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Prognostic value of Platelet-to-Lymphocyte Ratio (PLR) and IL-6 in patients with small cell lung cancer

Prognostyczna wartość wskaźnika płytkowo-limfocytowego (PLR) u chorych na drobnokomórkowego raka płuc

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Abstract

Background: In order to identify patients with the most favourable prognosis, the effect of baseline level of interleukin-6 (IL-6) and platelet-to-lymphocyte ratio (PLR) on survival was analysed in patients with small cell lung cancer.

Material and Methods: 159 patients with small cell lung cancer were enrolled. Full blood count enabling computing the PLR, as well as NSE, ProGRP and IL-6 levels were done in all participants.

Results: We demonstrated significant effect of disease stage, performance status, sex, initial NSE, ProGRP and IL-6 levels as well as PLR on survival of patients with SCLC. In subgroups with normal initial levels of ProGRP (below 50.36 ng/L) and NSE (below 20.95 µg/L), the IL-6 level above 6.0 ng/L worsens the prognosis by 28% and 29%, respectively. In a subgroup with elevated initial ProGRP, the difference in survival between patients with normal vs elevated IL-6 level at baseline was 25%, whereas in a subgroup with elevated initial NSE it was 14%. The between-subgroup differences in PLR were less considerable. There was a significant effect of PLR on patient survival in a subgroup with normal initial NSE level and elevated initial ProGRP level.

Conclusion: In subgroups of SCLC patients identified based on initial tumour marker levels, IL-6 level can be a source of reliable prognostic information, whereas the effect of PLR is less marked. Patients with normal tumour marker levels and IL-6 below 6 ng/L at baseline have the most favourable prognosis.

Streszczenie

Wstęp: W celu wyodrębnienia w grupie chorych z drobnokomórkowym rakiem płuc (SCLC) pacjentów z najkorzystniejszym rokowaniem przeanalizowano wpływ wyjściowego poziomu interleukiny-6 (IL-6) i wskaźnika płytkowo-limfocytowego (PLR) na 5-letnie przeżycie.

Materiał i metody: Do badań włączono 159 pacjentów z drobnokomórkowym rakiem płuca. U wszystkich chorych wykonano wyjściowo badania morfologii krwi umożliwiające wyliczenie PLR, jak również stężenia NSE, ProGRP i IL-6.

Wyniki: Wykazano istotny wpływ stadium zaawansowania choroby, stanu sprawności, płci, wyjściowych stężeń NSE, ProGRP i IL-6, a także wartości PLR na 5-letnie przeżycie chorych z SCLC. W podgrupach z prawidłowymi wyjściowymi poziomami ProGRP (poniżej 50,36 ng/L) i NSE (poniżej 20,95 mg/L), stężenie IL-6 powyżej 6,0 ng/L pogarszało rokowanie o odpowiednio 28% i 29%. W podgrupie z wyjściowo podwyższonym ProGRP, różnica przeżycia pomiędzy chorymi z prawidłowym lub podwyższonym stężeniem IL-6 na początku badania wynosiła 25%, podczas gdy w podgrupie z wyjściowo podwyższonym NSE wynosiła ona 14%. Różnice między podgrupami w PLR były mniejsze. Istotny statystycznie wpływ PLR na przeżycie chorych odnotowano w podgrupie z prawidłowym stężeniem NSE i podwyższonym przed leczeniem stężeniem ProGRP.

Wnioski: W podgrupach wyselekcjonowanych ze względu na wyjściowy poziom markerów, istotnej informacji odnośnie rokowania chorych na SCLC dostarcza IL-6, natomiast wpływ wskaźnika PLR jest słabiej zaznaczony. Najlepszym rokowaniem cechują się chorzy z prawidłowym przed leczeniem poziomem markerów nowotworowyc i stężeniem IL-6 niższym od 6 mg/L.

