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Usefulness of White Blood Cell Differential-based Indices in Patients With Extensive-stage Small Cell Lung Cancer

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Abstract

Background/Aim: Indices based on the white blood cell (WBC) count and WBC differential count are simple and can be easily calculated using routine blood tests. Many studies have examined the usefulness of these indices for predicting prognosis for various cancers, including lung cancer. However, no studies have focused on the relationships between indices based solely on WBC and WBC differential counts and the prognosis of patients with extensive-stage small cell lung cancer (ES-SCLC). The aim of this study was to evaluate the prognostic value of indices based on WBC and WBC differential counts in patients with ES-SCLC treated with platinum-doublet chemotherapy.

Patients and Methods: The pretreatment neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), neutrophil-to-monocyte ratio (NMR), monocyte-to-lymphocyte ratio (MLR), neutrophil-to-WBC ratio (NWR), lymphocyte-to-WBC ratio (LWR), monocyte-to-WBC ratio (MWR), neutrophil-to-eosinophil ratio (NER), lymphocyte-to-eosinophil ratio (LER), monocyte-to-eosinophil ratio (MER), eosinophil*neutrophil-to-lymphocyte ratio (ENLR), systemic inflammation response index (SIRI), and inflammatory related ratio (IRR) of patients with ES-SCLC who were treated with platinum-doublet chemotherapy as first-line treatment at Kainan Hospital were retrospectively analyzed.

Results: Data from 102 patients were analyzed. On multivariate analysis, patients with low MLR, MWR, NER, MER, and IRR values had significantly longer overall survival (OS) than patients with high MLR, MWR, NER, MER, and IRR values. In addition, patients with low WBC and monocyte counts had significantly longer OS than patients with high WBC and monocyte counts.

Conclusion: Indices based on WBC and WBC differential counts, especially monocyte-related indices, may be useful markers for predicting the prognosis of patients with ES-SCLC treated with platinum-doublet chemotherapy.

Keywords: Small cell lung cancer, WBC, WBC differential, prognosis.

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Introduction

Lung cancer is the third most common cancer and the leading cause of cancer death in Japan (1). Small cell lung cancer (SCLC) accounts for approximately 15% of all new lung cancer cases and is marked by an exceptionally high proliferative rate, strong predilection for early metastasis, and poor prognosis (2). Over two-thirds of patients present with extensive-stage (ES) disease at diagnosis, and ES-SCLC remains an incurable disease with a 5-year overall survival (OS) rate <5% (3).

Several clinical variables such as age, performance status (PS), weight loss, nutritional status, clinical stage, serum lactate dehydrogenase, albumin-bilirubin grade, and Glasgow prognostic score are considered to predict the prognosis of patients with SCLC (4-8). Furthermore, since inflammation has been suggested as a prognostic marker, general inflammation markers such as C-reactive protein (CRP) values, white blood cell (WBC) counts, and lymphocyte counts have been repeatedly studied and have shown some potential as prognostic markers in several cancers (9). In particular, the pretreatment neutrophil-to-lymphocyte ratio (NLR) and the monocyte-to-lymphocyte ratio (MLR) [or lymphocyte-to-monocyte ratio (LMR)] were major WBC differential count-based indices as cancer prognostic biomarkers, and the prognostic values of NLR and MLR (or LMR) for lung cancer patients have been reported in review articles (9-12).

However, there are no standard WBC differential-based prognostic parameters in patients with advanced SCLC because of conflicting results and different cutoff values in several studies. In addition to NLR and MLR, the derived neutrophil-to-lymphocyte ratio (dNLR), neutrophil-to-monocyte ratio (NMR), neutrophil-to-WBC ratio (NWR), lymphocyte-to-WBC ratio (LWR), monocyte-to-WBC ratio (MWR), neutrophil-to-eosinophil ratio (NER), lymphocyte-to-eosinophil ratio (LER), monocyte-to-eosinophil ratio (MER), eosinophil*neutrophil-to-lymphocyte ratio (ENLR), systemic inflammation response index (SIRI), and inflammatory-related ratio (IRR) have been reported as prognostic indices based on WBC and WBC differential counts for cancer patients (9-19). In this context, no report has focused on the prognostic value of indices based on WBC and WBC differential counts in patients with advanced SCLC treated with platinum-doublet chemotherapy. The aim of this study was to evaluate the prognostic value of 13 WBC and WBC differential count-based indices, namely NLR, dNLR, NMR, MLR, NWR, LWR, MWR, NER, LER, MER, ENLR, SIRI, and IRR, in patients with ES-SCLC who underwent platinum-doublet chemotherapy as first-line treatment. In addition, the associations of WBC and WBC differential count with prognosis were also evaluated in the same population.

