Neutrophil-to-Lymphocyte Ratio Predicts Overall Survival of Advanced Non-Small Cell Lung Cancer Harboring Mutant Epidermal Growth Factor Receptor

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Abstract

Background: Neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) have been demonstrated to be prognostic biomarkers in various cancers, including non-small cell lung cancer (NSCLC). However, little has been known about these two ratios for a specific population of NSCLC harboring active epidermal growth factor receptor (EGFR) mutation.

Methods: We retrospectively reviewed electrical medical records of 152 patients who met the following criteria: NSCLC harboring mutant EGFR, EGFR-tyrosine kinase inhibitor (EGFR-TKI) monotherapy initiated between October 2007 and February 2017 at our hospital, stage III-IV or post-surgical recurrence. We compared overall survival (OS) and progression-free survival (PFS) between dichotomized groups by the optimal cut-off points of the two biomarkers. Univariate and multivariate Cox hazard analyses also searched for prognostic factors of survival time.

Results: OSs of NLR < 2.11 (median 38.6 vs. 24.1 months, P < 0.01) and LMR ≥ 5.09 (median 39.4 vs. 26.4 months, P < 0.01) were significantly longer than those of NLR ≥ 2.11 and LMR < 5.09. Multivariate analyses found lower NLR (hazard ratio (HR) 1.07, 95% CI: 1.01 - 1.14; P = 0.03) as an independent prognostic factor for longer OS, in addition to Eastern Cooperative Oncology Group performance status 0 - 1, first-line EGFR-TKI, higher serum sodium concentration and lower lactate dehydrogenase. However, LMR was not detected as a significant prognostic factor for OS. None of these two biomarkers was selected as an independent prognostic factor for PFS.

Conclusions: This study demonstrated that elevated NLR is an independent prognostic factor for poor survival of patients with EGFR mutant NSCLC. NLR is a useful and simple biomarker for these patients.

Introduction

Epidermal growth factor receptor (EGFR) mutation status divides non-small cell lung cancer (NSCLC) into two genetic subsets, NSCLC with positive EGFR mutation and NSCLC with wild-type EGFR. For the former subset, EGFR tyrosine kinase inhibitors (EGFR-TKIs) provide better efficacy and longer survival than conventional cytotoxic chemotherapy. Thus, exclusively for these selected patients, EGFR-TKIs are prioritized over conventional chemotherapy. However, these drugs are not always effective for them. Overall response rate ranged 60-80%. Many patients experienced tumor progression 9 - 13 months after initiation of EGFR-TKIs [1-6].

Patient's systemic inflammatory response (SIR) plays an adverse role in development and prognosis of cancers [7-9]. Neutrophils, lymphocytes and monocytes are important for the cancer-induced SIR [10, 11]. These three types of circulating cells represent the patients' SIR. Their peripheral absolute counts can predict prognoses of various malignancies, including NSCLC. According to a Japanese analysis of 388 chemonaive NSCLC with stage IIIB or IV, pretreatment elevated neutrophil count was significantly associated with shorter overall survival (OS) and progression-free survival (PFS). However, this study failed to show any association between prognosis and lymphocyte or monocyte count [12]. On the other hand, another Japanese multivariate analysis of 237 node-negative NCSLC demonstrated that a preoperative peripheral lymphocyte count was an independent prognostic factor for OS rate, but the neutrophil count was not [13]. A Chinese multivariate analysis of 142 patients with NSCLC who had underwent lobectomy, lymph node dissection and adjuvant chemotherapy also detected preoperative lymphocyte count, but not neutrophil count, as an independent prognostic factor of disease-free survival [14]. These two studies considered that peripheral lymphocyte count was associated with vascular or lymphatic invasion [13, 14]. Regarding peripheral monocyte count, in a Chinese analysis of 370 patients who had received platinum-based doublet for pre-

Table 1. Comparisons of Backgrounds and Laboratory Data Between Two Groups Divided According to Neutrophil-to-Lymphocyte and Lymphocyte-to-Monocyte Ratios

