Original Article

Prognostic value of neutrophil-to-lymphocyte, platelet-to-lymphocyte and lymphocyte-to-monocyte ratio ratios in patients operated on due to non-small cell lung cancer

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Background: The aim of the study was to determine a prognostic value of the neutrophil to lymphocyte ratio (NLR), the platelet to lymphocyte ratio (PLR) and the lymphocyte to monocyte ratio (LMR) ratios for survival of patients, operated on due to non-small cell lung cancer (NSCLC).

Methods: The study was conducted on 532 patients, operated on due to NSCLC, in stages IA–IIIA. A total of 174 females and 358 males, aged 36–84 years (the mean age: 63.6 years) were included in the study. The following factors were subject to a statistical analysis, conducted for determination of potential prognostic values of NLR, PLR and LMR ratios: age, sex, nicotinism, the number of leukocytes, neutrophils, monocytes, platelets, histopathological diagnosis, T category, N category, the Charlson comorbidity index (CCI), kind of surgery, patient survival.

Results: The single-factor analysis revealed a relationship between NLR, PLR and LMR values, CCI values, the number of monocytes and the length of survival. The multi-factor analysis confirmed that for patients with expected 2-year survival, PLR above 138 (P=0.0008) is another negative prognostic factor, apart from the stage of the neoplastic disease and CCI above 4. For 5-year survival, such a relationship was not observed.

Conclusions: The PLR ratio is an independent and significant prognostic factor for expected, over 2-year survival of patients operated on due to NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); neutrophil to lymphocyte ratio (NLR); platelet to lymphocyte ratio (PLR); lymphocyte to monocyte ratio (LMR)

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Introduction

Lung cancer is the most frequently diagnosed malignant neoplasm (20% in males and 10% in females). Every year, about 22,000 Poles are affected by this disease. Of this number, 15,000 refer to males (1). In 2012, lung cancer claimed more than 1.6 million lives worldwide. It is estimated that in the year 2035, the disease will contribute to as many as 3 million deaths (2.1 million males and 0.9 million females) (2). The prognosis is bad. In Poland,

the 5-year survival does not exceed 13.5%. A particular kind of neoplasm, its advancement, involvement of lymph nodes and presence of distant metastases are the most important prognostic factors (1).

Oncological studies are focused on searching for factors that, as early as in the diagnostics stage, would enable to determine a preliminary prognosis, which would in turn, allow to implement proper treatment, adjusted to a particular case (3-5). The search is multidirectional and includes cancer markers, tumour growth factors as well as any laboratory parameters. Their elevated values imply a body response to an ongoing neoplastic process. One of body reactions to neoplasia is an inflammatory response, particularly when the tumour is extensive and its breakdown products are absorbed into the bloodstream. On the one hand, inflammation stimulates immunity processes so it can inhibit the development of tumour. On the other hand, however, it favours carcinogenesis, growth of the tumour and its spread. The mechanism of the last process is related to suppression of immune response, inhibition of apoptosis and activation of angiogenesis. The inflammatory response of a body is reflected in various biochemical and haematological indices, available in a laboratory test panel (6,7). The neutrophil to lymphocyte ratio (NLR), the platelet to lymphocyte ratio (PLR) and the lymphocyte to monocyte ratio (LMR) are regarded as reliable markers of inflammatory processes, ongoing oncological patients. An elevated level of these ratios is a consequence of increased numbers of neutrophils, monocytes and platelets and/or a decreased number of lymphocytes, accompanying the neoplastic process (8-10).

The aim of the study is to evaluate of NLR, PLR and LMR ratios, being potential prognostic factors in patients surgically treated due to non-small cell lung cancer (NSCLC).

Methods

Studied population

In 2007–2014, 1,013 patients were treated surgically due to lung malignant neoplasms. Prior to the operation, all the patients had undergone chest CT and bronchoscopy. In the event of lymphadenopathy, the patients underwent mediastinoscopy and from 2008, also endobronchial ultrasound (EBUS) examinations. The patients who did not demonstrate metastases to lymph nodes or in whom the neoplasm involved only one group of nodes and the nodes were not conglomerated (PET) were qualified for the therapy. Upon admission to hospital, all the patients underwent basic laboratory tests, required before the operation. NLR, being a ratio of the absolute number of neutrophils and the absolute number of lymphocytes, PLR, being a ratio of the absolute number of platelets and the absolute number of lymphocytes and LMR, identified as a ratio of the absolute number of lymphocytes and the absolute number of monocytes, were calculated in all the studied patients.

