research article

Neutrophil-to-lymphocyte ratio can predict outcome in extensive-stage small cell lung cancer

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Background. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) were analyzed in various carcinomas and their potential prognostic significance was determined. The objective of present study was to determine the correlation between these parameters and the survival of patients with small cell lung cancer (SCLC), since very few studies have been published on this type of carcinoma.

Patients and methods. One hundred and forty patients diagnosed with SCLC at University Hospital Center Zagreb, between 2012 and 2016 were retrospectively analyzed. Extensive-stage disease (ED) was verified in 80 patients and limited-stage disease (LD) in 60 patients. We analyzed the potential prognostic significance of various laboratory parameters, including NLR, PLR, and LMR, measured before the start of treatment.

Results. Disease extension, response to therapy, chest irradiation and prophylactic cranial irradiation (PCI), as well as hemoglobin, monocyte count, C-reactive protein (CRP), and lactate dehydrogenase (LDH) showed a prognostic significance in all patients. When we analyzed the patients separately, depending on the disease extension, we found that only skin metastases as well as LDH and NLR values, regardless of the cut-off value, had a prognostic significance in ED. Meanwhile, the ECOG performance status, chest irradiation, PCI, and hemoglobin and creatinine values had a prognostic significance in LD.

Conclusions. NLR calculated before the start of the treatment had a prognostic significance for ED, while PLR and LMR had no prognostic significance in any of the analyzed groups of patients.

Key words: small cell lung cancer; hematological markers; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; lymphocyte-to-monocyte ratio

Introduction

Lung cancer is still one of the most malignant diseases nowadays. It is the most commonly occurring cancer in men and the second most commonly occurring cancer in women according to the latest data by the International Agency for Research on Cancer (IACR).[1] At the same time, lung cancer is the leading cause of cancer death among both men and women. For the purposes of comparison, breast cancer in women occurs three times more often than lung cancer, while the mortality is almost equal. Moreover, prostate cancer and lung cancer have almost the same incidence in men, but the lung cancer mortality rate is four times higher than the prostate cancer mortality rate.[1,2]

Small cell lung cancer (SCLC) is the most aggressive subtype of lung cancer. Nowadays, small cell lung cancer makes up about 15% of all lung cancers and occurs almost only in smokers. The incidence of this lung cancer subtype has decreased in the last few decades, but primarily in developed

countries.[3,4] There are no global data on SCLC prevalence. In Croatia, there are no separate data on SCLC either, and the available epidemiological data relate to lung cancer as an entity. In the last twenty years, a slight reduction in the share of SCLC in relation to the total number of lung cancer patients has been observed at our institution, which is the largest thoracic oncology center in the country.

According to literature there are differences in survival rates for various tumors, including small cell lung cancer, depending on ethnic origin.[5] Therefore, the results of epidemiological and clinical studies in one geographic area are not applicable to some other geographic areas.

The main characteristics of small cell lung cancer are its rapid growth and early spread to distal body parts. This is the reason why in most cases this carcinoma is diagnosed late, when metastatic disease has already developed.[6] Surgical treatment is therefore rarely possible, but in the last few years it has been recommended for certain patients with early-stage disease.[7] Before the introduction of platinum-based antineoplastic drugs for the treatment of malignant disease, the median survival of patients diagnosed with small cell lung cancer was two to three months.[8,9] The survival rate has increased four to five times with chemotherapy, but for most patients with extensive-stage disease it does not exceed ten months. In fact, this tumor is extremely chemosensitive and usually responds to chemotherapy very well. However, it recurs very rapidly and most patients die after a relapse. Despite numerous clinical trials, progress in the treatment of small cell lung cancer has been modest. However, as treatment of limited disease (LD) became more successful with the introduction of thoracic radiotherapy and prophylactic cranial irradiation (PCI), concurrent chemoradiotherapy has been a standard in the treatment of LD for a long time now.[6] The optimal radiation therapy protocol has remained controversial until this day, although it has been established that there are no differences in either survival or toxicity between hyperfractionated and normofractionated radiotherapy.[10,11] The application of consolidation radiotherapy in selected patients with extensive-stage disease (ED) and a good initial response to chemotherapy have partly contributed to the improved survival rate, but application has been very inconsistent.[12,13] Immunotherapy has resulted in significant progress in the treatment of numerous malignant diseases, including non-small cell lung cancer (NSCLC). Expectations for the treatment of small cell lung cancer were high as well. For the time being, adding checkpoint inhibitors to first-line chemotherapy in ED has resulted in a slight increase of overall survival and progression-free survival, but the results are far from expected.[14-16]

