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Prognostic Significance of Total Lymphocyte Count, Neutrophil-to-lymphocyte Ratio, and Platelet-to-lymphocyte Ratio in Limited-stage Small-cell Lung Cancer

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Abstract

We sought markers of survival and disease control among patients treated for limited-stage small-cell lung cancer. High pretreatment total lymphocyte count was linked with superior (and high neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios with inferior) median and 2-year overall survival, findings confirmed in multivariate Cox regression. Baseline lymphopenia was an indicator of poor prognosis in patients with limited-stage small-cell lung cancer.

Background: We sought reliable markers of survival and disease control among patients treated for limited-stage small-cell lung cancer (LS-SCLC). **Patients and Methods:** Subjects were 122 patients given (chemo)radiotherapy for LS-SCLC at MD Anderson in 2002 through 2015. Pretreatment total lymphocyte count (TLC), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were analyzed for associations with overall (OS) and progression-free survival. Optimal cutoff values were identified with receiver operating characteristic curves and survival probabilities with the Kaplan-Meier method. **Results:** Pretreatment TLC was $1.86 \times 10^3/\mu L$ ($\pm$0.88); NLR, 3.44 ($\pm$3.69); and PLR, 170.53 ($\pm$101.56); corresponding cutoffs were 1.9, 2.9, and 140.1. Higher TLC was associated with superior median and 2-year OS (17.4 vs. 15.7 months and 33% vs. 29%; $P = .029$), and higher NLR and PLR with worse median and 2-year OS (NLR: 14.9 vs. 17.8 months, 29% vs. 31%; $P = .026$; PLR: 14.8 vs. 18.9 months, 24% vs. 37%; $P = .009$). Multivariate Cox regression adjusted for age, disease stage, number of chemotherapy cycles, and use of prophylactic cranial irradiation confirmed the links between high TLC and superior OS (hazard ratio [HR] 0.55; 95% confidence interval [CI], 0.32-0.94; $P = .028$) and between high NLR and PLR and inferior OS (NLR: HR, 1.86; 95% CI, 1.15-3.01; $P = .011$; PLR: HR, 1.72; 95% CI, 1.06-2.82; $P = .030$). **Conclusions:** Baseline lymphopenia was an indicator of poor prognosis in patients with LS-SCLC.

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Introduction

Small-cell lung cancer (SCLC) represents 13% of all lung cancers worldwide. An aggressive type of cancer, SCLC is characterized by rapid proliferation and a strong propensity for metastasis. Although technologic advances in radiotherapy have led to improved outcomes for this disease, 5-year survival rates remain disappointingly low at 10% to 15%.[1]

Several attempts have been made to identify factors other than disease stage as tools for selecting patients for various treatment approaches.[2,3] In one large pooled study, age and gender were identified as important prognostic factors for survival in patients with limited-stage (LS) SCLC.[3] However, including these factors does not allow efficient selection of patients for various treatment strategies, and additional reliable markers are needed to make choices among various treatment strategies to improve therapeutic efficacy for patients with LS-SCLC.

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Inflammation has critical roles in every aspect of tumor development and progression and in immune surveillance and response to therapy,[4] and each stage of cancer development is exquisitely susceptible to regulation by immune cells.[5] The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been evaluated in various types of cancers and proposed as inflammatory markers for predicting outcome.[6-11] Lymphocytes are one of the main components of the immune system and are indispensable in the immune response to cancer. Lymphopenia, defined in terms of total lymphocyte count (TLC), has been associated with poor prognosis in various types of cancers.[12-16] These markers of inflammation and immune status can be easily, inexpensively, and repeatedly acquired in routine clinical practice. However, information is scarce regarding the significance of TLC, NLR, and PLR in predicting outcomes for patients with LS-SCLC. We thus undertook this study to address this gap.