Patient characteristics

A total of 532 patients, operated on in 2007–2014 due to NSCLC, were subject to an analysis. The Bioethics Committee of the Medical University of Lodz gave its consent for the study to be conducted (No. RNN/83/19/KE). Patients who had undergone wedge resections or segmentectomies were excluded from analyses. There were 174 females and 358 males, aged 36–84 years (the mean age: 63.6 years). Among them, 55% of patients admitted to nicotine addiction. Squamous cell carcinoma (269 cases), adenocarcinoma (204 cases), large cell carcinoma (43 cases) and mixed carcinoma (adenosquamous carcinoma: 16 cases) were indications for a surgical procedure.

The tumour was localized the right lung in 312 patients and in the left lung in 220 patients. The majority of patients (375 people), on the base of the CCI index, were categorized into grades 4–6. One hundred patients were categorized into grades 2 and 3 (*Table 1*).

Surgical treatment

Anatomical procedures, i.e., lobectomies, bilobectomies and pneumonectomies, were performed with a standard technique, through anterolateral thoracotomy under general anaesthesia with the use of a double-lumen tube. In the event of involvement of the right lung, a lymphadenectomy procedure was performed for lymph nodes of groups: 2R, 3A, 4R, 7, 8, 9, 10, 11. Patients were removed lymph nodes of groups: 3A, 4L, 5, 6, 7, 8, 9, 10, 11 if the left lung was involved in the neoplastic process. Minimum 6 node groups of N1 and N2 categories were dissected. The degree of tumour advancement was determined on the base of the TNM Classification of Malignant Tumours [Union for International Cancer Control (UICC) 2017, 8thedition], whereas the collected lymph nodes were classified in compliance with the Naruke map.

Table 1 Patient characteristics

Parameter	n	%	Median of survival (years)	P
Sex				0.001
F	174	33	3.42	
M	358	67	2.46	
Nicotinism				0.006
Yes	295	55	2.36	
No	237	45	3.09	
CCI				
2	20	4		
3	80	15		0.0000
4	141	27	≤4: 3.76	
5	126	24	>4: 2.13	
6	108	20		
7	43	8		
8	12	2		
9	2	0.004		
Localization: lung				0.04
Right	312	59	2.9	
Left	220	41	2.42	
Localization: lobe				0.01
Lobe right upper	178	33	3.01	
Middle	16	3	3.71	
Right lower	118	22	2.62	
Left upper	119	22	2.89	
Left lower	101	19	1.74	

CCI, Charlson comorbidity index.

Statistical methods

The following factors were subject to a statistical analysis, conducted for determination of potential prognostic values of NLR, PLR and LMR ratios: age, sex, nicotinism, the number of leukocytes, neutrophils, monocytes, platelets, histopathological diagnosis, T category, N category, the Charlson comorbidity index (CCI), kind of surgery, patient survival.

- ❖ Continuous variables: verified with the Shapiro-Wilk test; due to lack of normal distribution, they were presented as medians and values of the lower and upper quartiles (25–75%) and further analyses—with the application of non-parametric tests;
- ❖ Comparisons of two groups—the U Mann-Whitney test. Comparisons of more groups—the Kruskall-Walis test with post-hoc comparisons, with the application of the Dunn-Bonferroni test;
- ❖ Nominal variables—as a number of observations and percent values, calculated for the study and control group. Comparisons—with the application of the Chi square test;
- ❖ Correlations—rank, non-parametric—the Spearman rank correlation;
- ❖ Survival analysis—the Kaplan-Meyer curves test, the Log-rank test, single-factor analysis of nominal parameters;
- ❖ Single-factor analysis of continuous parameters and multi-factor analysis—the Cox proportional hazard model.