It is well known that infection and deregulated inflammatory response are associated with the occurrence and progression of almost all chronic diseases, including cancers.[17] In the last few decades, a great number of researches investigating the role of different inflammatory markers in cancer development and outcome have been published.[18-20] Usually the investigated inflammatory markers include C-reactive protein (CRP), lactate dehydrogenase (LDH), erythrocyte sedimentation rate, platelet (Pc) and neutrophil counts.[21-23] In most cases, it has been found that elevated levels of these parameters are associated with poorer outcome of various cancers, including small cell lung cancer.[24,25] On the other hand, the lymphocyte count reflects the immunological status of a host, thus a low lymphocyte count is a predictor of poorer outcome.[26] The prognostic value of combinations of these and other parameters has also been extensively investigated. Among them, the neutrophil-to-lymphocyte ratio in various chronic diseases, including numerous malignant diseases, has been investigated the most.[27-29]

In this study, we have investigated CRP, LDH, Pc, hemoglobin (Hb), creatinine, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR) and their impact on the outcome of patients with SCLC. To the best of our knowledge, this is the first study carried out exclusively on a European population which investigated the prognostic significance of all three mentioned ratios in patients with limited-stage and extensive-stage small cell lung cancer.[29-31]

Patients and methods

Patients

For research purposes, we analyzed the medical records of 438 patients diagnosed with small cell lung cancer admitted to the University Hospital Center, Department for Lung Diseases Jordanovac between 2012 and 2016. We included only patients whose disease was verified by histopathological analysis and who had undergone first-line chemotherapy or chemoradiotherapy. Some additional criteria needed to be met in order to be included in the research: documented laboratory test results

with the investigated parameters measured up to three weeks before the first chemotherapy, as well as data on performance status, follow up, and outcome. The following patient categories were excluded from further research: surgically treated patients, patients with combined small cell lung carcinoma, patients with one or more synchronous tumors, patients who received no therapy, patients without the required medical records, and patients lost to follow-up. After exclusion of the mentioned groups, 140 patients remained who met all the required inclusion and exclusion criteria for further investigation. Out of the total number of patients, 80 were diagnosed with extensive-stage disease and 60 with limited-stage disease. The patients' performance status was measured before the start of the treatment and defined according to the Eastern Cooperative Oncology Group Performance Status (ECOG) scale.[32] Regarding the ECOG status, the patients were divided into two groups: good ECOG status (0–1) and poor ECOG status (2–3).

All patients underwent a thoracic and abdominal computed tomography (CT) scan before the start of the treatment. Skeletal scintigraphy was done only in cases with a clinical indication, because it was not routinely performed at our Department. The same applied to brain CT scanning. Disease extension was defined according to the staging system established by the International Association for the Study of Lung Cancer (IASLC) in 1989, which divides SCLC into two stages, "limited-stage disease" and "extensive-stage disease".[33] The patients underwent follow-up chest X-ray scans after every two chemotherapy cycles. A follow-up CT scan was performed after the treatment was completed, especially in cases of initial limited-stage disease. Regression of a primary tumor and metastasis or stable disease was marked as response to therapy what was in fact disease control after initial therapy, whereas progression of the disease was marked as no-response. Response to therapy was assessed radiologically and clinically (*e.g.*, if a patient had subcutaneous metastases or palpable lymph nodes in a region which had not been examined by CT).

In our institution, patients usually receive 4–6 cycles of the first-line platinum-doublet chemotherapy. Patients who received a minimum of two and a maximum of six cycles of the mentioned chemotherapy, with or without radiotherapy, were included in the study. A concomitant or sequential radiotherapy protocol was carried out, primarily in patients with limited-stage disease or as palliative treatment in patients with extensive-stage disease and a good response to chemotherapy. Prophylactic cranial irradiation was mainly performed in patients with limited-stage disease.