Keywords: small cell lung cancer, inflammation, interleukin-6, platelet-to-lymphocyte ratio
Słowa kluczowe: drobnokomórkowy rak płuca, stan zapalny, interleukina-6, wskaźnik płytkowo-limfocytowy PLR

Introduction

Small cell lung cancer (SCLC) is a lung cancer of distinct structural, biological and clinical characteristics. It affects 15-20% of all lung cancer cases and is highly invasive with a tendency to both local spread and distant metastases [1]. Whereas a significant percentage of patients respond to chemo– and radiotherapy in early stages of disease, antineoplastic treatment resistance may develop relatively quickly in some of them. Treatment in early stages involves chemoradiotherapy with prophylactic cranial irradiation (PCI). The survival median in this group ranges between 16-26 months as compared to 6-12 months in patients with advanced SCLC [2].

Among laboratory assays, tumour markers play an important role in oncology. They are increasingly more often considered as diagnostic and prognostic factors. Neuron-specific enolase (NSE) has been used in diagnosis and monitoring of patients with SCLC since 1999 [3]. A growing body of research evidence confirms its prognostic value [4, 5, 6]. Pro-gastrin releasing peptide (ProGRP) proved to be helpful in differential diagnosis of SCLC and non-small cell lung cancer or benign lung tumours. ProGRP assay offers high specificity and sensitivity in SCLC [7]. Even in early stages of SCLC, elevated ProGRP can be found in approx. 70-78% of cases. It is considered useful in assessing treatment response, especially in patients with limited disease [8]. The prognostic value of ProGRP, however, is debatable and remains controversial [9, 10, 11, 12].

Numerous reports point to the key role of inflammation in tumour development and progression, stimulating angiogenesis and metastases. Along with tumour cells, tumour microenvironment consists of immune cells, such as macrophages, neutrophils, mastocytes, myeloid-derived suppressor cells (MDSC), dendritic cells, natural killer (NK) cells, T-cells, B-cells and stromal cells (fibroblasts, endothelial cells, pericytes and mesenchymal cells) [13]. These cells can communicate directly or through chemokine and/or cytokine signalling, and exert autocrine or paracrine effect, thus modulating tumour growth. Expression of pro– and anti-inflammatory mediators and modulators along with different activated cell lines within the tumour microenvironment is thought to determine the direction, in which the shift of homeostasis will progress. Tumour-associated inflammation may promote tumour development or accelerate antineoplastic response [14]. Increased cell expression of interleukin 6 (IL-6) along with its elevated serum levels are found in a significant proportion of patients with SCLC. This translates into tumour invasiveness, treatment resistance and unfavourable prognosis [15, 16, 17]. Along with interleukin-1 (IL-1), granulocyte-macrophage colony-stimulating factor (GM-CSF), fibroblast growth factor (FGF) or oncostatin M (OM), IL-6 stimulates megakaryocyte proliferation and platelet production [18]. On the cellular level, this interaction is somehow reflected in fluctuating serum levels of acute phase proteins, platelets (PLT) or leucocytes subpopulation count as well as inflammatory indices computed based on these parameters, such as platelet-to-lymphocyte ratio (PLR) [19].

The aim of the research was to assess the prognostic value of PLR and IL-6 in patients with SCLC, in subgroups identified by baseline tumour marker levels.

