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The prognostic impact of the neutrophil-to-lymphocyte ratio in patients with small-cell lung cancer

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Background: The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are prognostic factors for various types of cancer. In this study, we assessed the association of NLR and PLR with the prognosis of small-cell lung cancer (SCLC) in patients who received the standard treatment.

Methods: We retrospectively reviewed patients who were diagnosed with SCLC and treated with platinum-based chemotherapy between July 2006 and October 2013 in Gyeongsang National University Hospital Regional Cancer Center and Changwon Samsung Hospital.

Results: In total, 187 patients were evaluated. Compared with low NLR (<4), high NLR ($\geqslant 4$) at diagnosis was associated with poor performance status, advanced stage, and lower response rate. Median overall survival (OS) and progression-free survival (PFS) were worse in the high-NLR group (high *vs* low, 11.17 *vs* 9.20 months, $P=0.019$ and 6.90 *vs* 5.49 months, $P=0.005$, respectively). In contrast, PLR at diagnosis was not associated with OS or PFS ($P=0.467$ and $P=0.205$, respectively). In multivariate analysis, stage, lactate dehydrogenase, and NLR at diagnosis were independent prognostic factors for OS and PFS.

Conclusions: NLR is easily measurable and reflects the SCLC prognosis. A future prospective study is warranted to confirm our results.

Small-cell lung cancer (SCLC) accounts for 15–20% of all lung cancers and has an extremely aggressive nature with a poor prognosis (Buccheri and Ferrigno, 2004). Without treatment, the median survival time is 2–4 months (Hayat *et al*, 2007).

Several clinical markers are related to prognosis in patients with SCLC. Stage is the most important predictor of survival in SCLC (Seifter and Ihde, 1988; Sagman *et al*, 1991; Buccheri and Ferrigno, 2004). The initial lactate dehydrogenase (LDH) level can indicate a high tumour burden and poor prognosis (Gronowitz *et al*, 1990; Buccheri and Ferrigno, 2004). Concurrent chemoradiotherapy (CCRT) in limited disease (LD) and prophylactic cranial irradiation (PCI) after complete response have improved the survival time of SCLC patients (Murray *et al*, 1993; Auperin *et al*, 1999). Performance status (PS) has been used traditionally to predict the outcome of patients with SCLC (Bremnes *et al*, 2003; Buccheri and Ferrigno, 2004). Gender, age,

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and body weight loss are also prognostic factors (Spiegelman *et al*, 1989; Paesmans *et al*, 2000; Bremnes *et al*, 2003). In addition to these clinical markers, many investigators have suggested that laboratory markers, such as neuron-specific enolase, carcinoembryonic antigen, cytokeratin fragment 19 (CYFRA 21-1), haemoglobin, albumin, alkaline phosphatase, and white blood cell count could be of prognostic value (Albain *et al*, 1990; Gronowitz *et al*, 1990; Sagman *et al*, 1991; Bremnes *et al*, 2003). However, the optimum prognostic factor for SCLC remains controversial.

The systemic inflammatory response was shown to be associated with a poor prognosis in various solid tumours. Several inflammatory markers, such as C-reactive protein (CRP), Glasgow Prognostic Score, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) have been evaluated in various types of cancer (Crumley *et al*, 2006; Kim *et al*, 2009; Kishi *et al*, 2009; Smith *et al*, 2009; Chua *et al*, 2011; Li *et al*, 2013; Stotz *et al*, 2014). Recently, tumour-associated neutrophils (TANs), which are distinct from naive neutrophils, were shown to be involved in tumour biology. Tumour cells themselves can recruit neutrophils into the tumour using specific chemokines (Bellocq *et al*, 1998; De Larco *et al*, 2004; Keane *et al*, 2004) and T cells (Stoppacciaro *et al*, 1993). TANs exert pro-tumourigenic effects (Fridlender *et al*, 2009), including tumour initiation by genotoxic reactive oxygen species (Gungor *et al*, 2010), anti-apoptosis and angiogenesis by matrix metalloproteinase-9 (Acuff *et al*, 2006; Kuang *et al*, 2011), tumour growth, invasion and metastasis via neutrophil elastase (Sun and Yang, 2004; Houghton *et al*, 2010) and suppression of the adaptive immune system (Fridlender *et al*, 2009). Therefore, NLR might be considered a surrogate marker for TANs, and is readily available and cost-effective. Several reports have suggested the prognostic value of NLR in colorectal cancer, gastric cancer, non-small-cell lung cancer, soft-tissue sarcoma, and pancreatic cancer (Kim *et al*, 2009; Kishi *et al*, 2009; Smith *et al*, 2009; Cedres *et al*, 2012; Lee *et al*, 2013; Stotz *et al*, 2013; Szkandera *et al*, 2013). Because platelet activation is stimulated by proinflammatory cytokines and participates in neutrophil recruitment (Ghasemzadeh and Hosseini, 2013), PLR has also been evaluated as an inflammatory marker; high PLR has been reported to be a risk factor for poor survival in pancreatic and colorectal cancers (Smith *et al*, 2009; Kwon *et al*, 2012). Although high CRP was reportedly related to poor survival in a retrospective study (Hong *et al*, 2012), the prognostic value of inflammatory markers, including NLR and PLR, is not well understood in SCLC.

