ORIGINAL RESEARCH

The Prognostic Significance of Preoperative Platelet-to-Lymphocyte and Neutrophil-to-Lymphocyte Ratios in Patients Operated for Non-Small Cell Lung Cancer

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Introduction:: The aim of the study was to determine the prognostic significance of PLR and NLR ratios in patients operated due to non-small cell lung cancer.

Material: The study group consisted of 532 (174 women, 358 men) patients with non-small cell lung cancer (NSCLC) staged IA-IIIA. The mean age was 63.6 years (range 36 to 84 years). Together with platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR), the following factors were included in the statistical analysis: age, sex, smoking history, the number of leukocytes, neutrophils, and platelets, histopathology, T-stage, N-stage, concomitant diseases according to the Charlson Comorbidity Index (CCI), type of operation, adjuvant chemotherapy, and overall survival.

Results: Univariate analysis showed an association between the value of PLR and NLR and the length of survival. Multivariate analysis found that the stage of advancement of the neoplastic disease (p=0.00003), adjuvant chemotherapy (p=0.009), CCI > 4 (0.00008), and PLR > 144 (p=0.001) were negative prognostic factors for survival > 2 years; however, this effect diminishes in patients surviving more than 5 years.

Conclusion: PLR might serve as a prognostic factor in patients affected by NSCLC with expected two-year overall survival.

Keywords: carcinoma, lymphocyte count, neutrophil count, non-small-cell, platelet count, ratio

Introduction

Lung cancer poses a serious threat, resulting in more than 1.6 million deaths worldwide annually.[1] Unfortunately, it is most often diagnosed when it is already locally advanced, and about one-fifth of the total number of cases of non-small cell lung cancer (NSCLC) can qualify for surgical treatment. Despite intensive treatment, the 5-year survival expectancy of those patients does not exceed 18%.

The most important prognostic factors are undoubtedly the histopathological type of cancer and its stage, ie lymph node involvement and presence of distant metastases.[2] The majority of ongoing studies are focused on the search for other factors that can be assessed at disease onset to predict the prognosis and qualify the patient for appropriate treatment. Such studies are typically performed on a large scale, including huge panels of laboratory parameters including protein and genetic biomarkers which might indicate a biological response to oncogenesis[3,4] This biological response is accompanied by a developing inflammatory process that can be induced by serum proteins and nucleic acid products released by the tumor, eg TNF-alpha, free fractions of microRNA or free circulating

DNA. Many of these molecules are undergoing testing as possible prognostic markers; however, their precise accuracy and specificity remain unknown and they are routinely used.[3] Nevertheless, it is possible to detect inflammatory processes with simple, easily available everyday tests, such as the standard complete blood count test and its calculated derivatives.[4,5] In addition, the platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR) are promising indices whose prognostic value has been discussed in cases of various malignancies.[2,4]

The aim of the present study is to evaluate the prognostic value of PLR and NLR in patients receiving surgical treatment due to NSCLC.

Materials and Methods
The Patient Group

The study included 532 patients surgically treated for stage IA-IIIA NSCLC in the period 2007 to 2014. Patients with operable small cell carcinoma and carcinoid were excluded from the study. Before the operation, all the patients had had to undergo a PET examination. Patients with N2 were qualified for an operation only if the metastases involved a single node and the node was not conglomerated.

The laboratory tests necessary for hospitalization were performed with a Sysmex XN 2000 flow cytometer (Sysmex Europe GmbH, Norderstedt, Germany). PLR, ie the ratio of the absolute number of platelets to the absolute number of lymphocytes, and NLR, the ratio of the absolute number of neutrophils to the absolute number of lymphocytes, were calculated in all analyzed patients.

Patient Characteristics

The study included 174 women and 358 men, aged 36–84 years (mean age: 63.6 years). Fifty-five percent of the patients indicated nicotine addiction. Imaging examinations revealed involvement of the right lung in 311 cases and involvement of the left lung in 221 cases. Squamous cell carcinoma (269 cases), adenocarcinoma (204 cases), large cell carcinoma (43 cases), and adenosquamous carcinoma (16 cases) were indications for surgical treatment. Most patients (375 cases) scored four to six points on the Charlson Comorbidity Index (CCI), while 100 patients scored 2 or 3 points (Table 1).