Results

Surgical treatment and post-operative degree of advancement

A total of 220 patients (41%) were in stage I, 180 patients (34%) were in stage II and 132 were in stage III. The most common procedure was lobectomy—400 cases (75%). Pneumonectomy was performed in 94 patients (18%), whereas—bilobectomy—in 37 patients (7%). R0 resection was obtained in all patients. Three patients died postoperatively (one due to an infarct, one due perforation of gastric ulcer and one due to a stroke). Within 30 days, following the operation, another 5 patients died. Complications were observed in 116 patients (22%). In most cases, they were prolonged air leak (49 patients), 15 reoperation due to bleeding and bronchial fistula. Atelectasis in the site of the lung operation was observed in 13 cases. Thirteen patients required postoperative transfusion of packed red blood cells and 11 patients were treated due to a paroxysm of atrial fibrillation.

Overall survival (OS) of patients

The mean OS was 50 months; 76% of patients survived 1 year, 57% of patients survived 2 years, 46% survived 3 years and 35% of patients survived 4 years. An analysis of OS revealed a significantly longer survival in females (median 3.42 *vs.* 2.46; P=0.00117) and non-smokers (median

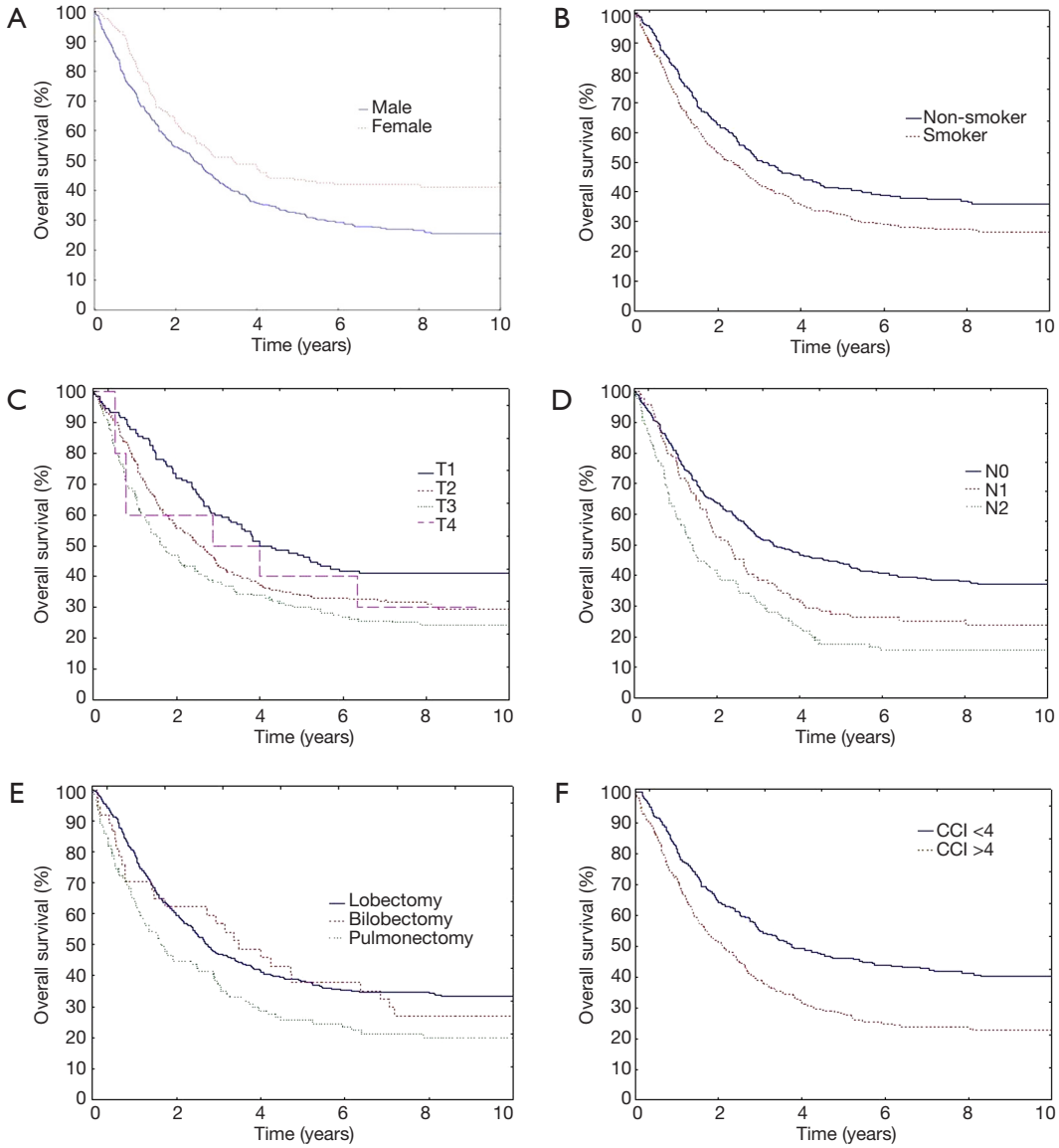

Figure 1 Kaplan-Meier curves of survival of patients operated on due to NSCLC for: (A) sex; (B) nicotine addiction; (C) T stage; (D) N stage; (E) kind of procedure; (F) CCI index. NSCLC, non-small cell lung cancer; CCI, Charlson comorbidity index.

3.09 *vs.* 2.36; P=0.006). Patients with T1 and T2 categories lived longer than those with T3 and T4 categories (P=0.0009); besides, the survival was longer in those with N0 category than in those with N1 and N2 categories (median respectively: 3.38 *vs.* 2.28 *vs.* 1.28; P=0.0000). Patients who underwent lobectomy or bilobectomy lived significantly longer than patients after pneumonectomy (median respectively 2.73 and 3.49 *vs.* 1.67; P=0.0046) (*Figure 1A*,*B*,*C*,*D*,*E*). Tumour localization (right lung/left lung; a particular lobe) did not contribute to statistical significance and did not significantly affect survival (respectively P=0.048; P=0.01). A kind of histopathological diagnosis did not have a significant effect on the lifespan (P=0.7) (*Table 2*). For CCI, being an index of comorbidity, the authors calculated the receiver operating characteristic (ROC) and determined the maximum values of sensitivity and specificity of the studied parameter. The optimal CCI limit value was 4. The lifespan of patients with CCI value above 4 was significantly shorter (3.76 *vs.* 2.13; P=0.0000) (*Figures 1F*,*2A*).