Patients and Methods

Study design and ethical considerations. This was a retrospective, observational study of patients with ES-SCLC who received standard platinum-doublet chemotherapy as first-line treatment at Kainan Hospital (Yatomi, Japan) between February 2009 and August 2019. Informed consent from patients in this study was obtained using an opt-out option provided on our hospital website. All patients' routine medical data were anonymized prior to the analyses. This study was approved by the Ethics Committee of Kainan Hospital Aichi Prefectural Welfare Federation of Agricultural Cooperatives (approved on May 15, 2025; No.: 20250515-02).

Patients and anticancer therapies. All included patients had pathologically (cytologically or histologically) confirmed SCLC. ES is defined as disease extending beyond limited-stage (LS), and LS is defined as disease confined to one hemithorax within a tolerable radiation field (3). For first-line chemotherapy, the patients were administered carboplatin (CBDCA) intravenously at an area under the concentration-time curve of 5 on day 1, in addition to etoposide (VP-16) 80-100 mg/m^2 on days 1-3, every 3-4 weeks. Alternatively, the patients were administered cisplatin (CDDP) 60 mg/m^2 on day 1 and irinotecan (CPT-11) 60 mg/m^2 on days 1, 8, and 15

intravenously, every four weeks. First-line chemotherapy was administered for up to six courses until disease progression was confirmed on imaging studies, withdrawal, unacceptable toxicity, or death. The dose and type of the first and subsequent chemotherapies were decided at the discretion of the physician in charge of each patient. The doses administered in and after the second treatment cycle were modified based on the patients' PS and previous hematological and non-hematological toxicities. Palliative radiation therapy was administered by the physician in charge in consultation with a radiologist. Patients treated with an immune checkpoint inhibitor (ICI), such as anti-programmed cell death ligand 1 (PD-L1) antibody, were excluded.

Patients' characteristics and measurement of serum biomarkers. Data on patients' characteristics, such as age, sex, PS, smoking status, and comorbid pulmonary disease [chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD)], were retrospectively extracted from the patients' medical records. The patients were assessed for disease stage, disease progression, and relapse by chest radiography, computed tomography of the chest and abdomen, and computed tomography or magnetic resonance imaging of the head. Sensitive relapse was defined as relapse occurring more than 90 days after completion of first-line chemotherapy, whereas refractory relapse was defined as relapse occurring at or less than 90 days after completion of first-line chemotherapy. Blood WBC and WBC differential counts were measured at the laboratory of our hospital; the Sysmex Automated Hematology Analyzer XE-Series was used until March 2015, and the Sysmex Automated Hematology Analyzer XN-Series was used after April 2015.

Definitions of NLR, dNLR, NMR, MLR, NWR, LWR, MWR, NER, LER, MER, ENLR, SIRI, and IRR. The scores for the 13 indices were calculated using the following formula: NLR = neutrophils ÷ lymphocytes; dNLR = neutrophils ÷ (WBC – neutrophils); NMR = neutrophils ÷ monocytes; MLR = monocytes ÷ lymphocytes; NWR = neutrophils ÷ WBC; LWR = lymphocytes ÷ WBC; MWR - monocytes ÷ WBC; NER = neutrophils ÷ eosinophils; LER = lymphocytes ÷ eosinophils; MER = monocytes ÷ eosinophils; ENLR = eosinophils × (neutrophils ÷ lymphocytes); SIRI = neutrophils × (monocytes ÷ lymphocytes); and IRR = (neutrophils × monocytes) ÷ (lymphocytes × eosinophils) (7-17). The indices combining other blood test markers, such as platelet counts, hemoglobin levels, CRP levels, and albumin levels, were excluded.