Data collection and ethical consideration

Data were collected by using the electronic information database, based on good clinical practice and complying with international standards including the Helsinki Declaration on Patient Safety. We obtained approval for data collection and analysis by the Ethics Committee of our institution. Since this was a retrospective study, informed consent was not required.

Demographic, laboratory, cytological, histopathological, clinical, and treatment data were collected on the patients included in the study. Laboratory test results obtained shortly before the start of treatment, that is, a maximum of three weeks before the first chemotherapy, were included in the study. Among all the hematological results, the following parameters were analyzed: leukocyte count, lymphocyte count, neutrophil count, monocyte count, platelets, hemoglobin, CRP, creatinine, and LDH. The neutrophil-to-lymphocyte ratio was calculated by dividing the total neutrophil count by the total lymphocyte count. The platelet-to-lymphocyte and lymphocyte-to-monocyte ratios were calculated in the same way.

Overall survival (OS) was defined as the length of time from the date of diagnosis to death from any cause, or the last follow-up for patients who were still alive. Progression-free survival (PFS) was defined as the length of time from diagnosis to progression or death, depending on what happened first.

Statistical analysis

For the analysis of demographic and clinical data, we used descriptive and inferential statistical methods. Parameters are indicated as sum and percentage, arithmetic mean +/- standard deviation, or as interquartile range limits with the median as a measure of the central tendency. Differences among the ranked parameters, *i.e.*, the investigated values, were calculated by using the Mann–Whitney U test. Differences among categorical data were tested by using the Chi-square test with Fisher's exact test for smaller samples. Intercorrelation among the variables was tested by using Spearman's rank correlation coefficient varying within the closed interval $-1 \leq r \leq +1$. For survival analysis, the Kaplan–Meier estimator was used, and the Log-rank test (Mantel-Cox) was used as a test of significance. The

TABLE 1. Patient characteristics regarding the disease stage

Variable	ED-SCLC (n = 80)	LD-SCLC (n = 60)	p-values
Age (years) x̄ (SD)	63.2 (9.1)	63.0 (9.4)	0.930
Gender			
Male	55 (68.8%)	34 (56.7%)	0.159
Female	25 (31.2%)	26 (43.4%)	
Smoking			
Yes	77 (96.2%)	57 (95.0%)	1.000
No	3 (3.8%)	3 (5.0%)	
PS (ECOG)			0.368
0–1	64 (80.0%)	52 (86.7%)	
2–3	16 (20.0%)	8 (13.3%)	
Chest irradiation			
Yes	9 (11.2%)	36 (60.0%)	**< 0.0001**
No	71 (88.8%)	24 (40.0%)	
PCI			
Yes	2 (2.5%)	10 (16.7%)	**0.004**
No	78 (97.5%)	50 (83.3%)	
Disease control			
Yes	63 (78.8%)	56 (93.3%)	**0.018**
No	17 (21.2%)	4 (6.7%)	
PFS (weeks) x̄ (SD)	30.1 (14.5)	60.3 (57.9)	**< 0.0001**
OS (weeks) x̄ (SD)	48.3 (23.4)	83.3 (59.3)	**< 0.0001**
Outcome			
dead	79 (98.8%)	46 (76.7%)	**0.013**
alive	1 (1.2%)	14 (23.3%)	
WBC count (x 10⁹/l) x̄ (SD)	9.1 (3.7)	9.2 (3.3)	0.686
Platelet count (x 10⁹/l) x̄ (SD)	293 (119)	304 (95)	0.249
Hemoglobin (g/l) x̄ (SD)	130.9 (17.8)	133.0 (16.8)	0.540
CRP (mg/l) x̄ (SD)	34.2 (44.6)	21.2 (26.6)	**0.048**
Creatinine (umol/l) x̄ (SD)	81.9 (20.0)	82.3 (29.6)	0.443
LDH (U/l) x̄ (SD)	336.2 (193.5)	311.1 (607.3)	**0.004**
Lymphocytes (x 10⁹/l) x̄ (SD)	1.6 (0.8)	1.7 (0.7)	0.202
Neutrophils (x 10⁹/l) x̄ (SD)	6.6 (3.4)	6.6 (3.2)	0.812
Monocytes (x10⁹/l) x̄ (SD)	0.7 (0.3)	0.7 (0.3)	0.700
NLR x̄ (SD)	5.1 (3.6)	4.6 (3.4)	0.485
PLR x̄ (SD)	217.9 (119.9)	213.4 (123.3)	0.714
LMR x̄ (SD)	2.5 (1.4)	3.0 (2.4)	0.271

CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; ED-SCLC = extensive-stage disease small cell lung cancer; LDH = lactate dehydrogenase; LD-SCLC = limited-stage disease small cell lung cancer; LMR = lymphocyte-to-monocyte ratio; NLR = neutrophil-to-lymphocyte ratio; OS = overall survival; SD = standard deviation; PCI = prophylactic cranial irradiation; PFS = progression- free survival; PLR = platelet-to-lymphocyte ratio; PS = performance status; WBC = white blood cells; x̄ = arithmetic mean

Cox regression was used for determining possible multiple interactions among the parameters. The Cox regression was performed in the case of $p < 0.3$ or for clinically relevant parameters. All P values were two-tailed. The level of significance was set at Alpha = 0.05. Statistical analysis was performed by using IBM SPSS Statistics for Windows, Version 21.0 (IBM SPSS Inc, Chicago, IL, USA).

Cut-off values suggested by the literature were used for testing the potential prognostic value of the investigated ratios, since the ROC curves of the investigated ratios did not have a statistical significance. All ratios were tested regarding two cut-off values. The cut-off values for NLR were 4 and 5, those for PLR were 150 and 250, and those for LMR were 2.64 and 4.19.[34-39]

Results

Patient characteristics

Patient characteristics regarding the disease stage are shown in Table 1. Out of 438 patients diagnosed with small cell lung cancer or mixed neuroendocrine carcinoma between 2012 and 2016, 140 met the inclusion and exclusion criteria and were included in the study. Of those 140 patients, 80 were diagnosed with extensive-stage disease and 60 with limited-stage disease. The mean patient age was 63.1 years with a mean deviation of 9.2 years (42–87 years of age). Slightly more males than females were involved in the study (89 or 63.6%). The majority of the patients were smokers (95.7%), of good performance status, 0–1 according to the ECOG scale (82.9%). Only 14 patients (10%) received less than 4 chemotherapy cycles. Forty-five patients (32%) underwent radiotherapy, most of whom were in the limited-stage disease group. Only twelve patients underwent PCI (8.6%), again significantly more in the limited-stage disease group. Disease control was observed in 119 patients (85%). After two years, 125 patients (89.2%) died. Fifteen out of the total number of patients included in the analysis (10.7%) survived for more than 2 years, and all of them belonged to the limited-stage disease group. According to the statistical analysis, disease control, PFS, OS, and outcome were significantly better in the limited-stage disease group. Of the laboratory parameters, a significant statistical difference regarding the disease stage was only observed for CRP and LDH. The mean NLR and PLR values were higher in the extensive-stage disease group of patients, while the mean LMR value was higher in the limited-stage disease group, but the difference was not statistically significant. In the extensive-stage disease group, a statistically significant difference of LMR values regarding patient

age was observed, *i.e.*, higher LMR values were observed in the younger age group.

Survival analysis

The median survival time for all patients was 52.6 weeks (95% confidence interval [CI] 47.5–57.7). The median survival time for the ED group of patients was 45.7 weeks (95% confidence interval [CI] 42.3–49.2) and for the LD patient group it was 64.1 weeks (95% confidence interval [CI] 56.70–71.6).