Patients and Methods

Patient Selection

With the approval of the institutional review board, we retrospectively identified patients with a diagnosis of LS-SCLC treated at a single tertiary cancer center from 2002 through 2015. Selection criteria were: (1) pathologically confirmed SCLC, (2) clinically limited disease (stage I-IIIB), (3) receipt of thoracic radiation therapy (TRT) with curative intent at a single institution, and (4) availability of laboratory data obtained at the same institution before initiation of any curative treatment (chemotherapy, TRT, or both). Patients were excluded if they had had upfront surgery or did not complete TRT. Patients received 1 of 3 treatments, all standard at our institution: 1 to 3 cycles of induction chemotherapy followed by sequential TRT; 1 to 3 cycles of chemotherapy followed by concurrent chemoradiotherapy; or upfront concurrent chemoradiotherapy followed by adjuvant chemotherapy. The standard chemotherapy regimen used was platinum and etoposide. Patients who achieved a clinical complete response or a good partial response, with lack of evidence of disease on brain magnetic resonance imaging (MRI) or computed tomography (CT) if MRI was contraindicated, were offered prophylactic cranial irradiation (PCI). Patients generally returned for follow-up every 3 months for the first 2 years, every 6 months from 3 to 5 years, and yearly thereafter. Thoracic CT or positron emission tomography(PET)/CT scans were obtained at every follow-up visit. Brain MRI or CT was also obtained at every follow-up visit for patients who did not undergo PCI, whereas patients who did receive PCI had brain imaging at the onset of symptoms or less frequently (eg, every 6 months for the first 2 years); however, this was not always done consistently.

Data Collection

Demographic, clinical, and treatment characteristics were extracted from electronic medical records and an institutional cancer database. Patient-specific variables included age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS) scores, smoking status, and laboratory values from pretreatment measurements of complete blood count (CBC) with differentials and lactate dehydrogenase (LDH). The most recent CBC and LDH measurements before the start of definitive treatment (chemotherapy, TRT, or both) was used. Tumor-specific variables included T status, N status, and TNM stage. Treatment variables included radiation technique, dose, and fractionation; receipt of PCI; receipt of induction or concurrent chemotherapy; and number of chemotherapy cycles. We assessed the following variables from the CBC: total (absolute) lymphocyte count (TLC); the absolute neutrophil count divided by the absolute lymphocyte count (NLR); and the absolute platelet count divided by the absolute lymphocyte count (PLR).

Statistical Analysis

Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values for TLC, NLR, and PLR in terms of their association with survival. Demographic, clinical, and treatment characteristics were summarized with descriptive statistics. Differences between patients stratified by the TLC cutoff were examined with the Mann-Whitney U test, χ^2 test or Fisher exact test according to the type of variable. The primary outcomes of interest were overall survival (OS) and progression-free survival (PFS). OS was calculated from the start date of definitive treatment to the date of death from any cause or the last contact. PFS was defined as the time from treatment start until radiographic or pathologic evidence of progression or recurrence. Survival and progression probabilities were estimated with the Kaplan-Meier method, and log-rank tests were used to compare Kaplan-Meier estimates of event rates between factors potentially associated with survival or disease control. Factors included in the final multivariate Cox regression analysis were those with a strong unadjusted association with survival and progression ($P < .10$) in univariate analysis. All analyses were 2-sided, and significance was set at a P value of .05. Statistical analyses were done with SPSS version 24 (SPSS, Chicago, IL) and Stata/MP 15.1 (Stata Corp LP, College Station, TX).

Results

We identified 174 patients as having had LS-SCLC during the study period. Of those patients, 52 were excluded from this analysis, 30 for having been initially treated at outside facilities, 12 for having had upfront surgery, 8 for missing lab data before treatment, and 2 for having had interruptions in curative TRT owing to pneumonia or disease progression during TRT. In total, 122 patients with LS-SCLC met the eligibility criteria; their demographic, clinical, and treatment characteristics are provided in Table 1. With regard to treatment, 53% of patients had had induction chemotherapy before TRT, 61% received TRT in twice-daily fractionation, and 61% received PCI.