Material and method

159 patients (34% of women) with SCLC aged 40 to 83 (median 63) treated at the Maria Sklodowska Curie Memorial Cancer Centre and Institute of Oncology, Cracow Branch in 2004-2014 were enrolled. Written informed consents for the collection of clinical data and blood specimens were obtained before treatment from each patients. The majority of patients had limited stage (LD) SCLC (67.3%) according to VALG system (Veterans Administration Lung Study Group) and ECOG performance status of 0-1 (60%). Patients with limited stage SCLC received combined chemoradiotherapy with prophylactic cranial irradiation (PCI) additionally used in those in complete or partial remission. Patients with extensive stage SCLC received palliative radiotherapy and/or chemotherapy. The reference group consisted of 67 healthy staff members of the Cancer Centre and Institute of Oncology, Cracow Branch. Full blood count, as well as serum ProGRP, NSE, and IL-6 levels were determined in all controls. Fasting blood samples for analyses were collected in regular conditions between 7 and 9 AM using the BD™ Vacutainer™ system (Becton Dickinson), to EDTA (full blood count) tubes and tubes with serum clot activator. Blood samples were allowed to clot for 30 minutes, after which they were centrifuged at 3,800 x g for 10 minutes at 18-25°C. The NSE, ProGRP and IL-6 levels were determined in the processed serum samples. The ProGRP concentrations were measured using a two-step fully automated chemiluminescent immunoassay (CMIA) in the Architect i1000 analyser (Abbott Laboratories, Germany). The NSE and IL-6 concentrations were measured using electrochemiluminescence immunoassays (ECLIA) in the Cobas e411 analyzer (Roche Diagnostics, Germany). The full blood count was determined using the ADVIA 2120 analyzer (Siemens Healthcare Diagnostics, Germany) The platelet-to-lymphocyte ratio (PLR) was computed for each participant based on the determined parameters.

All statistical analyses were carried out using Statistica v.12 software bundle (StatSoft, Poland). Data was presented as histograms. The correlations between the studied parameters were analysed using Pearson correlation coefficient. The areas under the ROC (Received Operating Characteristic) curves plotted for each studied parameter were determined to assess their clinical utility.

Qualitative and categorical variables were used for survival analysis. Log-rank test was used in order to determine values of studied parameters to discriminate between the patients with favourable and unfavourable survival prognosis at the lowest possible significance level. Kaplan-Meier estimator was used for plotting survival curves in individual subgroups and log rank test was used for assessing the differences between them. Cox proportional hazards model including only significant variables in a one-way analysis was used in order to identify independent prognostic factors.

P-values of less than 0.05 were considered significant.

Results

Diagnostic utility of ProGRP, NSE, IL-6 and PLR

NSE, ProGRP, and IL-6 concentration as well as PLR value were significantly higher in the study group as compared to the reference group. The median values of serum NSE, ProGRP, and IL-6 as well as PLR were 35.8 µg/L (range of 3.0 – 558.4) vs. 11.8 µg/L (range of

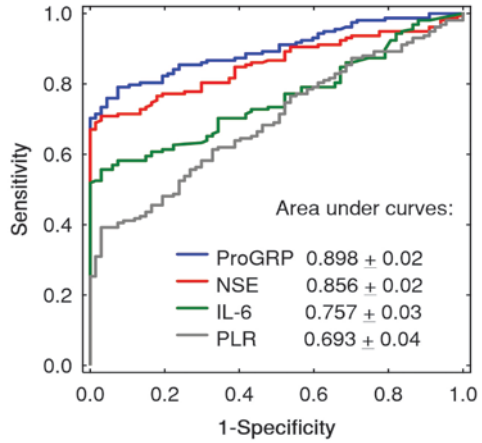

Figure 1. ROC curves for studied parameters for discrimination of SCLC patients from controls.

3.9 – 25.2), 298.5 ng/L (range of 5.9 – 2113.0) vs.17.7 ng/L (range of 3.7 – 72.9), 6.5 ng/L (range of 0.0 – 150.4) vs. 2.3 ng/L (range of 0.0 – 5.9) and 116.4 (range of 58.7 – 209.6) vs. 148.2 (range of 33.0 – 643.0) in patients and controls, respectively. The clinical utility of the studied parameters was determined using the ROC (Received Operating Characteristic) curve analysis. The area under the ROC curve for ProGRP was larger than under the one for NSE. The difference was not significant, though (P=0.176) (Figure 1). The areas under the ROC curve for IL-6 and PLR were smaller and the difference between them was not significant (P=0.150). The area under the ROC curve for ProGRP was significantly larger than under the ones for IL-6 (P=0.0003) and PLR (P<0.001). Similarly, the area under the ROC curve for NSE was significantly larger than under the ones for IL-6 (P=0.005) and PLR (P=0.0001). The cut-off values determined based on ROC curves were 50.4 ng/L, 20.95 µg/L, 5.19 ng/L and 176.8 for ProGRP, NSE, IL-6 and PLR, respectively.

