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Original Article

Predictive value of pre-operative prognostic nutritional index and systemic immune-inflammation index for efficacy and survival in patients with non-small cell lung cancer undergoing neoadjuvant chemotherapy

Jiaqi Lan[1], Wencong Lin[1], Yanjun Lai[2], Jiaxiang Zhang[1]

[1]Department of Oncology, Zhangzhou Municipal Hospital of Fujian Province, Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou 363000, Fujian, China; [2]Department of Digestive, Zhangzhou Municipal Hospital of Fujian Province, Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou 363000, Fujian, China

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Abstract: Objective: To explore the predictive value of preoperative prognostic nutritional index (PNI) and systemic immune inflammation index (SII) in relation to the efficacy and prognosis in patients with non-small cell lung cancer (NSCLC) undergoing neoadjuvant chemotherapy (NACT). Methods: Data of patients with stage IIIA-N2 NSCLC who received NACT in the 910th Hospital of Chinese People's Liberation Army from January 2017 to April 2020 were retrospectively analysed. Patients undergoing NACT were divided into the pCR group (80 cases with complete remission or partial remission) and the non-pCR group (46 cases with stable disease or progressive disease) in accordance with their treatment outcome. The pathologic and clinical data of the patients were collected and analysed to identify the factors affecting efficacy of NACT for stage IIIa-N2 NSCLC, and to evaluate the predictive value of PNI and SII in determining the efficacy of NACT. The patients were followed up for 3 years to observe the overall survival, and Cox regression analysis was employed to identify the risk factors affecting patient survival. Furthermore, the effect of PNI and SII on the survival time was analysed. Results: Multivariate regression analysis showed that tumor diameter, PNI, and SII were influencing factors for poor efficacy of NACT in patients with stage IIIa-N2 NSCLC. The non-pCR group exhibited a higher mortality within 3 years, thus a lower 3-year overall survival rate than the pCR group ($P<0.05$). Cox regression analysis revealed that both PNI and SII were risk factors for poor prognosis in patients with stage IIIa-N2 NSCLC undergoing NACT. Further analysis found a lower 3-year survival rate in patients with low PNI and high SII than in counterparts ($P<0.05$). Conclusion: Tumor diameter, PNI and SII are risk factors for poor efficacy in patients with stage IIIa-N2 NSCLC undergoing NACT. Low PNI and high SII can indicate a poor prognosis in these patients.

Keywords: Non-small cell lung cancer, prognostic nutritional index, systemic immune-inflammation index, efficacy, prognosis, correlation

Introduction

Lung cancer exhibits a high incidence and poses a significant threat to human health [1]. In China, lung cancer continues to hold the highest morbidity and mortality rates among malignant tumors [2]. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 80-85% [3]. About 1/3 of NSCLC are diagnosed at a locally advanced stage (stage III) [4-6]. The treatment approach for stage IIIa-N2 NSCLC has long been a subject of controversy due to its unique pathologic characteristics. Typically, the treatment plan involves a combination of surgery followed by postoperative chemotherapy [7]. With the popularity and proven clinical efficacy of neoadjuvant chemotherapy (NACT), a new treatment option has been brought to stage IIIa-N2 NSCLC: that is, NACT combined with surgery. NACT is done before the surgery. Commonly used NACT regimens for lung cancer include PP scheme (pemetrexed + platinum), TP scheme (paclitaxel + platinum), and GP scheme (gemcit-