The median time at which pretreatment laboratory values were obtained was 6 days before the start of any curative treatment (interquartile range [IQR], 1-12 days). The mean baseline value (± standard deviation)] of TLC was $1.86 \times 10^3/\mu L$ (±0.88); for NLR, 3.44 (±3.69); and for PLR, 170.53 (±101.56). According to ROC analysis, the optimal cutoff values were 1.9 for TLC (sensitivity 28% and specificity 51%), 2.9 for NLR (sensitivity 51% and specificity 70%), and 140.1 for PLR (sensitivity 57% and specificity 66%). The median patient age was 65 years, which was also used as a cutoff. Based on these cutoff values, patients were stratified into 2 groups, and OS and PFS were analyzed within these stratifications.

The median OS time for all patients was 16.6 months (IQR, 11.55-25.98 months). In univariate analysis, age $<$ 65 years,

Table 1 Patient Characteristics

Characteristic	All Patients (n = 122)	Pretreatment Lymphocyte Count Value or No. of Patients (%) TLC < 1.9 × 10^3/μL (n = 77)	TLC ≥ 1.9 × 10^3/μL (n = 45)	*P* Value
Demographics				
Gender				
Male	61 (50)	42 (55)	19 (42)	.260
Female	61 (50)	35 (45)	26 (58)	
Age at diagnosis, y				
Median (IQR)	65 (60-72)	65 (60-71)	64 (59-72)	.304
ECOG PS at diagnosis				
0-1	111 (91)	68 (88)	43 (96)	.211
>2	11 (9)	9 (12)	2 (4)	
Smoking status				
Current smoker	45 (37)	25 (32)	20 (44)	.396
Former smoker	73 (60)	49 (64)	24 (53)	
Never smoker	4 (3)	3 (4)	1 (2)	
Treatment				
Chemotherapy				
Induction chemo	65 (53)	42 (55)	23 (51)	.714
No induction chemo	57 (47)	35 (45)	22 (49)	
Concurrent chemo	106 (87)	63 (82)	43 (96)	.049
No concurrent chemo	16 (13)	14 (18)	2 (4)	
No. of chemotherapy cycles				
<4	20 (16)	17 (22)	3 (7)	.028
≥4	100 (82)	59 (77)	41 (91)	
Unknown	2 (2)	1 (1)	1 (2)	
Radiation technique				
3D conformal	7 (6)	6 (8)	1 (2)	.115
IMRT	99 (81)	61 (80)	38 (84)	
Proton	8 (7)	3 (4)	5 (11)	
SABR	8 (7)	7 (9)	1 (2)	
Twice-daily fractionation[a]				
Yes	75 (61)	44 (57)	31 (69)	.248
No	47 (39)	33 (43)	14 (31)	
Delivered dose, Gy or Gy [RBE]				
≤45	70 (57)	38 (49)	32 (71)	.023
>45	52 (43)	39 (51)	13 (29)	
Prophylactic cranial irradiation				
Yes	74 (61)	41 (53)	33 (73)	.035
No[b] or unknown	48 (39)	36 (47)	12 (27)	
T status				
T1	40 (33)	21 (27)	19 (42)	.501
T2	36 (30)	25 (32)	11 (24)	
T3	24 (20)	17 (22)	7 (16)	
T4	20 (16)	13 (17)	7 (16)	
TX	2 (2)	1 (1)	1 (2)	
N status				
N0	21 (17)	15 (19)	6 (13)	.493
N1	15 (12)	11 (14)	4 (9)	
N2	45 (37)	25 (32)	20 (44)	
N3	41 (34)	26 (34)	15 (33)	