Cutoff values of WBC count, WBC differential counts, and 13 indices. Patients were stratified into high and low value groups with reference to cutoff values derived from the receiver-operating characteristic curves for 300-day mortality. The cutoff values were 7,000/μl for WBC count, 5,000/μl for neutrophil count, 1,500/μl for lymphocyte count, 500/μl for monocyte count, and 100/μl for eosinophil count. The cutoff values for each index were defined as follows: NLR 2.8 (score <2.8 or ≥2.8), dNLR 1.75 (score <1.75 or ≥1.75), NMR 8.9 (score <8.9 or ≥8.9), MLR 0.25 (score <0.25 or ≥0.25), NWR 0.64 (score <0.64 or ≥0.64), LWR 0.24 (score <0.24 or ≥0.24), MWR 0.07 (score <0.07 or ≥0.07), NER 38 (score <38 or ≥38), LER 9.7 (score <9.7 or ≥9.7), MER 4.5 (score <4.5 or ≥4.5), ENLR 265 (score <265 or ≥265), SIRI 1.7 (score <1.7 or ≥1.7), and IRR 11 (score <11 or ≥11).

Statistical analyses. The data cutoff date was June 30, 2022. Differences in relapse patterns between two groups were evaluated using Fisher's exact test. OS was defined as the time from the pathological diagnosis of cancer to the time of death or the last follow-up. Univariate survival analyses were performed using log-rank tests, and multivariate analyses were performed using a Cox proportional hazards model to establish the associations between indices based on WBC and WBC differential counts and survival. Age, sex, PS, brain metastasis, liver metastasis, and ILD were included in the multivariate analysis. Additional multivariate analysis was also performed for WBC differentials, including age, sex, PS, brain metastasis, liver metastasis, ILD, neutrophil count, lymphocyte count, monocyte count, and eosinophil count.

The reported *p*-values were two-sided, and p-values less than 0.05 were considered significant. In this study, all statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria) (20).

Results

Patients' characteristics in this study. A total of 102 patients were included, and their clinical characteristics are presented in Table I. The median age of the patients was 71 (range=49-89) years. Of the 102 patients, 84 (82.4%) were male, 100 (98.0%) had a history of smoking, and 85 (83.3%) had good PS (0 or 1). Brain metastases were present in 21 patients (20.6%), and liver metastases were present in 39 patients (38.2%). Regarding comorbid pulmonary disease, 15 patients had ILD, of whom seven had both COPD and ILD. Eighty-three (81.4%) patients were treated with CBDCA and VP-16 as first-line chemotherapy, and the median number of platinum-doublet chemotherapy cycles administered as the first-line treatment was four (range=1-6). The median total number of chemotherapy regimens was two (range=1-8). Sixty-seven patients received palliative radiation therapy, 28 of whom received thoracic radiation therapy, and 39 received radiation therapy for brain metastases.

Values of 13 indices based on WBC and WBC differential counts and relationships between these indices and relapse patterns. There were 42 (42.2%) patients with low NLR, 30 (29.4%) with low dNLR, 33 (32.4%) with low NMR, 31 (30.4%) with low MLR, 32 (31.4%) with low NWR, 59 (57.8%) with low LWR, 63 (61.8%) with low MWR, 42 (41.6%) with low NER, 30 (29.7%) with low LER, 56 (55.4%) with low MER, 40 (39.2%) with low ENLR, 59 (57.8%) with low SIRI, and 41 (40.6%) with low IRR (Table II). The median follow-up duration from the time of cancer diagnosis was 263 (range=13-1,894) days. The associations between relapse patterns after first-line chemotherapy and indices based on WBC and WBC

Table I. *Clinical characteristics of the patients (n=102).*

Characteristics	Value
Age (y)	
Median	71
Range	49-89
Sex, n	
Male	84
Female	18
Smoking status, n	
Current or former smoker	100
Never smoked	2
ECOG PS, n	
0-1	85
2-3	17
Brain metastasis	
No	81
Yes	21
Liver metastasis	
No	63
Yes	39
Comorbid pulmonary disease	
COPD	20*
ILD	15*
Type of first-line therapy	
CDDP + CPT-11	19
CBDCA + VP-16	83
No. of first-line therapy cycles	
Median	4
Range	1-6
Sensitivity to first-line chemotherapy	
Sensitive relapse	14
Refractory relapse	74
Unknown	14
Type of second-line therapy	
Amurubicin	52
CBDCA + VP-16	4
PTX	4
CDDP + VP-16	1
CDDP + CPT-11	1
CPT-11	1
Number of total chemotherapy regimens	
1	39
2	30
3	15
4 or more	18
Palliative radiation therapy	
No	35
Yes	67
Thoracic radiation therapy	28*
Radiation therapy for brain metastases	39*