We hypothesised that inflammation is associated with the SCLC prognosis and that NLR or PLR may be good indicators of the inflammatory process. Therefore, in this retrospective study, we evaluated the association of NLR and PLR with the prognosis in SCLC patients who underwent the standard treatment.

Table 1. Baseline characteristics

	Number of patients (%) $n = 187$
Age, years ($n = 187$)	68 (range 43–84)
Sex ($n = 187$)	
Male	162 (86.6)
Female	25 (13.4)
Smoking at diagnosis ($n = 187$)	
Never smoker	15 (8.0)
Current or ex-smoker	172 (92.0)
ECOG PS at diagnosis ($n = 187$)	
0–1	163 (87.2)
2–3	24 (12.8)
Stage ($n = 187$)	
Limited disease	67 (35.8)
Extensive disease	120 (64.2)
LDH at initial diagnosis ($n = 187$)	
Normal range	72 (38.5)
Abnormally elevated	115 (61.5)
Chemotherapy regimen ($n = 187$)	
Etoposide-based	155 (82.9)
Irinotecan-based	32 (17.1)
Response for initial chemotherapy ($n = 187$)	
Complete response	14 (7.5)
Partial response	139 (74.3)
Stable disease	8 (4.3)
Progressive disease	7 (3.7)
Not evaluable	19 (10.2)
Second-line chemotherapy ($n = 125$)	
Yes	75 (60.0)
No	50 (40.0)
Thoracic radiotherapy ($n = 187$)	
Yes	62 (33.2)
No	125 (66.8)
Prophylactic cranial irradiation ($n = 187$)	
Yes	47 (25.1)
No	140 (74.9)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; PS = performance status.

MATERIALS AND METHODS

Study population. We retrospectively reviewed all patients diagnosed with SCLC between July 2006 and October 2013 in Gyeongsang National University Hospital Regional Cancer Center and Changwon Samsung Hospital. Histologically confirmed cases were included in the study. All patients received combination chemotherapy based on platinum agents such as cisplatin or carboplatin as first-line treatment for at least one cycle. Patients who received non-platinum-based chemotherapy only or who did not receive chemotherapy were excluded from the study. This study was approved by the Institutional Review Board of each participating hospital.

Clinical data collection. Baseline characteristics including demographics, smoking, PS, and medical history were collected using an electronic medical record system. Complete blood cell counts at diagnosis, after the first cycle of chemotherapy (immediately before the second cycle of chemotherapy), and at the time of progression were obtained. At diagnosis, LDH was also evaluated. Mean and peak standardised uptake values (SUVs) of initial positron-emission tomography and computed tomography (PET-CT) were obtained if possible. Both NLR and PLR were recorded at diagnosis, after the first cycle of chemotherapy, and at the time of disease progression.

Statistical analysis. The optimal cutoff values for NLR and PLR were determined using time-dependent receiver operating curve

Table 2. Change of NLR and PLR at diagnosis, after one cycle chemotherapy, and at progression

Value	At diagnosis	After one cycle of chemotherapy	*P*	After 1 cycle of chemotherapy	At progression	*P*
NLR, mean ± s.d.	3.78 ± 3.13	2.63 ± 2.80	<0.001	2.63 ± 2.80	4.50 ± 6.37	<0.001
PLR, mean ± s.d.	183.16 ± 98.21	173.16 ± 119.93	0.01	173.16 ± 119.93	181.69 ± 143.11	0.518

Abbreviations: NLR = neutrophil-lymphocyte ratio; PLR = platelet-lymphocyte ratio; s.d. = standard deviation.