Groups	ALL	NLR			LMR		
		< 2.11	≥ 2.11	P	< 5.09	≥ 5.09	P
N	152	54	98		105	47	
Backgrounds							
Age (years, mean ± SD)	70.3 ± 10.3	70.5 ± 8.6	70.2 ± 11.1	0.66[a]	70.4 ± 10.7	70.1 ± 9.4	0.69[a]
Sex (N, male/female)	57/95	15/39	42/56	0.08[b]	45/60	12/35	0.047[b]
Histology (N, Ad/others)	148/4	54/0	94/4	0.30[b]	101/4	47/0	0.31[b]
Stage (N, IIIA/IIIB/IV/Rec)	10/3/102/37	4/2/30/18	6/1/72/19	0.10[b]	6/1/74/24	4/2/28/13	0.32[b]
Distant met (N)	132	46	86	0.44[b]	95	39	0.28[b]
Brain met (N)	32	13	19	0.54[b]	21	11	0.67[b]
Liver met (N)	14	3	11	0.38[b]	10	4	1.00[b]
Bone met (N)	55	11	44	< 0.01[b]	45	10	0.01[b]
ECOG PS (N, 0 - 1/2/3/4)	111/32/7/2	49/5/0/0	62/27/7/2	< 0.01[b]	68/28/7/2	43/4/0/0	< 0.01[b]
BMI (mean ± SD)	21.8 ± 4.1	22.0 ± 3.3	21.6 ± 4.5	0.13[a]	21.7 ± 4.4	22.0 ± 3.4	0.30[a]
EGFR mt (N)[c]							
Ex 19del	74	27	47		50	24	
Ex 21 point mt	74	25	49		53	21	
Minor mt	6	3	3		3	3	
Ex19 del vs. other	74/78	27/27	47/51	0.87[b]	50/55	24/23	0.73[b]
Laboratory data							
Neut (cells/μL)	4,183 ± 1,956	3,075 ± 1,095	4,793 ± 2,060	< 0.01[a]	4,606 ± 2,093	3,237 ± 1,155	< 0.01[a]
Lymph (cells/μL)	1,496 ± 605	1,962 ± 554	1,239 ± 463	< 0.01[a]	1,338 ± 507	1,850 ± 659	< 0.01[a]
Mono (cells/μL)	411 ± 177	349 ± 123	446 ± 193	< 0.01[a]	468 ± 175	286 ± 101	< 0.01[a]

[a]Mann-Whitney test. [b]Fisher's extract test. [c]Double mutations. Exon 19del + Exon 21 L858R and Exon 21 L858R + Exon 18 G719S in each one case. Ad: adenocarcinoma; BMI: body mass index; del: deletion; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; LMR: lymphocyte-to-monocyte ratio; Lymph: lymphocyte; met: metastasis; Mono: monocyte; mt: mutation; Neut: neutrophil; NLR: neutrophil-to-lymphocyte ratio; Rec: post-surgical recurrence; SD: standard deviation.

viously untreated metastatic NSCLC, monocyte count was an independent prognostic factor for PFS and OS [15].

Recently, there has been increasing evidences of the prognostic value of combined scoring systems based on the SIR. Especially, neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) are easily calculated from leukocyte count and differentiation. Elevated NLR [16-18] and decreased LMR [15, 19] have been demonstrated to be associated with poor prognosis in various cancers, including advanced NSCLC. However, little has been known about these two ratios for a specific genetic subset of EGFR mutant NSCLC.

In this study, we evaluate the prognostic value of NLR and LMR in patients with EGFR mutant NSCLC.

