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RESEARCH ARTICLE

The prognostic nutritional index (PNI) predicts overall survival of small-cell lung cancer patients

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Abstract Recent studies have shown the prognostic nutritional index (PNI) had prognostic value in some solid tumors. However, no studies have examined its prognostic role in small-cell lung cancer (SCLC) patients. In this retrospective study, 724 consecutive SCLC patients were included between 2006 and 2013. Demographic, clinical, and laboratory data were collected. The PNI was calculated as 10 × serum albumin value (g/dl) + 0.005 × peripheral lymphocyte count (per mm^3). Univariate and multivariate analyses were performed to assess the prognostic value of relevant factors. The optimal cut-off value of PNI for OS stratification was determined to be 52.48. A total of 464 and 260 patients were assigned to low and high PNI groups, respectively. Compared with low PNI, high PNI was associated with older age, advanced stage, and elevated lactate dehydrogenase (LDH). Median overall survival (OS) was worse in the low PNI group (low vs high, 15.90 vs 25.27 months; HR, 0.62; $p<0.001$). In multivariate analysis, stage, performance status, LDH, and PNI were independent prognostic factors for OS. Subgroup analysis showed PNI was generally a significant prognostic factor in different clinical situations. The assessment of PNI could assist the identification of patients with poor prognosis and be a hierarchical factor in the future SCLC clinical trials.

Keywords Small cell · Lung cancer · Albumin · Lymphocyte · Prognosis

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Introduction

Lung cancer represents the leading cause of cancer-related mortality. In the USA, 159,260 deaths were attributed to lung cancer every year [1]. Small-cell lung cancer (SCLC) accounts for 15–20 % of all lung malignancies which is characterized by its aggressive nature and poor prognosis [2]. The median survival time is only 2–4 months for treatment-free patients [3]. Currently, platinum in combination with etoposide or irinotecan is the standard first-line treatment of SCLC, achieving a median overall survival (OS) of about 10 and 36 months in extensive and limited disease, respectively [4, 5]. Thoracic radiotherapy (TRT) is frequently given in combination with chemotherapy to improve clinical outcome while prophylactic cranial irradiation (PCI) has also been recommended to prevent cerebral metastases [6]. Even though initial response to chemotherapy is dramatic, most patients develop recurrence and/or remote metastases during early disease course, and the prognosis of such patients is poor [7]. There is an unmet need to further delineate prognostic factors of survival in order to better stratify those who are likely to benefit from

chemotherapy so that unnecessary toxicity and morbidity could be avoided.

Several clinical and laboratory markers are related to survival of SCLC patients. Among them, stage is the most important predictor of OS [8, 9]. Abnormally elevated lactate dehydrogenase (LDH) can imply high tumor burden as well as poor prognosis [9, 10]. Furthermore, performance status (PS) has traditionally been utilized to predict the outcome of SCLC patients [9]. Other variables, including age, gender, neuron-specific enolase, carcinoembryonic antigen, plasma sodium, albumin, hemoglobin, and alkaline phosphatase are also reported to be associated with OS in SCLC [9, 11–15]. However, the optimal prognostic factor for SCLC remains controversial.

There is increasing evidence showing that patient's nutritional and immunological status is closely related to the long-term outcome of malignant tumors. The prognostic nutritional index (PNI), which is calculated on the basis of serum albumin level and total lymphocyte count in peripheral blood, is originally designated for the assessment of perioperative immunonutritional status and risk of post-surgical complications [16]. Additionally, PNI can indicate systemic inflammatory reaction which has been shown to be related to tumorigenesis and cancer progression [17]. Recent studies also pointed out the prognostic value of PNI in a variety of cancer types including colorectal cancer, gastric cancer, malignant pleural mesothelioma, hepatocellular carcinoma, and pancreatic cancer [18–22]. Most of the studies used median or mean value as cut-off for PNI and showed that high PNI was a favorable prognostic factor. These methods might not be ideal for the determination of optimal cut-off to discriminate time-to-event end points like OS. However, there are currently no studies concerning the association between PNI and OS in SCLC patients.