In order to more accurately present the structure of the results of the examined parameters obtained before the treatment of the patients, histograms were used (figure 2). ProGRP concentration, higher than cut off value, was found in 74.8% of SCLC patients, while concentration higher than 250 ng/L was observed in 54% of patients. Similarly, NSE concentration above the cut-off value was demonstrated in 71.0% of patients, but higher than 100 µg/L only in 15%. IL-6 concentration higher than the cut-off value was observed in 56.6% of patients, wheras higher than 25 ng/L only in 10% of patients. In the studied group there were no patients with extremely high PLR values. The level of PLR higher than the cut-off value was found in 39.2%, while higher than 300 was observed only in 9% of the patients.

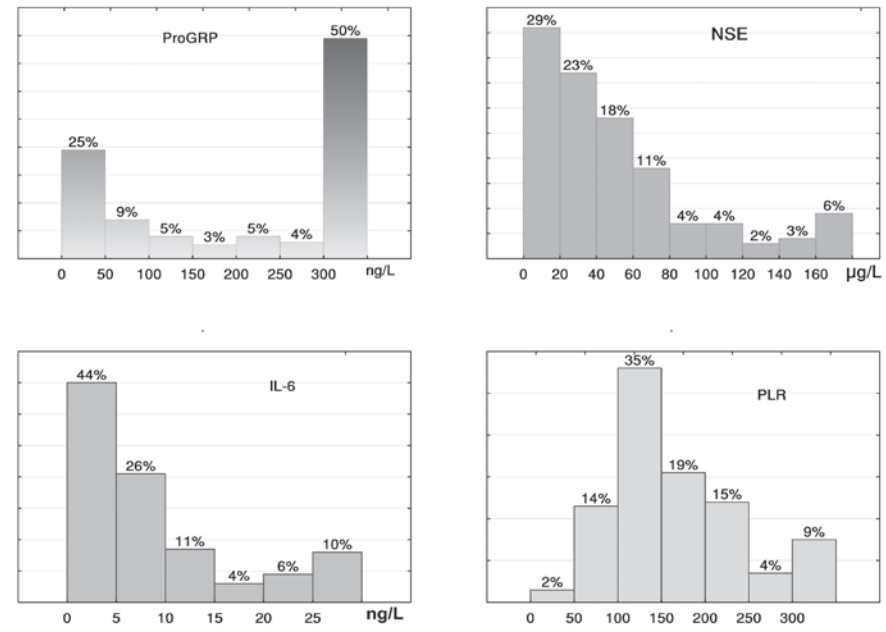

Figure 2. Distribution of ProGRP, NSE, IL-6 levels and PLR values in SCLC patients.
These histograms show the frequency of patients within chosen class intervals for studied parameters.

Table I. Results of univariate and multivariate analysis

Parameter	Variant	N	Median of survival	P	RR	CI	P
stage of disease	LD	107	21.0	**0.0000**	1		
	ED	52	9.0		3.40	2.44 – 5.15	**< 0.0001**
PS	0,1	96	18	**0.0002**	-	-	-
	≥ 2	63	10				
gender	females	54	19	**0.0130**	1		
	males	105	12		1.51	1.02 – 2.21	**0.0371**
age	≤ 63	115	15	**0.3851**	-	-	-
	> 63	44	13				
NSE, µg/L	≤ 28,0	60	23	**0.0000**	1		
	> 28,0	99	12		1.54	1.03 – 2.31	**0.0370**
ProGRP,ng/L	≤ 270	77	19.5	**0.0062**	-	-	-
	> 270	82	12				
IL-6, ng/L	≤ 6.0	77	21	**0.0000**	1		
	> 6.0	81	10		2.05	1.41 – 2.99	**0.0002**
PLR	≤ 210	119	16	**0.0330**			
	> 210	40	10		-	-	-

Correlation analysis

There was a fairly strong positive correlation between NSE and ProGRP levels (r=0.583; P=0.000). There were also slightly weaker positive correlations between IL-6 and NSE levels (r=0.197; P =0.013), IL-6 and PLT levels (r=0.174; P=0.028), as well as IL-6 level and PLR (r=0.205; P=0.009). There was no correlation between an absolute lymphocyte count, and platelets count as well IL-6 level.

