

Neutrophil-Lymphocyte ratio is prognostic in early-stage resected small-cell lung cancer

Zoltan Lohinai ^{Corresp., 1}, Laura Bonanno ², Aleksei Aksarin ³, Alberto Pavan ², Zsolt Megyesfalvi ⁴, Balazs Santa ¹, Virag Hollosi ¹, Balazs Hegedus ⁵, Judit Moldvay ¹, PierFranco Conte ⁶, Michail Ter-Ovanesov ⁷, Evgeniy Bilan ³, Balazs Dome ⁸, Glen Weiss ⁹

¹ National Koranyi Institute of Pulmonology, Budapest, Hungary

² Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy

³ Department of Oncology, Surgut District Clinical Hospital, Surgut, Russia

⁴ Department of Thoracic Surgery, Semmelweis University and National Institute of Oncology, Budapest, Hungary

⁵ Department of Thoracic Surgery, University Hospital Essen, Essen, Germany

⁶ Department of Surgical, Oncological and Gastroenterological Sciences, Università degli Studi di Padova, Padova, Italy

⁷ Department of Oncology and Hematology, Peoples' Friendship University of Russia, Moscow, Russia

⁸ Division of Thoracic Surgery, Department of Surgery, Medical University Vienna, Vienna, Austria

⁹ Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, United States of America

Corresponding Author: Zoltan Lohinai

Email address: zoltan.lohinai@koranyi.hu

Background: For selected early-stage small cell lung cancer (SCLC), curative intent surgery is often performed. Previous studies, predominantly from East Asia, reported that high neutrophil to lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) correlate with poor prognosis in several types of tumors including SCLC. The aim of our study was to investigate the prognostic value of NLR and PLR in Caucasian patients with resected SCLC, as potential tool to select patients for multimodal treatment including surgery. **Methods:** Consecutive patients with histologically confirmed and surgically resected SCLC evaluated between 2000 and 2013 at three centers were retrospectively analyzed. NLR and PLR at diagnosis was used to categorize patients into "high" (H) and "low" (L) groups based on ROC analysis. Univariate and multivariate analyses were used to evaluate the impact of clinical and pathological characteristics on outcome. **Results:** There were a total of 189 patients with a median age of 58 years, and the majority had stage I or II disease. We found a significant correlation between NLR and tumor stage ($p=0.007$) and age ($p=0.038$). LNLR was associated with significantly longer OS, while PLR had no prognostic impact. There were significant associations between NLR and PLR but not with gender, vascular involvement, tumor necrosis, peritumoral inflammation, or tumor grade. **Conclusion:** Pre-operative LNLR may be a favorable prognostic factor in stage I-II SCLCs. PLR is not prognostic in this population. LNLR is easy to assess and can be integrated into routine clinical practice. Further prospective studies are needed to confirm these observations.

Neutrophil-Lymphocyte ratio is prognostic in early-stage resected small-cell lung cancer

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¹National Koranyi Institute of Pulmonology, Budapest/Hungary

²Medical Oncology 2, Istituto Oncologico Veneto IOV IRCCS, Padova/Italy

³Surgut District Clinical Hospital, Surgut/Russia

⁴Department of Thoracic Surgery, Semmelweis University and National Institute of Oncology, Budapest/Hungary

⁵Department of Thoracic Surgery, Ruhrlandklinik, University Hospital Essen

⁶Department of Surgical, Oncological and Gastroenterological Sciences, Università degli Studi di Padova, Padova/Italy

⁷Peoples' Friendship University of Russia, Moscow/Russia

⁸Translational Thoracic Oncology Laboratory, Division of Thoracic Surgery, Department of Surgery, Comprehensive Cancer Center, Medical University Vienna, Vienna/Austria

⁹Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA, United States of America

Corresponding author:

Zoltan Lohinai, MD, PhD, Department of Tumor Biology, National Koranyi Institute of Pulmonology, H-1121, Pihenó ut 1-3., Budapest, Hungary; Phone: +36 1 3913310; Fax: +36 1 3913357, Email: zoltan.lohinai@koranyi.hu

Abstract

Background For selected early-stage small cell lung cancer (SCLC), curative intent surgery is often performed. Previous studies, predominantly from East Asia, reported that high neutrophil to lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) correlate with poor prognosis in several types of tumors including SCLC. The aim of our study was to investigate the prognostic value of NLR and PLR in Caucasian patients with resected SCLC, as potential tool to select patients for multimodal treatment including surgery.

Methods Consecutive patients with histologically confirmed and surgically resected SCLC evaluated between 2000 and 2013 at three centers were retrospectively analyzed. NLR and PLR at diagnosis was used to categorize patients into "high" (H) and "low" (L) groups based on ROC analysis. Univariate and multivariate analyses were used to evaluate the impact of clinical and pathological characteristics on outcome.