Methods

This study was retrospective and single institutional. We collected the following patients: 1) patients who started EGFR-TKIs monotherapy between October 2007 and February 2017, 2) histologically or cytologically proven NSCLC, and positive EGFR mutation status confirmed by the peptide nucleic acid-locked nucleic acid PCR clamp method by LSI Medience Cooperation (Tokyo, Japan) [20], 3) c-stage IIIA-B, IV or post-surgical recurrence, based on the 7th TNM classifica-

tion of lung cancer by the Union for International Cancer Control (UICC) [21], 4) patients who received blood test within 1 week before the initiation of EGFR-TKIs. In Japan, gefitinib, erlotinib and afatinib were approved for NSCLC in July 2002, October 2007 and January 2014, respectively. EGFR mutation tests became covered by insurance in June 2007. The definitions of overall response rate (RR), disease control rate (DCR), PFS and OS in this study followed those of our previous studies [22, 23]. When RR, DCR and PFS were calculated, sequential change from a TKI to another TKI due to adverse effects was arbitrarily defined as one regimen treatment in this study. When we calculated creatinine clearance (Ccr) by means of Cockcroft-Gault equation, we added 0.2 mg/dL on serum creatinine values determined by the enzymatic method [24]. Peripheral venous blood (approximately 2 mL) was collected into a sterile ethylene-diamine-tetra-acetic acid (EDTA) tube. Hematological parameters were analyzed using hematology analyzers (Sysmex XE-2100 until 2012, and thereafter Sysmex XE-5000; Sysmex, Kobe, Japan). NLR and LMR were obtained by dividing pretreatment venous absolute circulating neutrophil count by lymphocyte count, and venous absolute circulating lymphocyte count by monocyte count, respectively. The data cut-off was September 1, 2017. The Osaka Police Hospital Ethics Committee approved this study (number 685), and waived the requirement for informed consent because de-

Table 2. Treatment and Outcomes

Group	All	NLR			LMR		
		< 2.11	≥ 2.11	Pa	< 5.09	≥ 5.09	Pa
N	152	54	98		105	47	
TKI choice (N, Gef/Erl/Afa)	107/36/9	43/10/1	64/26/8	0.12	72/27/6	35/9/3	0.68
TKI line (N, first/second/≥ third)	104/38/11	37/14/4	67/24/7	1.00	71/27/7	33/11/3	0.96
Pre TKI treatment (N)	49	18	31	0.86	34	10	0.18
Platinum-based	39	14	25	1.00	30	7	0.10
Curative-intent TRT	8	3	5	1.00	6	2	1.00
Post TKI treatment (N)	98	41	57	0.03	64	34	0.20
Cytotoxic drugs	62	26	36	0.23	40	22	0.37
Platinum-based	27	10	17	1.00	18	13	0.19
Osimertinib	14	5	9	1.00	9	5	0.76
Re-challenge of TKI	62	27	35	0.12	42	22	0.48
Palliative radiotherapy (N)	57	18	39	0.49	38	19	0.72
TKI Response (N)							
Complete response	5	3	2		2	3	
Partial response	88	36	52		55	33	
Stable disease	29	11	18		21	8	
Progressive disease	19	2	17		18	1	
Not evaluated	11	2	9		9	2	
RR (%) (95% CI)	61.2 (53.0 - 69.0)	72.2 (58.4 - 83.5)	55.1 (44.7 - 65.2)	0.055	54.3 (44.3 - 64.0)	76.6 (62.0 - 87.7)	0.01
DCR (%) (95% CI)	80.3 (73.0 - 86.3)	92.6 (82.1- 97.9)	73.5 (63.6 - 81.9)	< 0.01	74.3 (64.8 - 82.3)	93.6 (82.5 - 98.7)	< 0.01

aFisher's extract test. Afa: afatinib; CI: confidence interval; DCR: disease control rate; Erl: erlotinib; Gef: gefitinib; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; RR: response rate; TKI: tyrosine kinase inhibitor; TRT: thoracic radiotherapy.

identified data were retrospectively collected.

