Value of neutrophil-to-lymphocyte ratio for predicting lung cancer prognosis: A meta-analysis of 7,219 patients

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Abstract. Current evidence suggests that the neutrophil-to-lymphocyte ratio (NLR) may be a biomarker for poor prognosis in lung cancer, although this association remains controversial. Therefore, a meta-analysis was performed to evaluate the association between NLR and lung cancer outcome. A systematic literature search was performed through the PubMed, Embase and Cochrane Library databases (until July 30, 2016), to identify studies evaluating the association between NLR and overall survival (OS) and/or progression-free survival (PFS) among patients with lung cancer. Based on the results of this search, data from 18 studies involving 7,219 patients with lung cancer were evaluated. The pooled hazard ratio (HR) suggested that elevated pretreatment NLR predicted poor OS [HR=1.46, 95% confidence interval (CI): 1.30-1.64] and poor PFS (HR=1.42, 95% CI: 1.15-1.75) among patients with lung cancer. Subgroup analysis revealed that the prognostic value of NLR for predicting poor OS increased among patients who underwent surgery (HR=1.50, 95% CI: 1.21-1.84) or patients with early-stage disease (HR=1.64, 95% CI: 1.37-1.97). An NLR cut-off value of ≥4 significantly predicted poor OS (HR=1.56, 95% CI: 1.31-1.85) and PFS (HR=1.54, 95% CI: 1.13-1.82), particularly in the cases of small-cell lung cancer. Thus, the results of the present meta-analysis suggested that an elevated pretreatment NLR (e.g., ≥4) may be considered as a biomarker for poor prognosis in patients with lung cancer.

Introduction

Lung cancer is a leading cause of morbidity and mortality worldwide (1,2). The two main types of lung cancer are non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC), which account for 85 and 15% of all cases, respectively (3). However, despite improvements in the modalities for diagnosing and treating lung cancer, the prognosis remains poor. Thus, novel and effective prognostic factors, which may allow clinicians to use effective therapeutic strategies, are urgently needed.

The traditional prognostic markers for lung cancer prognosis include patient age (4), sex (5), smoking (6), and TNM classification (7). There are also novel biomarkers that are able to predict prognosis and guide clinical treatment, including elevated levels of carcinoembryonic antigen, cytokeratin-19 fragments, squamous cell carcinoma antigen, progastrin-releasing peptide, tumor M2-pyruvate kinase, and C-reactive protein (8). However, patients with the same TNM stage may have a different prognosis (9), whereas some of the abovementioned prognostic biomarkers are costly and, thus, not included in routine tests for the majority of the patients.

During recent years, an increasing number of studies have revealed an association between systemic inflammation and tumorigenesis-related factors, including tumor angiogenesis, progression, invasion and metastasis (10-13). Accumulating evidence also indicates that tumor-associated inflammation may be detected in the peripheral blood as neutrophilia and/or lymphopenia (14). This finding suggests that the levels of neutrophils and lymphocytes may function as a combined factor, which may more accurately reflect the inflammatory response, compared with a single factor. Thus, the neutrophil-to-lymphocyte ratio (NLR) has been developed as a novel indicator of inflammation, and an elevated NLR may be associated with a poor prognosis (15). Moreover, routine laboratory and blood tests are performed during the pre-treatment work-up for all patients, and these results may be used to evaluate the patient's NLR. Therefore, NLR is a minimally invasive and inexpensive biomarker that may be used to predict prognosis among patients with lung cancer. However, there is controversy regarding whether NLR is a convincing or effective clinical indicator, and the association between NLR and lung cancer remains unclear. The aim of the present meta-analysis was to evaluate whether NLR is of value for predicting the prognosis of lung cancer.

Data collection methods

Search strategy. A systematic search was performed through the PubMed, Embase and Cochrane Library databases from inception up to July 30, 2016. The search used the following terms: Neutrophil-to-lymphocyte ratio, neutrophil to lymphocyte ratio,

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neutrophil-lymphocyte ratio, neutrophil lymphocyte ratio, and MeSH terms (lung neoplasms AND prognosis). The reference lists from the identified reports were also reviewed, in order to retrieve other potentially relevant studies.

Study selection criteria. Articles were considered eligible if they fulfilled the following criteria: i) The patients were pathologically diagnosed with lung cancer (NSCLC or SCLC); ii) the study investigated the association between pretreatment NLR and various outcomes, including overall survival (OS), progression-free survival (PFS), disease-free survival, or recurrence-free survival; iii) reported hazard ratios (HRs) and 95% confidence intervals (CIs) or provided sufficient information to estimate the HRs and 95% CIs; and iv) the full text was accessible and written in English.