Results There were a total of 189 patients with a median age of 58 years, and the majority had stage I or II disease. We found a significant correlation between NLR and tumor stage ($p=0.007$) and age ($p=0.038$). LNLR was associated with significantly longer OS, while PLR had no prognostic impact. There were significant associations between NLR and PLR but not with gender, vascular involvement, tumor necrosis, peritumoral inflammation, or tumor grade.

Conclusion Pre-operative LNLR may be a favorable prognostic factor in stage I-II SCLCs. PLR is not prognostic in this population. LNLR is easy to assess and can be integrated into routine clinical practice. Further prospective studies are needed to confirm these observations.

Introduction

Small cell lung cancer (SCLC) is a highly aggressive malignancy with a poor prognosis.¹ In most cases it is diagnosed in advanced-stages, therefore surgical resection is rarely possible and serves little clinical benefit.² In recent years, for selected early-stage cases, curative intent surgery has been offered. There remains no validated predictive or prognostic biomarker for these patients. In a large cohort of 2,476 SCLC patients underwent surgical resection and chemotherapy had improved five-year overall survival (OS) compared to those who received nonsurgical therapy alone (according to stages: IA 54% vs. 18%, IB 36% vs. 19%, IIA 24% vs. 17%, IIIA 18% vs. 12%, in stage IIB there was no significant difference, though only 43 out of 1689 patients underwent surgery).³ A recent study suggests an increased role of surgery in multimodality therapy for early-stage SCLC.⁴ These results might indicate that surgery could be a treatment option even in locally-advanced disease after appropriate patient selection. Since the late 1990s evidence is available concerning the role of tumor infiltrating immune system cells in tumor progression.⁵ Inflammation plays a key role and enhances tumor initiation, promotion, stimulates angiogenesis, contributes to metastatic progression through reactive oxygen and nitrogen species, cytokines (e.g. IL1, Tumor Necrosis Factor (TNF), Transforming Growth Factor (TGF), Interleukin (IL) 6, IL11, IL23), transcription factors (Activator protein 1 (AP-1), nuclear factor- κ B (NF- κ B), and Signal transducer and activator of transcription 3 (STAT3)), growth factors Epidermal Growth Factor (EGF), Vascular Endothelial Growth Factor (VEGF), prostaglandins, and matrix degrading enzymes.⁶ Routine blood test based neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are potential biomarkers of the systemic inflammatory response and can be prognostic biomarkers for survival across a variety of malignancies.^{7, 8} Previous studies, predominantly from East-Asia, showed that high neutrophil to lymphocyte ratio (HNLR) and high platelet to lymphocyte ratio (HPLR) correlate with poor prognosis in several tumor types.⁹ Others showed a significant association between PLR and OS, NLR, and disease-free survival (DFS) in non-metastatic non-small-cell lung cancer (NSCLC) patients treated with chemoradiotherapy.¹⁰ A meta-analysis showed that HPLR is associated with poor prognosis in patients with NSCLC.¹¹ Another meta-analysis reported that pretreatment HPLR was associated with poor OS, progression-free survival (PFS), and DFS in NSCLC patients.¹² The potential role of NLR and PLR have also been retrospectively investigated in Asian patients with SCLC and NLR was identified as an independent negative prognostic marker in extensive stage (ES) disease, whereas its role in limited stage (LS) is more controversial. Two different groups reported HNLR as negative prognostic factor in SCLC series, including both ES and LS.^{13 14} but others found that pretreatment NLR in ES-SCLC was an independent significant prognostic factor for OS, while in LS-SCLC PLR was a significant prognostic factor.^{15, 16} Another study established and validated a novel nomogram for the prediction of OS in predominantly advanced-stage SCLC patients found that increased levels of NLR and PLR were associated with worse clinical outcome.¹⁷ All in all, NLR is established in ES but controversial in LS and published data primarily focuses on Asian patients. The individualization of prognostic factors is essential in LS disease, since the optimal multimodal approach has not been clearly defined yet and we have no elements to identify patients who may benefit from more intensive treatment

including surgery. The aim of this retrospective study was to investigate the prognostic value of NLR and PLR in Caucasian patients with resected SCLC.