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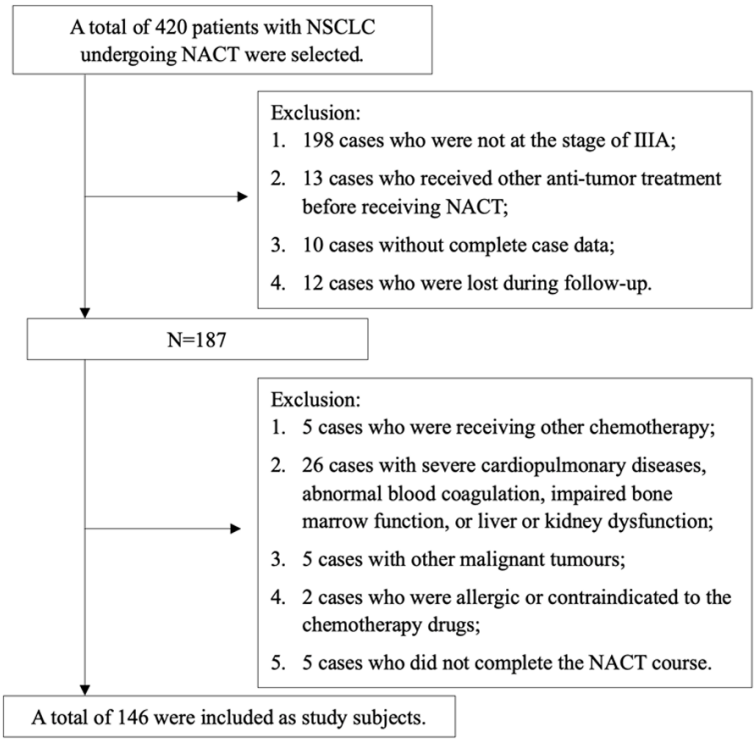

Figure 1. Flow chart of this study. NSCLC: non-small cell lung cancer; NACT: neoadjuvant chemotherapy.

abine + platinum) [8]. Studies have found that NACT can shrink tumors, thereby reducing the scope and difficulty of surgery, as well as decreasing postoperative complications [9, 10]. Although various treatment options for patients with stage IIIa-N2 NSCLC have prolonged the survival time of the patients, the 5-year survival rate is still only about 15% [11].

In recent years, studies have confirmed the influence of patients' autoimmune and nutritional status on prognosis, in addition to the pathologic type and tumor size [12-14]. The prognostic nutritional index (PNI) is a clinical indicator that integrates nutritional and immune markers. Studies have established an association between PNI and the prognosis of various malignant tumors. Patients with oral cancer or gastric cancer who had a low PNI tended to have a poorer prognosis, resulting in reduced overall survival time [15, 16]. The systemic immune-inflammation index (SII) can reflect both local and systemic reactions in the body. Studies have validated the significant predictive value of SII in assessing the prognosis of patients with malignant tumors [17, 18]. However, currently, no studies have been conducted to investigate the predictive value of PNI and SII for assessing the efficacy and survival of NACT in NSCLC patients. In this study, the preoperative PNI and SII of patients with stage IIIA-N2 NSCLC were collected to explore the predictive value of PNI and SII for that purpose.

Materials and methods

General data

Retrospectively, we analyzed the data of 146 patients with stage IIIA-N2 NSCLC who received NACT in the 910th Hospital of Chinese People's Liberation Army from January 2017 to April 2020. The patients aged 29-74 years old, with an average age of (62.3 ± 6.9). A flow chart of the study is presented in **Figure 1**. This study was approved by the Ethics Committee of the 910th Hospital of Chinese People's Liberation Army.

Inclusion criteria for patients undergoing NACT: patients who were pathologically diagnosed with NSCLC [19]; patients at a clinical stage of IIIA-N2 (T1-3N2M0) [20]; patients who did not receive other relevant treatment before admission; patients who underwent pulmonary lobe resection after NACT in accordance with multidisciplinary treatment; patients who were aged no more than 70 years old; patients whose KPS scores were no less than 80; patients who submitted complete clinical data one week before treatment; patients who had complete clinical and follow-up data.

Exclusion criteria: patients who had previously received or were receiving other chemotherapy; patients with severe cardiopulmonary disease; patients with other malignant tumors; patients with abnormal blood coagulation or bone marrow function; patients with liver or kidney insufficiency; patients who were allergic or contraindicated to the chemotherapy drugs; patients who died from non-NSCLC causes; patients with poor compliance; patients with missing clinical data.