The study was granted approval by the Bioethics Committee of the Medical University of Lodz (consent

Table 1 Patient Characteristics and Results of Surgical Treatment with Survival Time

Parameter	n	%	Median of Survival [Years]		p
Sex					
F	174	33	3.42		0.001
M	358	67	2.46		
Nicotinism					
Yes	295	55	2.36		0.006
No	237	45	3.09		
Charlson Comorbidity Index					
2	20	4			
3	80	15			
4	141	27	≤4	3.76	0.0000
5	126	24	>4	2.13	
6	108	20			
7	43	8			
8	12	2			
9	2	0.004			
Localization – lung					
Right	312	59	2.90		0.04
Left	220	41	2.42		
Localization – lobe					
Lobe right upper	178	34	3.01		0.01
Middle	16	3	3.71		
Right low	118	22	2.62		
Left upper	119	22	2.89		
Left lower	101	19	1.74		
Stage of the disease					
T IA1	3	1	7.37		0.0000
T IA2	40	8	7.48		
T IA3	39	8	5.39		
T IB	138	25	3.27		
T IIA	8	2	0.78		
T IIB	172	32	2.08		
T IIIA	132	24	1.81		
Diagnosis					
Squamous cell carcinoma	269	50	2.84		0.7
Adenocarcinoma	204	38	2.39		
Large cell carcinoma	42	8	2.83		
Mixed type carcinoma	16	4	2.14		
Surgical treatment					
Lobectomy	400	75	2.73		0.004
Bilobectomy	37	7	3.49		
Pneumonectomy	94	18	1.67		

No. RNN/83/19/KE). Due to the retrospective character of the study, individual consent was not required from the patients for the review of medical records. The authors conformed to the principles of the Helsinki Declaration and kept the personal data of the participants confidential.

Treatment Method

All patients underwent typical anatomical resections, ie lobectomies, bilobectomies, and pneumonectomies. The operations were performed under general anesthesia, through the anterolateral approach with the use of a double-lumen tube. The surgeries involved the resection of at least six N1 and N2 lymph node groups according to the Classification of the Japan Lung Cancer Society.[6] The tumor stage was identified with the use of the eighth edition of TNM (UICC from 2017).[7] The resected lymph nodes were identified according to the Naruke map.[8]

Statistical Analysis

To determine the potential prognostic values of PLR and NLR parameters, the following factors were included in the analysis: patient age, sex, smoking history, the number of leukocytes, neutrophils, and platelets, histopathology, TNM staging, the Charlson Comorbidity Index, type of surgery, adjuvant chemotherapy, and overall patient survival.

The distribution of continuous variables was tested with the Shapiro–Wilk test. Continuous or ordinal variables without a normal distribution were presented as medians and lower and upper quartiles (25–75%), and further analyses were made with the use of nonparametric tests. Normally distributed variables were presented as percentages and numbers. Pairs were compared using the Mann–Whitney *U*-test. Groups of more than two were compared with the Kruskal-Wallis ANOVA test, with the post hoc Dunn-Bonferroni analysis, if indicated. Nominal variables were analyzed using the chi-square test, and Spearman Rank for correlation.

Survival analysis was performed using the Kaplan-Meier test. Univariate analysis (UA) was performed using the Log rank test for nominal variables, and the Cox proportional hazard (CPH) model for continuous variables. For multivariate analysis, a CPH model was constructed including all factors presented as significant during UA; both backward and forward stepwise analyses were performed.

Receiver Operating Characteristic (ROC) curves were created based on these findings, and the optimal combination of sensitivity and specificity of the studied parameters was determined by means of the Youden method and calculated cut-off points.

Results

Surgical Treatment and Postoperative Stages of Advancement

The most commonly performed surgery was lobectomy (400 cases). Pneumonectomy was performed in 94 cases (18%), whereas bilobectomy was administered in 37 cases. A postoperative histopathological analysis revealed R0 resection in all patients. Stage I was noted in 220 (41%) cases, stage II in 180 (34%) cases, and stage III in 132 (25%) cases. Three patients died during postoperative hospitalization and another five within 30 days following surgery. The deaths were caused by myocardial infarct, cerebral stroke, and gastric ulcer perforation. Postoperative complications were observed in 112 cases (21%); these included prolonged air leak, which occurred most frequently (59 cases), atelectasis (20 cases) requiring interventional bronchoscopy and postoperative anemia (19 cases), which required blood transfusion. Ten patients had to be treated for postsurgical arrhythmia. In addition, 228 patients received adjuvant chemotherapy based on combined administration of cisplatin with either vinorelbine or gemcitabine. When cisplatin was contraindicated, carboplatin was used. A total of 76 patients did not receive adjuvant treatment due to contraindication or lack of consent.