Table 1 Continued

Characteristic	All Patients (n = 122)	Pretreatment Lymphocyte Count Value or No. of Patients (%)		*P* Value
		TLC < 1.9 × 10^3/μL (n = 77)	TLC ≥ 1.9 × 10^3/μL (n = 45)	
Disease stage				
IA/B	15 (12)	10 (13)	5 (11)	.805
IIA/B	12 (10)	9 (12)	3 (7)	
IIIA	49 (40)	30 (39)	19 (42)	
IIIB	46 (38)	28 (36)	18 (40)	
Pretreatment laboratory findings				
Median LDH, U/L (IQR)	489 (404-560)	493 (397-560)	487 (452-553)	.803
Median Hb, g/dL (IQR)	13.2 (12.3-14.2)	13.1 (12.0-13.9)	13.6 (12.7-14.6)	.020
Median WBC, × 10^3/μL (IQR)	7.7 (6.4-9.0)	6.9 (5.7-8.4)	8.5 (7.7-9.7)	<.001
Median neutrophils, × 10^3/μL (IQR)	4.7 (3.8-5.8)	4.5 (3.6-5.8)	5.0 (4.3-6.0)	.144
Median platelets, × 10^3/μL (IQR)	251 (203-310)	246 (198-307)	263 (223-328)	.335

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; Hb = hemoglobin; IMRT = intensity-modulated radiation therapy; IQR = interquartile range; LDH = lactate dehydrogenase; SABR = stereotactic ablative radiation therapy; TLC = total lymphocyte count; WBC = white blood cells.
[a]Excludes 1 patient for whom twice-daily fractionation was used only for boost dosing.
[b]Includes 1 patient for whom PCI was cancelled in the middle of the treatment.

ECOG PS score 0 to 1, receipt of ≥ 4 cycles of chemotherapy, receipt of PCI, higher TLC (≥ 1.9 × 10^3/μL), lower NLR (< 2.9), and lower PLR (< 140.1) were all associated with better survival ($P < .10$) (Table 2).

Patients with higher pretreatment TLC (≥ 1.9 × 10^3/μL) had superior median OS time and 2-year OS rate than did patients with lower pretreatment TLC (< 1.9 × 10^3/μL) (17.4 vs. 15.7 months and 33% vs. 29%; $P = .029$) (Figure 1A). Conversely, patients with higher pretreatment NLR (≥ 2.9) and PLR (≥ 140.1) had worse median OS times and 2-year OS rates than did patients with lower pretreatment NLR (< 2.9) and PLR (< 140.1) (NLR: 14.9 vs. 17.8 months and 29% vs. 31%; $P = .026$; PLR: 14.8 vs. 18.9 months, 24% vs. 37%; $P = .009$) (Figure 1B,C). Because of the strong colinearity among TLC, NLR, and PLR, these factors could not be tested simultaneously and were examined separately in multivariate analysis.

The final multivariate Cox regression analysis was adjusted for age, receipt of ≥ 4 cycles of chemotherapy and receipt of PCI ($P < .10$ in univariate analysis) plus disease stage and each of the CBC values (Table 3). The results showed that, along with the positive effect of receipt of ≥ 4 cycles of chemotherapy on OS (hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.21-0.82; $P = .011$), higher baseline TLC (≥ 1.9 × 10^3/μL) was associated with superior OS (HR, 0.55; 95% CI, 0.32-0.94; $P = .028$). Conversely, higher baseline NLR (≥ 2.9) and higher PLR (≥ 140.1) were associated with inferior OS (NLR: HR, 1.86; 95% CI, 1.15-3.01; $P = .011$; PLR: HR, 1.72; 95% CI, 1.06-2.82; $P = .030$).

The median PFS time for these patients was 9.5 months (IQR, 6.57-19.01 months). No factors investigated in this analysis were found to be associated with PFS.

Discussion

Inflammation and the immune system have important roles in cancer development and progression. In this study, we found that pretreatment TLC, NLR, and PLR were associated with OS—but not PFS—in patients with LS-SCLC.