Methods

All included patients were treated with NACT, and the PNI and SII before NACT were collected. NACT regimens included PP regimen (pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC=5-6, 21 d as a cycle, 4-6 cycles), TP regimen (paclitaxel 135-175 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC=5-6, 21 d as a cycle, 4-6 cycles), and GP regimen (gemcitabine 1000-1250 mg/m^2 + cisplatin 75 mg/m^2 or carboplatin AUC=5-6, 21 days as a cycle, 4-6 cycles) [21]. All the included patients underwent and completed the NACT, but 20 patients did not receive surgery due to a poor response from NACT or general poor conditions. The other 126 patients were evaluated to be suitable for open pulmonary lobectomy. For the surgery, a 22 cm incision was made on the posterolateral side of the 5th or 6th rib to access the chest. Blunt dissection of the chest wall muscle was performed, and a rib retractor was selected for lobectomy based on the specific conditions. Dissection of the lateral mediastinum and hilar lymph nodes was carried out, followed by flushing of the pleural cavity with 0.9% normal saline and placement of a drainage tube.

One month after the NACT, two-dimensional dual-diameter measurements were used to calculate the tumor size (a*b), where a represents the maximum horizontal diameter, and b signifies the maximum vertical diameter. This calculation aligns with the response evaluation criteria in solid tumors (RECIST) [22]. The tumour size was calculated according to the results from color Doppler ultrasound before and after NACT. The change in tumor size was used to determine the efficacy of the NACT. Complete remission (CR) referred to the disappearance of all target lesions, no new lesions, and normal range of tumor markers for at least 4 weeks; partial response (PR) was indicated by a reduced sum (over 30%) of the maximum diameters of the target lesions for at least 4 weeks; stable disease (SD) was defined as the sum of the maximum diameters of the target lesions not meeting the criteria for PR by showing shrinkage, nor did they reach the threshold for progressive disease (PD) by exhibiting an increase in size; PD was considered when the sum of the maximum diameters of target lesions increased by at least 20% or there was development of new lesions. According to results of RECIST, the patients were divided into a pCR group (CR+PR) and a non-pCR group (SD+PD).

All included patients were followed up for 3 years by telephone or outpatient visits, and the deadline of follow-up was June 2023. The overall survival (OS) of the patients was recorded.

Outcome measures

a. The PNI and SII before treatment were compared between the two groups, PNI = 5× lymphocyte count (×10^9/L) + serum albumin (g/L), and SII = peripheral platelet count (×10^9/L) * peripheral neutrophil count (×10^9/L)/peripheral lymphocyte count (×10^9/L), where PNI refers to the prognostic nutritional index [15], and SII to the systemic immune-inflammation index [17]. PNI≥50 indicates a normal nutritional status, and PNI<50 indicates malnutrition, while there is no commonly agreed normal level for SII. b. The predictive value of PNI and SII for the efficacy of NACT in patients with stage IIIA-N2 NSCLC was evaluated. c. The included patients were followed up for 3 years, and the number of deaths was recorded. d. According to the survival time, Cox regression analysis was employed to identify the risk factors affecting the survival of the patients, and the effects of PNI and SII before treatment on the OS of patients was analysed.

Statistical analyses

SPSS 22.0 statistical software was used to analyse the data. Normally distributed continuous variables were expressed as mean ± standard deviation ($\bar{x}$ ± sd) and processed by independent sample t test. The non-normally distributed measured data were expressed by median (lower quartile, upper quartile) and compared between the two groups using Mann-Whitney U test. The enumerated data were subjected to Pearson chi-square test. With a test level of $P<0.05$, univariate analysis was conducted to identify variables with a significant difference between the groups. These significant variables were included in a binary logistic regression analysis to examine the influencing factors for the efficacy, incorporating PNI and SII based on whether patients benefitted from the NACT. Receiver operating characteristic (ROC) curves were generated to calculate the area under the ROC curve (AUC). Survival analy-

Table 1. Comparison of general data between the two groups ($\bar{x}$ ± sd/n (%))