Materials and Methods

Ethics Statement

The study was conducted in accordance with the guidelines of the Helsinki Declaration of the World Medical Association and with the approval of the national level ethics committee (Hungarian Scientific and Research Ethics Committee of the Medical Research Council, ETTTUKEB-7214-1/2016/EKU), which waived the need for individual informed consent for this retrospective study. The Ethics Committee of Istituto Oncologico Veneto in Padova (Italy) evaluated and approved the study and patients provided informed consent to be signed for the collection, analysis and publication of data, when the investigators have the possibility to collect it from patients, according to Italian data protection authority dispositions. The ethics Committee of the Department of Health in Ugra (Russia) has evaluated and approved the study, which waived the need for individual informed consent for this retrospective study. Clinical information was collected and patients were de-identified. Subsequently, patients cannot be identified either directly or indirectly.

Study Population

Consecutive SCLC patients underwent surgical resection between 1999 and 2013 at the National Koranyi Institute of Pulmonology (cohort #1) were included in this study. Consecutive SCLC patients underwent surgical resection at Università degli Studi di Padova between 2000 and 2013 (cohort #2), and between 1999 and 2013 at the Surgut District Clinical Hospital (cohort #3). Clinicopathological data collected included gender, age, smoking history, chemo- and radiotherapy treatments, type of operation (segmentectomy, lobectomy, and pneumonectomy), and OS or DFS. TNM stage according to the Union for International Cancer Control (7th edition)¹⁸, and age at the time of diagnosis were recorded. OS was estimated from the time of diagnosis, until death, or last available follow-up. The study and all treatments were conducted in accordance with the current National Comprehensive Cancer Network guidelines.

Date of last follow-up included in this analysis was April 2017. Most studies examining NLR and PLR did not explicitly state the timeframe of blood sample analysis prior to surgery, thus we set the time point to be within 30 days prior to surgery, so that the data could be broadly applicable to clinical practice. The NLR and PLR was calculated according to the absolute neutrophil and platelet counts and absolute lymphocyte counts on routine blood tests obtained within 30 days prior to surgery. For patients who received neoadjuvant chemotherapy, blood tests prior to initiation of neoadjuvant chemotherapy were analyzed.

Based on the relatively low case numbers in each individual patients cohort and the lack of significant differences in OS and DFS according to cohorts ($p=0.360$ and $p=0.744$, respectively), we pooled cohorts #1-3 together. There were no significant differences in gender or stage across the three individual cohorts, however there were significant differences in age, CHT, and RT administration Supplemental Data 1 (Supplementary Table 1), and Supplemental Data 2 (Supplementary Table 2).

Treatment

Patients who underwent complete tumor resection including segmentectomy, lobectomy, and pneumonectomy with mediastinal lymph node dissection were included in this retrospective analysis. Selected patients were treated with postoperative systemic CHT with a platinum-etoposide doublet regimen or with a combination of cyclophosphamide, epirubicin, and vincristine (CEV). Selected patients with positive mediastinal lymph node status received preoperative CHT with the aforementioned regimens.

Statistical Methods

Time-dependent receiver operating curve (ROC) analysis was used to identify the optimal cut-off values for NLR and PLR according to OS and DFS. Next, patients were divided into "high" and "low" groups according to their preoperative NLR and PLR. ROC was applied to determine the optimal cutoff values, which was selected by using the largest possible sensitivity and specificity combination. Kaplan-Meier curves and two-sided log-rank tests were used for univariate survival analysis. Two sided p-values less than 0.05 were considered statistically significant. All variables with p-values less than 0.05 were included in the multivariate analysis. The Cox proportional hazards model was used for univariate and multivariate survival analyses to calculate the hazard ratios (HR) and corresponding 95% confidence intervals (CI). For multivariate survival analyses, the Cox regression model was adjusted for significant variables in the univariate analysis. Metric data are shown as median or mean and corresponding range or, in case of OS, as median and corresponding 95% CI. Clinical characteristics of patients with LPLR (vs HPLR) or LNLR (vs HNLR) were analyzed by the Chi-square test in each individual cohorts and then inter-cohort heterogeneity was assessed with the same test. Age (<65 years vs. ≥ 65 years) was considered as a categorical variable. To address the problem of multiple comparisons between clinicopathological parameters of the individual cohorts, Bonferroni's correction was applied. Thus, with six comparisons comprising three cohorts according to LNLR (vs HNLR) or LPLR (vs HPLR), p-values less than 0.008333 were considered to indicate statistical significance. All p-values were two-sided. Next, we evaluated the associations of preoperative NLR or PLR with clinicopathological characteristics (age, gender, stage, vascular involvement, tumor necrosis, peritumoral inflammation, and tumor grade) using Spearman's rank correlation which assess linear correlation coefficient as it measures the strength of linear relationship between the variables. The value of linear correlation coefficient (r) varies from -1 to 1 both values inclusive. No Linear Correlation ($r = 0$), weak positive linear correlation ($0.2 < r \leq 0.5$), moderate positive

linear correlation ($0.5 < r \leq 0.8$), strong positive linear correlation $0.8 < r < 1$. All statistical analyses were performed using the PASW Statistics 22.0 package (SPSS Inc., Chicago, IL, USA).