Prognostic value of ProGRP, NSE, IL-6 and PLR

Stage of disease, performance status, sex and initial NSE, ProGRP, IL-6 levels as well as PLR were demonstrated to significantly affect 5-year survival (Table 1).

Multivariate analysis demonstrated that the extensive-stage SCLC, male sex, as well as serum NSE level above 28 µg/L and serum IL-6 above 6 ng/L were independent negative prognostic factors. Whereas with the baseline NSE level above 28 µg/L the prognosis worsened 1.5-fold, with the baseline IL-6 level above 6 ng/L, it worsened even 2-fold.

The above results were obtained when assessing the effect of individual parameters on patient survival in the whole studied group of SCLC patients. Due to the complexity of processes co-occurring during tumorigenesis and the associated fluctuations in biomarker concentrations, the additive effect of inflammatory markers on patient survival in subgroups identified based on their baseline tumour marker levels was assessed.

Elevated IL-6 levels significantly worsened prognosis in subgroups with normal initial tumour marker levels (ProGRP ≤ 50.36 ng/L and NSE ≤ 20.95 µg/L) (Figure 3). In subgroups with normal initial NSE and ProGRP levels, the difference in 5-year survival between patients with IL-6 below 6.0 ng/L and above 6 ng/L was 29% (P=0.0218) and 28% (P=0.0276), respectively. In subgroups with elevated initial NSE and ProGRP levels, the difference in 5-year survival between patients with IL-6 below 6.0 ng/L and above 6 ng/L was 14% (P=0.0002) and 25% (P<0.0001), respectively.

The results for the PLR were fairly dissimilar. Whereas the PLR above 210 significantly worsened prognosis in patients with initial NSE level below 20.95 µg/L (P=0.049), it did not affect survival of patients with initial ProGRP below 50.36 ng/L (P=0.417) (Figure 4). It should be noted that the percentage of patients with normal tumour marker levels and PLR above 210 was low, (10.9% and 25% in subgroups with normal initial NSE and ProGRP levels, respectively). Furthermore, there was no effect of PLR on survival in a subgroup with elevated initial NSE level (P=0.566), whereas in a subgroup with elevated initial ProGRP, patients with PLR above 210 had significantly worse prognosis than those with lower PLR (P=0.045). The percentage of patients with NSE level above 20.95 µg/L and PLR above 210 was 30.9%, whereas the percentage of patients with ProGRP level above 50.36 ng/L and PLR above 210 was 25.2%.

Discussion

Diagnostic management of patients with cancer aims to determine tumour morphology and its biological characteristics along with blood tumour marker levels [11]. However, a number of studies point to host immune response to tumour and gradually increasing systemic inflammation, regulated by various mediators and modulators, as equally important [14].

Interleukin-6 (IL-6), a cytokine released both in tumour cells and tumour microenvironment is one of inflammatory mediators. Its binding to a specific receptor α triggers intracellular signalling cascade. The JAK-STAT signalling pathway activation results in enhanced expression of genes essential for tumour cell proliferation