ECOG PS: Eastern Cooperative Oncology Group performance status; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; CDDP: cisplatin; CPT-11: irinotecan; CBDCA: carboplatin; VP-16: etoposide; PTX: paclitaxel. *There is some overlap.

differential counts are shown in Table III. High values of MLR and IRR before treatment were weakly associated with a high refractory relapse rate (p=0.056 and p=0.072, respectively).

Survival analysis according to the indices based on WBC and WBC differential counts. Univariate survival analysis showed that high NMR (p=0.018), low MLR (p=0.002), low MWR (p<0.001), low MER (p<0.001), low SIRI (p=0.038), and low IRR (p=0.001) were associated with better OS (Table IV). Multivariate analyses showed that low MLR (p=0.005), low MWR (p<0.001), low NER (p=0.021), low MER (p=0.002), and low IRR (p<0.001) were prognostic factors for better OS. MLR, MWR, MER, and IRR were significantly associated with OS on both univariate and multivariate analyses.

Survival analysis by WBC and WBC differential counts. Low WBC count (<7,000 /μl) and low monocyte count (<500/μl) were significantly associated with better OS on both univariate and multivariate analyses (Table V). The additional multivariate analysis performed for WBC differential counts showed that low monocyte count (<500/μl) (p=0.011) and high eosinophil count (>100/μl) (p<0.042) were prognostic factors for better OS. In contrast, neutrophil count and lymphocyte count were not significantly associated with OS in any analysis. Furthermore, no association was identified between relapse patterns subsequent to first-line chemotherapy and WBC or WBC differential counts.

Discussion

In this study, the prognostic values of the 13 indices based on WBC and WBC differential counts, namely NLR, dNLR, NMR, MLR, NWR, LWR, MWR, NER, LER, MER, ENLR, SIRI, and IRR, were evaluated in patients with ES-SCLC who underwent CBDCA plus VP16 or CDDP plus CPT-11 as first-line chemotherapy. The results showed that low values of MLR, MWR, MER, and IRR before platinum-doublet chemotherapy were associated with longer OS on

Table II. *Scores of white blood cell differential-based indices (n=102).*

Models	Values
NLR	
Median (range)	3.213 (1.279 to 17.627)
<2.8	n=42
≥2.8	n=60
dNLR	
Median (range)	2.246 (1.027 to 10.835)
<1.75	n=30
≥1.75	n=72
NMR	
Median (range)	10.544 (8.413 to 28.805)
<8.9	n=33
≥8.9	n=69
MLR	
Median (range)	0.309 (0.098 to 1.083)
<0.25	n=31
≥0.25	n=71
NWR	
Median (range)	0.692 (0.507 to 0.916)
<0.64	n=32
≥0.64	n=70
LWR	
Median (range)	0.214 (0.052 to 0.402)
<0.24	n=59
≥0.24	n=43
MWR	
Median (range)	0.066 (0.031 to 0.112)
<0.07	n=63
≥0.07	n=39
NER*	
Median (range)	41.8 (3.595 to 689)
<38	n=42
≥38	n=59
LER*	
Median (range)	13.143 (1.259 to 169)
<9.7	n=30
≥9.7	n=71
MER*	
Median (range)	3.818 (0.371-63)
<4.5	n=56
≥4.5	n=45
ENLR	
Median (range)	329.234 (0-3,926.625)
<265	n=40
≥265	n=62
SIRI	
Median (range)	1.480 (0.393-7.227)
<1.7	n=59
≥1.7	n=43
IRR*	
Median (range)	12.533 (0.976-556.5)
<11	n=41
≥11	n=60

NLR: Neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; NMR: neutrophil-to-monocyte ratio; MLR: monocyte-to-lymphocyte ratio; NWR: neutrophil-to-white blood cell ratio; LWR: lymphocyte-to-white blood cell ratio; MWR: monocyte-to-white blood cell ratio; NER: neutrophil-to-eosinophil ratio; LER: lymphocyte-to-eosinophil ratio; MER: monocyte-to-eosinophil ratio; ENLR: Eosinophil*Neutrophil-to-Lymphocytes ratio; SIRI, systemic inflammation response index; IRR: inflammatory related ratio. *One case with an eosinophil count of 0 was excluded.