Table 3. Clinical manifestations and laboratory parameters according to NLR at diagnosis

	NLR <4 Number of patients (%) *n* = 128	NLR ⩾4 Number of patients (%) *n* = 59	*P*
Age, years (*n* = 187)	68 (range 43–84)	68 (range 43–82)	0.976
Sex (*n* = 187)			0.383
Male	109 (85.2)	53 (89.8)	
Female	19 (14.8)	6 (10.2)	
Smoking at diagnosis (*n* = 187)			0.671
Never smoker	11 (8.6)	4 (6.8)	
Current or ex-smoker	117 (91.4)	55 (93.2)	
ECOG PS at diagnosis (*n* = 187)			<0.001
0–1	119 (93.0)	44 (74.6)	
2–3	9 (7.0)	15 (25.4)	
Stage (*n* = 187)			0.001
Limited disease	56 (43.8)	11 (18.6)	
Extensive disease	72 (56.3)	48 (81.4)	
Platelet, × 10^9/l, mean ± s.d. (*n* = 187)	267 ± 109	324 ± 400	0.484
PLR at diagnosis, mean ± s.d. (*n* = 187)	150.19 ± 78.13	254.69 ± 99.79	<0.001
LDH at diagnosis (*n* = 187)			0.579
Normal range	51 (39.8)	21 (33.6)	
Abnormally elevated	77 (60.2)	38 (64.4)	
Chemotherapy regimen (*n* = 187)			0.225
Etoposide-based	109 (85.2)	46 (78.0)	
Irinotecan-based	19 (14.8)	13 (22.0)	
Response for initial chemotherapy (*n* = 187)			0.037
Complete response	11 (8.6)	3 (5.1)	
Partial response	98 (76.6)	41 (69.5)	
Stable disease	6 (4.7)	2 (3.4)	
Progressive disease	6 (4.7)	1 (1.7)	
Not evaluable	7 (5.5)	12 (20.3)	
Mean SUV at initial PET-CT, mean ± s.d. (*n* = 164)	7.15 ± 2.43	7.10 ± 3.07	0.341
Peak SUV at initial PET-CT, mean ± s.d. (*n* = 164)	9.71 ± 3.14	10.29 ± 6.38	0.188
Second-line chemotherapy (*n* = 125)			0.379
Yes	55 (62.5)	20 (54.1)	
No	33 (37.5)	17 (45.9)	
Thoracic radiotherapy (*n* = 187)			<0.001
Yes	54 (42.2)	8 (13.6)	
No	74 (57.8)	51 (86.4)	
Prophylactic cranial irradiation (*n* = 187)			0.005
Yes	40 (31.2)	7 (11.9)	
No	88 (68.8)	52 (88.1)	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; NLR = neutrophil-lymphocyte ratio; PET-CT = positron-emission tomography and computed tomography; PLR = platelet-lymphocyte ratio; PS = performance status; s.d. = standard deviation; SUV = standardised uptake value.

(ROC) analysis. Time-dependent ROC analysis was performed using R software, version 3.03 (The R foundation for statistical computing, Vienna, Austria. http://www.r-project.org) and the 'timeROC' package (Adams *et al*, 2009; Blanche *et al*, 2013). The NLR was calculated from the differential counts by dividing the neutrophil number by the lymphocyte number. The NLR values were categorised into two groups: <4 and $\geqslant 4$. The PLR was calculated by dividing the platelet count by the lymphocyte count; a PLR $\geqslant 160$ was considered to be elevated.

Statistical analyses were performed using SPSS 21.0 for Windows software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means with standard deviation (s.d.) and range, and compared between the low- and high-NLR groups using the Mann–Whitney *U*-test or Wilcoxon signed-rank test. The categorical variables were presented as the numbers of patients and percentages and compared using the χ^2- or Fisher's exact test.

The overall survival (OS) was calculated from the time of diagnosis to the time of death. The progression-free survival (PFS) was defined as the period from the time of therapy initiation to the time of disease progression or death. Survival analyses were performed using the Kaplan–Meier method. Significant differences between groups were identified using the log-rank test. Multivariate analysis of survival was performed using the Cox proportional hazards model, and the associated 95% confidence interval was calculated. All tests were two-sided, and $P<0.05$ was considered to indicate statistical significance.

RESULTS

Patient characteristics. In total, 187 patients were enrolled in this study between July 2006 and October 2013. The median follow-up time was 40.28 months (range, 2.60–89.26 months). The baseline characteristics of the patients are shown in Table 1. The median age was 68 years (range, 43–84 years) and 162 patients (86.6%) were male and 25 (13.4%) were female. The majority of patients were current or ex-smokers ($n=172$, 92%). performance status was generally good, 163 patients (87.2%) were Eastern Cooperative Oncology Group (ECOG) PS 0 or 1. Only 67 patients (35.8%) were LD and 120 (64.2%) were ED at the time of diagnosis.