We hypothesized that immunonutritional status, which can be assessed by PNI, is associated with OS of SCLC patients. Therefore, in this retrospective study, we aimed to investigate the association between PNI and clinicopathological factors as well as its prognostic value in SCLC patients receiving standard first-line chemotherapy.

Materials and methods

Study population

We retrospectively reviewed all patients who were histologically diagnosed as SCLC between May 2006 and December 2013 in Sun Yat-sen University Cancer Center (SYSUCC). Other inclusion criteria were as follows: (I) ≥18 years old, (II) received at least one cycle of standard chemotherapy (irinotecan- or etoposide-based chemotherapeutic regimens), (III) available pretreatment blood samples or sufficient laboratory data, and (IV) complete clinicopathological information. Patients with previous or coexisting cancers other than SCLC, hematological disorders, or autoimmune diseases were excluded. The study protocol was approved by the institutional review board of SYSUCC, and written informed consent was obtained for each participant. All patients were followed up to March 30th 2014 or death from any cause.

Clinical data collection

Baseline characteristics including demographics, smoking status, PS, pathological diagnosis, cancer stage, and therapeutic information were collected using an electronic medical record system. Smokers were defined as those who had more than 100 lifetime cigarettes. Cancer stage was determined according to the modified Veterans Administration Lung Cancer Group (VALG) staging system dividing patients into limited and extensive disease [23]. Limited disease (LD) was defined as tumor confined to one hemithorax with/without regional lymph node metastasis (including both ipsilateral and contralateral hilar, supraclavicular and mediastinal nodes), as well as ipsilateral pleural effusion. Extensive disease (ED) was defined as any tumor that extended beyond the abovementioned boundaries. Pretreatment complete blood cell counts, serum albumin, and LDH level were evaluated. PNI was then calculated with the following formula as previously described [16]: 10×serum albumin value (g/dl)+0.005×peripheral lymphocyte count (per mm^3).

Statistical analyses

The overall survival (OS) was calculated from the time of pathological diagnosis to the date of death from any cause or last follow-up. All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). The optimal cut-off value of PNI was determined using a R software-engineered, web-based system designed by Budczies et al. (http://molpath.charite.de/cutoff/) [24]. Continuous variables were expressed as medians and ranges and were categorized at the median value. Categorical variables were presented as the number of patients and percentages and were compared using Chi-square or Fisher's exact test with odds ratio (OR) and corresponding 95 % confidence interval (CI). Survival analyses were carried out using Kaplan–Meier methodology. Univariate and multivariate analyses for survival difference were performed using the Cox proportional hazards model and were expressed as hazard ratios (HRs) and 95 % CIs. PNI and other variables including age, gender, smoking status, cancer stage, PS, and LDH were used in the multivariate analysis model. A two-sided p value of less than 0.05 was taken to be significant.

Results

Patient characteristics

A total of 1216 SCLC patients diagnosed in Sun Yat-sen University Cancer Center were screened. After eligibility review, a total of 724 SCLC patients treated with standard chemotherapy were included for the analysis. The details of patients' selection process are shown in Fig. 1. The median follow-up time was 39.47 months (range, 1.30–116.07 months). The baseline characteristics of all the patients are shown in Table 1. The median age of the study population was 59 years (range: 19–86 years), and 627 (86.6 %) patients were males and 97 (13.4 %) were females. The majority of the patients were current or ex-smokers (n=600, 82.9 %). Performance status was generally good. A total of 667 (92.1 %) patients had Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1. For cancer stage, 401 (55.4 %) patients were initially diagnosed as LD and 323 (44.6 %) as ED.

The most commonly used first-line chemotherapy regimen was etoposide-based combination (n=606, 83.7 %). Irinotecan-based combination agents were also used in 281 (38.8 %) patients. In LD patients, 271 of 401 patients (67.6 %) had TRT, and 165 of 724 patients (22.8 %) received PCI after first-line chemotherapy.