Overall Survival (OS) of Patients

The mean OS was 50 months, with 76% of patients surviving 1 year, 57% surviving 2 years, and 46% surviving 3 years. In the studied group of patients, the mean OS was 50 months; one-year OS was noted in 76% of patients, two-year OS in 57%, and three-year OS in 46%.

The survival analysis revealed that stages T3 and T4 and stages N1 and N2 most significantly contributed to shorter survival (p=0.0009 and p=0.0000, respectively). The mean survival periods were 4.605 for stage T1 and T2, 3.934 for T3 and T4, 4.80 for N0, 3.66 for N1, and 2.76 for N2 (p=0.0000). Sex and nicotine addiction most significantly affected patient survival (p=0.00117 and p=0.006, respectively). The mean survival periods were 4.87 years for women and 3.91 years for men and 3.88 years for nicotine smokers and 4.63 years for nonsmokers. Longer OS was observed after lobectomies and bilobectomies (respectively: 4.42 years and 4.51 years)
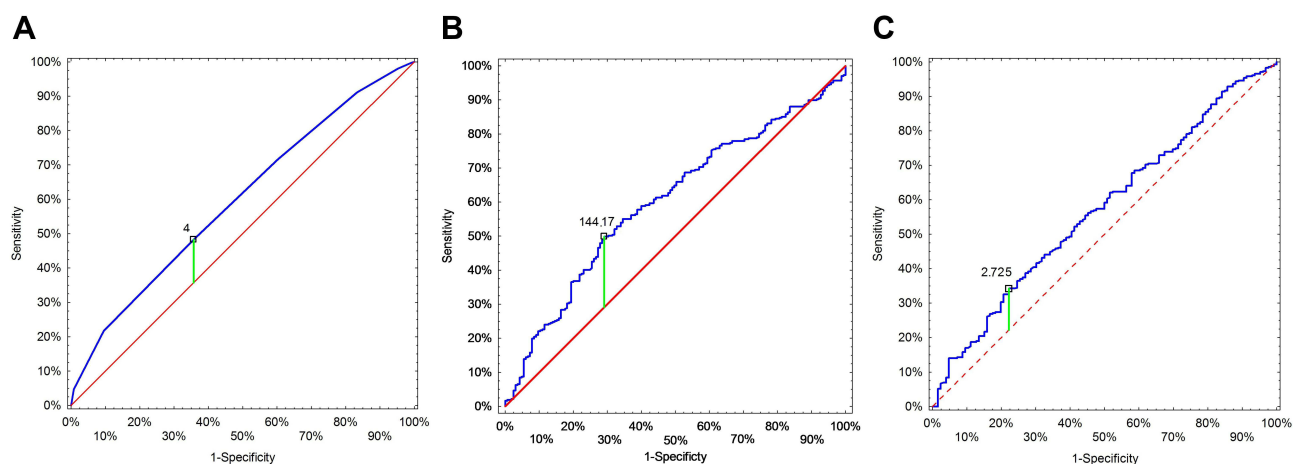
Figure 1 Youden index with receiver-operating characteristic (ROC) curves. (**A**) Charlson comorbidity index (CCI). (**B**) Platelet to lymphocyte ratio. (**C**) Neutrophil to lymphocyte ratio.

than after pneumonectomies (3.23 years; p=0.0046). To a lesser extent, localization of the tumor in the right upper and middle lung lobe resulted in better survival (3.01 years and 3.71 years; p=0.01). No significant relationship was observed between tumor type and patient OS (p=0.7). The CCI value was found to be 4, based on the ROC value (p=0.005). Patients with CCI > 4 demonstrated significantly shorter OS (3.55 versus 5.02; p=0.0000), as can be seen in Table 1.

PLR and NLR as Prognostic Factors

The obtained AUCs were 0.567 for PLR (95% CI: 0.509–0.624; p=0.0238) and 0.587 for NLR (95% CI: 0.531–0.642; p=0.0024).. The cutoff point values for PLR and NLR were 144.017 and 2.725, respectively (Figure 1).

Univariate analysis indicated that NLR and PLR had a significant effect on patient OS, as did CCI and application of adjuvant chemotherapy (Table 2 and Figure 2).