Data extraction. All the retrieved articles were independently reviewed by two investigators (Yu Yu and Lei Qian). The extracted data included the first author's name, year of publication, study duration, country, ethnicity, sample size, sex, age, stage, tumor type, follow-up period, treatment, study design, and cut-off value for elevated NLR with the HRs and/or 95% CIs. Disagreements were discussed and resolved through consensus.

Statistical analysis. Based on the methods of Tierney *et al* (16), the HRs and 95% CIs were estimated or extracted to evaluate the significance of NLR according to OS and PFS. A poorer prognosis was defined as an elevated NLR being associated with an HR of >1. Heterogeneity of the pooled results was tested using Cochran's Q test and Higgins' I-squared statistic, with an I^2 of >50% representing significant heterogeneity. The pooled HRs and 95% CIs were calculated using a random-effects model (Der Simonian-Laird method) or a fixed-effects model (Mantel-Haenszel method), as appropriate The random-effects model was defined as the preferred method when heterogeneity was detected. Inter-study heterogeneity was also investigated using subgroup analysis and meta-regression analysis. Sensitivity analysis was also performed to evaluate the stability and credibility of the results. Publication bias was assessed using Egger's funnel plot. All statistical tests were two-sided and P-values <0.05 were considered to indicate statistically significant differences. All statistical analyses were performed using Stata software, version 13.1 (StataCorp LP, College Station, TX, USA).

Results

Study characteristics. The study selection flow chart is shown in Fig. 1. The initial search through the PubMed, Embase and Cochrane Library databases identified 125 studies. After excluding duplicate reports, irrelevant reports, reviews and conference abstracts, aa total of 37 full-text reports were included in the evaluation. Subsequently, 19 studies were excluded for the following reasons: 7 studies failed to provide sufficient data for the analyses, 6 studies did not report the NLR cut-off value, 4 studies did not report specific NLR data according to OS, and 2 studies had data duplication. Thus, the final analyses included 18 studies (19 cohorts) (17-34) with 7,219 patients, published between 2009-2016. The patients in the report by Botta *et al* (22) were split into two independent cohorts (Botta 1 and Botta 2) due to the cohort design of the article.

The characteristics of the 18 studies are summarized in Table I. A total of 7 studies were conducted in Western countries, including the UK (17,26,34), USA (28), Spain (20) and Italy (22,34), 1 study was performed in Turkey (23), and 10 studies were performed in East Asian countries, including Japan (18,19,31,32), Korea (21,25) and China (24,27,30,33). The study published by Mitchell *et al* (29) included patient data from 33 countries. The included studies evaluated 16 populations of patients with NSCLC (17-24,26-29,31-34) and 2 populations of patients with SCLC (25,30). The 2 studies on SCLC reported tumor staging information as limited and extensive disease, so only the staging information from the studies regarding NSCLC were considered Only 1 study by Sarraf *et al* (17) evaluated all tumor stages, 8 studies evaluated early-stage tumors (23,26-29,31-33), and 6 studies evaluated late-stage tumors (18,20-22,24,34). The study by Tomita *et al* (19) evaluated stages IA/III/IV. The cut-off values for elevated NLR ranged from 2.5 to 5.

NLR and OS in lung cancer. A total of 17 studies with 17 cohorts (17-21,23-34) including 7,107 patients evaluated the association between elevated pretreatment NLR and OS among patients with lung cancer. The random-effects model was used for this analysis, as significant heterogeneity was detected (I^2=84.2%, $P_{heterogeneity}$<0.001). The pooled HR was 1.46 (95% CI: 1.30-1.64, P<0.001; Fig. 2), which suggested that elevated pretreatment NLR predicted poor OS after treatment for lung cancer.

NLR and PFS in lung cancer. A total of 7 studies with 8 cohorts (18,21,22,24,25,30,34) including 1,581 patients evaluated the association between elevated pretreatment NLR and PFS among patients with lung cancer. Significant heterogeneity was also detected among these studies (I^2=76.2%, $P_{heterogeneity}$<0.001). A pooled HR of 1.42 (95% CI: 1.15-1.75, P=0.001; Fig. 3) suggested that elevated pretreatment NLR predicted shorter PFS after treatment for lung cancer.