The most often used chemotherapeutic regimen was etoposide-based combination chemotherapy ($n=155$, 82.9%). Irinotecan ($n=32$, 17.1%) was also used as a first-line combination agent in place of etoposide. Clinical response was evaluated after two or three cycles of chemotherapy. Among the 187 patients, 153 (81.8%) obtained at least partial response; the disease control rate was 86.1%. Of the 125 patients with disease progression, 75 (60.0%) received second-line chemotherapy. In LD, 62 of 67 patients (92.5%) were treated with thoracic radiotherapy (RT). Forty-seven of 187 patients (25.1%) received PCI after the first-line chemotherapy.

NLR and PLR according to disease and treatment status. Mean NLR and PLR values were compared according to disease and

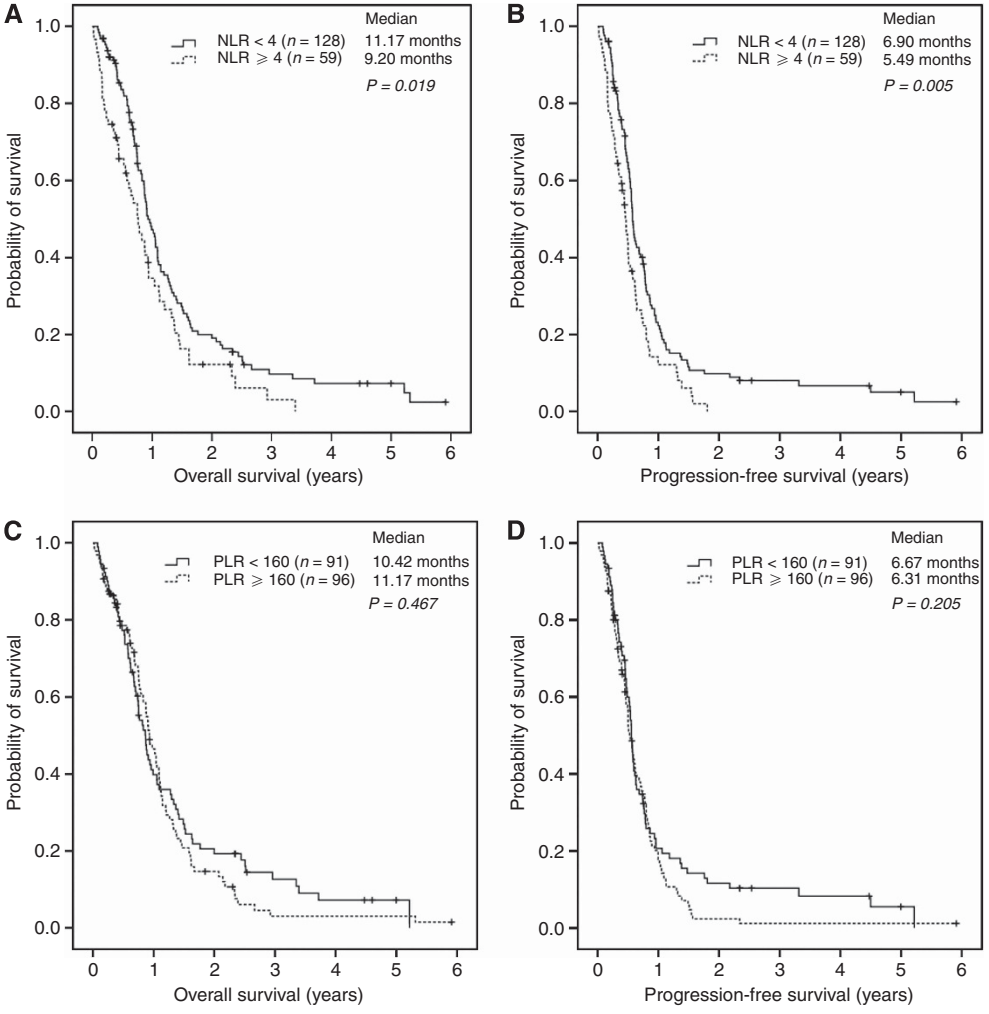

Figure 1. Kaplan–Meier curves for survival according to NLR and PLR at diagnosis. (**A**) OS stratified by NLR. (**B**) PFS stratified by NLR. (**C**) OS stratified by PLR. (**D**) PFS stratified by PLR. Abbreviations: NLR = neutrophil-to-lymphocyte ratio; OS = overall survival; PFS = progression-free survival; PLR = platelet-to-lymphocyte ratio.

treatment status (Table 2). Mean ± s.d. NLR was 3.78 ± 3.13 at diagnosis, and decreased significantly to 2.63 ± 2.80 after one cycle of chemotherapy ($P<0.001$). Compared with after one cycle of chemotherapy, mean ± s.d. NLR increased significantly to 4.50 ± 6.37 at disease progression ($P<0.001$). Mean ± s.d. PLR after one cycle of chemotherapy also decreased significantly from 183.16 ± 98.21 at diagnosis to 173.16 ± 119.93 ($P=0.01$). However, there was no significant difference in mean ± s.d. PLR at disease progression (*vs* after one cycle of chemotherapy, $P=0.518$).

