the ones treated with chemotherapy ($p=0.049$) than those with lower PNI. Moreover, PNI was significantly higher in patients diagnosed with stage IIIB cancer compared with those with stage IV disease ($p<0.001$). No significant correlation was observed between PNI and age, gender, smoking or pathology.

Prognostic value of PNI. The correlation between clinicopathological factors and OS is shown in Figure 1. The PNI values of all the patients ranged from 5.15 to 73.25 (mean, 48.1; median, 49.35). The cutoff value of the PNI for clinically significant malnutrition was set at below 50 in this study. Then, 315 patients were divided into low-PNI group ($n=179$; 56.8%) and high-PNI group ($n=136$; 43.2%). The median OS of patients with low PNI ($PNI \leq 50$) and high PNI ($PNI > 50$) was 14.4 and 17.95 months, respectively, and low PNI was highly associated with a short survival time ($HR=1.331$; 95% CI: 1.05–1.688, $p=0.018$). One-year OS rates of $PNI > 50$ group were higher than those of $PNI \leq 50$ group (74%; 67%) (Figure 1).

PNI and other prognostic factors for OS. To further identify the risk factors linked to postoperative OS, PNI and other clinicopathologic factors were evaluated by univariate analysis and the Cox regression model. Univariate analysis (Table 3) showed that the significant prognostic factors for OS in advanced NSCLC patients were disease stage ($p=0.017$), smoking ($p=0.001$), pathology ($p<0.001$) and PNI ($p=0.018$). All clinicopathological characteristics were further investigated in multivariate analysis. After multivariate analysis (Table 4), we found that smoking ($p<0.001$), disease stage ($p=0.005$) and PNI ($p=0.001$) were significant independent predictors of OS. However, pathology ($p=0.423$) had no influence on OS.

Table 3. Univariate analysis of clinicopathological parameters for the prediction of OS in patients with NSCLC.

Parameters	Univariate HR	analysis (95% CI)	p-value
Age (years)			0.070
<58	1.00		
≥ 58	1.244	0.982–1.576	
Gender			0.080
Female	1.00		
Male	1.248	0.974–1.601	
Smoking			0.001
No smoking	1.00		
Smoking	1.974	1.524–2.556	
Disease stage			0.017
IIIB	1.00		
IV	0.749	0.592–0.949	
Treatment			0.113
Chemotherapy	1.00		
EGFR-TKIs	0.801	0.609–1.054	
PNI			0.018
≥ 50	1.00		
<50	1.331	1.05–1.688	
Pathology			< 0.001
AD	1.00		
SQ	0.677	0.554–0.827	
others			

AD, adenocarcinoma; PNI, prognostic nutritional index; SQ, squamous cell carcinoma; EGFR-TKIs, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors.

Table 4. Multivariate analysis of clinicopathological parameters for the prediction of OS in patients with NSCLC.

Parameters	Multivariate HR	analysis (95% CI)	p-value
Disease stage			0.005
IIIB	1.00		
IV	0.703	0.550–0.897	
Smoking			< 0.001
No smoking	1.00		
Smoking	2.418	1.478–3.957	
PNI			0.001
≥ 50	1.00		
<50	1.525	1.194–1.947	
Pathology			0.423
AD	1.00		
SQ	1.151	0.816–1.626	
others			

AD, adenocarcinoma; PNI, prognostic nutritional index; SQ, squamous cell carcinoma; EGFR-TKIs, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors.

Discussion

PNI, determined by two factors, the serum albumin concentration and lymphocyte count in the peripheral blood, was used to assess the immunological and nutritional status of cancer patients after digestive surgery [9]. In 2011, Proctor et al. reported that Onodera's PNI could predict the outcome of cancer patients, regardless of the primary site of origin [8]. Yao et al. found that PNI was a useful indicator of prognosis in patients with malignant pleural mesothelioma [13]. Similar results can be seen in other cancers such as colorectal and hepatocellular carcinomas [11], and lung cancer is no exception.

Notably, many previous reports have shown that a lower PNI signifies a shorter OS in the in patients with completely resected NSCLC [14, 15]. Studies about the prognostic value of the PNI in patients with advanced NSCLC are very few. In 2016, Sheng et al. studied 144 patients with advanced NSCLC following EGFR-TKIs and found that PNI was a significant prognostic factor [16]. In our study, we investigated PNI in 315 patients for advanced (IIIB/IV) NSCLC who received chemotherapy or EGFR-TKIs. After univariate and multivariate analysis, we found that PNI was independently associated with overall cancer-specific survival of patients ($p=0.001$). Patients with a higher PNI had a better prognosis.

The mechanisms that regulate the association between PNI and the survival of patients with cancer are not yet completely elucidated. Several explanations have been proposed.

Firstly, malnutrition can be seen in various malignancies, especially in advanced cancers. Due to the characteristic of cancer rapid reproduction, large quantities of nutrients are consumed and deprived from the body, causing the impairment of normal metabolism. Besides, nutritional disorders have been reported to be associated with the severity of depression, anxiety and pain, which lead to poor outcomes in cancer patients [17]. Serum albumin, synthesized by hepatocytes, is commonly used to estimate the nutritional status [18]. Decreased albumin expression has been considered an indication of malnutrition and its drastic reduction often gives a hint of a contributor to cachexia, which is associated with reduced survival [19]. In addition, increasing evidence has emphasized the contributing role of the inflammatory response, which can exacerbate tumor-related malnutrition and the albumin reduction in many cancer patients.