Subgroup analysis. A subgroup analysis was performed to identify the possible reason(s) for the significant heterogeneity in the meta-analysis (Table II). The OS-related subgroup analysis included 7 subgroups: Treatment (surgery and non-surgery), ethnicity (Caucasian and Asian), tumor stage (late stage: IIIB-IV; and early stage: I-IIIA), sample size (<200 and ≥200), NLR cut-off value (<4 and ≥4), tumor type (NSCLC and SCLC), and analysis method (multivariate and univariate). The results consistently demonstrated that elevated pretreatment NLR predicted poor OS after treatment for lung cancer. The PFS-related subgroup analysis included 5 subgroups (ethnicity, sample size, cut-off value, tumor type and analysis method), and the combined results were similar to those for OS. Interestingly, an NLR cut-off of ≥4 was found to be associated with significantly lower heterogeneity (OS: I^2=14.3%, $P_{heterogeneity}$=0.323; PFS: I^2=57.2%, $P_{heterogeneity}$=0.029), suggesting that an NLR of ≥4 was a useful prognostic indicator for both OS and PFS.

Heterogeneity. Meta-regression analysis was performed to explore the potential source(s) of heterogeneity in the

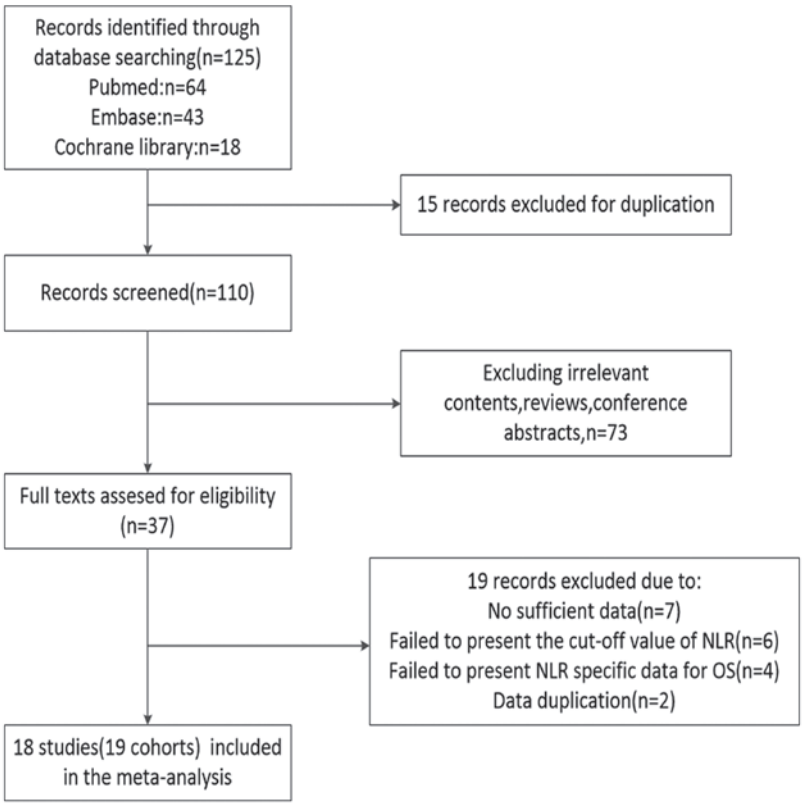

Figure 1. Flow chart of the included studies. NLR, neutrophil-to-lymphocyte ratio; OS, overall survival.

associations of NLR with OS and PFS. The results revealed that heterogeneity in the OS results was not significantly affected by treatment (P=0.725), ethnicity (P=0.976), tumor stage (P=0.305), sample size (P=0.156), cut-off value (P=0.807), or tumor type (P=0.884). The results also revealed that heterogeneity in the PFS results was not significantly affected by ethnicity (P=0.696), sample size (P=0.942), cut-off value (P=0.137), or tumor type (P=0.844).

Publication bias and sensitivity analysis. Egger's test revealed statistically significant publication bias for both OS and PFS (both P<0.05). A sensitivity analysis was performed by sequentially removing each study, and evaluating whether any individual study significantly affected the results. However, the pooled HRs and 95% CIs revealed that no single study significantly affected OS or PFS (Figs. 4 and 5).