Factors associated with NLR. Clinical and laboratory factors according to NLR group are shown in Table 3. Age, gender, smoking status, first-line chemotherapy regimen, mean or peak SUV at initial PET-CT, and LDH were similar between the groups. However, PS was significantly worse (ECOG PS 2–3 in low *vs* high, 7.0% *vs* 25.4%, respectively, $P<0.001$) and clinical stage was relatively more advanced (ED in low *vs* high, 56.3% *vs* 81.4%, respectively, $P=0.001$) in the high-NLR group compared with the low-NLR group. Additionally, more patients received thoracic RT (low *vs* high, 42.2% *vs* 13.6%, respectively, $P<0.001$) and PCI (low *vs* high, 31.2% *vs* 11.9%, respectively, $P=0.004$) in the low-NLR group. Although platelet count did not show a significant difference ($P=0.484$), the mean PLR at diagnosis was higher in the high-NLR group (low *vs* high, 150.19 *vs* 254.69, respectively, $P<0.001$).

Additionally, the rate of objective response (complete and partial response) to first-line chemotherapy was significantly lower in the high-NLR group than in the low-NLR group (low *vs* high, 85.2% *vs* 74.6%, respectively, $P=0.037$).

Association of NLR and PLR with survival. In total, median OS was 10.84 months and median PFS was 6.67 months. NLR and PLR levels at diagnosis had different impacts on survival (Figure 1). High NLR at diagnosis was associated with worse OS (NLR < 4 *vs* NLR ⩾ 4, median OS 11.17 *vs* 9.20 months, respectively, $P=0.019$) and PFS (NLR < 4 *vs* NLR ⩾ 4, median PFS 6.90 *vs* 5.49 months, respectively, $P=0.005$). In contrast, PLR at diagnosis was not associated with OS (PLR < 160 *vs* PLR ⩾ 160, median OS 10.42 *vs* 11.17 months, respectively, $P=0.467$) and PFS (PLR < 160 *vs* PLR ⩾ 160, median PFS 6.67 *vs* 6.31 months, respectively, $P=0.205$).

Patients with a high NLR at both diagnosis and after one cycle of chemotherapy showed worse OS and PFS than patients with low or high NLR at diagnosis and low NLR after one cycle of chemotherapy (Figure 2A, $P<0.001$ and $P=0.007$, respectively). In addition, patients with a high NLR at disease progression and a

