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The clinical value of the systemic immune-inflammation index for major pathological response in non-small cell lung cancer patients receiving neoadjuvant chemoimmunotherapy

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Abstract: This study attempted to investigate the clinical value of systemic immune-inflammation index (SII) for Major Pathologic Response (MPR) in non-small cell lung cancer(NSCLC) patients receiving neoadjuvant chemoimmunotherapy. A total of 56 non-small cell lung cancer patients who were diagnosed and received neoadjuvant chemoimmunotherapy in the First Affiliated Hospital of Chongqing Medical University from April 2019 to April 2023 December 2023 were retrospectively analyzed,all patients were divided into the MPR group (35 cases) and No-MPR group (21 cases) according to their postoperative pathological results. The baseline neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-infammation index (SII) and clinicopathological variables were assessed for their association with MPR.The receiver operating characteristic (ROC) curve analysis and area under the ROC curve (AUC) values were used to evaluate the optimal cutoff values of the NLR,PLR and SII,and independent influencing factors of postoperative MPR were analyzed by binary logistic regression. Results indicated that NLR, PLR, and SII levels were significantly lower in the MPR group compared to those of the No-MPR group (P<0.05).The results of the ROC analysis showed that the area under the curve for the NLR,PLR and SII were 0.794,0.728and 0.838,respectively. Univariate Logistic regression analysis showed that the NLR, PLR, and SII level were significantly related to MPR (P<0.05).According to multivariate Logistic regression analysis,only SII level(OR=0.12,95%CI 0.02-0.17,P=0.019) was independent influence factors for MPR. In conclusion, NSCLC patients with low SII level (<947.6) are more likely to achieve MPR receiving neoadjuvant chemoimmunotherapy. It is likely to become a clinical monitoring index for the efficacy of neoadjuvant chemoimmunotherapy.

1. Introduction

Lung cancer is one of the malignant tumors with the highest morbidity and mortality

worldwide[1].Among patients diagnosed with NSCLC,surgery is still the main therapy, accounting for 20% to 25%[2].However, 30% to 55% of NSCLC patients will relapse and die of the disease[3].And more recently, nivolumab with platinum doublet chemotherapy has been approved by the Food and Drug Administration (FDA) for patients with resectable NSCLC in the neoadjuvant setting[4].Previous studies have demonstrated that the combination of neoadjuvant chemotherapy and immunotherapy results in a higher MPR(defined as ≤ 10% viable tumor in resected tumor specimens) compared to chemotherapy alone[5].Importantly, this combined treatment approach did not increase the incidence of adverse events or impede the feasibility of surgery.Thus in several clinical trials,CheckMate816, IMpower030, AEGEAN,BGB-A317,and CANOPY-N all consider MPR as the primary endpoint and use it as an alternative endpoint for overall survival (OS). Therefore, it is important to find effective biomarkers to predict which NSCLC patients will benefit most from neoadjuvant chemoimmunotherapy.

1.1. Treatment scheme

Previous studies have indicated a close relationship between tumor-related inflammatory response and tumor occurrence,progression and prognosis in patients[6].Detecting the count of neutrophils,lymphocytes,and platelets in peripheral blood can provide valuable insights into systemic inflammatory response. Moreover,in various advanced solid tumors treated with immune checkpoint inhibitors(ICIs),peripheral blood inflammatory biomarkers such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune inflammatory index (SII) have shown promising predictive abilities for patient prognosis in hepatocellular carcinoma,esophageal cancer,nd uroepithelial carcinoma[7-9].Additionally, they have been established as prognostic indicators for advanced NSCLC immunotherapy[10].However,it is unknown, whether these inflammatory biomarkers could also be used to predict immunotherapeutic efficacy in neoadjuvant chemoimmunotherapy settings.Therefore,we aims to investigate the clinical value of NLR, PLR, and SII in patients with NSCLC after neoadjuvant chemoimmunotherapy.