We described the continuous, categorical and survival variables as the mean ± standard deviation (SD), frequency, median (95% confidential intervals (CIs)), respectively. We used Fisher's exact and Mann-Whitney tests for comparison of the relative frequencies and continuous variables that were not normally distributed, respectively. Using receiver operating characteristic (ROC) curve and Youden index, we selected the optimal cut-off values of NLR and LMR, and then divided our patients into two groups. We arbitrary defined complete and partial responses of EGFR-TKIs as the outcome variables of ROC analysis. The results of ROC analyses were expressed as sensitivity, specificity, area under the curve (AUC) with 95% CI. We used Kaplan-Meier method to evaluate PFS and OS, and compared two groups by log-rank test.
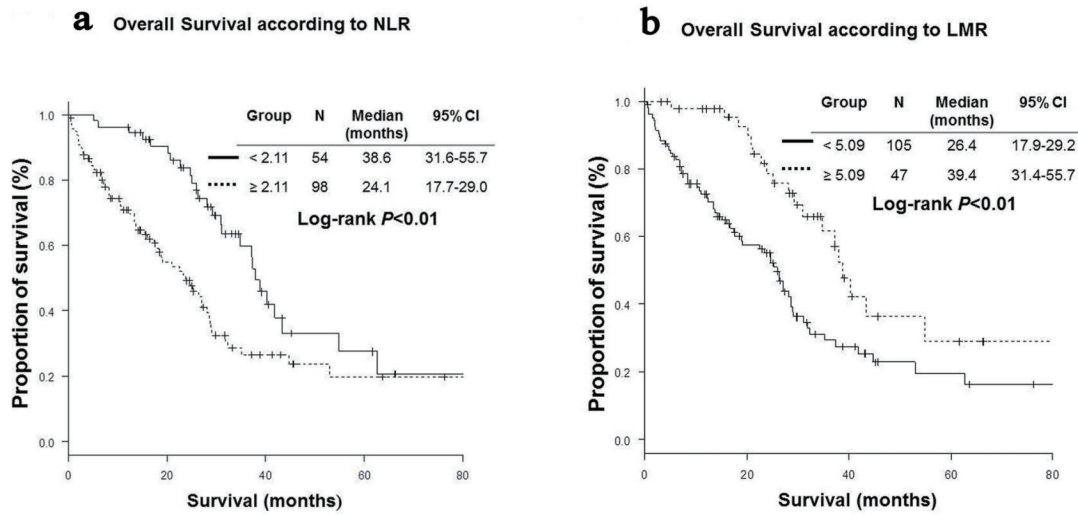
To investigate independent prognostic factors, we used Cox proportional hazard analyses. After the univariate analysis, only variables with P-value < 0.1 were used in the multivariate analysis. The results were described as hazard ratios (HR) and 95% CI. P-value < 0.05 was defined as statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [25].

Results

We collected 152 patients for this study. At the time of data-cut off, 85 patients were dead, 39 still alive and 28 lost to follow-up. As for the first TKI treatment, 15 patients still continued TKI, while the other 137 discontinued TKI because of PD in 84, adverse effects in 20, deteriorated comorbidity or general condition in 17, change regimens from EGFR-TKI to cytotoxic drugs before PD in 5, patients' refusal in 3, transfer to other hospitals in 6 and unidentified death in 2. Eleven patients changed TKIs mainly due to adverse effects. As the optimal cut-off points of NLR and LMR, ROC curves defined 2.11 (sensitivity 0.75, specificity 0.42, AUC 0.54, 95% CI 0.44 - 0.64) and 5.09 (sensitivity 0.83, specificity 0.39, AUC 0.60, 95% CI 0.51 - 0.69), respectively.

High NLR group (NLR ≥ 2.11) included more patients with bone metastases (45% vs. 20%, P < 0.01) and severe Eastern Cooperative Oncology Group performance status (ECOG PS) (P < 0.01) than low NLR group (NLR < 2.11). High LMR group (LMR ≥ 5.09) was characteristics of more female (74% vs. 57%, P = 0.047), less frequent bone metastases (21% vs. 43%, P = 0.01), better PS (P < 0.01) than low LMR group (LMR < 5.09) (Table 1). Patients with low NLR were more likely to receive further line chemotherapy (76% vs. 58%, P = 0.03). RR were significantly higher in high LMR group than in low LMR group (76.6% vs. 54.3%, P = 0.01). DCRs were significantly higher in low NLR (92.6% vs. 73.5%, P < 0.01) and high LMR (93.6% vs. 74.3%, P < 0.01) groups than in high NLR and low LMR groups (Table 2). OS of low NLR (OS, 38.6 vs. 24.1 months in median, P < 0.01) and high LMR (OS, 39.4 vs. 26.4 months, P < 0.01) groups were significantly longer than those of high NLR and low LMR groups (Fig. 1).