According to the Kaplan-Meier estimator, survival analysis of all 140 patients showed a statistically significant difference in the overall survival regarding disease extension, radiotherapy to the primary tumor, prophylactic brain irradiation and disease control. Therefore, patients with limited-stage disease, patients with disease control, irradiated patients and patients who underwent PCI had a better survival. Of the laboratory parameters, a statistically significant difference in the overall survival was observed regarding the hemoglobin, CRP, LDH, and boundary monocyte values, whereas a statistically significant difference in the overall survival regarding the ECOG status, NLR, PLR, and LMR was not observed (Table 2).

Separate testing showed a statistically significant difference in overall survival in patients with extensive-stage disease, considering the presence of skin metastases and laboratory parameters including LDH and NLR, regardless of the cut-off values. Therefore, a better overall survival was observed in the patients who did not have skin metastases and had lower LDH and NLR values (Table 3). No positive correlation between overall survival and ECOG status, number of metastatic sites, and disease control was observed in the subjects with metastatic disease.

A statistically significant difference in overall survival, regarding the ECOG status, radiotherapy of the primary tumor, prophylactic cranial irradiation, and laboratory values such as hemoglobin and creatinine levels, was determined in the limited-stage disease group of patients (Table 4).

As we have already mentioned, Cox regression was used for determining possible multiple interactions among the variables. Thus, all statistically significant parameters from the Kaplan-Meier analysis were included in the multiple regression model. In this model LDH became the most significant prognostic factor in extensive-stage disease, while the ECOG performance status became the most powerful one in limited-stage disease. The data are presented in Table 5.

TABLE 2. Prognostic parameters for survival – all patients

Variable		No. of patients	Median survival (weeks) - 95% CI	p-values (log-rank test)
Extent of disease	LD ED	60 80	64.1 (56.7–71.6) 45.7 (42.3–49.2)	**< 0.0001**
Chest irradiation	Yes No	45 95	69.1 (63.3–75.0) 45.3 (39.0–51.6)	**< 0.0001**
PCI	Yes No	12 128	69.0 (12.3–125.7) 49.1 (43.4–54.9)	**0.003**
Disease control	Yes No	119 21	53.4 (49.5–57.3) 36.4 (25.3–47.5)	**0.013**
Hemoglobin (g/l)	M ≥ 138 F ≥ 119 < 138 < 119	78 62	57.1 (50.6–63.6) 40.6 (28.9–52.3)	**0.006**
CRP (mg/l)	< 5.0 ≥ 5.0	35 104	57.1 (48.9–65.4) 47.9 (41.4–54.3)	**0.026**
LDH (U/l)	< 241 ≥ 241	55 56	63.0 (53.0–73.0) 37.0 (27.7–46.3)	**0.002**
Monocytes ($x10^9$/l)	≤ 0.84 > 0.84	99 41	55.0 (49.5–60.5) 44.3 (33.2–55.4)	**0.048**

CRP = C-reactive protein; ED = extensive-stage disease; LD = limited-stage disease; LDH - lactate dehydrogenase; PCI = prophylactic cranial irradiation

TABLE 3. Prognostic parameters for survival – extensive-stage disease (ED)

Variable		No. of patients	Median survival (weeks) - 95% CI	p-values (log-rank test)
Skin metastases	Yes No	4 76	15.9 (0.7–31.0) 46.9 (42.7–51.0)	**< 0.0001**
LDH (U/l)	< 241 ≥ 241	26 36	54.0 (45.4–62.6) 33.7 (22.8–44.6)	**0.017**
NLR	< 4 ≥ 4	40 40	50.1 (43.5–56.8) 44.7 (37.4–52.0)	**0.026**
NLR	< 5 ≥ 5	50 30	50.1 (44.7–55.6) 39.6 (30.7–48.5)	**0.036**

LDH = lactate dehydrogenase; NLR = neutrophil-to-lymphocyte ratio

Discussion

Numerous prognostic factors were investigated in various cancer types in order to find the factor which would most accurately define the patient groups that could benefit from a certain therapy and consequently expect a better survival.[39] The established fact about the important role inflammation plays in the process of carcinogenesis has led to research into the prognostic significance of various inflammatory markers. In the past decade numerous papers have been published on such research in relation to non-small cell lung cancer[29,31], but, very few studies of this kind have been done for small cell lung cancer. The present study