2. Data and methods

2.1. Clinical data collection

The general clinical data of 56 patients with NSCLC who were diagnosed and received neoadjuvant neoadjuvant chemoimmunotherapy in the first affiliated Hospital of Chongqing Medical University from April 2019 to December 2023 were collected retrospectively, including age, sex, smoking status, tumor size, lymph node metastasis,tissue type,clinical stage(according to the AJCC Lung Cancer Staging, 8th edition) and Eastern Cooperative Oncology Group (ECOG) performance status,peripheral blood neutrophil count, lymphocyte count, platelet count, NLR, PLR, SII before therapy.Inclusion criteria:(1)preoperative fiberoptic bronchoscopy or CT-guided puncture biopsy was pathologically diagnosed as NSCLC;(2)according to Response Evaluation Criteria in Solid Tumors (version 1.1),patients were required to have measurable lesions (3)did not receive other anti-tumor therapy before neoadjuvant therapy;(4)blood routine examination was performed within 3 days before treatment.(5)Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.Exclusion criteria:(1)patients with obvious abnormal blood routine before neoadjuvant therapy,such as other tumor history,hematological diseases, kidney diseases,autoimmune diseases and recent infectious diseases;(2)known EGFR mutations and ALK translocations sensitive to targeted therapy, unknown or uncertain EGFR status in patients with non-squamous cell carcinoma.(3)patients must stop taking corticosteroids 2 weeks before the first treatment, or take a stable or decreasing dose of 10mg or less prednisone daily.(4)those who willingly give up

chemotherapy or change the treatment plan due to the progression of the disease. (5) patients with serious lack of medical records.

Preoperative neoadjuvant therapy involved the use of immunotherapy in combination with platinum-containing dual-drug chemotherapy. The chemotherapy regimen used was the standard first-line treatment for advanced NSCLC. For patients with squamous cell carcinoma, the treatment consisted of nedaplatin (75 mg/m2, d1) in combination with albumin-bound paclitaxel (200 mg/m2, d1). For patients with adenocarcinoma, the treatment consisted of nedaplatin (75 mg/m2, d1) in combination with pemetrexed (500 mg/m2, d1). The immunosuppressants used were all PD-1 inhibitors (200 mg, d1). Chemoimmunotherapy was administered every 3 weeks for 2-4 cycles prior to surgical resection. After two treatment cycles, a chest CT scan was performed to assess tumor response using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Preoperative evaluation included blood routine, blood biochemistry, blood coagulation, tumor markers, chest and abdomen CT scans, and other imaging examinations. Pulmonary dissection and lymph node dissection were performed within 4 weeks after the completion of neoadjuvant therapy.

2.2. Observation index

NLR and PLR were defined as the absolute value of neutrophils (×10^9) and the absolute value of platelet count (×10^9)/lymphocyte count (×10^9),respectively.The SII formula is calculated as SII = (P × N) / L, where P, N, and L represent the peripheral platelet count, neutrophil count, and lymphocyte count, respectively.The curative effect index includes both imaging effect and pathological effect.Imaging efficacy is evaluated according to the RECIST1.1:Complete Response (CR) is defined as the complete disappearance of the target focus compared to the contrast baseline.Partial Response (PR) is defined as a reduction of at least 30% in the sum of the target lesion diameter compared to the contrast baseline.Progressive Disease (PD) is defined as an increase of more than 20% in the target lesion or the appearance of new lesions.Stable Disease (SD) is defined as neither meeting the criteria for PR nor PD.The objective response rate (ORR) after 2 cycles of neoadjuvant therapy was calculated as the total number of ORR=(CR+PR)/×100%.Thepathological efficacy index MPR was defined as pathological biopsy after neoadjuvant therapy indicating that the remaining living tumor cells were less than 10%,regardless of whether there were tumor cells in the lymph nodes or not.Pathological complete remission (PCR) was considered when no residual cancer cells were found in the pathological biopsy after neoadjuvant therapy.

2.3. Statistical analysis

To compare continuous data that followed a normal distribution in the MPR group and non-MPR group, we conducted an independent sample t-test. In cases where the data did not follow a normal distribution, we used the Wilcoxon test to compare the two groups. For analyzing categorical data, we employed either the $\chi 2$ test or Fisher's exact test to compare groups. Receiver operating characteristic (ROC) curve analysis was employed to examine the association of NLR, PLR, and SII with MPR and determine the optimal cut-off values. These values were used as thresholds to group all patients above or below the points. A logistic regression model was used for both univariate and multivariate analysis. Only significant parameters from the univariate logistic regression model were included in the multivariate analysis to determine independent influence factors for MPR in NSCLC patients receiving neoadjuvant chemoimmunotherapy. All analyses were performed using SPSS 26.0 and R Software 4.1.0. ($P < 0.05$) was considered statistically significant.