a Overall Survival according to NLR

b Overall Survival according to LMR

Group	N	Median (months)	95% CI
< 2.11	54	38.6	31.6-55.7
≥ 2.11	98	24.1	17.7-29.0

Log-rank *P*<0.01

Group	N	Median (months)	95% CI
< 5.09	105	26.4	17.9-29.2
≥ 5.09	47	39.4	31.4-55.7

Log-rank *P*<0.01

Figure 1. Kaplan-Meier curves of overall survival. (a) Neutrophil-to-lymphocyte ratio (NLR). (b) Lymphocyte-to-monocyte ratio (LMR).
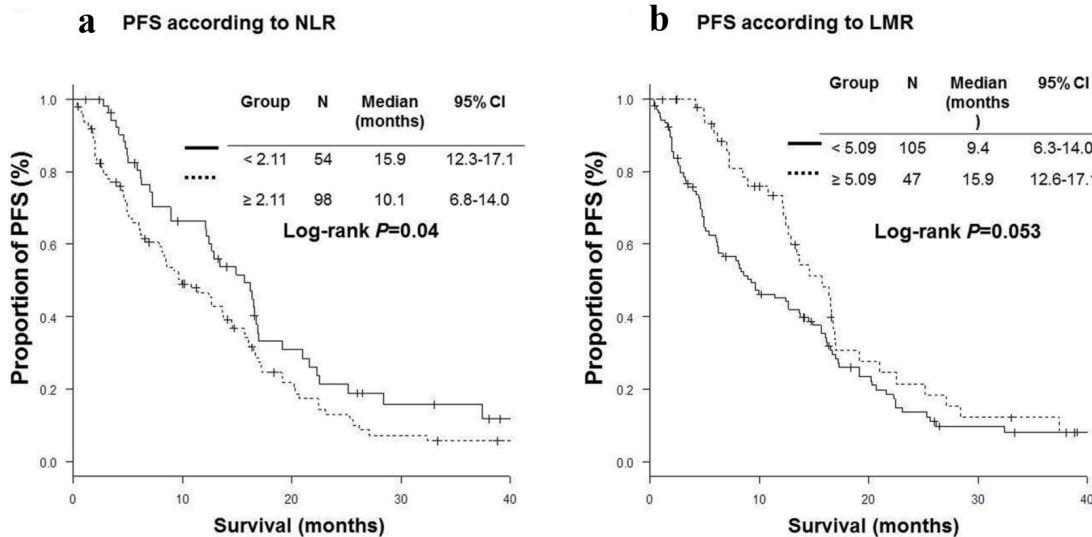
However, PFS of low NLR (PFS, 15.9 vs. 10.1 months in median, P = 0.04) group was significantly longer than those of high NLR group, while there was no statistically significant difference in PFS according to LMR (Fig. 2).

Univariate analyses detected ECOG PS 0 - 1, higher Ccr, higher sodium concentration, lower lactate dehydrogenase (LDH), lower C-reactive protein (CRP), lower NLR and higher LMR as prognostic factors for longer OS; no distant metastasis, ECOG PS 0 - 1, body mass index (BMI) ≥ 18.5, EGFR-TKI introduction in first-line setting, treatment with erlotinib or afatinib, higher Ccr, higher sodium concentration, lower LDH, lower CRP, lower NLR and higher LMR as predictive factors for longer PFS (Table 3). The subsequent multivariate

analyses found lower NLR (HR 1.07, 95%CI: 1.01 - 1.14; P = 0.03) as an independent prognostic factor for longer OS, in addition to ECOG PS 0 - 1, first-line introduction of EGFR-TKI, higher sodium concentration and lower LDH. However, LMR was not detected as a significant prognostic factor for OS (Table 4). Neither NLR nor LMR was selected as a significant prognostic factor for PFS (Table 5).