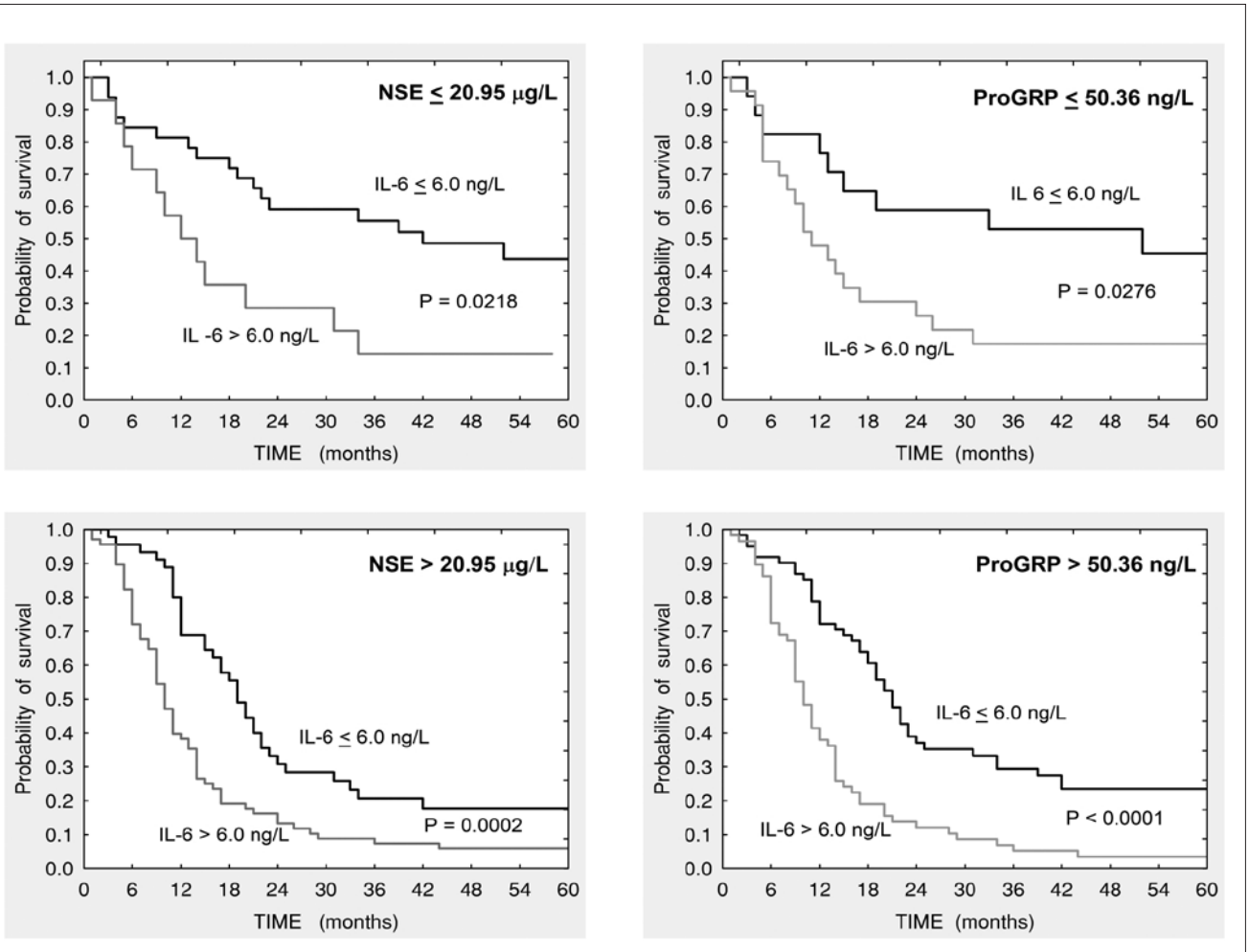

Figure 3. Kaplan-Meier survival curves for IL-6 in subgroups identified based on the initial tumour marker levels.

and survival, angiogenesis and metastases, as well as upregulation of immunosuppressive factors, which determine the MDSC phenotype, macrophages and dendritic cells [20]. A number of studies demonstrated unfavourable effect of elevated IL-6 levels on prognosis in patients with different cancers, including lung cancer [17, 21]. Our findings appear to confirm that. In the study group of SCLC patients we have demonstrated that IL-6 level significantly affects survival and is an independent prognostic factor. Furthermore, tumour-associated inflammation manifesting as elevated IL-6 levels, decreases 5-year survival by even 28% in patients with normal tumour marker levels at baseline.