3. Results

3.1. Characteristics of clinical data

A total of 56 patients diagnosed with NSCLC were enrolled in the study from April 2019 to December 2023. The inclusion and exclusion criteria were fully met, as previously described. Among the patients, 49 (87.5%) were male and 7 (12.5%) were female. The majority of cases were squamous cell carcinoma (89.3%), while a smaller proportion had adenocarcinoma (10.7%). Out of the patients, 42 (75%) were smokers and 14 (25%) were non-smokers. Most patients were classified as clinical stage III, with 30 cases (53.6%) in stage IIIA and 18 cases (31.0%) in stage IIIB. A total of 31 patients (55.4%) received 2 cycles of neoadjuvant therapy.

Radiologically, the overall response rate (ORR) after 2 cycles of neoadjuvant chemoimmunotherapy was 62.5% (35/56). Patients who achieved partial remission (PR) or complete remission (CR) were more likely to reach major pathological response (MPR) compared to patients with stable disease (SD) (68.57% vs 52.38%), although this difference was not statistically significant (Table 1). Pathologically, 35 patients (62.5%) achieved MPR, with 22 (62.9%) of them achieving complete pathological response (PCR). The overall rate of pathological complete remission was 39.3% (22/56) (Table 1).

3.2. Comparison of clinical data between MPR group and No-MPR group

The study included a total of 56 cases, with 35 cases in the MPR group and 21 cases in the No-MPR group. The demographic and clinical characteristics of the two groups, including age, sex, smoking status, ECOG status, tissue type, tumor size, lymph node metastasis, clinical stage, neoadjuvant cycle, and imaging effect, did not show any significant differences.However, the MPR group exhibited significantly lower levels of NLR, PLR, and SII compared to the No-MPR group($P < 0.05$).Furthermore,the MPR group had significantly lower levels of neutrophil count and platelet count compared to the control group.Additionally,the neoadjuvant therapy regimen was similar between the two groups. (Table 1)

Continuous data that conform to the normal distribution are expressed as (mean ± standard) deviation,while those that do not conform to the normal distribution are expressed as Md(P25,P75).Abbreviations viations:MPR,major pathological response;SQQ,squamous carcinoma; LUAD,lungadenocarcinoma;RECIST1.1,Response Evaluation Criteria in Solid Tumors 1.1; SD, stable disease; PR, partial response;CR,complete response;ECOG,Eastern Cooperative Oncology Groupperformance status score(ranging from 0 to 5, with higher scores indicating greater disability); NLR, neutrophil-to-lymphocyte ratio;PLR,platelet-to-lymphocyte ratio;SII,systemic immune-infammation index; clinical staging using TNM staging criteria from the 8th edition of the American Joint Committee on Cancer for NSCLC.

Table 1: Comparison of clinical data characteristics between MPR group and No-MPR group

Characteristics	MPR(n=35)	No-MPR(n=21)	t/χ2/Z value	P value
Age	58.8±6.13	59.38±8.05	0.305	0.762
Gender			0	1.000
Fmale	4(11.43%)	3(14.29%)		
male	31(88.57%)	18(85.71%)		
Smoking status			0.025	0.873
Yes	26(74.29%)	16(76.19%)		
No	9(25.71%)	5(23.81%)		

EOCG status			1.026	0.311
0	24(68.57%)	17(80.95%)		
1	11(31.43%)	4(19.05%)		
Histology			0.05	0.823
SQQ	32(91.43%)	18(85.71%)		
LUAD	3(8.57%)	3(14.29%)		
Tumour lesion			0.395	0.941
T1	3(8.57%)	1(4.76%)		
T2	18(51.43%)	12(57.14%)		
T3	11(31.43%)	6(28.57%)		
T4	3(8.57%)	2(9.52%)		
Nodal stage			0.986	0.805
N0	7(20%)	4(19.05%)		
N1	6(17.14%)	3(14.29%)		
N2	18(51.43%)	13(61.9%)		
N3	4(11.43%)	1(4.76%)		
Clinical Stage			3.236	0.357
I	2 (5.71%)	2(9.52%)		
II	4(11.43%)	0(0%)		
IIIA	17(48.57%)	13(61.9%)		
IIIB	12(34.29%)	6(28.57%)		
Neoadjuvant cycle			0.558	0.757
2	20(57.14%)	11(52.38%)		
3	8(22.86%)	4(19.05%)		
4	7(20%)	6(28.57%)		
RECIST1.1			1.468	0.226
SD	11(31.43%)	10(47.62%)		
CR/PR	24(68.57%)	11(52.38%)		
Neutrophil	4.07(3.58,4.5)	5.93(5.25,6.38)	4.291	<0.001
lymphocyte	1.5(1.23,1.83)	1.59(1.17,1.95)	-0.313	0.754
Platele	207(173,241)	285(232,351)	3.165	0.002
NLR	2.65(2.01,3.53)	4.15(3.31,4.75)	3.647	<0.001
PLR	132.3(118.5,164.9)	171.9(159.4,231.3)	2.835	0.005
SII	589.2(457.1,687.3)	1039.7(758.9,1324.1)	4.206	<0.001