A multivariate analysis of patients treated for NSCLC with OS >2 years revealed that adjuvant chemotherapy; p=0.009, CCI > 4; p=0.00008 and PLR > 144, p=0.001 can be considered independent prognostic factors of advanced stage of lung cancer. However, the prognostic value of these parameters decreases for OS greater than 5 years (Table 3). Figure 3 presents the Kaplan–Meier curves of OS >2 years in the multivariate model.

Discussion

The chronic inflammatory process accompanying neoplasia can be easily confirmed by simple blood tests. The most frequently observed abnormalities include quantitative changes in simple blood tests, such as leukocytosis, neutrophilia, thrombocytopenia, and lymphocytopenia.[5] They occur during the growth and lysis of the tumor. Immunoregulatory cytokines secreted by inflammation facilitate the recruitment of tumor-associated neutrophils, causing disease progression and increasing the risk of distant metastasis; platelets also appear to have a similar role.[5] In contrast, lymphocytes display completely different behavior and are believed to have anticancer activity; indeed, lymphocytosis itself is considered a favorable prognostic factor.[9]

These abnormalities demonstrate a mutual relationship, as reflected in the PLR and NLR parameters.[5,9] Although

Table 2 Results of Studied Parameters and Univariate Analysis in Patients Operated on Due to NSCLC

Parameter	Median	Range	HR	95% CI	p
Neutrophils [$\times 10^3$]	5.8	1.4–31.0	1.03	1.01–1.04	0.02
Lymphocytes [$\times 10^3$]	1.9	0.5–9.3	0.84	0.72–0.97	0.02
Platelets [$\times 10^3$]	262.5	30.0–674.0	1.00	1.00–1.00	0.16
NLR	2.7	0.5–12.3	1.05	1.02–1.09	0.00
PLR	144.0	17.6–570	1.00	1.00–1.00	0.00
CCI	4.2	2–9	1.21	1.12–1.30	0.00
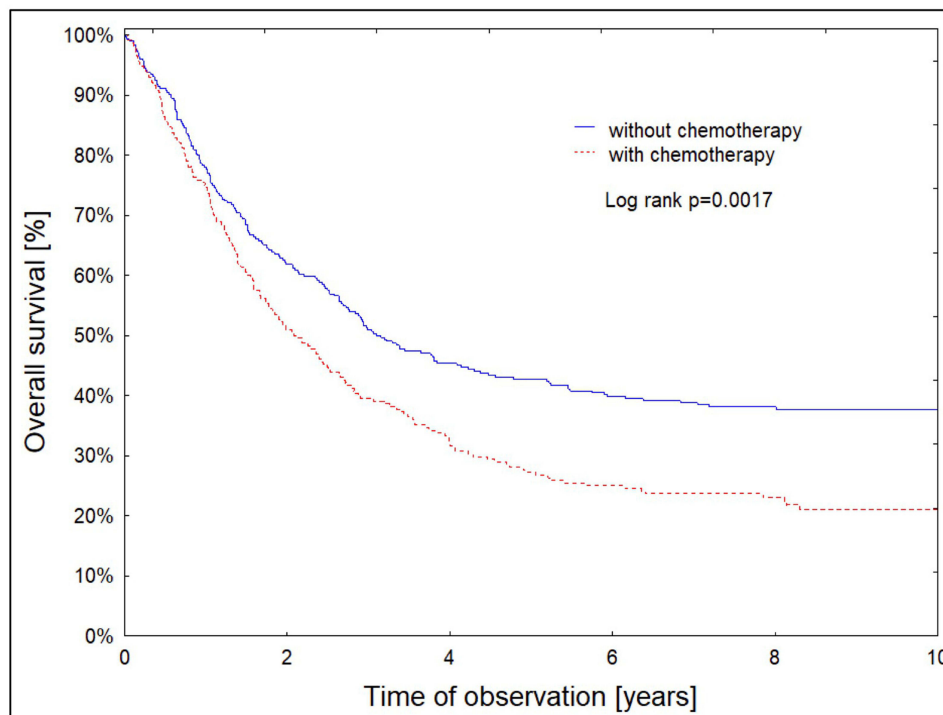
|	Median OS [y]	Mean OS [y]	SD OS [y]	N - non censored	N censored	N total
No chemotherapy	3,12	4,72	3,85	189	115	304
Chemotherapy	2,11	3,55	3,36	178	50	228
Total	2,68	4,22	3,69	367	165	532

Figure 2 Impact of adjuvant chemotherapy on patient survival.

their prognostic role of these parameters in NSCLC has been widely discussed in meta-analyses, the authors recommend caution in their interpretation and use in clinical practice.[10,11] Nevertheless, as the test is widely available and easy to perform, and the results are obtained quickly afterwards, it was included in the present study.