Cut-off determination of PNI

The median value of PNI was 50.4 (range, 22.85–68.70). Using the biostatistical tool Cutoff Finder [24], we found that a wide range of cutoff points for PNI were significant (176 out of 252 tests, 69.8 %) (Fig. 2). The optimal cut-off points of PNI for the stratification of OS in SCLC was determined to be 52.48. Based on this cut-off value, 260 (35.90 %) patients were categorized as PNI-high group while the remaining 464 (64.1 %) patients as PNI-low group.

Association between clinicopathological variables and PNI

Clinical and laboratory factors according to PNI groups were presented in Table 1. Gender, smoking status, and chemotherapy regimens were similar between the two groups. However, patients were significantly older (≥59 years in low vs high PNI, 69.7 vs 30.3 %, respectively, p=0.002), and cancer stage was more advanced (ED in low vs high PNI, 72.4 vs 27.6 %, respectively, p<0.001) in the PNI-low group compared with the PNI-high group. Additionally, more patients received TRT (high vs low, 40.6 vs 49.4 %, respectively, p=0.043) and PCI (high vs low, 46.7 vs 53.3 %, respectively, p=0.001) in the high PNI group than that in low PNI group. Also, low PNI was significantly associated with abnormally elevated LDH level (p=0.007). For ECOG PS, patients with low PNI tended to have worse PS though no significant difference was reached (PS 2–3 in low vs high PNI, 75.4 vs 24.6 %, p=0.063).

Association of PNI with OS

At the date of last follow-up, 456 (63.0 %) patients had died. Median OS of the total patients was 18.6 months (95 % CI 17.56–19.78 months). In univariate analyses of survival, high PNI was significantly associated with longer OS compared with low PNI group (median OS in high vs low PNI group, 25.27 vs 15.90 months; HR, 0.62; 95 % CI, 0.51–0.75; p<0.001), yielding a significant reduction in the mortality risk of 38 % (Fig. 3a). Other variables including LDH (HR for elevated vs normal LDH, 1.75; p<0.001), PS (HR for PS 2–3 vs PS 0–1, 2.58; p<0.001), and cancer stage (HR for ED vs LD, 2.44; p<0.001) were also significantly associated with OS (Fig. 3b–d). However, no significant difference in OS was noted regarding age (p=0.121), gender (p=0.149), smoking status (p=0.453), and chemotherapy regimens (p=0.605). In multivariate analyses, PNI was an independent prognostic factor in SCLC. Patients with high PNI had 29 % decrease