3.3. ROC curve analysis of MPR by NLR, PLR and SII

ROC curve analysis was conducted to evaluate the predictive ability of NLR, PLR, and SII in determining MPR in NSCLC patients who underwent neoadjuvant chemoimmunotherapy (Figure 1). The analysis revealed that NLR, PLR, and SII were able to predict the ROC curve for MPR in these patients. The area under the curve (AUC) and the corresponding optimal critical values were as follows: NLR - AUC: 0.794 (95%CI: 0.67-0.92), with an optimal critical value of 3.65; PLR - AUC: 0.728 (95%CI: 0.58-0.87), with an optimal critical value of 157.9; SII - AUC: 0.838 (95%CI: 0.72-0.96), with an optimal critical value of 947.6 (Table 2).

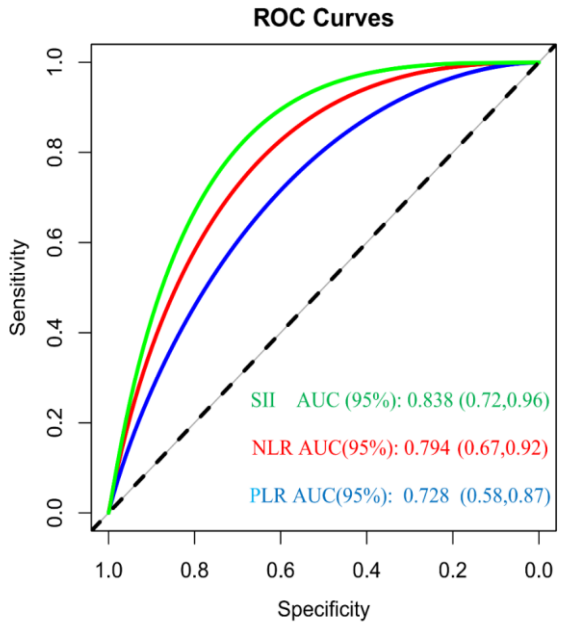


Figure 1: ROC curve of the NLR, PLR and SII for MPR of NSCLC

Table 2: ROC curve analysis results of NLR, PLR and SII for MPR of NSCLC

Characteristics	Cut-off value	sensitivity	specificity	AUC	95%CI
NLR	3.65	0.800	0.714	0.794	0.67-0.92
PLR	157.9	0.714	0.810	0.728	0.58-0.87
SII	947.6	0.943	0.667	0.838	0.72-0.96

3.4. Influencing factors of postoperative MPR in patients with NSCLC

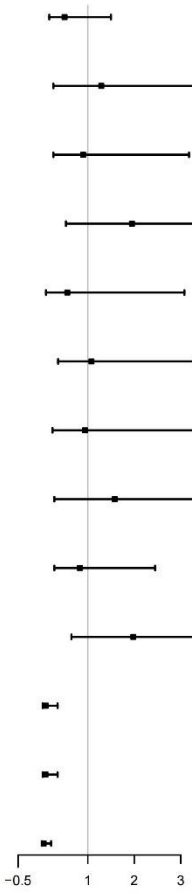
Based on the optimal critical value, a total of 56 NSCLC patients were divided into two groups based on their NLR, PLR, and SII values before neoadjuvant therapy. The groups were categorized as high NLR (≥ 3.65) and low NLR (< 3.65), high PLR (≥ 157.9) and low PLR (< 157.9), and high SII (≥ 947.6) and low SII (< 947.6). Univariate analysis revealed a significantly higher MPR rate in the low NLR, PLR, and SII groups compared to the high NLR, PLR, and SII groups (P<0.001).(Table 3) Furthermore, multivariate logistic regression analysis demonstrated that the SII level (OR=0.12,95%CI 0.02-0.17,P=0.019) was independently associated with MPR after neoadjuvant chemotherapy and immunotherapy in NSCLC patients (Table 4).