Item	pCR group (n=80)	non-pCR group (n=66)	χ^2/t/Z value	*P* value
Sex			0.668	0.414
Male	49	36		
Female	31	30		
Age (years old)			0.376	0.540
≥60 years old	42 (52.50)	38 (57.58)		
<60 years old	38 (47.50)	28 (42.42)		
Smoking			0.832	0.362
Yes	50 (62.50)	46 (69.70)		
No	30 (37.50)	20 (30.30)		
Pathologic type			0.231	0.891
Squamous cell carcinoma	32 (40.00)	24 (36.36)		
Adenocarcinoma	45 (56.25)	39 (59.09)		
Others	3 (3.75)	3 (4.55)		
BMI (kg/m^2)	23.78 ± 2.64	22.23 ± 2.83	3.418	<0.001
Tumor diameter (cm)			6.612	0.010
≥3 cm	53	56		
<3 cm	27	10		
PNI	50.92 ± 7.76	47.04 ± 7.47	3.155	0.002
SII	(261.42, 595.32)	(418.51, 1050.24)	2.588	0.011

Note: χ^2 is the result of chi-square test; t is the result of t test; Z is the result of rank sum test. pCR: partial remission + complete remission; BMI: body mass index; PNI: prognostic nutritional index; SII: systemic immune inflammation index.

sis was employed to observe the 3-year survival of the two patient groups. Multivariate Cox regression was used to analyse the correlation of PNI and SII with the prognosis of patients with stage IIIA-N2 NSCLC undergoing NACT. P<0.05 was considered significant.

Results

Comparison of general data

There were 80 patients (8 cases of CR and 72 cases of PR) in the pCR group and 66 patients (63 cases of SD and 3 cases of PD) in the non-pCR group. Comparison of the general data between the two groups showed that the pCR group exhibited lower body mass index (BMI), tumor diameter, and SII, as well as higher PNI than the non-pCR group (all P<0.01). See **Table 1**.

Logistic regression analysis of factors influencing the efficacy of NACT

Taking pCR as the dependent variable (1= yes, 0= no) and the significant indicators in univariate analysis as independent variables, multivariate binary logistic regression analysis found that tumor diameter (OR (95% CI): 1.687 (1.263-2.543), P=0.003), PNI (OR (95% CI): 0.598 (0.396-0.769), P<0.001) and SII (OR (95% CI): 2.156 (1.674-2.756), P<0.001) were factors associated with the efficacy of NACT in patients with stage IIIa-N2 NSCLC. See **Table 2**.

Predictive value of PNI and SII in the efficacy of NACT

The AUC of PNI for predicting the efficacy of NACT in IIIa-N2 NSCLC patients was 0.747. When PNI was at the cut-off value of 46.22, the Youden index was 0.442, the specificity was 0.700, and the sensitivity was 0.742. The AUC of SII for predicting the efficacy of NACT was 0.699, and when the SII was at the cut-off value of 580.34, the Youden index was 0.314, the specificity was 0.864, and the sensitivity was 0.450. See **Figure 2**.

Comparison of the mortality between the two groups within 3 years

The 3-year mortality rate was 35.00% (28/80) in the pCR group and 45.45% (30/66) in the non-pCR group. The average OS of the non-pCR group was 36.8 months, which was shorter

Table 2. Logistic regression analysis of factors influencing the efficacy of NACT

Variable	OR value (95% CI)	*P* value
Constant	-	<0.001
Tumor diameter (cm)	1.687 (1.263-2.543)	0.003
PNI	0.598 (0.396-0.769)	<0.001
SII	2.156 (1.674-2.756)	<0.001

Note: Tumor diameter ≥3 cm=1, tumor diameter <3 cm=0; PNI≥50=0, PNI<50=1; SII values were input using the normal numeric values. OR: odds ratio; NACT: neoadjuvant chemotherapy; PNI: prognostic nutritional index; SII: systemic immune inflammation index.

than 44.7 months for the pCR group (χ^2=5.462, P=0.019). See **Table 3** and **Figure 3**.