Discussion

This study was a comprehensive evaluation of two biomarkers and prognosis in patients with EGFR mutant NSCLC treated

a PFS according to NLR

b PFS according to LMR

Group	N	Median (months)	95% CI
< 2.11	54	15.9	12.3-17.1
≥ 2.11	98	10.1	6.8-14.0

Log-rank *P*=0.04

Group	N	Median (months)	95% CI
< 5.09	105	9.4	6.3-14.0
≥ 5.09	47	15.9	12.6-17.1

Log-rank *P*=0.053

Figure 2. Kaplan-Meier curves of progression-free survival (PFS). (a) Neutrophil-to-lymphocyte ratio (NLR). (b) Lymphocyte-to-monocyte ratio (LMR).

Table 3. Univariate Cox Hazard Analyses of Factors Associated With Overall Survival and Progression-Free Survival

	OS			PFS		
	HR	95% CI	P	HR	95% CI	P
Age (years < 75 vs. ≥ 75)	1.18	0.75 - 1.85	0.48	0.97	0.67 - 1.41	0.88
Sex (female vs. male)	1.33	0.86 - 2.07	0.19	1.17	0.81 - 1.68	0.41
Distant metastasis (no vs. yes)	2.08	0.99 - 4.38	0.054	2.10	1.12 - 3.93	0.02
ECOG PS (0 - 1 vs. 2 - 4)	4.08	2.56 - 6.50	< 0.01	1.98	1.33 - 2.93	< 0.01
BMI (≥ 18.5 vs. < 18.5)	1.58	0.95 - 2.64	0.08	1.60	1.04 - 2.47	0.03
EGFR mutation (exon 19 del vs. others)	1.27	0.82 - 1.95	0.29	1.14	0.79 - 1.63	0.49
EGFR-TKI line (first vs. second or later)	1.46	0.94 - 2.26	0.09	1.47	1.01 - 2.15	0.04
EGFR-TKI (Gef vs. Erl or Afa)	0.84	0.50 - 1.41	0.51	0.61	0.40 - 0.92	0.02
Hemoglobin (g/dL)	0.89	0.77 - 1.02	0.09	0.94	0.85 - 1.05	0.29
Ccr (mL/min) (/10)	0.86	0.74 - 0.998	0.047	0.88	0.78 - 0.99	0.04
Sodium (mEq/L) (/10)	0.19	0.10 - 0.39	< 0.01	0.34	0.19 - 0.62	< 0.01
LDH (IU/L) (/100)	1.36	1.19 - 1.54	< 0.01	1.24	1.11 - 1.39	< 0.01
CRP (mg/dL)	1.17	1.08 - 1.27	< 0.01	1.19	1.10 - 1.29	< 0.01
NLR	1.12	1.07 - 1.18	< 0.01	1.08	1.03 - 1.13	< 0.01
LMR	0.78	0.69 - 0.89	< 0.01	0.89	0.81 - 0.98	0.02

Afa: afatinib; BMI: body mass index; Ccr: creatinine clearance; CI: confidence interval; CRP: C-reactive protein; del: deletion; ECOG PS: Eastern Cooperative Oncology Group performance status; EGFR-TKI: epidermal growth factor receptor- tyrosine kinase inhibitor; Erl: erlotinib; Gef: gefinitib; HR: hazard ratio; LDH: lactate dehydrogenase; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; OS: overall survival; PFS: progression-free survival.

with EGFR-TKIs. To our knowledge, there were only four studies and one study that had investigated association of NLR [26-29] and LMR [30] with prognosis, respectively (Table 6).