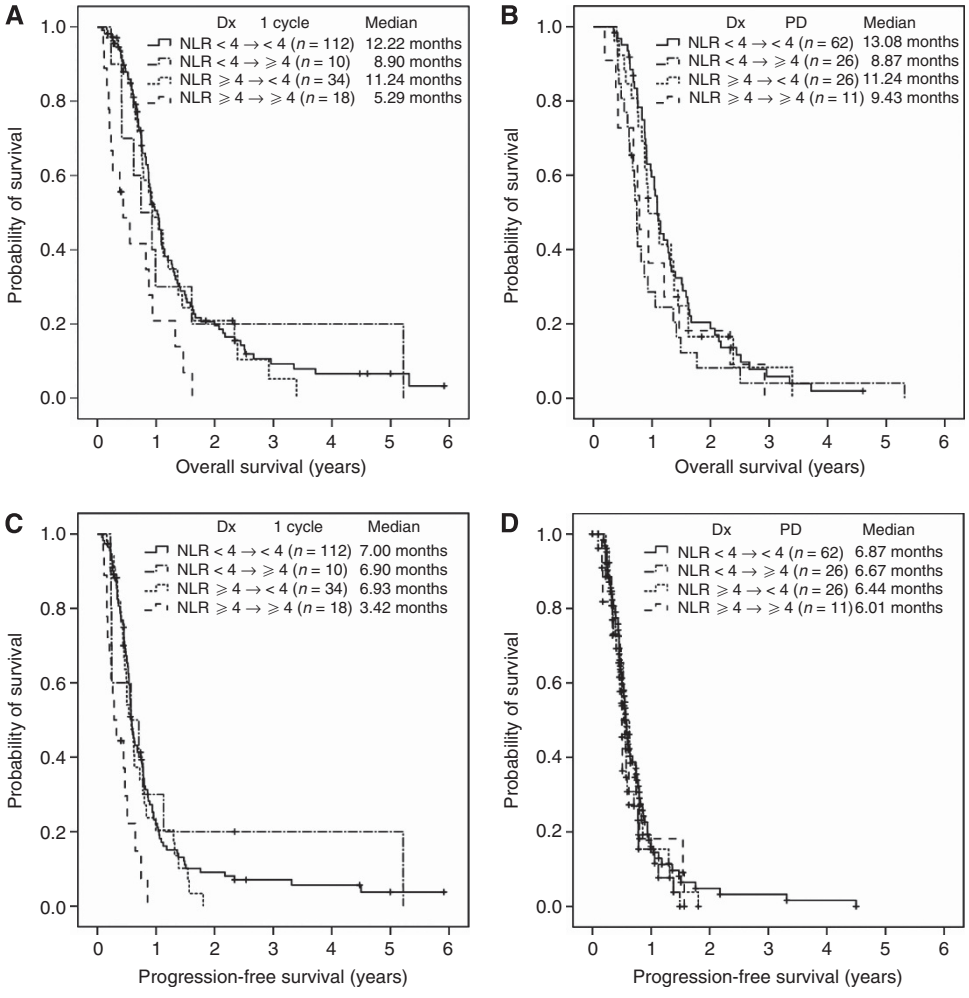

Figure 2. Kaplan–Meier curves for survival according to NLR and treatment course. (**A**) OS and (**C**) PFS stratified by NLR at diagnosis and after one cycle of chemotherapy. Patients with high NLR both at diagnosis and after one cycle of chemotherapy showed worse OS and PFS than patients with low or high NLR at diagnosis and low NLR after one cycle of chemotherapy ($P<0.001$ and $P=0.007$, respectively). (**B**) OS and (**D**) PFS stratified by NLR at diagnosis and at disease progression. Among patients with low NLR at diagnosis, patients with high NLR at disease progression showed worse OS than patients with low NLR at disease progression ($P=0.033$). Abbreviations: Dx = at diagnosis; NLR = neutrophil-to-lymphocyte ratio; OS = overall survival; PD = at disease progression; PFS = progression-free survival; 1 cycle = after 1 cycle of chemotherapy.

low NLR at diagnosis had a worse OS than patients with low NLR both at diagnosis and disease progression ($P = 0.033$, Figure 2B). Similarly, PFS was worse in patients with a high NLR both at diagnosis and after one cycle of chemotherapy compared with those with low NLR after one cycle of chemotherapy ($P < 0.001$ *vs* an initial low NLR, and $P = 0.004$ *vs* initially high NLR; Figure 2C). However, there was no significant difference in the PFS between changes in NLR according to progression time (Figure 2D).

According to clinical stage and disease course, NLR had a slightly different impact on survival. At the time of diagnosis, the ED survival curve showed significant differences according to the NLR ($P = 0.018$) compared with LD, which consisted of only 11 high-NLR patients ($P = 0.946$; Figure 3A and B). This survival curve pattern was statistically more significant in ED patients after one cycle of chemotherapy ($P = 0.001$), whereas no significant differences according to NLR status were observed in LD patients