PNI and SII were risk factors for poor prognosis

Multivariate Cox regression analysis showed that PNI and SII were both risk factors for death in patients with stage IIIa-N2 NSCLC undergoing NACT. See **Table 4**.

Correlation of PNI and SII with the prognosis of patients

The cut-off values (AUC) of ROC curves for predicting patient death were used to categorize the high and low values of PNI and SII. Using 46.22 as the cut-off value of PNI, 86 cases were included in a high PNI group, and 60 cases in a low PNI group. Using 580.34 as the cut-off value of SII, 46 cases were included in a high SII group, and 100 cases in a low SII group. Survival analysis showed that the survival rate of patients with high PNI was higher than that of patients with low PNI (χ^2=7.921, P=0.005), while the survival rate of patients with high SII was lower than that of patients with low SII (χ^2=86.153, P<0.001). See **Figure 4**.

Discussion

Since the efficacy of surgery alone is poor in patients with stage IIIA-N2 NSCLC, and the rates of postoperative metastasis and recurrence are high, effective alternative treatment is needed [23]. Studies have demonstrated that preoperative NACT combined with surgery can provide benefits for patients with stage IIIa-N2 NSCLC. A meta-analysis of 15 randomized controlled trials has revealed that preoperative chemotherapy can significantly improve the survival of NSCLC patients and

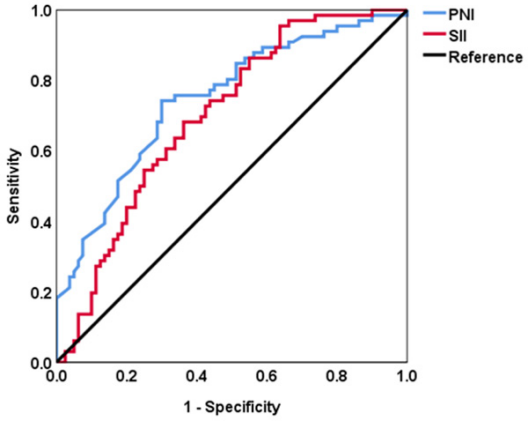

Figure 2. ROC curve of the predictive values of PNI and SII for the efficacy of NACT. ROC: receiver operating characteristic; PNI: prognostic nutritional index; SII: systemic immune inflammation index; NACT: neoadjuvant chemotherapy.

reduce the risk of postoperative mortality [24]. Another study reported that NACT combined with concurrent radiotherapy could significantly improve the disease-free survival of patients [25]. NACT had a clinical response rate of 25%-74% and a pathologic downstaging rate of 19%-67% in patients with lung cancer. Our study found that an objective response rate of 54.80% (80/146) in patients with stage IIIa-N2 NSCLC after NACT. This suggests that preoperative NACT can effectively improve the objective response rate, consistent with previous research [26].

In this study, regression analysis showed that tumor diameter, PNI, and SII were factors influencing the efficacy of NACT. Tumour diameter as an influencing factor indicates that NACT is less sensitive to tumor with strong proliferation and invasion. This is consistent with previous research results [27]. Immune and nutritional indicators have been reported to play an important role in the development, invasion, and metastasis of tumors [28]. PNI and SII can reflect the nutritional status and systemic inflammation, respectively. PNI is calculated from serum albumin and lymphocytes. Hypoalbuminemia has been confirmed by multiple studies to be closely associated with the prognosis of cancer patients [29, 30], and studies on lung cancer patients have reported a correlation between nutritional status and prognosis [31, 32]. Lymphocytes can activate cytotoxic T cells, which can then inhibit the proliferation

Table 3. Comparison of mortality between the two groups within 3 years (n (%))

Group	Death within 1 year	Death within 2 years	Death within 3 years
pCR group (n=80)	6 (7.50)	15 (18.75)	28 (35.00)
Non-pCR group (n=66)	10 (15.15)	24 (36.36)	34 (51.51)
χ^2	2.174	5.731	4.037
P value	0.141	0.017	0.045

Note: χ^2 is the result of chi-square test. pCR: partial remission + complete remission.