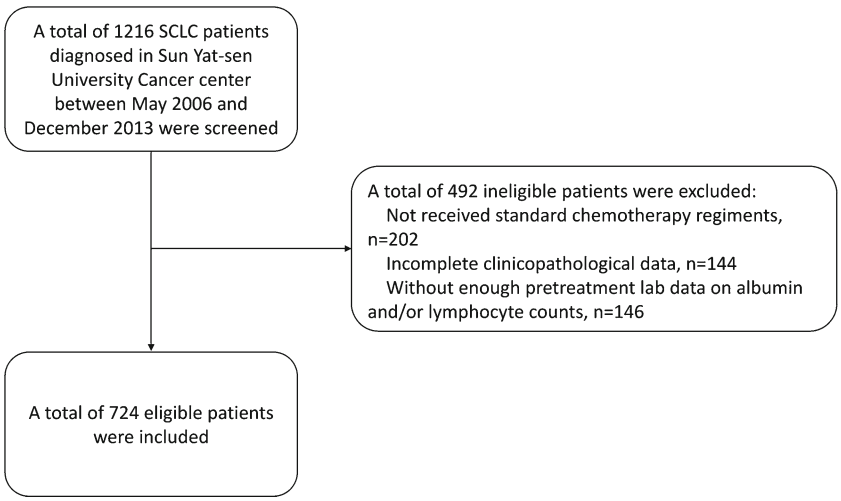

Fig. 1 Flow chart of patients' selection. *SCLC* small-cell lung cancer

Table 1 Baseline characteristics stratified by pretreatment PNI level

Characteristics	*N* (%)	PNI-low, *N* (%)	PNI-high, *N* (%)	OR (95 % CI)[a]	*P*
Age, years					
<59	368 (50.8)	216 (58.7)	152 (41.3)	1 (Referent)	
≥59	356 (49.2)	248 (69.7)	108 (30.3)	1.62 (1.19–2.20)	0.002
Gender					
Male	627 (86.6)	401 (64.0)	226 (36.0)	1 (Referent)	
Female	97 (13.4)	63 (64.9)	34 (35.1)	1.04 (0.67–1.63)	0.850
Smoking					
Current or ex-smoker	600 (82.9)	380 (63.3)	220 (36.7)	1 (Referent)	
Never smoker	124 (17.1)	84 (67.7)	40 (32.3)	1.22 (0.81–1.83)	0.352
ECOG PS at diagnosis					
0–1	667 (92.1)	421 (63.1)	246 (36.9)	1 (Referent)	
2–3	57 (7.9)	43 (75.4)	14 (24.6)	1.79 (0.96–3.35)	0.063
Stage					
Limited disease	401 (55.4)	230 (57.4)	171 (42.6)	1 (Referent)	
Extensive disease	323 (44.6)	234 (72.4)	89 (27.6)	1.95 (1.43–2.68)	<0.001
LDH at diagnosis, U/L					
Normal range	443 (61.2)	267 (60.3)	176 (39.7)	1 (Referent)	
Abnormally elevated	281 (38.8)	197 (70.1)	84 (29.9)	1.55 (1.12–2.13)	0.007
Chemotherapy regimen					
Etoposide-based	606 (83.7)	393 (64.9)	213 (35.1)	1 (Referent)	
Irinotecan-based	118 (16.3)	71 (60.2)	47 (39.8)	0.82 (0.55–1.23)	0.333
Thoracic radiotherapy					
Yes	271 (37.3)	161 (59.4)	110 (40.6)	1 (Referent)	
No	453 (62.7)	303 (66.9)	150 (33.1)	1.38 (1.01–1.88)	0.043
Prophylactic cranial irradiation					
Yes	165 (22.8)	88 (53.3)	77 (46.7)	1 (Referent)	
No	559 (77.2)	376 (67.3)	183 (32.7)	1.80 (1.26–2.56)	0.001

ECOG Eastern Cooperative Oncology Group, *PS* performance status, *LDH* lactate dehydrogenase, *PNI* prognostic nutritional index

[a] Denoted as the risk of having low PNI between the given groups

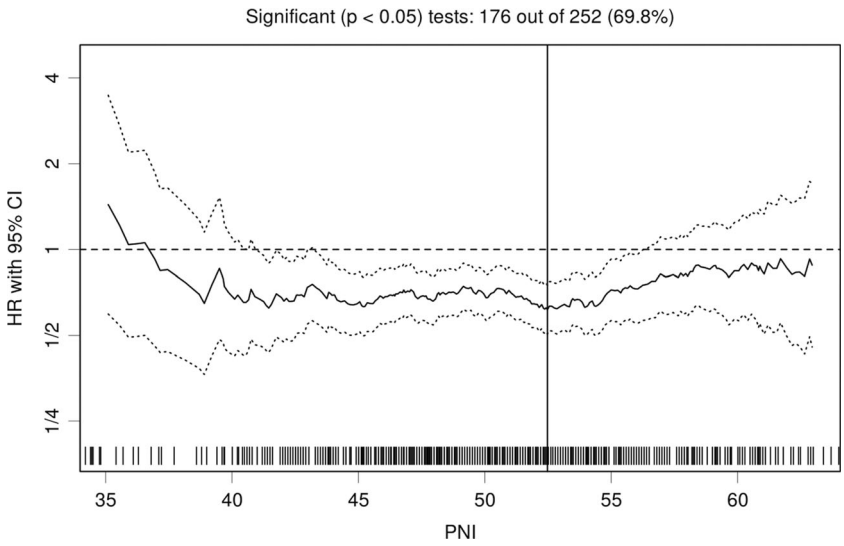

Fig. 2 Hazard ratio (*HR*) for overall survival (*OS*) in dependence of cut-off point for PNI in small-cell lung cancer patients. The *vertical line* designates the optimal cut-off point with the most significant (log-rank test) split. *PNI* prognostic nutritional index. The plots were generated using the biostatistical tool Cut-off Finder