Results

Clinicopathological characteristics

A total of 189 patients were identified for this study: 91, 54, and 44 according to cohorts # 1, #2, and #3; respectively. One hundred fifty-five cases had PLR and NLR data available and were included for further analyses. The median age at diagnosis was 58 years. According to AJCC tumor staging, there were 60, 39, and 40 patients with Stage I, II, and III; respectively (16 patients had inaccurate staging data). During the follow-up period, 100 patients received adjuvant chemotherapy. The median preoperative neutrophil, lymphocyte and thrombocyte counts were 4.621, 2.115, and 241.00; respectively, while NLR and PLR median values were 2.214 and 111.489. Major clinicopathological characteristics of resected SCLC patients in pooled cohorts #1-3 (n=155) are shown according to PLR and NLR (Table 1). Clinicopathological characteristics of resected SCLC patients in cohorts #1, #2, and #3 (n=189) are shown according to NLR (Supplemental Data 1 [Supplemental Table 1]) and PLR (Supplemental Data 2 [Supplemental Table 2]). The 44 cases without NLR/PLR vs. 155 with NLR/PLR have no differences for clinicopathological characteristics. We found significant differences only in pathological stage according to PLR and NLR in the full cohort. Higher percentage of stage I patients showed pre-treatment LNLR. The identified cut-off NLR and PLR values for OS were 111.253 (sensitivity: 0.566, specificity: 0.589) and 2.258 (sensitivity: 0.545, specificity: 0.661), respectively. For DFS, NLR and PLR value cut-offs of 112.174 (sensitivity: 0.531, specificity: 0.614) and 2.254 (sensitivity: 0.551, specificity: 0.649) were used, respectively.

Prognostic factors for OS and DFS

Univariate survival analysis identified significantly longer OS in patients with lobectomy and segmentectomy (vs. pneumonectomy, median OS, 56.2 vs 31.7 months, $p=0.0015$), pN 0-1 (vs pN 2, median OS, 64.9 vs 30.3 months, $p=0.001$), and LNLR (vs HLNR, median OS, 74.8 vs 44.5 months, $p=0.033$, Fig 1A). There was no significant OS difference with LPLR (vs. HPLR, median OS, 73.6 vs 40.4 months, $p = 0.084$, Fig 1C). Furthermore, univariate survival analysis identified significantly longer DFS in patients with lobectomy and segmentectomy (vs. pneumonectomy, median OS, 55.2 vs 18.8 months, $p=0.033$), pN 0-1 (vs pN 2, median OS, 55.7 vs 23.0 months, $p=0.002$). There were no significant differences in DFS in patients with LNLR (vs. HNLR median OS, 68.8 vs 34.9 months, $p=0.051$, Fig 1B) or LPLR (vs. HPLR, median OS, 68.8 vs 32.8 months, $p = 0.086$, Fig 1D). The Cox multivariate analysis found pN 0-1 (vs. pN 2, HR, 2.07; 95% CI, 1.237-3.448; $p=0.006$), but not lobectomy and segmentectomy (vs. pneumonectomy, HR, 1.61; 95% CI, 0.977-2.666; $p=0.062$), or LNLR (vs HLNR, HR, 1.36;

95% CI, 0.879-2.103; $p=0.167$) as a significant independent prognostic factor for OS. Next, the Cox multivariate analysis identified only pN 0-1 (vs. pN 2, HR, 2.041; 95% CI, 1.241-3.357; $p=0.005$), but not lobectomy and segmentectomy (vs. pneumonectomy, HR, 1.48; 95% CI, 0.904-2.445; $p=0.119$), or LNLR (vs. HLNR, HR, 1.27; 95% CI, 0.833-1.939; $p=0.226$) as a significant independent prognostic factor for DFS. Since the prognosis is significantly different for pN2 patients, we performed multivariate analysis only including stage I and II patients. The univariate and Cox multivariate analysis (Table 2) found LNLR (vs. HNLR, HR, 1.582; 95% CI, 1.010-2.478; $p=0.045$), but not lobectomy and segmentectomy (vs. pneumonectomy, HR, 1.697; 95% CI, 0.974-2.958; $p=0.062$) as a significant prognostic factor for OS. We also performed the Spearman test (Table 3) and found a weak positive correlation between NLR and tumor stage ($r=0.226$, $p=0.007$) and a weak positive correlation between NLR and age ($r=0.167$, $p=0.038$) and a weak positive correlation of NLR and PLR ($r=0.035$, $p<0.0001$). Thus higher NLR indicates a higher grade in tumor stage. Also, higher PLR correlates with a higher NLR value. Of note, based on the limited case numbers in each individual cohort, we were not able to use ROC curves to identify individual cut-off values for combined analysis