Table 2 Results of surgical treatment with survival time

Parameter	n	%	Median of survival (years)	P
Stage of the disease				0.0000
T IA1	3	1	7.37	
T IA2	40	8	7.48	
T IA3	39	7	5.39	
T IB	138	26	3.27	
T IIA	8	2	0.78	
T IIB	172	32	2.08	
T IIIA	132	25	1.81	
Diagnosis				0.7
Squamous cell carcinoma	269	51	2.84	
Adenocarcinoma	204	38	2.39	
Large cell carcinoma	42	8	2.83	
Mixed type carcinoma	16	3	2.14	
Surgical treatment				0.004
Lobectomy	400	75	2.73	
Bilobectomy	37	7	3.49	
Pneumonectomy	94	18	1.67	

Morphological indices of inflammation as prognostic factors

In order to optimally determine limit values of NLR, PLR and LMR, the authors used ROC curves. The ROC curve enabled to calculate the area under the curve. The values for NLR, LMR and PLR were respectively: 0.587 (95% CI: 0.531–0.642, P=0.0024), 0.587 (95% CI: 0.531–0.642, P=0.0024) and 0.567 (95% CI: 0.509–0.624, P=0.0238). The optimal limit values for NLR, LMR and PLR were: 2.235, 2.86 and 138.017, respectively (*Figure 2B*,*C*,*D*).

A single-factor analysis revealed significant relationships between the values of NLR, PLR and LMR ratios, the CCI Index, the number of monocytes and OS of the patients (*Table 3*).

A multi-factor analysis of over 2-year survival showed that the stage of a neoplastic disease, the CCI value above 4 and the PLR value above 138 (P=0.0008) can be considered negative prognostic factors in patients operated on due to NSCLC. For over 5-year survival, none of the studied ratios (NLR, PLR and LMR) appeared to be an independent prognostic factor (*Table 4*).

Discussion

Clinical studies definitely confirm that there is a close relationship between neoplasia and chronic inflammation. Leukocytosis, thrombocytosis, neutrophilia and lymphocytopenia, which occur in the inflammatory course, are considered negative prognostic factors (6). Inflammatory reaction which is ongoing in the tumour becomes generalised in the course of its growth, which leads to an increased number of leukocytes. The generalization of the inflammatory process results in weaker cell resistance, which is manifested with a reduced number of T lymphocytes (6,7). Cytokines which appear as a response to inflammation, stimulate megacariocytes, which in turn, increases the number of platelets in the course of neoplastic disease. Thrombocytaemia occurs in 39–57% of patients with NSCLC and is considered one of risk factors for metastasis (6). NLR, PLR and MLR ratios reflect mutual quantitative relationships of these haematocytes.