Along with its tumorigenic effect, IL-6 also mediates the antitumor immune response, facilitating T-cell proliferation, whereas interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) suppress lymphocyte proliferation [20, 22, 23]. The lack of association between serum IL-6 level and lymphocyte count, and on the other hand, the tendency for the PLT count to increase with serum IL-6 level elevation demonstrated in patients with SCLC in our study appear to confirm the multidimensional and multidirectional nature of discussed interactions on a cellular level.

Activated platelets use adhesion molecules to bind tumour cells, thus protecting them from the host's immune response [24]. Following platelet activation, a number of proangiogenic factors are released, such as VEGF, FGF and MMP-9 which promote tumour spread [25]. Given that immune response inhibitors present in tumour microenvironment, such as IL-10 and TGFβ decrease lymphocyte count and impair their function, the platelet-to-lymphocyte ratio (PLR) was proposed as a severity index of systemic inflammatory response.

Recent reports indicate that high PLR at baseline may adversely affect the prognosis in patients with ovarian, colorectal, kidney and lung cancer [26, 27, 28]. This, however, mostly applies to the cases of non-small cell cancer or those with mixed histologic type (non-small cell and small cell) tumours [29, 30, 31].

The study by Unal et al. carried out in patients with grade IIA – IIIB NSCLC eligible for chemoradiotherapy demonstrated significantly worse prognosis in patients with baseline PLR above 195 [29]. Along with an increase in baseline PLR (expressed as terciles of <193, 193-328 and >328), the survival median in patients with metastatic lung cancer eligible for treatment with nivolumab decreased (>14 vs. 7.70 vs. 3.15 months for the three terciles, respectively). PLR above 262 (i.e. median PLR in this group of patients) was associated with significantly worse prognosis (survival of 13.2 vs. 4.8 months. P=0.006) [30].

The prognostic value of PLR in SCLC remains debatable and controversial. Studies carried out in Asian populations tend to demonstrate the lack of prognostic value of PLR. Although the participants had different stages of disease, the PLR values assumed to discriminate between the different survival groups were relatively low (122.7 in a study by Wang et al., 125 in a study