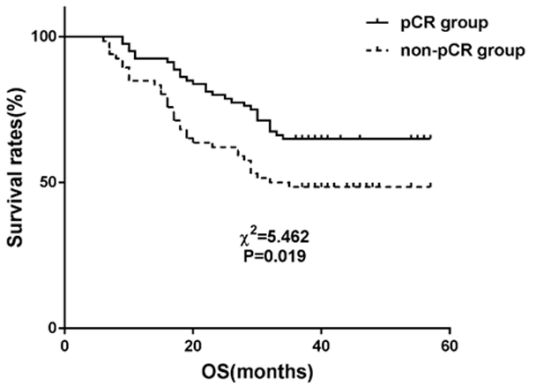

Figure 3. Comparison of 3-year survival between the pCR group and the non-pCR group. χ^2 is the result of chi-square test. pCR: partial remission + complete remission; OS: overall survival.

and migration of malignant tumor cells [33]. Inflammatory factors play a vital role in the development and progression of tumors, including lung cancer. Inflammatory factors can promote lung cancer proliferation, as well as enhance tumor invasion and metastasis [34]. SII is calculated from neutrophil, lymphocyte and platelet counts. Neutrophils can secrete a large amount of nitric oxide and arginase after proliferation to promote angiogenesis [35]. T lymphocytes have been shown to have an anti-tumor effect [36]. As for platelets, studies have shown that they can promote the release of inflammatory factors and anti-apoptotic factors, thereby enhancing the invasion and metastasis of tumor cells [37]. Therefore, SII serves as a comprehensive measure that integrates and reflects these three indicators, providing an overall evaluation of the level of host inflammation and immune response within the body. Prior studies have demonstrated that elevated SII in lung cancer patients portends a poorer prognosis [38, 39].

This study further analysed the cut-off values of PNI and SII in predicting the efficacy of NACT, and the optimal cut-off value was 46.22 for PNI and 580.34 for SII. At present, nutrition and immune inflammation have been shown to be associated with efficacy of chemotherapy and prognosis in different tumor studies [40, 41]. Nevertheless, the use of nutritional and immune inflammatory factors to predict the efficacy of chemotherapy and patient prognosis is still in an exploratory stage, lacking a standardized diagnostic cut-off criterion.

The prognosis of patients with tumor is a crucial clinical consideration. It has been observed in clinical practice that the variation in treatment efficacy among patients holds great significance for their prognosis. NACT, as an essential approach in the treatment of NSCLC, contributes to improving surgical resection rate and holds substantial importance in enhancing patient prognosis [42]. This study revealed that NSCLC patients who achieved a favorable treatment response following NACT exhibited a higher 3-year survival rate.

Further analysis showed that patients with low PNI and high SII had a lower 3-year survival rate. A prior retrospective study showed that low PNI (≤46) was an independent risk factor for poor OS in NSCLC patients [43]. Another study reported that patients with high PNI (≥49.17) had a longer OS than those with low PNI (<49.17) (13 months *vs.* 12 months, P=0.03) [44]. A study involving 157 NSCLC patients observed the impact of preoperative SII on prognosis. Their results demonstrated that the patients with a preoperative SII greater than or equal to 620.2 exhibited a significantly reduced average OS [45]. Another study including 127 NSCLC patients employed the combination of PNI and SII to assess the prognosis of NSCLC. The findings revealed that both a low PNI and a high SII were associated with a poor prognosis [46], which aligns closely with the results obtained in this study. The mechanisms by which low PNI and high SII lead to poor prognosis or survival might be associated with advanced TNM stage, high tumor grade, increased proliferation, invasion or metastasis capabilities of the tumor. Reduced albumin lev-

Table 4. Correlation of PNI and SII with prognosis analysed by Cox regression

Variable	β	SE	Wald value	OR value (95% CI)	P
PNI	-0.058	0.022	6.986	0.944 (0.904-0.985)	0.008
SII	0.564	0.132	24.652	1.214 (1.189-1.362)	<0.001

Note: PNI: prognostic nutritional index; SII: systemic immune inflammation index.