Discussion

Preoperative complete blood count (CBC) is often used as a broad screening test before lung cancer resection. CBC includes neutrophils, lymphocytes, and platelets, therefore NLR and PLR can easily be assessed in the routine clinical practice. An increasing body of literature reports that tumor progression appears to be linked to the inflammatory response. Diverse immune cells play critical roles in carcinogenesis.^{19 20 21 22 23} These studies reveal signaling molecules released by inflammatory cells that possess tumor-promoting features. These include the tumor growth factor EGF, the angiogenic growth factor VEGF, other proangiogenic factors such as Fibroblast Growth Factor 2 (FGF2), chemokines, and cytokines that amplify the inflammatory state. Additionally, they may produce proangiogenic and/or proinvasive matrix-degrading enzymes, including Matrix Metallo Protease-9 (MMP-9) and other matrix metalloproteinases, cysteine cathepsin proteases, and heparanase.^{24 23} Consistent with their expression of these diverse effectors, tumor-infiltrating inflammatory cells have been shown to induce and help sustain tumor angiogenesis, stimulate cancer cell proliferation, facilitate, via their presence at the margins of tumors, tissue invasion, and support the metastatic dissemination and seeding of cancer cells.^{19, 21, 23, 24, 25, 26, 27, 28} Previous studies investigated the role of PLR and NLR in other cancers including NSCLC. NLR and PLR (colorectal, gastroesophageal, pancreatic, ovarian, hepatocellular, lung, and renal) appears to be prognostic in patients with advanced stage and can predict treatment response, which might be helpful in selecting patients for further therapy.⁷ PLR was also reported to have prognostic value for poor prognosis in many cancers including ovarian cancer, gastric cancer, colorectal cancer, hepatocellular carcinoma and NSCLC.⁹ One group reported significant associations between PLR and OS and NLR and DFS; respectively, in NSCLC patients treated with chemoradiotherapy. There was no significant relationship between chemoradiotherapy and NLR or PLR, which shows that these markers of survival are

independent from chemotherapy.¹⁰ Others have found NLR and PLR significantly elevated in patients with different lung cancer subtypes compared to healthy controls, however, they did not examine the association between these markers and prognosis.²⁹ A meta-analysis showed that HPLR is associated with poor prognosis in patients with NSCLC.^{11, 12} On the contrary, in line with others studies in SCLC, PLR alone did not show prognostic significance in our study.¹³ This latter fact can be explained by the completely different biological behavior, molecular and pathological structure of SCLC compared to NSCLC. Consistent with our study, another meta-analysis of 11 lung cancer studies reported that PLR had prognostic value for OS in patients with NSCLC treated with chemo-radiotherapy, but not in SCLC patients and not for PFS. In that meta-analysis, PLR had prognostic value in later stage⁹ which may explain why our study of early stage SCLC did not show this association. Currently, there are no available reliable cut-off values, and previous studies reported combined LD and ED SCLC patient cohorts. Surgically resected SCLC patients also have a different prognosis.^{17, 30} Therefore, we used ROC analysis to determine the optimal cut-off values in resected SCLC patients. In our study multivariate (and univariate) analysis identified LNLR (vs. HNLR) but not lobectomy and segmentectomy (vs. pneumonectomy) as a significant independent prognostic factor for OS in stage I and II. This may be particularly relevant considering that the main known prognostic marker for LS-SCLC is the involvement of mediastinal lymph-nodes, whereas no clear prognostic marker is available to individuate different prognostic groups among stage I and II disease. Others investigated the role of PLR and NLR in a large study of 320 patients of East Asian origin with LD and ED SCLC patients.³¹ They used the Cox proportional hazard model that showed that $NLR \geq 2.65$ (HR = 1.35; 95% CI 1.02–1.79; p=0.039), $LDH \geq 210$ (HR = 1.46; 95% CI 1.10–1.96; p=0.002), patients with surgery (HR = 0.55; 95% CI 0.33–0.93; p=0.025), thoracic RT (HR = 0.66; 95% CI 0.50–0.88; p=0.005) and PCI (HR = 0.71; 95% CI 0.53–0.96; p=0.023) were independent prognostic factors for OS in SCLC patients. In our study, we had no data on LDH and we did not include to our analysis PCI or thoracic RT as an initial prognostic factor since patients received these modalities only at disease recurrence. In our study the cut-off value with ROC analysis was similar (NLR, 2.25). The difference can be explained by the early stage, resected patient cohort in our study, compared to a predominantly ED SCLC cohorts in other studies. However, the underlying pathological mechanism is similar. Compared to pure SCLC, in histologically combined-SCLC with NSCLC, Shao et al. and Wang et al. showed that HNLR was associated with poor prognosis and recurrence.^{32 33} In line with our study, Hong et al. found that HNLR appeared to be associated with worse prognosis, however, this study could only show in univariate, but not in multivariate analysis.³⁴ Kang et al. also demonstrated that HNLR was an independent prognostic factor for OS and PFS.¹⁴ Nevertheless, in our study, higher PLR weakly correlated with a higher NLR value. Also, higher NLR indicated a higher grade in tumor stage independent of LN status. However, in contrast to our SCLC study, in lung cancer, NLR was associated with pathological factors such as tumor invasiveness, lymph node metastasis, poor differentiation, and vascular invasion.³⁵