Inflammatory mediators secreted by tumor, including tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) result in low appetite and thus affecting the nutritional intake. Some studies have suggested that hypoalbuminemia is caused by these cytokines, which all participate in downregulating the gene expression of albumin and decrease the synthesis of albumin [20]. Furthermore, inflammation can also promote and reflect tumor progression by affecting

host immunity and the antitumor response. Therefore, nutrition plays a vital role in the process of the maintenance of immune function and malnutrition may have bad effects on the function of immune system.

The above-mentioned evidence suggests that hypoalbuminemia correlates with poor outcome in cancer patients. A study of 191 esophageal cancer patients after surgery demonstrated that an insufficient postoperative albumin recovery was a poor predictor of survival [21]. Another study conducted in 59 elderly patients with advanced NSCLC, who received chemotherapy or best supportive care, found that in elderly advanced NSCLC patients with poor performance status (PS), low serum albumin level was associated with poor prognosis in chemotherapy group [22]. A meta-analysis conducted to assess the prognostic significance of serum albumin in urothelial carcinoma found that reduced preoperative serum albumin level was an independent prognostic factor of urothelial carcinoma [23]. Besides, serum albumin level has been identified to have a prognostic impact on survival of patients with multiple cancer types [24–30].

On the other side, accumulating evidence support that the immunity is closely related to the occurrence and development of tumor [31]. Lymphocytes as important components of immune cells, have long been reported to inhibit the growth of cancer by T-cell-mediated immune response [32]. It is true that CD4+ T helper lymphocytes (CD4+Th) and CD8+T lymphocytes work together to induce an immune response to tumor. When tumor antigens are presented to CD8+T lymphocytes, CD8+T lymphocytes are transferred into CD8+cytotoxic T lymphocyte (CTLs) to exhibit the activity against cancer. With direct roles of killing tumor cells, CD8+CTLs also increase tumor cell apoptosis by secreting cytokines such as interferon- γ (IFN- γ) [33, 34], tumor necrosis factor (TNF). Additionally, substantial evidence shows that chronic inflammatory reactions contribute to promoting tumor growth and invasion. We found that CD4+Th became capable of enhancing the effect of CD8+CTLs and inducing antitumor inflammation response via generating and releasing interleukin-2. As discussed above, high concentrations of lymphocytes were shown to be strongly associated with antitumor activity and infection control.

Several reports support using the lymphocyte count as a prognostic factor. Mehrazin et al. observed that patients with lymphopenia risk had a worse prognosis in papillary renal cell carcinoma [35]. In 2005, Sato et al. reported that intraepithelial CD8+ tumor infiltrating lymphocytes were associated with a good prognosis in ovarian cancer [36]. Similarly, several studies suggested that there was a positive correlation between the infiltration of lymphocytes in tumor tissue and prognosis in breast, head and neck cancer patients [37–39].

In advanced patients with NSCLC, Lee and colleagues reported that the lymphocyte count was a significant prognostic factor [40], while Song et al. found that it was useful in patients with NSCLC treated with chemoradiotherapy [41].

Based on these reports, both the serum albumin and lymphocytes are obviously related to the prognosis of cancer patients, which may explain the association between low PNI and poor prognosis in cancer patients.

In our present study, we also found that the high PNI tend to be in patients of stage IIIB ($p < 0.001$) and treated with chemotherapy ($p = 0.049$). It is easy to understand that patients of stage IIIB have a better prognosis than that of stage IV. We know that stage IIIB has better nutritional and immune state than stage IV, which could explain why stage IIIB are more likely to have a higher PNI. As we know, chemotherapy leads to sickness and vomiting, then patients may lose appetite and have a rapid weight loss. Compared with chemotherapy, the side effects of EGFR-TKIs tend to be accepted [42]. However, in our present study, patients treated with EGFR-TKIs have a lower PNI. Our explanation is that the number of enrolled patients was too small. If we have a large sample, maybe we can come to a completely different conclusion. Another reason is that some patients with EGFR-TKIs developed drug resistance early and refused further treatment.

In addition, we also explored other factors that may influence the OS of cancer patients, such as age, gender, smoking habits, pathology stage, historic types. As previous reports mentioned, age, male, smoking, patients with advanced stage were negative factors that affect survival in lung cancer patients. However, significant differences were observed in patients with advanced clinical stage (IV) and those having smoking habits (p -value both < 0.05). Age and gender were not correlated to survival of advanced NSCLC patients in our study.

This study has several limitations that should be considered when interpreting the results. Firstly, the number of patients is small, which may have potentially biased the results of our study. Secondly, the relapse free survival of patients was not statistically analyzed in the study, so the obtained results are correspondingly short of conviction.

In conclusion, we demonstrated that PNI was a favorable and promising marker to predict OS of patients with advanced (IIIB/IV) NSCLC. A low PNI is correlated with the poor prognosis of cancer patients. As to patients with decreased PNI, some alternative treatment methods can be provided, which may prolong their survival.

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