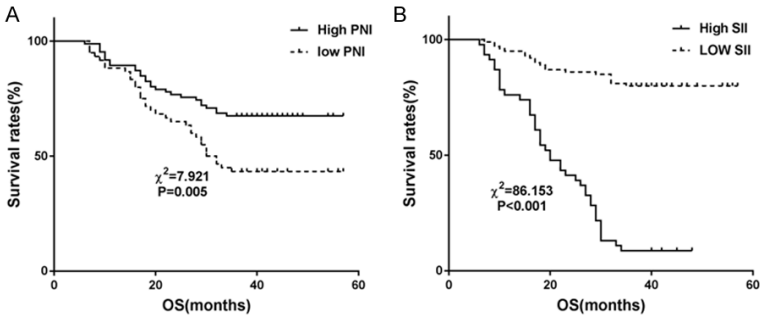

Figure 4. Correlation of PNI and SII with prognosis of the patients. A: Survival curve of patients with different PNI; B: Survival curve of patients with different SII. χ^2 is the result of chi-square test; PNI: prognostic nutritional index; SII: systemic immune inflammation index; OS: overall survival.

els and deterioration in nutritional status can reflect tumor aggressiveness. The immune functions of patients also decline, accompanied by rising levels of their systemic inflammatory markers. In addition, the onset and progression of tumor are associated with lower immune functions of patients. Both low PNI and high SII could result in a reduction in lymphocytes, which in return inhibits the anti-tumor immune response, impairing the ability to recognize, reject and clear tumor cells from the body. Consequently, there is proliferation, invasion, and metastasis of tumor cells.

UsingROC and survival analyses, this study also found that patients with high inflammatory response and poor nutritional status exhibited poorer chemotherapy efficacy and prognosis. Previous studies have demonstrated that increased secretion of neutrophils can promote tumour growth, stimulate angiogenesis, and enhance the invasiveness of tumor cells, playing an important role in tumour progression [47]. Platelets have the ability to release angiogenic factors that stimulate angiogenesis, thereby facilitating the development of blood vessels around tumors. An increased blood supply to tumors can promote progression [48]. Lymphocytes, as key components of the immune system, play a crucial role in immune regulation within the body. They possess an ability to modulate the tumor microenvironment, thereby inhibiting migration and micrometastasis [49]. Infiltration of neutrophils and platelets and reduction of lymphocytes can be found in the progression of tumor cells due to the various roles of these inflammatory cells. Malnourished tumor patients are more likely to experience a poorer prognosis, primarily becasue of depletion of serum albumin caused by tumor cell progression [29, 30].

Limitations and prospects: Considering the small sample size in this study, expanding the sample size would be beneficial to investigate the effect of PNI and SII on the efficacy and prognosis of patients with stage IIIA-N2 NSCLC undergoing NACT combined with surgery or surgery combined with postoperative chemotherapy. Future studies may concentrate on the underlying mechanisms and factors that contribute to the changes of PNI and SII in patients with stage IIIa-N2 NSCLC.

In summary, tumor diameter, PNI (≥46.22), and SII (≥580.34) were risk factors for poor efficacy in patients with stage IIIa-N2 NSCLC undergoing NACT, and the patients who do not benefit from NACT have a poor prognosis. Thus, low PNI and high SII are early markers for poor prognosis in these patients.

Disclosure of conflict of interest

None.

Address correspondence to: Jiaxiang Zhang, Department of Oncology, Zhangzhou Municipal Hospital of Fujian Province, Zhangzhou Affiliated Hospital of Fujian Medical University, No. 59, Shengli West Road, Xiangcheng District, Zhangzhou 363000, Fujian, China. Tel: +86-18059706745; E-mail: zhangjiaxiang0729@163.com

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