In our study, the single-factor analysis revealed a significant influence of preoperative values of NLR, PLR and LMR ratios on OS of patients after surgical treatment of NSCLC. Chen *et al.* confirmed preoperative values of the above ratios in patients with IB stage, operated on due to NSCLC. The multi-factor analysis revealed prognostic values of LMR and PLR ratios in patients with this disease stage (11). Results of our study indicate that the PLR ratio is characterised with the highest preoperative prognostic value. For PLR >138, over 2-year survival (OS >2) was significantly short (P=0.001). Such a relationship was not observed for OS >5. The multi-factor analysis confirmed that not only increased PLR values but also CCI >4 and IIA, IIB and IIIA stages are independent, negative prognostic factors.

Lee *et al.* made a similar observation. Apart from preoperative values of the PLR ratio, exceeding 180 and stages II and III according to the TNM Classification of Malignant Tumours, also age, male sex and postoperative radiotherapy appeared to be independent, negative prognostic factors of OS (12). Similarly, Xu *et al.* showed that PLR >135 constitutes an independent predictive factor for T category (13). A different study, conducted by Tod *et al.*, revealed that the PLR ratio is a negative prognostic factor for patients treated surgically due to NSCLC and administered complementary chemotherapy (9). This

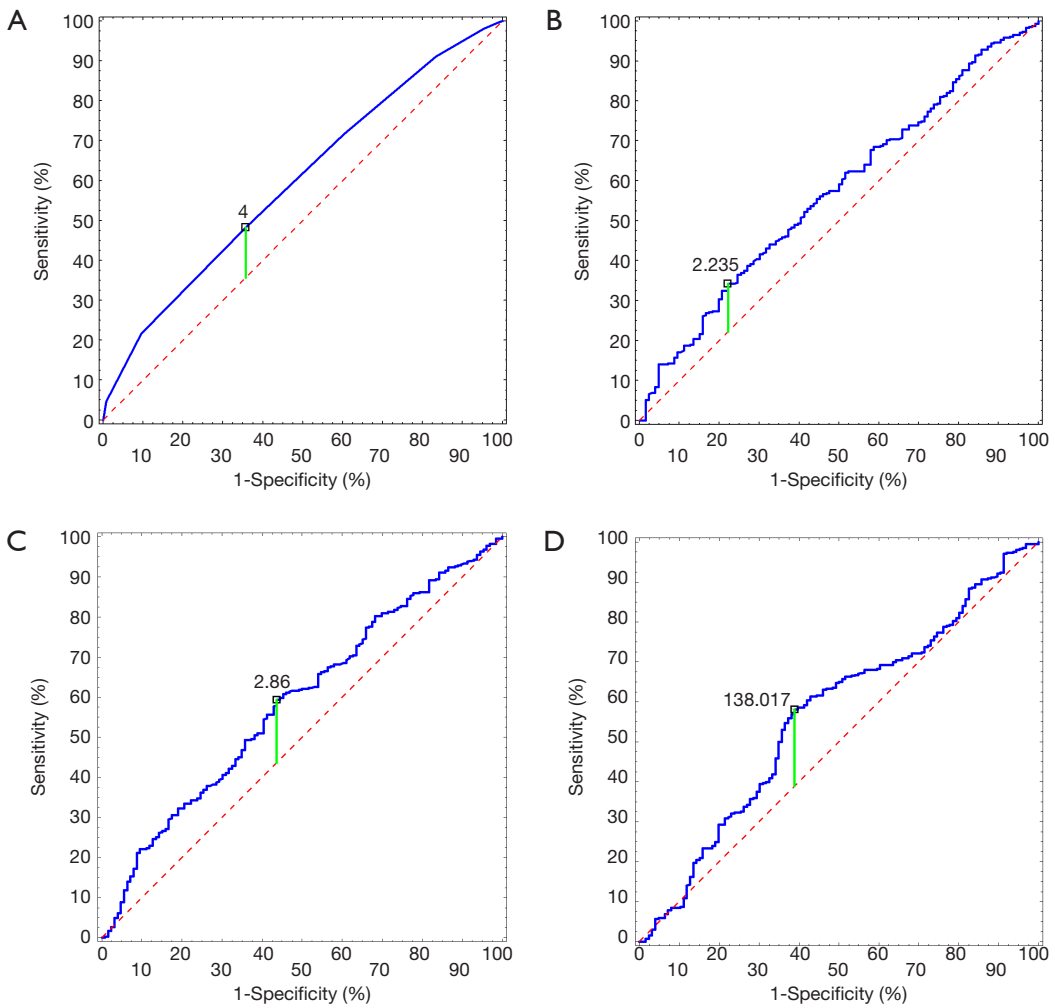

Figure 2 Youden index with ROC curves. For: (A) CCI; (B) NLR; (C) LMR; (D) PLR. ROC, receiver operating characteristic; CCI, Charlson comorbidity index; NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio.

Table 3 Results of studied parameters and single-factor analysis in patients operated on due to NSCLC

Parameter	Median	Range	HR	95% CI	P
Neutrophils (×10^3)	5.8	1.4–31.0	1.03	1.01–1.04	0.02
Lymphocytes (×10^3)	1.9	0.5–9.3	0.84	0.72–0.97	0.02
Monocytes (×10^3)	0.7	0.3–2.4	1.76	1.25–2.48	0.00
Platelets (×10^3)	262.5	30.0–674.0	1.00	1.00–1.00	0.16
LMR	2.9	0.7–26.1	0.83	0.76–089	0.00
NLR	2.7	0.5–12.3	1.05	1.02–1.09	0.00
PLR	148.0	17.6–570	1.00	1.00–1.00	0.00
CCI	4.2	2–9	1.21	1.12–1.30	0.00

NSCLC, non-small cell lung cancer; NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio; CCI, Charlson comorbidity index.