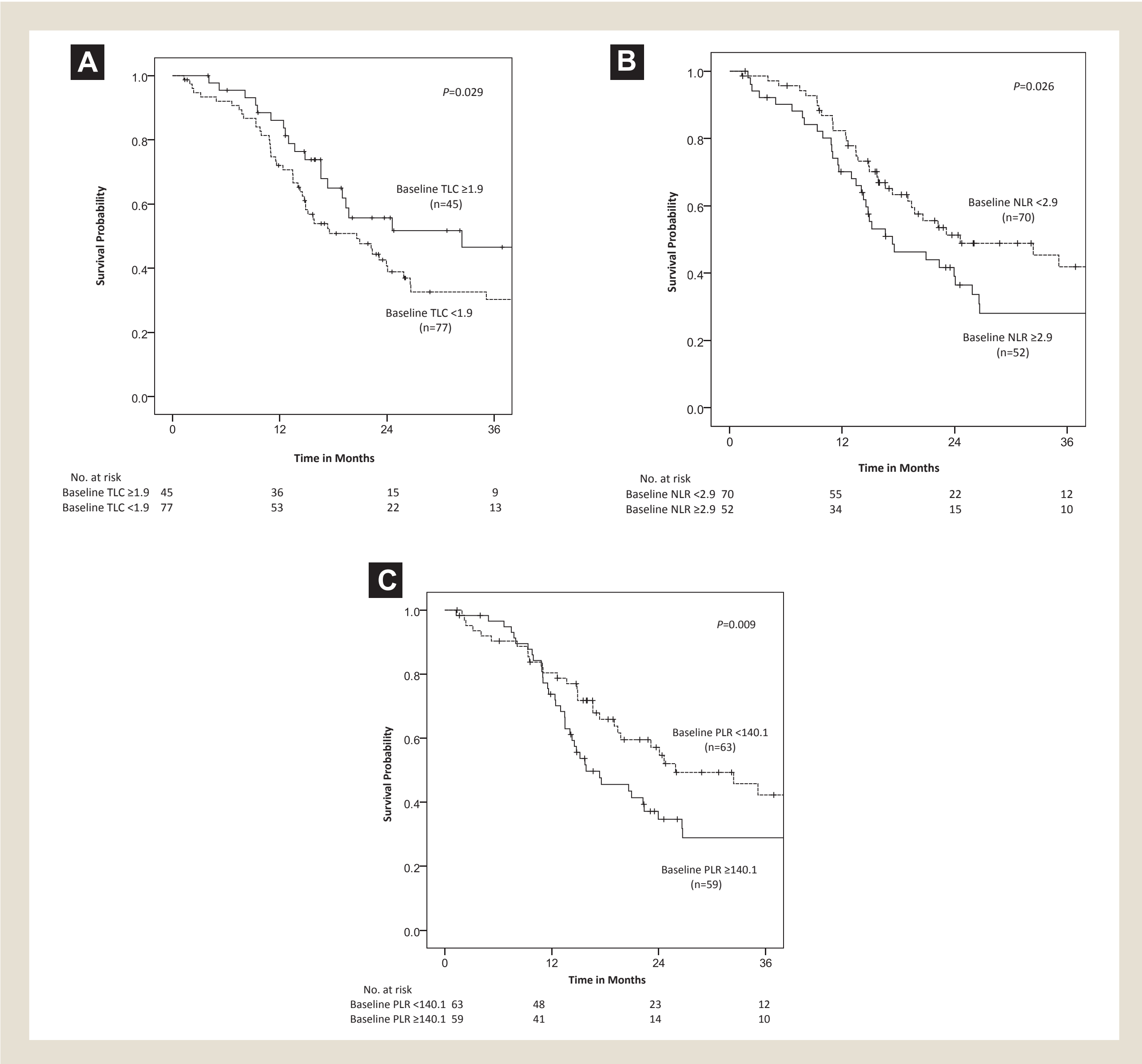
Inflammation within the tumor microenvironment can affect every aspect of tumor development and progression as well as response to therapy.[4] Elevated NLR and PLR in the peripheral blood of patients with cancer could be a manifestation of systemic inflammation provoked by cancer cells. NLR and PLR have been evaluated in various types of cancers and proposed as reliable inflammatory markers for predicting outcome.[6-11] Elevated NLR in patients with SCLC has been linked with worse survival in several studies,[17-20] but as far as we know, only one study other than ours found an association between elevated PLR and survival in SCLC.