The key limitations to our study are the retrospective nature and SCLC patients were pooled from three different institutions.

Conclusions

To our knowledge, this is the first study in Caucasian patients with resected SCLC which shows that LNLR (<111) with blood collected up to 30 days before surgical resection, may be a favorable prognostic factor for longer OS. The determination of LNLR should be further evaluated in other series of surgical resected patients and should be evaluated when planning trials addressed to define the optimal multimodal treatment in stage I-II SCLC. We also conclude that accurate mediastinal LN staging and NLR and PLR may help in selecting patients for surgery in the future. Further prospective studies are needed to confirm these observations.

Conflict of interest statement

GJW reports personal fees from Paradigm, Merck, Novartis, Amgen, Pfizer, IDEA Pharma, GLG Counsel, Guidepoint Global, Ignyta, Circulogene-all outside this work; has received travel reimbursement from NantWorks, Cambridge HealthTech Institute, and Tesaro; ownership interest in Circulogene-outside the submitted work; and has a patent for methods and kits to predict prognostic and therapeutic outcome in small cell lung cancer issued, outside the submitted work. Other authors declare no potential conflicts of interest.

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Table 1(on next page)

Major clinicopathological characteristics of resected SCLC patients according to neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in the pooled cohorts #1-3 (n=155).

		Total					Total				
		NLR				P	PLR				P
		LNLR		HNLR			LPLR		HPLR		
		Count	Column N %	Count	Column N %		Count	Column N %	Count	Column N %	
Gender	Male	59	71.95%	55	75.34%	0.63	56	73.68%	58	73.42%	0.97
	Female	23	28.05%	18	24.66%		20	26.32%	21	26.58%	
	Total	82	100.00%	73	100.00%		76	100.00%	79	100.00%	
Age	<65	63	44.44%	45	62.50%	0.04*	58	76.32%	50	64.94%	0.06
	≥65	18	22.22%	27	37.50%		18	23.68%	27	35.06%	
	Unknown	1		1			0		2		
Smoking	Non-smoker	11	15.49%	3	4.48%	0.08	10	14.49%	4	6.25%	0.28
	Smoker	54	76.06%	56	90.32%		54	78.26%	56	87.50%	
	Ex-smoker	6	8.45%	3	4.84%		5	7.25%	4	6.25%	
Preoperative CHT	Unknown	11		11		0.87	7		15		0.68
	No	53	71.62%	51	72.86%		48	70.59%	56	73.68%	
	Yes	21	32.43%	19	27.14%		20	29.41%	20	26.32%	
Adjuvant CHT	Unknown	8		3		0.64	8		3		0.054
	No	17	25.37%	14	21.88%		10	16.13%	21	30.43%	
	Yes	50	74.63%	50	78.13%		52	83.87%	48	69.57%	
Thoracic RT	Unknown	15		9		0.26	14		69		0.99
	No	39	68.42%	32	58.18%		33	63.46%	38	63.33%	
	Yes	18	31.58%	23	41.82%		19	36.54%	22	36.67%	
PCI	Unknown	25		18		0.9	24		19		0.53
	No	45	77.59%	44	78.57%		40	75.47%	49	80.33%	
	Yes	13	22.41%	12	21.43%		13	24.53%	12	19.67%	
Stage	Unknown	24		17		0.02*	23		18		0.04*
	I	38	54.29%	22	31.88%		31	47.69%	29	39.19%	
	II	17	24.29%	12	31.88%		22	33.85%	17	22.97%	
pT	III	15	21.43%	25	36.23%	0.73	12	18.46%	28	37.84%	0.42
	Unknown	12		14			11		5		
	1	21	29.58%	17	24.64%		18	27.69%	20	26.67%	
	2	38	53.52%	36	52.17%		37	56.92%	37	49.33%	
	3	10	14.08%	12	17.39%		9	13.85%	13	17.33%	
	4	2	2.82%	4	5.80%		1	1.54%	5	6.67%	
	Unknown	11		4			11		4		