Table 3 Multivariate Analysis in Patients Operated on Due to NSCLC

Parameter	Model of OS>2 Years			Model of OS>5 Years		
	HR	95% CI	p	HR	95% CI	p
Neutrofile [x10³]	1.145	0.986–1.331	0.075	1.032	0.882–1.207	0.686
Limfocyty [x10³]	1.137	0.643–2.012	0.656	0.965	0.550–1.694	0.903
Platelets [x10³]	0.997	0.992–1.002	0.366	0.996	0.991–1.001	0.124
NLR >2.725	0.947	0.7131–1.395	0.988	0.939	0.742–1.427	0.606
PLR >144	1.004	1.001–1.006	**0.001**	1.005	0.997–1.014	0.177
CCI >4	1.319	1.149–1.514	**0.00008**	0.725	0.628–0.838	**0.00001**
Stages:	1.754	1.086–1.833	**0.00003**	1.154	1.047–1.273	**0.0002**
Chemotherapy	1.163	0.916–1.477	**0.009**	1.281	0.906–1.811	0.498
Sex	0.912	0.590–1.407	0.677	1.233	0.804–1.893	0.335
Smoking	1.345	0.911–1.986	0.135	1.257	0.850–1.858	0.251

Note: Statistically significant values are printed as bold.
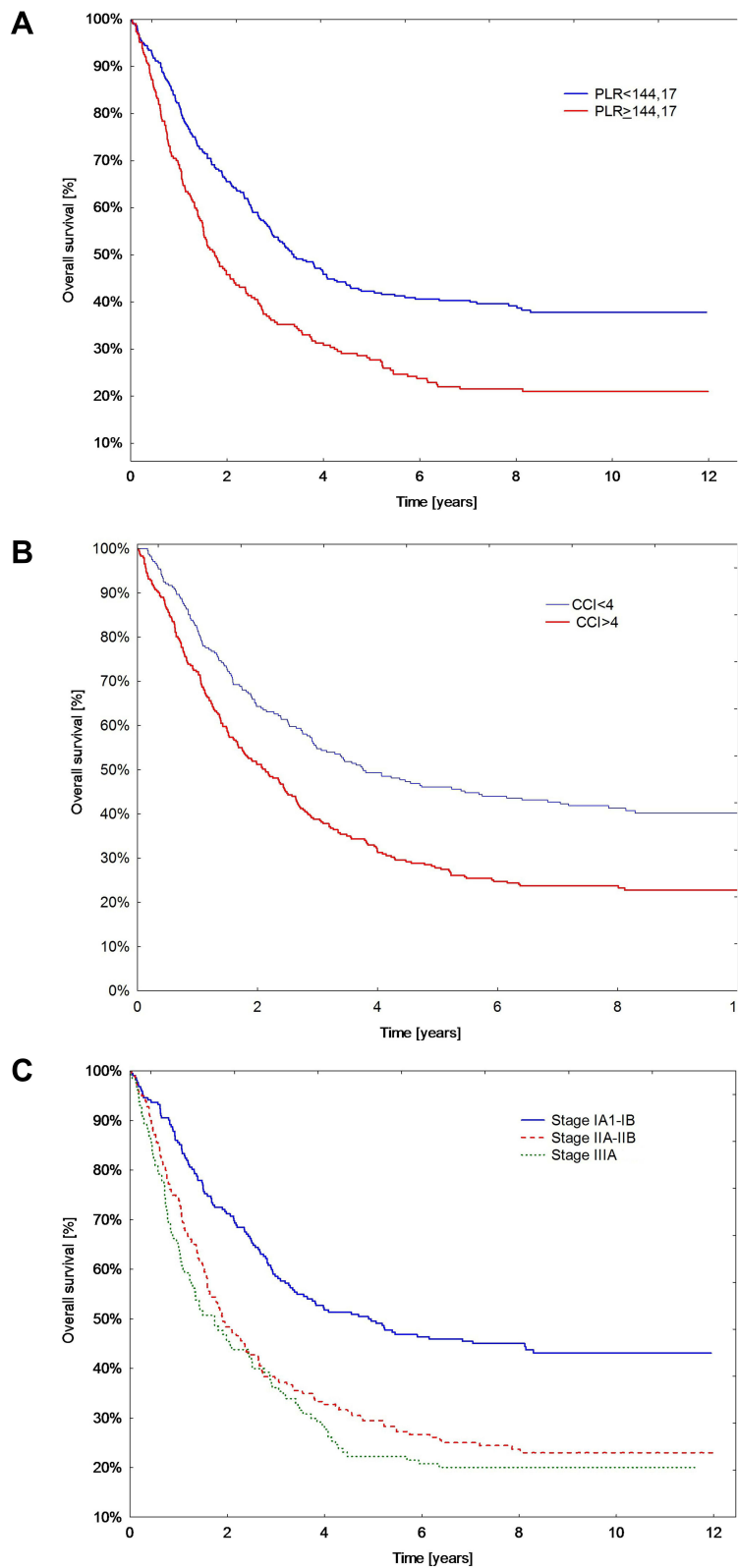
Figure 3 Kaplan–Meier curves of survival of patients operated on due to non-small cell lung cancer. (**A**) Platelet to lymphocyte ratio. (**B**) Charlson comorbidity index (CCI). (**C**) Stage of disease.