Table 3: Multivariate Logistic regression analysis of MPR

Characteristics	B	SE	Wald value	OR value	[95%CI]	Pvalue
NLR						
Low	Reference					
High	-0.984	0.840	-1.711	0.37	[0.07,1.94]	0.242
PLR						
Low	Reference					
High	-0.870	0.891	-0.976	0.42	[0.07,2.4]	0.329
SII						
Low	Reference					
High	-2.084	0.885	-2.353	0.12	[0.02,0.71]	0.019

Table 4: Univariate Logistic regression analysis of MPR

Characteristics	Number	OR[95%CI]	P.value
Age			
>59	30		
<=59	26	0.5[0.17−1.5]	0.216
Gender			
Male	49		
Female	7	1.29[0.26−6.43]	0.755
Smoking status			
Yes	42		
No	14	0.9[0.26−3.18]	0.873
EOCG status			
1	15		
0	41	1.95[0.53−7.16]	0.316
Histology			
SQQ	50		
LUAD	6	0.56[0.1−3.08]	0.507
Tumour lesion			
T1+T2	34		
T3+T4	22	1.08[0.36−3.29]	0.888
Nodal stage			
N0	11		
Other	45	0.94[0.24−3.7]	0.931
Clinical Stage			
III	49		
I+II	7	1.58[0.28−9]	0.604
Neoadjuvant cycle			
2	31		
3+4	25	0.83[0.28−2.45]	0.729
RECIST1.1			
CR/PR	35		
SD	21	1.98[0.65−6.05]	0.229
NLR			
Low	34		
High	22	0.1[0.03−0.35]	<0.001
PLR			
Low	29		
High	27	0.09[0.03−0.35]	<0.001
SII			
Low	39		
High	17	0.05[0.01−0.21]	<0.001



4. Discussion

In this study, we conducted an analysis to examine the relationship between NLR, PLR, and SII and MPR, as well as the clinical significance of NLR, PLR, and SII in predicting MPR in patients with NSCLC receiving chemoimmunotherapy. Our multivariate analysis revealed that the level of SII was independently associated with MPR, suggesting its potential as a predictor of MPR in NSCLC.

In previous clinical trials, patients with resectable NSCLC who received neoadjuvant chemoimmunotherapy showed improved pathological effects, with MPR rates ranging from 57% to 83%[11-13].This study also found a postoperative MPR of 62.5% in NSCLC patients, which aligns with previous research. Shuetal reported on CheckMate816[5], revealing that the median disease-free survival time of patients in the MPR group after neoadjuvant chemotherapy immunization was significantly higher than that in the non-MPR group (14.3 months vs 34.5 months, $P < 0.01$). Therefore, it is predicted that the biomarkers of MPR after neoadjuvant chemotherapy and immunotherapy may offer a promising approach for resectable NSCLC in the future.

The tumor microenvironment, influenced by inflammatory cells, plays a critical role in tumor progression. It supports cell proliferation, survival, and metastasis, and is closely associated with