NLR is an independent prognostic factor for OS of those selected population. Our survival comparisons and multivariate analyses demonstrated that higher NLR was associated with poorer OS, and were consistent with previous three studies [26-28]. On the other hand, despite of significantly longer OS in patients with LMR ≥ 5.09, our multivariate analysis failed to detect LMR as a significant prognostic factor for OS. This result was different from the previous larger-scaled study [30]. Our study scale might be insufficient to evaluate LMR.

Both NLR and LMR are still controversial as prognostic

factors for PFS of EGFR-TKI treatment. In our survival comparisons, PFSs of patients with NLR ≥ 2.11 and LMR < 5.09 were significantly shorter than those of patients with NLR < 2.11 and LMR ≥ 5.09, respectively. However, our multivariate analyses did not detect NLR and LMR as independent prognostic factors for PFS. As an independent prognostic factor for shorter PFS, NLR ≥ 3.5 [27, 28] and NLR ≥ 5 [26] were demonstrated by previous studies. However, a Korean study failed to demonstrate NLR ≥ 3 as a significant prognostic factor [29]. On the other hand, a Taiwan study found that high baseline LMR was an independent prognostic factor for PFS of first-line TKIs [30], which was contrary to ours. Between the Taiwan and our studies, there seemed to be some differences in

Table 4. Multivariate Cox Hazard Analyses of Factors Associated With Overall Survival

	NLR			LMR		
	HR	95% CI	P	HR	95% CI	P
Distant metastasis (no vs. yes)	1.59	0.73 - 3.50	0.25	1.44	0.64 - 3.24	0.38
ECOG PS (0 - 1 vs. 2 - 4)	3.46	2.03 - 5.89	< 0.01	3.41	1.99 - 5.82	< 0.01
BMI (≥ 18.5 vs. < 18.5)	1.62	0.89 - 2.93	0.12	1.58	0.87 - 2.87	0.14
EGFR-TKI line (first vs. second or later)	1.71.	1.07 - 2.73	0.02	1.72	1.08 - 2.74	0.02
Hemoglobin (g/dL)	1.14	0.97 - 1.34	0.11	1.15	0.98 - 1.36	0.08
Ccr (mL/min) (/10)	0.86	0.73 - 1.02	0.08	0.86	0.73 - 1.01	0.07
Sodium (mEq/L) (/10)	0.30	0.13 - 0.71	< 0.01	0.27	0.11 - 0.64	< 0.01
LDH (IU/L) (/100)	1.24	1.05 - 1.48	0.01	1.27	1.07 - 1.50	< 0.01
CRP (mg/dL)	1.01	0.90 - 1.14	0.82	0.98	0.86 - 1.11	0.74
NLR	1.07	1.01 - 1.14	0.03	-	-	-
LMR	-	-	-	0.88	0.76 - 1.01	0.07

BMI: body mass index; Ccr: creatinine clearance: CI: confidence interval; CRP: C-reactive protein; ECOG PS: Eastern Cooperative Oncology Group performance status; EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitors; HR: hazard ratio; LDH: lactate dehydrogenase; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio.

Table 5. Multivariate Cox Hazard Analyses of Factors Associated With Progression-Free Survival

	NLR			LMR		
	HR	95% CI	P	HR	95% CI	P
Distant metastasis (no vs. yes)	1.69	0.87 - 3.27	0.12	1.77	0.92 - 3.42	0.09
ECOG PS (0 - 1 vs. 2 - 4)	1.55	0.97 - 2.47	0.07	1.63	1.01 - 2.61	0.04
BMI (≥ 18.5 vs. < 18.5)	1.53	0.94 - 2.47	0.09	1.57	0.96 - 2.55	0.07
EGFR-TKI line (first vs. second or later)	1.47	0.99 - 2.19	0.058	1.49	1.00 - 2.23	0.049
EGFR-TKI (Gef vs. Erl or Afa)	0.63	0.40 - 0.99	0.046	0.64	0.41 - 1.01	0.06
Ccr (mL/min) (/10)	0.94	0.82 - 1.08	0.37	0.94	0.82 - 1.07	0.36
Sodium (mEq/L) (/10)	0.60	0.30 - 1.20	0.15	0.60	0.30 - 1.21	0.16
LDH (IU/L) (/100)	1.11	0.97 - 1.27	0.15	1.12	0.98 - 1.29	0.10
CRP (mg/dL)	1.10	0.99 - 1.22	0.08	1.10	0.99 - 1.23	0.07
NLR	1.03	0.97 - 1.10	0.29	-	-	-
LMR	-	-	-	1.00	0.90 - 1.12	0.99