Table 2 Univariate Analysis of Factors Potentially Associated With Overall Survival

Characteristics	HR	95% CI	*P* Value
Age ≥65 y	1.48	0.93-2.35	.095
Female	0.95	0.60-1.49	.808
ECOG PS ≥2	3.08	1.37-6.90	.006
TNM stage IIIA-IIIB	1.48	0.84-2.60	.180
Current smoker	0.79	0.49-1.29	.350
Receipt of induction chemotherapy	0.75	0.47-1.17	.204
Receipt of concurrent chemotherapy	0.89	0.45-1.73	.722
Receipt of ≥4 cycles of chemotherapy	0.33	0.18-0.61	<.001
Receipt of twice-daily fractionation	0.93	0.59-1.48	.768
Prescribed dose >45 Gy	1.29	0.81-2.05	.280
Receipt of prophylactic cranial irradiation	0.57	0.36-0.91	.017
Pretreatment LDH >500	0.97	0.59-1.59	.901
Pretreatment TLC ≥1.9 × 10^3/μL	0.57	0.34-0.95	.031
Pretreatment NLR ≥2.9	1.68	1.06-2.66	.028
Pretreatment PLR ≥140.1	1.85	1.16-2.96	.010

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; LDH = lactate dehydrogenase; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; TLC = total lymphocyte count; TNM = tumor-nodes-metastasis.

Figure 1 Kaplan-Meier Plots of Overall Survival Among Patients Who Received (Chemo)Radiation Therapy for Limited-stage Small Cell Lung Cancer Stratified by Baseline TLC (A), Baseline NLR (B), and Baseline PLR (C)



Abbreviations: NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; TLC = total lymphocyte count.

That study, which included 383 patients with LS-SCLC, showed that PLR was associated with OS.[17] In contrast to this and our results, findings from 2 lung cancer meta-analyses[18,21] and 2 single-institution studies[19,20] revealed that PLR was not associated with survival in patients with SCLC. Larger cooperative studies may be needed to confirm the significance of PLR for this purpose.

Higher NLR or PLR values indicate increased neutrophil or platelet counts in combination with relative decreases in TLC. Systemic inflammation induces neutrophilia and thrombocytosis, the latter a common finding in patients with cancer (10%-57%)[22] that has been linked with poor prognosis in variety of cancers including lung.[23-26] Use of inflammation inhibitors such as cyclooxygenase-2 (COX-2) inhibitors could be effective in preventing or treating some forms of cancer. Increased amounts of COX-2 are commonly detected in both premalignant and malignant tissues in a variety of organs, and several preclinical studies have sought to establish a link between COX-2 and carcinogenesis.[27] Many epidemiologic studies have found that use of nonsteroidal anti-inflammatory drugs, which are prototypic COX inhibitors, is associated with reduced risk of several types of cancer.[28]

Lymphocytes are a crucial component of the immune system and have a fundamental role in the immune response to cancer. Lymphopenia defined in terms of TLC has been shown to be associated with dismal prognosis in many types of cancer.[12-16] In another series of patients with extensive-stage SCLC, we found baseline TLC and baseline NLR to be significantly associated with survival.[29] As for patients with LS-SCLC, one study showed that a lower TLC nadir during TRT and a lower TLC at 1 month after TRT were associated

Table 3 Multivariate Analysis of Factors Potentially Associated With Overall Survival

Characteristics	Model 1 (TLC Included)			Model 2 (NLR Included)			Model 3 (PLR Included)		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age ≥65 y	1.41	0.86-2.33	.177	1.53	0.92-2.54	.100	1.41	0.86-2.31	.176
TNM stage IIIA-IIIB	1.94	1.08-3.50	.027	1.77	0.99-3.17	.054	1.64	0.91-2.96	.101
Receipt of ≥4 cycles of chemotherapy	0.41	0.21-0.82	.011	0.40	0.21-0.79	.008	0.42	0.21-0.83	.012
Receipt of prophylactic cranial irradiation	0.73	0.43-1.23	.238	0.73	0.44-1.22	.227	0.72	0.43-1.21	.214
Pretreatment TLC ≥1.9 × 10^3/μL	0.55	0.32-0.94	.028	—	—	—	—	—	—
Pretreatment NLR ≥2.9	—	—	—	1.86	1.15-3.01	.011	—	—	—
Pretreatment PLR ≥140.1	—	—	—	—	—	—	1.72	1.06-2.82	.030

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; TLC = total lymphocyte count; TNM = tumor-nodes-metastasis.

with poor survival.[30] In line with these studies, our results suggest that lower baseline TLC was associated with poor prognosis in LS-SCLC.