Most of the reports on NLR and PLR parameters are from eastern Asia.[9–12] The authors of this study wanted to investigate the behavior of these indicators in the population of an Eastern European country.

Our observations indicate that increased values of PLR and NLR, assessed preoperatively, are related to the OS of NSCLC patients after radical surgical treatment. Similar preoperative prognostic findings have been obtained previously,[12] as well as in NSCLC patients treated with Nivolumab.[13]

Our analysis showed that PLR demonstrates a greater preoperative prognostic value than NLR. The survival time of patients over 2 years (OS > 2) was significantly associated with a worse prognosis (p=0.001) for PLR > 144; no such association was noted for NLR. However, no prognostic value was observed for either of the parameters in the analysis of OS > 5 years. Similarly, Huang et al report that PLR values >122 significantly affect the OS of patients, and this parameter shows a higher prognostic value than NLR.[14] Lan et al observed the highest prognostic value of PLR, ie >148, for one-year survival.[12] A meta-analysis by Qiang et al highlights the value of PLR as a cheap and easily available negative prognostic marker for DFS and OS in patients diagnosed with NSCLC.[10]

Our own multivariate analysis showed that PLR >144, CCI > 4, advancement stages IIA-B and IIIA and application of adjuvant chemotherapy are all independent prognostic factors contributing to a worse prognosis in patients surgically treated for NSCLC. Lee et al obtained similar results, noting that age, male sex, PLR > 180, TNM stages II and III and postoperative radiotherapy are prognostic disadvantages for NSCLC patients.[15] Xu et al report a relationship between PLR > 135 and T stage,[2] while Toda et al indicate that PLR is an unfavourable prognostic factor in NSCLC patients who were treated surgically and received adjuvant chemotherapy.[16] This latter observation is consistent with our present findings, which indicate that PLR values are related to TNM stages II and III and adjuvant chemotherapy.

Our work has several limitations. This study was retrospective in character, and it was performed in a single center for which only patients with operable NSCLC were included. As such, the selection of patients had an influence on the obtained results. Secondly, the postoperative staging in the study group revealed stages IIB and IIIA; therefore, these patients received complementary treatment, which also had an impact on the analyzed

survival time. Thirdly, the authors did not have any data on the molecular profile of the patients, which to some extent was a limitation of this study.

Conclusions

1. In NSCLC patients, elevated PLR values appear to be an independent prognostic factor, in addition to advanced stage and coexistent diseases defined by the Charlson Comorbidity Index.
2. Further prospective multi-center research should be carried out on larger groups of patients before inflammatory markers can be confidently interpreted as prognostic markers in lung cancer and applied in clinical practice.

Abbreviations

AUC, area under curve; CCI, Charlson Comorbidity Index; CPH, cox proportional hazard; CT, computed tomography; EBUS, endobronchial ultrasound; NLR, neutrophil-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; OS, overall survival; PET-CT, positron-emission tomography with computed tomography; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic; TNM, tumor node metastasis classification; UA, univariate analysis; UICC, union of international cancer control.

Disclosure

All authors declare no conflicts of interest.

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