the prognosis of various advanced solid tumors[14]. In patients with advanced NSCLC who underwent immunotherapy, elevated levels of baseline NLR, PLR, and SII were significantly linked to poor progression-free survival (PFS) and overall survival (OS)[15,16]. Although the reason why inflammatory biomarkers in peripheral blood can predict the effectiveness of immunotherapy remains unclear, studies have shown that neutrophils not only promote cancer cell proliferation and metastasis, but also aid in evading immune surveillance by cancer cells[17]. On the other hand, platelets can protect cancer cells from immune clearance, and their numerous receptors on the surface may facilitate the adhesion of cancer cells to the vascular endothelium, thereby promoting tumor growth and metastasis[18].Conversely, lymphocytes inhibit tumors by inducing cell death. Lymphopenia, characterized by a low lymphocyte count, is considered a poor prognostic indicator for other types of solid cancer[19]. Understanding these mechanisms will provide valuable insights into the roles of neutrophils, platelets, and lymphocytes in cancer, as well as their relationship with immunity and inflammation. Additionally, Li [20]discovered and verified for the first time that in patients with resectable NSCLC who received neoadjuvant chemoimmunotherapy, the levels of NLR, PLR, and SII during treatment were significantly lower compared to non-MPR patients. Moreover, SII during treatment was found to be independent of MPR ($P<0.001$). However, no significant relationship has been found between NLR, PLR, and SII before neoadjuvant treatment and postoperative MPR. In this study, we did not include inflammatory markers during treatment due to observed myelosuppression in some patients, which required clinical intervention. Including these patients would have compromised the reliability of the data. Instead, our focus was on collecting patients' inflammatory indicators before neoadjuvant treatment to accurately reflect their current inflammation and immune status. Our findings revealed a significant relationship between NLR, PLR, and SII levels before neoadjuvant treatment and MPR. Notably, SII emerged as an independent influencing factor for MPR after NSCLC surgery. These results suggest that these biomarkers can be utilized to evaluate the prognosis of immunotherapy in advanced NSCLC and predict its effectiveness in the neoadjuvant setting.

Previous studies have shown that programmed cell death ligand 1 (PD-L1) and tumor mutation burden (TMB) can provide valuable insights into the tumor immune microenvironment. However, their utility in selecting patients with advanced NSCLC who will benefit from immunotherapy treatment is even more significan[21,22]. The NEOSTAR trial and CheckMate159 studies have found a significant correlation between PD-L1/TMB expression levels and the response to neoadjuvant immunization in patients with resectable NSCLC. However, it is important to note that these biomarkers may not accurately predict the anti-tumor response to immune checkpoint inhibitors (ICIs) due to limitations in tissue sampling, their dynamic and heterogeneous nature during cancer progression and treatment, and the relatively lower expression of PD-L1 and TMB in early-stage tumors compared to late-stage tumors. Additionally, the shorter treatment cycles of ICIs in early-stage tumors may also impact the predictive value of neoadjuvant immunotherapy efficacy. Therefore, complete blood count or differential detection, which are low-cost and routinely performed in patients receiving immunotherapy, offer promising potential as routine methods for predicting immunotherapy efficacy in clinical practice. Consequently, NLR, PLR, and SII are expected to gain prominence in predicting the effectiveness of immunotherapy.

However, the study has some limitations. Firstly, it was conducted retrospectively at a single facility and included a relatively small number of samples. Secondly, although we have established the prognostic importance of SII, we did not compare its discriminatory ability with other inflammatory markers such as PCT and CRP. Lastly, it should be noted that the patients in our study underwent surgery after being evaluated by different surgeons at our medical center, potentially introducing a selection bias. More NSCLC patients who have received neoadjuvant neoadjuvant chemoimmunotherapy from diverse facilities nationwide are needed to study the relationship

between SII and MPR.

5. Conclusion

This study demonstrated the association between infammatory biomarkers in the peripheral blood and MPR and suggested that baseline SII is an independent factor that affects MPR in patients with NSCLC who undergo neoadjuvant chemoimmunotherapy. If these hematological parameters are validated in large prospective studies, they could potentially be utilized to classify patients with resectable NSCLC in randomized trials of immune checkpoint inhibitors (ICIs), allowing them to optimize the benefits of the therapy.

Data availability statement

The data that support the finding of our study are available on request from the corresponding author.

Ethics Approval

This study was approved by in the first affiliated Hospital of Chongqing Medical University. The IRB waived the patient's informed consent as this was a non-interventional study using routinely collected data.