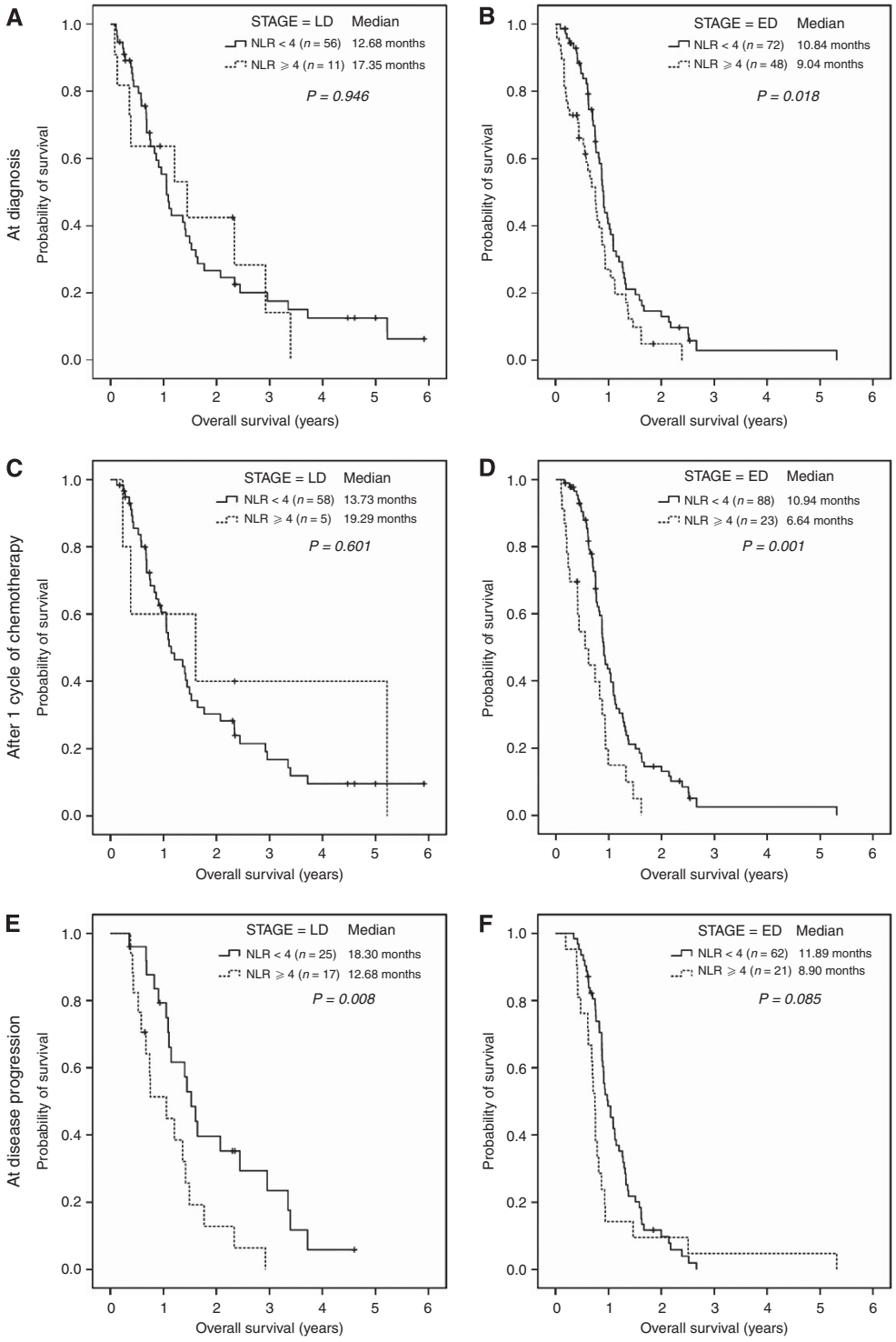

Figure 3. Kaplan–Meier curves for OS according to NLR, stage and treatment course. OS stratified according to the NLR at diagnosis in (**A**) LD and (**B**) ED patients. OS stratified according to the NLR after one cycle of chemotherapy in (**C**) LD and (**D**) ED patients. OS stratified according to the NLR at disease progression in (**E**) LD and (**F**) ED patients. Abbreviations: ED = extensive disease; LD = limited disease; NLR = neutrophil-to-lymphocyte ratio; OS = overall survival.

after one cycle of chemotherapy ($P = 0.601$; Figure 3C and D). At the time of disease progression, LD patients showed a significant difference in survival according to the NLR ($P = 0.008$). However, no statistical significance was found in ED patients according to the NLR ($P = 0.085$; Figure 3E and F).

In subgroup analysis of PLR according to clinical stage and disease course, PLR and OS were not correlated, except when survival of LD patients was compared using the PLR level at disease progression (PLR < 160 *vs* PLR ⩾ 160, median OS 24.87 *vs* 13.73 months, respectively, $P = 0.022$).

Univariate analysis was performed for clinical and laboratory factors. Factors associated with poor OS were ED, elevated LDH, and high NLR at any time. Factors related to poor PFS were ED, elevated LDH, irinotecan-based first-line regimen, and high NLR at diagnosis. Stage, LDH, NLR, and PLR at diagnosis were included in the multivariate analysis (Table 4). ED, elevated LDH, and high NLR, but not high PLR, at diagnosis were independent prognostic factors for OS and PFS.

DISCUSSION

In this study we reviewed the prognostic significance of NLR and PLR with other clinical factors in SCLC patients. PLR had little influence on survival; however, ED, elevated LDH, and high NLR at diagnosis were associated with poor OS and PFS in SCLC patients who underwent first-line chemotherapy.

The high-NLR group included significantly more ED patients than the low-NLR group in this study. Therefore, worse survival in the high-NLR group might be explained in part by selection bias, because the low-NLR group included more LD patients, who had a better prognosis than ED patients and who received additional curative treatments such as CCRT and PCI. However, several findings suggest that NLR was an independent prognostic marker regardless of stage. For OS and PFS, NLR was demonstrated as a prognostic factor via multivariate analysis including stage and LDH. In addition, subgroup analysis according to stage showed that OS in the high-NLR group was significantly shorter than in the low-NLR group in ED patients. Although no significant difference in OS in LD patients was found, the numbers of LD patients with a high NLR at diagnosis ($n = 11$) and after one cycle of chemotherapy ($n = 5$) were too small for statistically significant evaluation, and the high-NLR group at disease progression showed significantly decreased OS in LD patients ($n = 17$). Furthermore, the high-NLR group had worse PS at diagnosis than the low-NLR group. For these reasons, we suggest that NLR is an independent prognostic factor for survival in SCLC patients.