Table III. *Relapse patterns and white blood cell differential-based indices (n=88*).*

	Sensitive relapse	Refractory relapse	*p*-Value⁺
NLR			
<2.8	8	27	0.233
≥2.8	6	47	
dNLR			
<1.75	7	18	0.102
≥1.75	7	56	
NMR			
<8.9	3	25	0.534
≥8.9	11	49	
MLR			
<0.25	8	20	0.056
≥0.25	6	54	
NWR			
<0.64	7	20	0.116
≥0.64	7	54	
LWR			
<0.24	6	46	0.238
≥0.24	8	28	
MWR			
<0.07	12	45	0.125
≥0.07	2	29	
NER**			
<38	8	28	0.241
≥38	6	45	
LER**			
<9.7	7	21	0.132
≥9.7	7	52	
MER**			
<4.5	10	38	0.245
≥4.5	4	35	
ENLR			
<265	4	31	0.392
≥265	10	43	
SIRI			
<1.7	9	42	0.770
≥1.7	5	32	
IRR**			
<11	9	26	0.072
≥11	5	47	

NLR: Neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; NMR, neutrophil-to-monocyte ratio; MLR, monocyte-to-lymphocyte ratio; NWR: neutrophil-to-white blood cell ratio; LWR(lymphocyte-to-white blood cell ratio; MWR: monocyte-to-white blood cell ratio); NER: neutrophil-to-eosinophil ratio; LER: lymphocyte-to-eosinophil ratio; MER: monocyte-to-eosinophil ratio; ENLR: Eosinophil*Neutrophil-to-Lymphocytes ratio; SIRI, systemic inflammation response index; IRR, inflammatory related ratio. *14 cases were not evaluable. **One case with an eosinophil count of 0 was excluded. ⁺Fisher's exact test.

both univariate and multivariate analyses. Furthermore, multivariate analyses of WBC and WBC differential counts showed that longer OS was associated with low WBC count, low monocyte count, and high eosinophil count. In contrast, in the present study population, pretreatment NLR, dNLR, NWR, LWR, LER, ENLR, neutrophil count, and lymphocyte count were not significantly associated with OS in any analysis.

It is known that a close relationship exists between carcinogenesis and systemic inflammation, and WBCs are the primary effectors of the immune system protecting the body against infection and resolving tissue injury (21, 22). Recently, in a large epidemiological study, elevated WBC counts were associated with the risk of lung cancer (21). In addition, there have been several reports that elevated WBC counts are associated with poor survival in non-small cell lung cancer (NSCLC) patients (23, 24). Although the present study involved patients with ES-SCLC, similar to those past studies, elevated WBC counts were associated with shorter OS.

The roles of each WBC differential count in cancer-related inflammation and immune responses to cancer are described as follows. Neutrophils are classified into two types: high-density neutrophils, which directly target tumor cells and stimulate T-cell-mediated immune responses to enhance antitumor effects, and low-density neutrophils, which suppress antitumor T cell responses *via* the increase of vascular endothelial growth factor, leukotrienes, and arginases (19). During the initial stages of inflammation, neutrophils predominantly display the high-density neutrophil phenotype, whereas the low-density neutrophil phenotype becomes more prevalent as inflammation subsides. Lymphocytes, which are responsible for mediating both cellular and humoral immune responses, play a pivotal role in defending against pathogens, eliminating tumor cells, and regulating immune responses through the induction of apoptosis and the inhibition of tumor cell proliferation and migration (19). Monocytes release various pro-inflammatory cytokines, including interleukins (IL)-1, IL-6, IL-10, and tumor necrosis factor-α, which are linked to reduced survival and a worse prognosis in patients with malignant tumors (19). However, the precise role of eosinophils in cancer is not fully understood. Although eosinophils have been studied