References

[1] SUNG H, FERLAY J, SIEGEL R L, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries [J]. CA: A Cancer Journal for Clinicians, 2021, 71(3): 209-249.
[2] LIANG Y, WAKELEE H A. Adjuvant chemotherapy of completely resected early stage non-small cell lung cancer (NSCLC) [J]. Translational lung cancer research, 2013, 2(5): 403-410.
[3] URAMOTO H, TANAKA F. Recurrence after surgery in patients with NSCLC [J]. Translational lung cancer research, 2014, 3(4): 242-249.
[4] AKINBORO O, DREZNER N, AMATYA A, et al. US Food and Drug Administration Approval Summary: Nivolumab Plus Platinum-Doublet Chemotherapy for the Neoadjuvant Treatment of Patients With Resectable Non-Small-Cell Lung Cancer [J]. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2023, 41(17): 3249-3259.
[5] FORDE P M, SPICER J, LU S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer [J]. New England Journal of Medicine, 2022, 386(21): 1973-1985.
[6] KUNDU J K, SURH Y J. Inflammation: gearing the journey to cancer [J]. Mutation research, 2008, 659(1-2): 15-30.
[7] DHARMAPURI S, ÖZBEK U, LIN J Y, et al. Predictive value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in advanced hepatocellular carcinoma patients treated with anti-PD-1 therapy [J]. Cancer medicine, 2020, 9(14): 4962-4970.
[8] JOMRICH G, PAIREDER M, KRISTO I, et al. High Systemic Immune-Inflammation Index is an Adverse Prognostic Factor for Patients With Gastroesophageal Adenocarcinoma [J]. Annals of Surgery, 2021, 273(3): 532-541.
[9] TACHINAMI H, TOMIHARA K, YAMADA S I, et al. Neutrophil-to-lymphocyte ratio as an early marker of outcomes in patients with recurrent oral squamous cell carcinoma treated with nivolumab [J]. The British journal of oral & maxillofacial surgery, 2023, 61(4): 320-326.
[10] LIU J, LI S, ZHANG S, et al. Systemic immune-inflammation index, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio can predict clinical outcomes in patients with metastatic non-small-cell lung cancer treated with nivolumab [J]. Journal of clinical laboratory analysis, 2019, 33(8): e22964.
[11] PROVENCIO M, NADAL E, INSA A, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial [J]. The Lancet Oncology, 2020, 21(11): 1413-1422.
[12] SHU C A, GAINOR J F, AWAD M M, et al. Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial [J]. The Lancet Oncology,

2020, 21(6): 786-795.
[13] CASCONE T, LEUNG C H, WEISSFERDT A, et al. Neoadjuvant chemotherapy plus nivolumab with or without ipilimumab in operable non-small cell lung cancer: the phase 2 platform NEOSTAR trial [J]. Nature medicine, 2023, 29(3): 593-604.
[14] COUSSENS L M, WERB Z. Inflammation and cancer [J]. Nature, 2002, 420(6917): 860-867.
[15] JIANG M, PENG W, PU X, et al. Peripheral Blood Biomarkers Associated With Outcome in Non-small Cell Lung Cancer Patients Treated With Nivolumab and Durvalumab Monotherapy [J]. Frontiers in oncology, 2020, 10: 913.
[16] ROMANO F J, RONGA R, AMBROSIO F, et al. Neutrophil-to-Lymphocyte Ratio Is a Major Prognostic Factor in Non-small Cell Lung Carcinoma Patients Undergoing First Line Immunotherapy With Pembrolizumab [J]. Cancer diagnosis & prognosis, 2023, 3(1): 44-52.
[17] ANDERSON R, TINTINGER G R, FELDMAN C. Inflammation and cancer: The role of the human neutrophil [J]. South African Journal of Science, 2014, 110(1/2): 1-6.
[18] BENCSIKOVá B, GREPLOVá K, PILáTOVá K, et al. [Platelets in the pathogenesis of solid tumors] [J]. Casopis lekaru ceskych, 2014, 153(2): 78-85.
[19] EL HOUAT Y, MASSARD C, QUILLIEN V, et al. Meta-analysis and Critical Review: Association Between Radio-induced Lymphopenia and Overall Survival in Solid Cancers [J]. Advances in radiation oncology, 2023, 8(2): 101038.
[20] LI C, WU J, JIANG L, et al. The predictive value of inflammatory biomarkers for major pathological response in non-small cell lung cancer patients receiving neoadjuvant chemoimmunotherapy and its association with the immune-related tumor microenvironment: a multi-center study [J]. Cancer Immunology, Immunotherapy, 2022, 72(3): 783-794.
[21] RECK M, SCHENKER M, LEE K H, et al. Nivolumab plus ipilimumab versus chemotherapy as first-line treatment in advanced non-small-cell lung cancer with high tumour mutational burden: patient-reported outcomes results from the randomised, open-label, phase III CheckMate 227 trial [J]. European journal of cancer (Oxford, England : 1990), 2019, 116: 137-147.
[22] HERBST R S, GIACCONE G, DE MARINIS F, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC [J]. The New England journal of medicine, 2020, 383(14): 1328-1339.