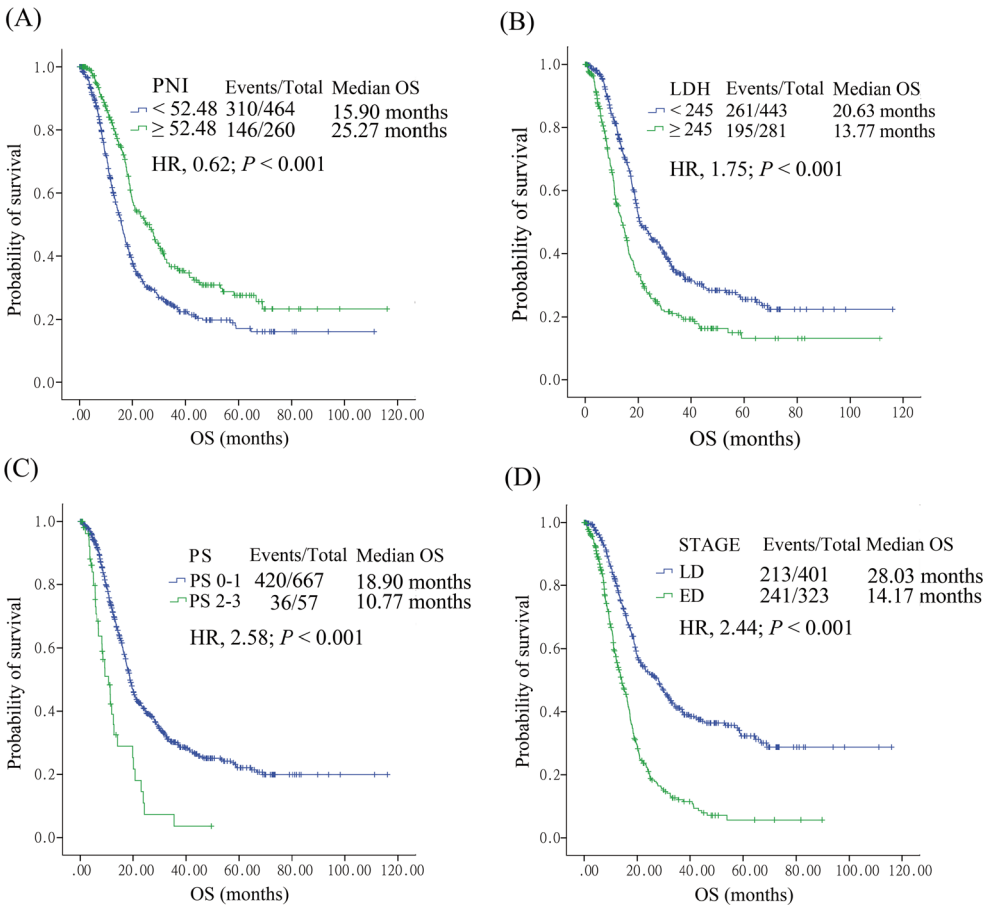

Fig. 3 Kaplan–Meier survival curves comparing patients with small-cell lung cancer with **a** high PNI vs low PNI, **b** low LDH vs low LDH, **c** good vs bad PS, **d** limited disease vs extensive disease. *PNI* prognostic nutritional index, *LDH* lactate dehydrogenase, *PS* performance status score, *LD* limited disease, *ED* extensive disease

in the risk of death compared with those with low PNI (HR, 0.71; 95 % CI, 0.58–0.87; $p<0.001$). Poor PS, extensive disease, and abnormally elevated LDH also independently predicted worse OS in SCLC. All the univariate and multivariate survival analyses are presented in Table 2.