Afa: afatinib; ALP: alkaline phosphatase; BMI: body mass index; Ccr: creatinine clearance; CI: confidence interval; CRP: C-reactive protein; ECOG PS: Eastern Cooperative Oncology Group performance status; EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitors; Erl: erlotinib; Gef: gefitinib; HR: hazard ratio; LDH: lactate dehydrogenase; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio.

age (65.2 ± 12.4 vs. 70.3 ± 10.3 years) and proportion of TKI in the first-line setting (100% vs. 68.4%). Furthermore, significant prognostic factors detected by multivariate analyses for PFS were different. Our study found ECOG PS (0 - 1 vs. 2 - 4) and TKI line setting (first vs. second or later line), while the Taiwan study detected LMR, the 1-month-to-basline ratio of LMR, EGFR mutation (common vs. uncommon) and distant metastases (0 - 2 vs. > 2). Thus, there is no established view on these two biomarkers as prognostic factors for PFS.

Our study included some limitations. First, we are afraid that our study was too small to find these two biomarkers as significant factors. Especially, our study underestimated LMR

as a prognostic factor for OS. Second, our study might include case bias because of a single-centered and retrospective study. Multi-centered, prospective and larger-sized studies are ideal for such a specific cancer population.

Conclusions

This study demonstrated that elevated NLR is an independent prognostic factor for poor survival of patients with EGFR mutant NSCLC. NLR is a useful and simple biomarker for these patients, while LMR requires further studies as a significant

Table 6. Review of Previous Studies of Multivariate Analyses for Prediction of Survival Outcomes in Patients With EGFR Mutant NSCLC

Author (year)	Country	N	Treatment	Variable	Cut-off	Multivariate analyses			
						OS		PFS	
						HR (95% CI)	P	HR (95% CI)	P
Lin et al [27] (2014)	China	81	Gef (30%) Erl (70%) All first-line	NLR	3.5	3.29 (1.62 - 6.71)	< 0.001	3.89 (1.98 - 7.68)	< 0.001
Chen et al [30] (2015)	Taiwan	253	All first-line	LMR	3.29	2.36 (1.66 - 3.35)	< 0.001	1.71 (1.14 - 2.56)	0.009
Sim et al [29] (2016)	Korea	85	All first-line	NLR	3	NA	NA	1.239 (0.693 - 2.215)	0.469
Meriggi et al [28] (2017)	Italy	63	Gef (71%) Erl (29%)	NLR	3.5	2.699 (1.187 - 6.137)	0.018	2.275 (1.257 - 4.116)	0.007
Ding et al [26] (2017)	Australia	85	First-line (85%)	NLR	5	0.43 (0.19 - 0.94)	0.04	0.40 (0.18 - 0.87)	0.02
Ours	Japan	152	Gef (70%) Erl (24%) First-line (68%)	NLR	-	1.07 (1.01 - 1.14)	0.03	1.03 (0.97 - 1.10)	0.29
				LMR	-	0.88 (0.76 - 1.01)	0.07	1.00 (0.90 - 1.12)	0.99

CI: confidence interval; Erl: erlotinib; Gef: gefitinib; HR: hazard ratio; NA: not assessed; LMR: lymphocyte-to-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; OS: overall survival; PFS: progression free survival.

biomarker.

Acknowledgments

Conflict of Interest

The authors declare that they have no conflict of interest.

Grant Support

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