Table IV. *Univariate analysis of overall survival (OS) by the log-rank test and multivariate analysis of OS by the Cox proportional hazard model.*

Index	n	Median OS (days)	*p*-Value in log-rank test	Multivariate adjusted[#] HR (95%CI)	*p*-Value in cox proportional hazards model
NLR					
<2.8	42	311 (244-474)		1.00	
≥2.8	60	229 (194-295)	0.231	1.232 (0.815-1.862)	0.323
dNLR					
<1.75	30	298 (213-520)		1.00	
≥1.75	72	245.5 (198-322)	0.864	1.120 (0.715-1.753)	0.621
NMR					
<8.9	33	213 (174-255)		1.00	
≥8.9	69	322 (218-434)	0.018	0.616 (0.380-1.001)	0.051
MLR					
<0.25	31	474 (288-627)		1.00	
≥0.25	71	216 (183-258)	0.002	1.979 (1.228-3.191)	0.005
NWR					
<0.64	32	298 (194-520)		1.00	
≥0.64	70	245.5 (198-322)	0.809	1.140 (0.730-1.782)	0.565
LWR					
<0.24	59	240 (194-295)		1.00	
≥0.24	43	300 (217-474)	0.270	0.835 (0.553-1.260)	0.390
MWR					
<0.07	63	345 (258-541)		1.00	
≥0.07	39	198 (142-245)	<0.001	2.547 (1.541-4.210)	<0.001
NER*					
<38	42	336.5 (217-573)		1.00	
≥38	59	245.0 (194-283)	0.0851	1.686 (1.082-2.626)	0.021
LER*					
<9.7	30	367 (218-627)		1.00	
≥9.7	71	245 (194-283)	0.067	1.507 (0.934-2.433)	0.093
MER*					
<4.5	56	351.5 (240-541)		1.00	
≥4.5	45	216.0 (183-260)	<0.001	1.979 (1.294-3.028)	0.002
ENLR					
<265	40	245.5 (183-283)		1.00	
≥265	62	329.5 (216-395)	0.195	0.729 (0.475-1.121)	0.150
SIRI					
<1.7	59	300 (244-396)		1.00	
≥1.7	43	216 (161-260)	0.038	1.486 (0.945-2.336)	0.087
IRR*					
<11	41	386 (240-627)		1.00	
≥11	60	217 (183-266)	0.001	2.232 (1.438-3.467)	<0.001

HR: Hazard ratio; CI: confidence interval; NLR: neutrophil-to-lymphocyte ratio; dNLR: derived neutrophil-to-lymphocyte ratio; NMR: neutrophil-to-monocyte ratio; MLR: monocyte-to-lymphocyte ratio; NWR: neutrophil-to-white blood cell ratio; LWR: lymphocyte-to-white blood cell ratio); MWR: monocyte-to-white blood cell ratio; NER: neutrophil-to-eosinophil ratio; LER: lymphocyte-to-eosinophil ratio); MER: monocyte-to-eosinophil ratio; ENLR: Eosinophil×Neutrophil-to-Lymphocytes ratio; SIRI: systemic inflammation response index; IRR: inflammatory related ratio. [#]Age, sex, Eastern Cooperative Oncology Group performance status, brain metastasis, liver metastasis, and interstitial lung disease adjusted. *One case with an eosinophil count of 0 was excluded.

for their potential prognostic value in NSCLC patients, most clinical data provided are heterogenous, and both pro- and anti-tumorigenic activities have been reported in pre-clinical models (25).

In the present study, both univariate and multivariate analyses showed that monocyte counts and monocyte-based indices were associated with OS in patients with advanced SCLC, suggesting that monocyte counts may be

Table V. *Univariate analysis of overall survival (OS) by the log-rank test and multivariate analysis of OS by the Cox proportional hazards model.*