Table 4. Multivarate analysis for overall survival and progression-free survival

	Overall survival			Progression-free survival		
	HR	95% CI	*P*	HR	95% CI	*P*
Stage						
LD	Reference			Reference		
ED	1.546	1.072–2.230	0.020	1.700	1.193–2.422	0.003
LDH						
Normal	Reference			Reference		
Elevated	1.507	1.078–2.107	0.016	1.658	1.199–2.294	0.002
NLR at diagnosis						
<4	Reference			Reference		
⩾4	1.465	1.012–2.119	0.043	1.474	1.033–2.105	0.032
PLR at diagnosis						
<160	Reference			Reference		
⩾160	0.896	0.628–1.280	0.547	0.961	0.685–1.347	0.816

Abbreviations: CI = confidence interval; ED = extensive disease; HR = hazard ratio; LDH = lactate dehydrogenase; NLR = neutrophil-lymphocyte ratio; PLR = platelet-lymphocyte ratio.

As shown in Tables 2 and 3, the NLR level changed with the disease and treatment course, and the response rate was lower in patients with high NLR at diagnosis. The NLR level decreased significantly even after only one cycle of chemotherapy. Given that the treatment response was over 80% in this study, a decrease in the tumour burden may be achieved in most patients after one cycle of chemotherapy. At disease progression, the NLR level increased significantly compared with after one cycle of chemotherapy. These results imply that the NLR may reflect tumour burden and help in assessing the treatment response and monitoring recurrence or progression of SCLC. The clinical importance of the NLR is supported by our findings that the subgroup of patients who failed to achieve a low NLR after one cycle of chemotherapy and patients with a high NLR at disease progression showed poor survival.

A high NLR indicates an increased neutrophil count and/or a decreased lymphocyte count, as well as relative lymphopaenia. Lymphocytes have a crucial role in tumour defence by inducing cytotoxic cell death and inhibiting tumour cell proliferation and migration (Coussens and Werb, 2002; Mantovani *et al*, 2008). In contrast, large numbers of neutrophils affect the cytolytic activity of lymphocytes or natural killer cells and could negatively affect tumour growth (Pillay *et al*, 2012). In addition to the TANs described above, neutrophil extracellular traps (NETs), which are fibres composed of chromatin and neutrophil proteins (Berger-Achituv *et al*, 2013), are known to be associated with cancer. TANs are more prone to NETs than their normal counterparts (Berger-Achituv *et al*, 2013; Demers and Wagner, 2013). An experimental study demonstrated that widespread deposition of NETs induced by sepsis sequesters circulating tumour cells and promotes metastasis (Cools-Lartigue *et al*, 2013). NETs may protect circulating tumour cells by adhering to them and recruiting platelets (Demers and Wagner, 2013). These theoretical considerations support the role of NLR, reflecting the extent of neutrophilia in malignancy.

NLR is an easily measurable and repeatable parameter and thus clinically useful. However, several problems exist. NLR may occasionally not be a tumour-specific marker because other inflammatory conditions and steroid treatments could be confounding factors. Some authors have suggested that NLR should be assessed together with other inflammatory markers such as CRP (Nakamura *et al*, 2013; Yalcinkaya *et al*, 2013). In addition, numerous articles have reported on NLR using different cutoff levels that require validation. In a study that showed a significant correlation between the NLR and survival in patients with stage IV gastric cancer, the authors used a NLR level of 2.5 and median survival was significantly longer in the group with a low-NLR level (Yamanaka *et al*, 2007). Other studies reported a correlation between NLR and survival, using various cutoff values (Yamanaka *et al*, 2007; Kishi *et al*, 2009; Chua *et al*, 2011; Stotz *et al*, 2013).

This study had several limitations. First, the sample size was relatively small, which limits generalising our findings. Second, as with all retrospective studies, there are several limitations inherent to its design, including the retrospective data collection. Nevertheless, to our knowledge, this is the first study to suggest the usefulness of NLR and investigate the prognostic role of NLR in SCLC patients.

In conclusion, NLR at the time of diagnosis is a readily available and effective measurement that reflects the prognosis in SCLC patients. NLR determination during treatment and monitoring may help in assessing the treatment response and predicting recurrence. Further prospective studies are needed to evaluate cutoff values and confirm our results.

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