TABLE 4. Prognostic parameters for survival – limited-stage disease (LD)

Variable		No. of patients	Median survival (weeks) - 95% CI	p-values (log-rank test)
PS (ECOG)	0–1 2–3	52 8	66.3 (57.6–75.0) 35.9 (8.3–63.4)	**0.007**
Chest irradiation	Yes No	36 24	70.7 (51.8–89.6) 36.7 (16.1–57.3)	**0.003**
PCI	Yes No	10 50	102.0 (0.0–209.6) 58.3 (46.7–69.8)	**0.032**
Hemoglobin (g/l)	M ≥ 138 F ≥ 119 < 138 < 119	35 25	71.9 (57.0–86.8) 54.3 (17.7–90.9)	**0.033**
Creatinine (umol/l)	M < 125 F < 107 ≥ 125 ≥ 107	57 3	66.3 (58.6–74.0) 32.9 (27.8–37.9)	**0.001**

ECOG = Eastern Cooperative Oncology Group; PCI = prophylactic cranial irradiation; PS = performance status

TABLE 5. Results of Cox regression analysis

Variable		HR	95.0% CI for HR		p-value
ED-SCLC			Lower	Upper	
Skin metastases	Yes vs No	0.034	0.006	0.192	0.000
LDH	< 241 vs. ≥ 241	**1.691**	1.130	2.530	**0.011**
Monocytes	≤ 0.84 vs. > 0.84	1.057	0.675	1.655	0.809
NLR	< 4 vs. ≥ 4	1.497	0.757	2.961	0.246
NLR	< 5 vs. ≥ 5	0.795	0.391	1.615	0.525
LD-SCLC					
ECOG	0–1 vs. 2–3	**2.865**	1.032	7.953	**0.043**
Chest irradiation	Yes vs. No	1.558	0.793	3.047	0.195
PCI	Yes vs. No	2.038	0.893	4.654	0.091
Hemoglobin	Normal vs. Anemia	1.439	0.773	2.678	0.251
Creatinine	Normal vs. Elevated	1.432	0.155	13.198	0.751

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group, ED-SCLC = extensive-stage disease small cell lung cancer; HR = hazard ratio; LDH = lactate dehydrogenase; LD-SCLC = limited-stage disease small cell lung cancer; NLR = neutrophil-to-lymphocyte ratio; PCI = prophylactic cranial irradiation

was conducted with the intention to determine potential prognostic parameters of survival in a European population of patients diagnosed with SCLC. Survival parameters were identified for the whole population of patients, as well as separately for patients with extensive-stage and those with limited-stage disease, in order to determine differences between these two groups.

As disease extension and performance status are generally among the most investigated prognostic parameters, they were verified as the most important for SCLC as well.[23] Our study also showed that disease extension was a significant prognostic factor, and certainly the most significant predictor of longer survival. On the other hand, performance status showed a prognostic value only for the limited-stage disease patient group, which can be explained by the fact that it was possibly assessed more accurately in this patient group. As a matter of fact, performance status assessment is a subjective method and in retrospective studies there is always a possibility that the criteria for certain patients varied. Unlike in other neoplasms, age did not have a prognostic significance in most of the studies regarding SCLC, which was confirmed in our study, too.[23] Neither gender nor smoking status had a prognostic significance, but, it is noteworthy that the number of non-smokers in the study was negligible. Of all the variables, radiotherapy, PCI and disease control had a survival impact in the whole research patient group. When we separated the patients with extensive-stage from those with limited-stage disease, radiotherapy and PCI retained a survival impact in the patients with limited-stage disease, as we expected. However, disease control showed prognostic value neither in LD nor in ED.

In the last few decade various laboratory parameters regarding prognostic value have been investigated. Their ratios have also been investigated recently. Some studies verified a prognostic significance of hemoglobin, leukocyte count, CRP, LDH, and serum sodium concentration in SCLC.[23,25,40] The prognostic significance of hemoglobin and LDH was confirmed in our patients, along with a lower significance of CRP and monocyte count as prognostic factors. When we excluded disease extension from the analysis, LDH retained a prognostic significance in the ED group, while hemoglobin retained a prognostic significance in the LD group of patients. Besides, creatinine level occurred as an independent prognostic factor for survival in the LD group of patients, but again only in the extremely small number of patients with increased creatinine levels.