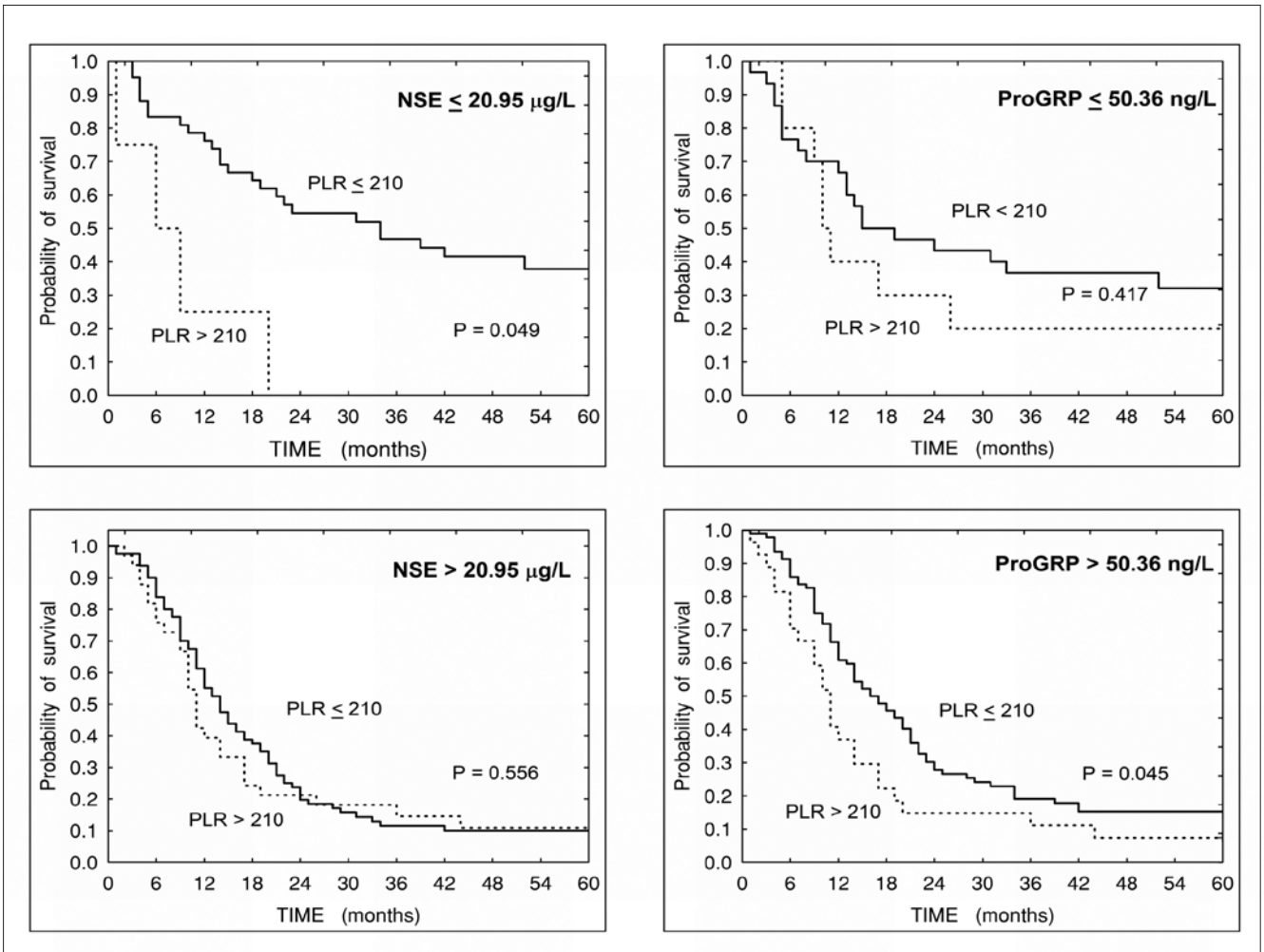

Figure 4. Kaplan-Meier survival curves for PLR in subgroups identified based on the initial tumour marker levels.

by Deng et al. and 160 in a study by Kang et al.) [32, 33, 34]. The cut-off values in these studies were determined based on survival ROC curve analysis. In our opinion, the discriminatory value determination method was erroneous, as the areas under the ROC curve for PLR were small (0.531-0.623), which indicates that PLR lacks clinical utility in this regard. Accepting such low discriminatory values would also result in unfavorable prognosis for the majority of people from the reference groups, because, as shown by the results of our research, the cut-off value determined in the healthy group was 176, and the median for PLR 116.

Xie et al. demonstrated that PLR may also be associated with the stage of disease. In their study, the PLR median in patients with limited stage SCLC was 160 as compared to 190 in those with extensive stage SCLC. The authors, using the log-rank test, determined the differential value of PLR for patients due to their survival and confirmed a worse prognosis in patients with PLR higher than 210 [35]. Similarly, in our sample, the patients with initial PLR above 210 had worse prognosis as compared to those with lower initial PLR.

Hong et al. evaluated prognostic value of PLR in a sample of 919 patients with SCLC, with disease staging distribution across the sample similar to the one in our population. They demonstrated unfavourable effect of PLR above 250 on overall survival [36].

Our analysis of tumour and inflammatory marker levels as prognostic factors indicates that PLR is a poorer survival predictor than IL-6, NSE and ProGRP. Elevated IL-6 levels in cancer patients may result from its increased production in tumour cells and host response to the tumour [21]. Presented study results confirm that pre-existent inflammation (i.e. present before treatment commencement) significantly worsens 5-year survival in patients with SCLC, both those with elevated and normal tumour marker levels. Patients with normal tumour marker levels and IL-6 below 6 ng/L at baseline have the most favourable prognosis.

The differences in PLR were significantly smaller, which could be due to the fact, that the interaction between platelets which stimulate tumour growth and tumour cells which trigger platelet activation is regulated by numerous components of tumour microenvironment, which enhance tumour spread. It seems that PLR reflects more the immune functional status of the host rather than the severity of inflammation.

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