In order to investigate the consistency of PNI as a prognostic factor in SCLC, we also did subgroup analyses according to baseline characteristics (Fig. 4). Higher PNI predicted favorable OS both in extensive and limited diseases (HR, 0.63 and 0.74, respectively). PNI was also a significant prognostic factor in etoposide-based as well as irinotecan-based chemotherapy. However, in patients with PS 2–3, females, and non-smokers, higher PNI only non-significantly predicted better OS.

Discussion

In this study, we retrospectively enrolled 724 consecutive SCLC patients treated with standard first-line chemotherapy to explore the prognostic significance of PNI with other clinical factors. To our knowledge, this is the first report on this issue. We showed that high PNI was a significant indicator of favorable OS in SCLC patients, independent of cancer stage, performance status, and LDH level.

The PNI, which was initially designed to assess the immunological and nutritional function of patients undergoing surgery of gastrointestinal tracts, could serve as a predictor of post-operational complications [16]. PNI is calculated based on standard laboratory measurement of albumin and total lymphocyte count and is therefore easily obtained. A low PNI indicates a decrease in albumin and/or lymphocyte count. Serum albumin is an important indicator of the host's inflammatory reaction and nutritional status and has been shown to be related to the prognosis of various cancer types (either alone or in combination with other factors) [25–28]. Malnutrition, or cachexia, which is partially reflected by hypoalbuminemia, was also closely related to elevated inflammatory markers including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein, and the modified Glasgow prognostic score (mGPS) [29, 30]. These markers have intensively been studied as a significant prognostic factor in cancer patients [31–33], suggesting the unfavorable role of chronic inflammation on the clinical outcome of malignancies. Actually, the production of albumin by hepatocytes was regulated by proinflammatory cytokines including interleukin-1 (IL-1), IL-6, and necrosis factor α

Table 2 Univariate and multivariate analysis of clinicopathological parameters for the prediction of overall survival in patients with small-cell lung cancer

Parameters	Median OS (95 % CI)	Univariate analysis		Multivariate analysis	
		HR (95 % CI)	*P*	HR (95 % CI)	*P*
Age, years					
<59	19.43 (17.49–21.37)	1 (Referent)		1 (Referent)	
≥59	17.60 (15.97–19.23)	1.16 (0.96–1.39)	0.121	1.03 (0.86–1.25)	0.741
Gender					
Male	18.67 (17.50–19.84)	1 (Referent)		1 (Referent)	
Female	19.50 (15.23–23.78)	0.82 (0.61–1.08)	0.149	0.92 (0.65–1.32)	0.655
Smoking					
Never smoker	18.73 (17.56–19.90)	1 (Referent)		1 (Referent)	
Current or ex-smoker	18.03 (14.14–21.92)	1.10 (0.86–1.41)	0.453	1.14 (0.82–1.58)	0.440
ECOG PS					
0–1	18.90 (17.62–20.18)	1 (Referent)		1 (Referent)	
2–3	10.77 (7.78–13.77)	2.58 (1.83–3.64)	<0.001	2.33 (1.64–3.31)	<0.001
Stage					
Limited disease	28.03 (22.90–33.16)	1 (Referent)		1 (Referent)	
Extensive disease	14.17 (12.27–16.07)	2.44 (2.02–2.95)	<0.001	2.11 (1.73–2.57)	<0.001
LDH, U/L					
Normal range	20.63 (17.94–23.32)	1 (Referent)		1 (Referent)	
Abnormally elevated	13.77 (11.78–15.76)	1.75 (1.45–2.10)	<0.001	1.44 (1.18–1.74)	<0.001
Chemotherapy					
Etoposide-based	18.40 (17.13–19.67)	1 (Referent)		1 (Referent)	
Irinotecan-based	20.37 (15.68–25.06)	0.94 (0.74–1.19)	0.605	1.01 (0.80–1.29)	0.910
PNI at diagnosis					
<52.48	15.90 (14.45–17.36)	1 (Referent)		1 (Referent)	
≥52.48	25.27 (20.44–30.10)	0.62 (0.51–0.75)	<0.001	0.71 (0.58–0.87)	<0.001