Although the combinations of various laboratory indicators, including NLR, PLR, and LMR, have already been examined as prognostic factors in SCLC, a relatively small number of studies have been published regarding this type of cancer. Most of the published papers investigating the predictive significance of these parameters in patients with lung cancer address non-small cell lung carcinoma.[29-31] Consulting the literature in English until May, 2020, we found a total of twenty studies, seven of which had been published in 2019, which investigated one or more of these three ratios in patients with small cell lung cancer. It is interesting to note that most of the studies relate to the Asian population. For example, the prog-

nostic significance of LMR in SCLC was only investigated in two studies, both conducted in the Asian population.[38,41] Out of twelve studies which investigated the prognostic value of PLR alone or in combination with NLR, only one was done in Europe.[35] NLR, as the most researched ratio, was the subject of investigation in seventeen studies, of which only three were European.[25,35,42] There are only two studies investigating the prognostic role of NLR and/or PLR exclusively in the ED group of patients.[34,43] To our knowledge, to date neither of these two parameters have been investigated on a European population in cases of extended SCLC.

As race has been determined as a significant prognostic factor in SCLC patients, in the sense that being Caucasian represents a favorable independent prognostic factor, we were interested in whether our results would differ from the ones obtained elsewhere so far.[5]

It is important to mention that the results of the former studies are inconsistent, that is, some studies showed a statistically significant correlation between the NLR and PLR ratios and overall survival of the patients, while others did not yield a statistical significance. In fact, some studies didn't investigate these ratios in correlation with survival at all.[44-46] The only prospective study conducted in the USA on more than 900 patients verified that NLR was a prognostic parameter for OS only in the extensive-stage disease group of patients, which is consistent with our results.[47] The same study established that PLR was a prognostic parameter for OS only in limited-stage disease, which was different from our results. There are no prospective studies for LMR. Most retrospective studies which investigated NLR established its prognostic value, regardless of whether it was investigated in LD, ED, or simultaneously in both patient groups. Among twelve retrospective studies investigating PLR, only three showed a prognostic significance of this parameter.[48-50] Out of the two studies investigating LMR, only one showed a prognostic significance of this parameter.[38]

In the prospective study mentioned above, among other things it was established that NLR and PLR were statistically significantly greater in patients with extended disease.[47] In our study, the mean values of NLR and PLR were also higher in ED patients, while LMR was higher in LD, although the difference was not statistically significant. On the other hand, we found statistically significant differences in LMR values in correlation with patient age in the ED group, *i.e.*, higher LMR values in the younger age group of these patients.

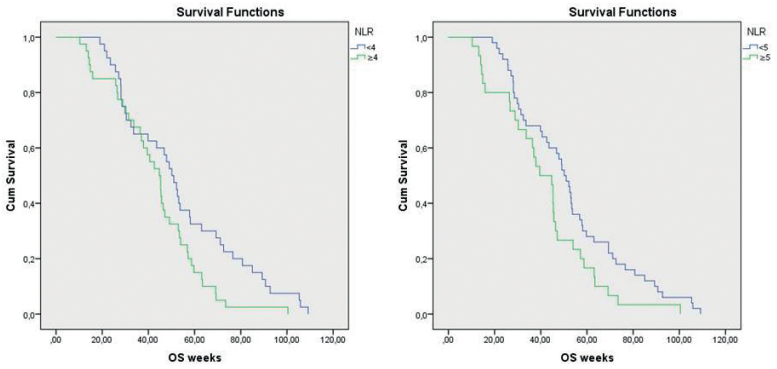

FIGURE 1. Probability of survival of all patients according to stage ($p < 0.0001$).