Table 4 Multi-factor 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 (×10^3)	1.145	0.986–1.331	0.075	1.032	0.882–1.207	0.686
Limfocyty (×10^3)	1.137	0.643–2.012	0.656	0.965	0.550–1.694	0.903
Monocyty (×10^3)	1.735	0.404–7.443	0.458	1.856	0.387–8.897	0.438
Płytki krwi (×10^3)	0.997	0.992–1.002	0.366	0.996	0.991–1.001	0.124
NLR >2.23	0.947	0.7131–1.395	0.988	0.939	0.742–1.427	0.606
PLR >138	1.004	1.001–1.006	0.001	1.005	0.997–1.014	0.177
LMR >2.86	0.841	0.681–1.407	0.107	1.027	0.739–1.427	0.87
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
Sex M	0.912	0.590–1.407	0.677	1.233	0.804–1.893	0.335
Nicotinism	1.345	0.911–1.986	0.135	1.257	0.850–1.858	0.251

OS, overall survival; NSCLC, non-small cell lung cancer; NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio; CCI, Charlson comorbidity index.

observation corresponds to results of our study, in which we confirmed a prognostic relationship between the PLR ratio and the degree of advancement, i.e., stages II and III, according to the TNM Classification of Malignant Tumours, where a complementary therapy is usually implemented.

A meta-analysis, carried out by Qiang *et al.* on 1,554 patients from 7 centres, confirmed a high negative prognostic value of the PLR ratio in patients with NSCLC, shortening OS and disease-free survival (DFS). The authors pointed out that PLR, being a potential biomarker, is easily available and cheap (14).

A mutual interaction of platelets and leukocytes, being a response to an ongoing inflammatory process, might in future appear to be a useful and cheap marker, which will enable to implement a proper treatment and foresee prognosis. The presented results correspond to those obtained by other authors.

Conclusions

Increased values of NLR, PLR and LMR as well as the number of monocytes affect the survival period of NSCLC patients. The PLR ratio, the stage of the neoplastic disease and CCI above 4 are an independent and significant prognostic factor for expected, over 2-year survival of patients operated on due to NSCLC. The stage of tumour advancement and the CCI value are independent prognostic factors for 5-year survival.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Bioethics Committee of the Medical University of Lodz gave its consent for the study to be conducted (No. RNN/83/19/KE).

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