Although beyond the scope of this study, preclinical and clinical evidence exists to support the importance of lymphocyte subpopulations in the tumor microenvironment.[31-33] One study showed the accumulation of immunosuppressive Foxp3$^+$ regulatory T cells in lung tumors and metastatic lymph nodes in combination with a considerable decrease in the natural killer (NK) cell numbers, which implicated Foxp3$^+$ regulatory T cells in the creation of an immunosuppressive tumor microenvironment.[32] Another study suggested increased proportions of regulatory, CD8+, and CD8$^+$CD28$^-$ T cells and decreased CD4$^+$ T cells and CD4/CD8 ratio in patients with non−small-cell lung cancer at first relapse relative to patients at initial diagnosis.[33] That group also found that increased regulatory T cells were independently associated with worse PFS after receipt of TRT. Further studies incorporating analysis of lymphocyte subpopulations may be a path to develop more effective therapeutic interventions.

The emergence of immunotherapy has changed the standard of care for treatment of lung cancer. After recognition of its role in first-line treatment of advanced non−small-cell lung cancer, immunotherapy is also being used in first-line treatments for extensive-stage SCLC.[34] If our findings are validated, baseline TLC, NLR and PLR could be included as stratification factors in future clinical trials incorporating immunotherapy.

This study was limited by its retrospective nature and relatively small sample size in addition to variations in the timing of laboratory value measurements. Also, other variables that more comprehensively describe lymphocytes, including subpopulations, may be more prognostic than absolute numbers. Despite these limitations, this study investigated the potential association between baseline TLC, NLR, and PLR (all inflammatory and immunologic markers that are easily available in routine clinical practice) and survival outcomes in patients with LS-SCLC. All 3 of these markers were found to be associated with better or worse OS.

Findings from the current study should be validated in a larger, multicenter study. If these inflammatory and immunologic markers can be validated as reliable indicators of survival, they could be used to guide more personalized treatment for patients with LS-SCLC, perhaps including such innovations as immune preservation or modulation and inflammatory regulation before or after treatment.

Clinical Practice Points

- Inflammation and immunity have crucial roles in tumor development and progression, immune surveillance, and response to therapy. The NLR and PLR have been proposed as inflammatory markers to indicate outcome in various types of cancer. Low TLC has also been associated with poor prognosis. These markers can be readily acquired in routine clinical practice. Nevertheless, little is known of their influence on outcomes, if any, for patients with LS-SCLC.
- We found that TLC, NLR, and PLR, all measured before treatment, were significantly associated with OS in LS-SCLC. Specifically, median survival time was longer for patients with higher pretreatment TLC (≥ 1.9 × 10^3/μL) than for patients with lower pretreatment TLC (17.4 vs. 15.7 months). Conversely, patients with higher NLR (≥ 2.9) and PLR (≥ 140.1) before treatment had shorter median OS times than did patients with lower NLR (14.9 vs. 17.8 months) or lower PLR (14.8 vs. 18.9 months). Multivariate Cox regression also showed that higher pretreatment TLC (≥ 1.9 × 10^3/μL) was associated with superior OS (HR, 0.55; P = .028). Conversely, higher baseline NLR (≥ 2.9) and higher PLR (≥ 140.1) were associated with inferior OS (NLR: HR, 1.86; P = .011; PLR: HR, 1.72; P = .030).
- Although further validation is necessary with larger groups of patients, these markers could be used to guide the choice of treatment for patients with LS-SCLC, perhaps including new approaches such as immune preservation or modulation or regulation of inflammation before or after treatment.

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Disclosure

The authors have stated that they have no conflicts of interest.

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