OS overall survival, *HR* hazard ratio, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *LDH* lactate dehydrogenase, *PNI* prognostic nutritional index

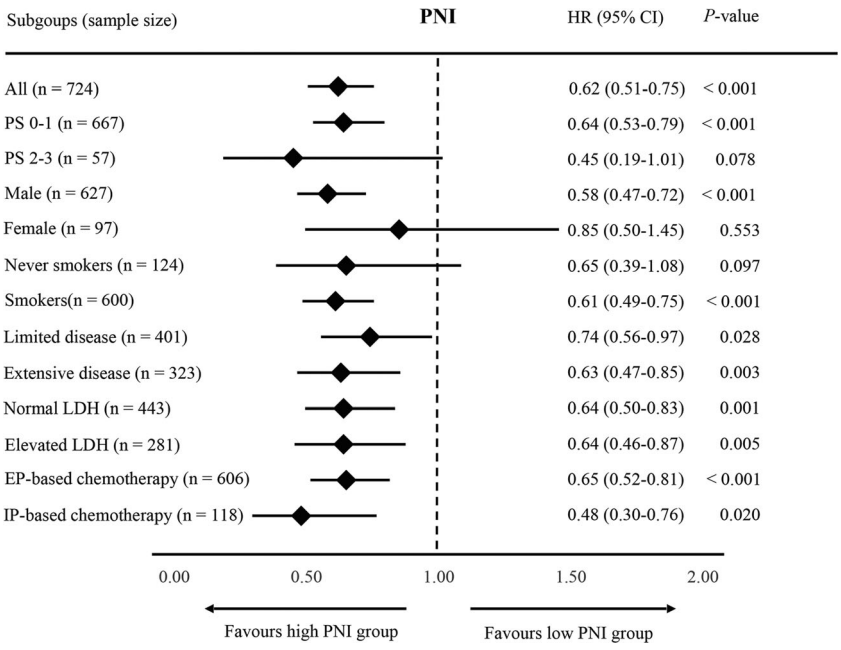

Fig. 4 Forest plot for subgroup analysis of overall survival. Survival is for high PNI vs low PNI. Data are derived from Cox's analysis without covariates. *HR* hazard ratio, *CI* confidence interval, *PS* performance status score, *LDH* lactate dehydrogenase, *PNI* prognostic nutritional index

(TNF-α) [34]. These cytokines, either from tumor itself or as a host reaction, are crucial for malignant transformation, neoangiogenesis and cancer progression [35]. Another aspect of PNI, the lymphocyte, has critical role in the defense of cancer cells by initiating cytotoxic immune response and inhibiting cancer cell proliferation, invasion, and migration [35, 36]. Lymphocytopenia, which could be induced by systemic inflammatory reaction, reveals the impairment of innate cellular immunity. Decreased lymphocytes are associated with disease severity and poor prognosis [37, 38]. Taken together, serum albumin and total lymphocyte may serve as indicators of chronic inflammation, immunity, and nutritional status, all of which are of prognostic significance.

Previous studies have investigated a number of potential prognostic factors in SCLC. In particular, disease extent, patient performance status and LDH level are the most validated ones [14]. In the present study, we further proved that extensive disease, poor PS, and abnormally elevated LDH were significantly associated with decreased OS. More importantly, we established the prognostic value of PNI in SCLC. In univariate survival analysis, we found that high PNI was an indicator of favorable OS, achieving a 38 % decrease in the mortality risk.