pN	0	42	56.76%	34	46.58%	0.33	40	57.14%	36	46.75%	0.13
	1	22	29.73%	20	27.40%		21	30.00%	21	27.27%	
	2	10	13.51%	19	26.03%		9	12.86%	20	25.97%	
	Unknown	8		0			6		2		
Vascular involvement	0	32	74.42%	26	60.47%	0.17	34	72.34%	24	61.54%	0.29
	1	11	25.58%	17	39.53%		13	27.66%	15	38.46%	
	Unknown	39		30			29		40		
Tumor necrosis	0	18	32.14%	16	25.00%	0.36	15	25.86%	19	30.16%	0.6
	1	38	67.86%	49	76.56%		43	74.14%	44	69.84%	
	Unknown	26		8			18		16		
Peritumoral inflammation	0	20	46.51%	11	25.58%	0.22	20	42.55%	11	42.31%	0.4
	1	12	27.91%	16	37.21%		12	25.53%	3	11.54%	
	2	8	18.60%	13	30.23%		11	23.40%	10	38.46%	
	3	3	6.98%	3	6.98%		4	8.51%	2	7.69%	
	Unknown	39		30			29		53	100.00%	
Operation	Lob+seg	67	81.71%	57	78.08%	0.57	66	86.84%	58	73.42%	0.52
	PNO	15	18.29%	16	21.92%		10	13.16%	21	26.58%	
	Unknown	0		0			0		0		

- 1 HNLR: high neutrophil to lymphocyte ratio, LNLR: low neutrophil to lymphocyte ratio
- 2 HPLR: high platelet to lymphocyte ratio, LPLR: low platelet to lymphocyte ratio
- 3 Data shown in parentheses are column percentages
- 4 P: Chi-square (Fisher's exact) test;
- 5 *Statistically significant
- 6 CHT: chemotherapy
- 7 PCI: prophylactic cranial irradiation
- 8 RT: radiation therapy
- 9 Lob: lobectomy
- 10 Seg: segmentectomy
- 11 PNO: pneumonectomy

Table 2(on next page)

Clinical variables and survival of patients with stage I/II SCLC in the Cox proportional hazards model for overall survival.

	Univariate			Multivariate		
Prognostic factor	HR	95 % CI	p-value	HR	95 % CI	p-value
NLR (LNLR vs HNLR)	1.621	1.036-2.537	0.035	1.582	1.010-2.478	0.045*
Type of operation (lobectomy and segmentectomy vs. pneumonectomy)	1.780	1.061-2.986	0.029	1.697	0.974-2.958	0.062

1 **HR**: hazard ratio; **CI**: confidence interval;

2 **HNLR**: high neutrophil to lymphocyte ratio, **LNLR**: low neutrophil to lymphocyte ratio

3 *Statistically significant

Table 3(on next page)

Correlations of clinicopathological variables (n=189)

Factors		Preop PLR	Preop NLR
Age	r	0.125	0.167*
	p	0.124	0.038*
	N	153	153
Gender	r	0.003	-,038
	p	0.970	0.635
	N	155	155
Smoking	r	0.089	,088
	p	0.306	0.314
	N	133	133
Vascular involvement	r	0.115	0.149
	p	0.293	0.171
	N	86	86
Tumor necrosis	r	-0.048	0.084
	p	0.603	0.363
	N	121	121
Peritumoral inflammation	r	0.074	0.191
	p	0.500	0.078
	N	86	86
pN	r	0.139	0.135
	p	0.092	0.103
	N	147	147
pT	r	0.074	0.084
	p	0.388	0.322
	N	140	140
Stage	r	0.158	0.226**
	p	0.064	0.007*
	N	139	139
Preop NLR	r	0.357**	1.000
	p	<0.001*	-
	N	155	155

1 *Indicates significant correlation with Spearman test (Mean OS cut)