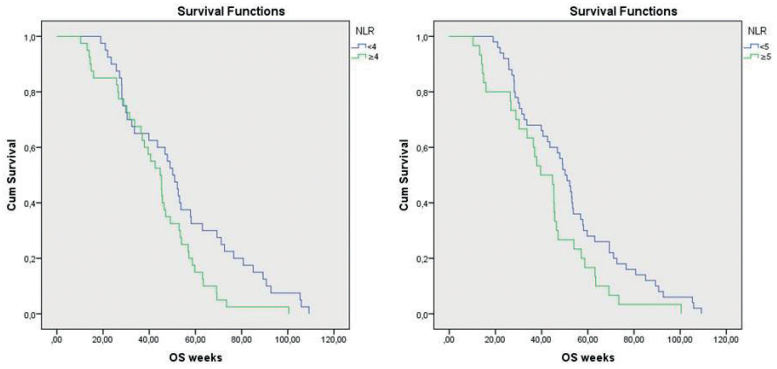

FIGURE 2. Probability of survival of extensive-stage disease small cell lung cancer patients according to neutrophil-to-lymphocyte ratio (NLR) cut-off 4 ($p = 0.026$) and NLR cut-off 5 ($p = 0.036$).

In spite of the fact that some of our results were consistent with those from the only prospective study, our study had numerous limitations. In every study where data are collected from available records, there is a possibility that some of it may not be reliable, particularly data undergoing subjective assessment. As mentioned earlier, performance status is one of such parameters, thus making it more difficult for analysis in retrospective studies. A similar situation may arise in the assessment of peripheral lymph node regression during patient follow up and evaluation of the response to treatment.

Furthermore, in the determination of disease extent, especially in concomitant chemoradiotherapy candidates, assessment based only on clinical examination, bronchoscopy, and CT is not sufficient. Since this type of carcinoma is characterized by rapid spread, complete staging should be done prior to treatment, including brain CT and bone scintigraphy. This is the standard procedure at our

institution today, but was not always possible in the past for technical reasons.

The relatively small number of subjects enrolled in the study was also a limitation. However, two published studies enrolled approximately the same number of patients.[51,52] Also, some of the published studies were conducted in even smaller groups of participants.[44,51,53] Although some studies had a large number of patients, they didn't analyze patients separately considering disease extension.[54]

It is important to note that the number of patients enrolled in the study was probably not adequate for the analysis of certain variables. Namely, only a very small number of patients with skin metastases and increased creatinine participated in the study, as well as very few patients with a low performance status. This presents a problem for many studies, since low-performance status patients are usually not candidates for differential treatment and are rarely included in clinical studies. The same applies for kidney failure patients. On the other hand, since the skin is an uncommon metastatic site, such patients are rare. Considering the confidence interval, it is clear that according to this study skin metastases are not a favorable indicator of survival. On the contrary, creatinine can be considered a favorable indicator of survival despite the small number of patients.

As far as the investigated treatment procedures and their prognostic values are concerned, there are certain limitations as well. In the group of all patients, statistically significant differences were found for survival in relation to PCI and thoracic irradiation. However, when the patients were analyzed separately in relation to the extent of the disease, those differences disappeared in the ED group. This is due to the fact that disease extent is one of the most important prognostic factors for SCLC, which was established in 2003 in a prospective study involving 436 patients.[23] Therefore, these two patient groups should always be investigated separately, because the differences in their prognoses entail different modes and aims of treatment. In our study, PCI remained prognostically valuable in the LD patient group, but with an insufficient number of subjects for the result to be considered reliable. This treatment procedure has always been controversial, presenting an issue for confrontation and opposing research.[55] The prognostic value of PCI was certainly not the primary aim of our study. In spite of its limitations, we believe that our study will contribute to the elucidation of small cell lung cancer, as well as stimulate further research on this type of carcinoma, which has somehow always remained in the margins of lung cancer research.

Conclusions

The objective of this study was to determine a potential prognostic value of the neutrophil-to-lymphocyte, platelet-to-lymphocyte, and lymphocyte-to-monocyte ratios in patients diagnosed with extensive-stage and limited-stage small cell lung cancer. To the best of our knowledge, this is the first study carried out on a European population which analyzed all three of the mentioned ratios. According to the study, NLR could be a good prognostic marker in patients with extensive-stage SCLC. Further prospective studies are definitely needed for this type of cancer.

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