We also explored the association between clinicopathological variables and PNI in order to exclude potential bias. Low PNI was significantly associated with older patients, advanced cancer disease, and higher LDH. Therefore, worse OS in low PNI group might be explained by selection bias because high PNI group included more LD patients who had better survival than ED patients and who received more curative TRT and PCI. However, several results indicate that PNI was an independent prognostic determinant regardless of stage. PNI was shown as a prognostic factor through multivariate analysis including stage, LDH, and PS. Additionally, subgroup analysis according to stage demonstrated that OS in low PNI group was significantly shorter than that in high PNI group both in LD and ED patients. Although the prognostic power of PNI was more remarkable in ED patients than in LD patients, this may be due to more unfavorable markers in ED patients apart from low PNI. However, we found that higher PNI only non-significantly predicts favorable OS in patients with PS 2–3, females, or smokers. The most obvious reason is that the sample size of these subgroups are relatively small, which merits future investigation to draw final conclusions regarding these subgroups. For the abovementioned reasons, we postulated that PNI is a new and independent prognostic factor for OS in SCLC patients.

Currently, etoposide-based and irinotecan-based regimens are the standard first-line chemotherapy for SCLC patients. Consistent with previous studies, these two chemotherapeutic regimens failed to exhibit significant OS difference [4, 5]. The present study showed that in SCLC patients receiving either regimen, low PNI was significantly associated with shorter OS, indicating its general applicability in SCLC patients undergoing chemotherapy. Malnutrition reduces the quality of life in cancer patients and may result in treatment delay and even discontinuity which ultimately lead to decreased survival. Chemotherapy itself might have some adverse effects such as chemotherapy-induced nausea and vomiting (CINV) and myelosuppression and anorexia which impair the immune system as well as the nutritional status of patients. More recently, several studies have shown that systemic inflammation may impair the activity of cytochrome p450 3A4 (CYP3A4) [39, 40]. As CYP3A4 is an important drug-metabolizing enzyme for many cytotoxic agents including etoposide and irinotecan, decreased CYP3A4 activity might be related to impeded drug response or increased toxicity. Malnutrition may also change the pharmacokinetics of many anticancer drugs via altered protein binding and P450 activity [40]. It is therefore important to keep a balance between curative chemotherapy and the toxicities. In addition, immunonutritional intervention can be considered as adjuvants for chemotherapy [41]. Though not investigated in the present study, dynamic monitoring of PNI beyond baseline in SCLC patients receiving chemotherapy can provide interesting information on the association of PNI, treatment efficacy and toxicities.

PNI is a readily available and reproducible parameter and hence clinically useful. However, several problems need to be counted. PNI may be a non-specific marker for tumor burden because other non-cancer situation (e.g., autoimmune and infectious diseases, hematological malignancies, and steroid usage) could be confounding. In the present study, we excluded such patients and clearly showed that PNI is an independent prognostic determinant in SCLC. Whether this conclusion can be extended to SCLC patients with the abovementioned situation remains to be elucidated. Our study also points out a potential role of anti-inflammation treatment in patients with SCLC.

One major limitation of the present study is its retrospective nature, which may suffer from some selection bias. However, we included consecutive SCLC patients to minimize such bias. Despite its preliminary character, this study can clearly indicate similar significant prognostic value of PNI for both limited and extensive stage SCLC, so we think the results of this study could be convincing. However, it would be important to compare the utility of PNI with other prognostic parameters in an independent validation cohort, ideally collected in a prospective fashion. This step is needed before the PNI can be confidently used to estimate overall survival in individual patient. Furthermore, it is of clinical significance to correlate the PNI with possible proinflammatory cytokines as well as patient-generated subjective global assessment (PGSGA), the more robust measurement of cachexia.

In summary, the results of our study suggest that the presence of a systemic inflammation and impaired nutritional

status, as indicated by PNI, is a useful tool in the assessment of overall survival in SCLC patients. The PNI could serve as a surrogate marker for the complex interaction between inflammatory pathways, immunity, nutritional status, and tumor progression that are known to impact patient survival. The PNI is a cost-effective prognostic marker and therefore should be included in routine clinical practice and in the stratification of patients entering clinical trials.

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Conflicts of interest None

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