2 NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio

3 r: Correlation Coefficient

4 p: probability value

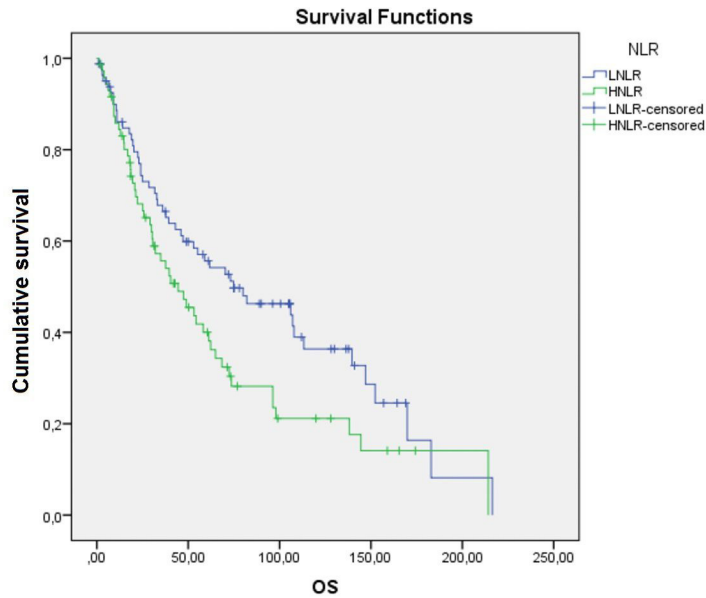
5 N: number of patients

Figure 1(on next page)

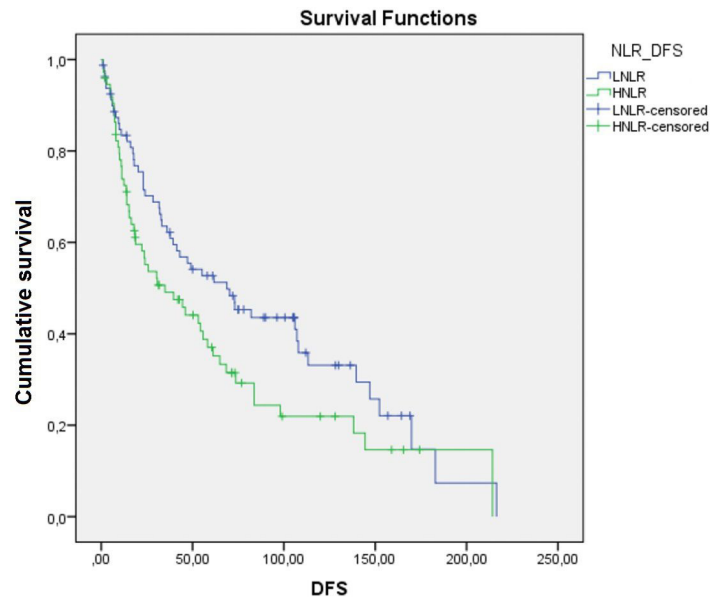
Kaplan–Meier survival curves for overall survival (OS) and disease-free survival (DFS) in resected SCLC patients (n=189).

(A) OS of patients with LNLR (<2.25) was significantly longer (vs HLNR, median OS, 74.8 vs 44.5 months, $p=0.033$, log-rank test). (B) DFS of patients with LNLR (<2.25) (vs. HNLR median OS, 68.8 vs 34.9 months, $p=0.051$, log-rank test [not statistically significant]). (C) OS of patients with LPLR (<111) (vs. HPLR, median OS, 73.6 vs 40.4 months, $p=0.084$, log-rank test [not statistically significant]). (D) DFS of patients with LPLR (<111) (vs. HPLR, median OS, 68.8 vs 32.8 months $p = 0.086$, log-rank test [not statistically significant]).

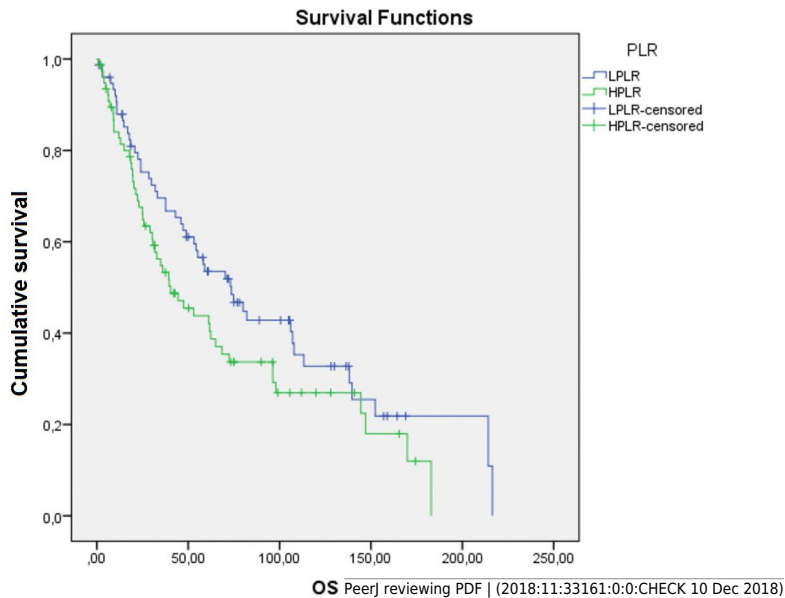
A



B



C



D