Index	n	Median OS (days)	*p*-Value in log-rank test	Multivariate adjusted# HR (1) (95%CI)	*p*-Value in cox proportional hazards model	Multivariate adjusted* HR (2) (95%CI)	*p*-Value in cox proportional hazards model
WBC count (/μl)							
<7,000	44	339.5 (200-573)		1.00		–	
≥7,000	58	244.5 (194-295)	0.013	1.601 (1.009-2.542)	0.046	–	–
Neutrophil count (/μl)							
<5,000	51	300 (213-483)		1.00		1.00	
≥5,000	51	244 (183-295)	0.173	1.214 (0.803-1.834)	0.358	0.845 (0.513-1.389)	0.506
Lymphocyte count (/μl)							
<1,500	48	239 (191-396)		1.00		1.00	
≥1,500	54	262 (217-322)	0.819	1.151 (0.755-1.755)	0.514	1.041(0.653-1.658)	0.867
Monocyte count (/μl)							
<500	61	322 (255-483)		1.00		1.00	
≥500	41	194 (146-258)	0.001	1.858 (1.186-2.908)	0.007	2.060 (1.177-3.603)	0.011
Eosinophil count (/μl)							
<100	40	245.5 (183-283)		1.00		1.00	
≥100	62	325 (217-395)	0.11	0.678 (0.447-1.026)	0.066	0.636 (0.411-0.9846)	0.042

HR: Hazard ratio; CI: confidence interval; WBC: white blood cell. #Age, sex, Eastern Cooperative Oncology Group performance status, brain metastasis, liver metastasis, and interstitial lung disease adjusted. *Age, sex, Eastern Cooperative Oncology Group performance status, brain metastasis, liver metastasis, interstitial lung disease, neutrophil count, lymphocyte count, monocyte count, and eosinophil count adjusted.

useful for predicting prognosis in cancer patients. Regarding NLR, for which no significant results were obtained in the present study, systematic reviews and meta-analyses have reported a significant association with prognosis in lung cancer patients (7, 10, 11). However, there was considerable heterogeneity among the studies of NLR, cutoff values varied between studies, and some studies did not find significant associations (10, 11, 22, 26-29). This may be because NLR is not a tumor-specific marker, and it may be strongly affected by bacterial infections, steroid use, and other factors (7). In contrast, monocyte counts might be less affected by bacterial infections and/or steroid use than neutrophil and/or lymphocyte counts. However, even for indices other than NLR, there seemed to be room for discussion regarding indices based on WBC and WBC differential counts, such as the issue of optimal cutoff values (7). Furthermore, it should be noted that the differences in the relative importance of these indices and the underlying mechanisms causing these differences remain unclear.

Study limitations. This was a single-center study with a small number of patients and a retrospective study design. Larger validation studies are warranted to re-evaluate the present findings. In addition, the associations between basophil counts or indices using basophils and OS were not investigated in this study, since the number of basophils is very small, and indices using basophils are extremely rare. However, in future research, it might be necessary to evaluate the usefulness of basophils for predicting the prognosis of cancer patients. Regarding chemotherapy regimens, in the present study, more than 80% of patients received chemotherapy using CBDCA and VP16, and patients who received chemotherapy including anti-PD-L1 antibody were excluded. Therefore, although the type of chemotherapy may affect the association between indices based on WBC and WBC differential counts and the prognosis of patients with ES-SCLC, the impact of differences in types of chemotherapy could not be evaluated in this study. Last, the present study failed to examine the associations between the indices combined with other blood test markers, namely platelet counts, hemoglobin levels, CRP levels and albumin levels, and prognosis in patients with ES-SCLC. Due to the substantial number of indices in existence, the present study was focused exclusively on WBC and WBC differential counts.

In conclusion, the present findings suggest that WBC counts, monocyte counts, MLR, MWR, MER, and IRR before platinum-doublet chemotherapy are prognostic markers in patients with ES-SCLC. Future larger-scale and multicenter studies, including those using anti-PD-L1 antibody, are warranted to validate these findings. We believe that these findings will provide clinicians an opportunity to reconsider the importance of indices based on WBC and WBC differential counts in patients with advanced SCLC. Finally, the findings of this study appear to demonstrate the potential usefulness of monocyte counts and/or indices using monocytes as simple, cost-effective prognostic biomarkers in clinical practice, providing valuable information for predicting cancer patient outcomes.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Makoto Nakao designed the study and wrote the initial drafts of the manuscript. Mamiko Kuriyama contributed to raw data collection, analyses, and interpretation. Hideki Muramatsu provided support throughout the study and assisted in the preparation of the manuscript. All other Authors contributed to interpretation and critically reviewed the manuscript. All the Authors read and approved the final manuscript.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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