Discussion

The present meta-analysis evaluated the prognostic value of elevated pretreatment NLR in 18 studies and 7,219 patients with lung cancer. To the best of our knowledge, this is the largest meta-analysis regarding this topic to date. The pooled HRs suggest that elevated pretreatment NLR was associated with poor OS (HR=1.46, 95% CI: 1.30-1.64) and poor PFS (HR=1.42, 95% CI: 1.15-1.75). Furthermore, the subgroup analysis revealed that an elevated pretreatment NLR of ≥4 effectively predicted poor OS and PFS after treatment for lung cancer, regardless of the analytical method. One previous study had used an NLR cut-off of 4 (35), and another study used a cut-off of 5 (35). Our results confirmed that an NLR of 4 is a more stable threshold for predicting prognosis, as our subgroup analysis with an NLR of ≥4 revealed significantly lower heterogeneity. We suggest that the setting of the reliable threshold of the NLR for predicting prognosis of lung cancer may be very helpful for clinical use. Of note, NLR may also better predict a poor OS for patients who undergo surgery (HR=1.50, 95% CI: 1.21-1.84) or patients with early-stage tumors (HR=1.64, 95% CI: 1.37-1.97), suggesting that NLR may be used as an independent prognostic indicator to monitor the postoperative outcome of patients with early-stage lung cancer. In cases with SCLC, NLR provided significantly improved prognostic value, without any heterogeneity in the OS and PFS analysis. The use of NLR may be promising in evaluating the prognosis of SCLC patients. However, additional studies are required to validate this association, as only 2 studies evaluating SCLC cases were identified.

Accumulating evidence suggests that a dysregulated inflammatory response plays a vital role in cancer (36). Infiltration by immune cells is increasingly accepted as an important part of the tumor microenvironment, which may lead to cancer-related inflammation (37). In this context, NLR has recently been introduced as a simple index of the systemic inflammatory response, as inflammation leads to more neutrophils and fewer lymphocytes in the peripheral blood. Together, these changes result in an elevated NLR. Neutrophils are the dominant leukocytes in the blood, and are the first line of defense against inflammation and infection (38). Neutrophil infiltration is also observed in a number of tumor types, and tumor-associated neutrophils in lung cancer are associated with malignant potential and a poor prognosis (39). According to Proctor *et al*, NLR may be a more sensitive

Table I. Characteristics of all the included studies.

First author	Year	Duration	Country	Ethnicity	Median follow-up, months (range)	Sample size	Sex (M/F)	Median/mean age, years ± SD (range)	Stage	Type	Treatment	Cut-off value	Survival analysis	Study design	Method	(Refs.)
Sarraf	2009	1999-2005	UK	Caucasian	29 (8-56)	177	104/73	63±10	I–IV	NSCLC	S	3.81	OS	R	MV	(17)
Teramukai	2009	2001-2005	Japan	Asian	18.9 (2.3-57)	388	276/112	65 (33-81)	IIIB/IV	NSCLC	C	4.74	OS, PFS	P	MV	(18)
Tomita	2011	2000-2005	Japan	Asian	60.7-131.7	284	178/106	67 (26-85)	IA/III/IV	NSCLC	S	2.5	OS	R	MV/UV	(19)
Cedrés	2012	2004-2009	Spain	Caucasian	9.1 (1-70.37)	171	143/28	63 (30-81)	IV	NSCLC	C	5	OS	R	MV/UV	(20)
Lee	2012	2005-2007	Korea	Asian	36 (33.6-37.9)	199	17/182	57 (19-74)	IIIB/IV	NSCLC	C or T	3.25	OS, PFS	P	MV/UV	(21)
Botta	2013	2008-2011	Italy	Caucasian	15	73	55/18	58.57±10.54[a]	IIIB/IV	NSCLC	C	4	PFS	R	UV	(22)
Botta	2013	2008-2011	Italy	Caucasian	15	39	26/13	67.85±9.67[a]	IIIB/IV	NSCLC	C+T	4	PFS	R	UV	(22)
Unal	2013	NR	Turkey	Caucasian	NR	94	88/6	58.1±8.6 (30-78)[a]	IIA-IIIB	NSCLC	C+R	3.44	OS, DFS	R	MV/UV	(23)
Yao	2013	2007-2010	China	Asian	NR	182	119/63	59 (28-79)	III-IV	NSCLC	C	2.63	OS, PFS	R	MV/UV	(24)
Kang	2014	2006-2013	Korea	Asian	40.28 (2.60-89.26)	187	162/25	68 (43–84)	L+E	SCLC	C	4	OS, PFS	R	MV	(25)
Pinato	2014	2004-2011	UK	Caucasian	13 (1-87)	220	110/110	65	IA-IIIA	NSCLC	NR	5	OS	P	MV/UV	(26)
Zhang	2014	2006-2009	China	Asian	46 (1-78)	400	272/128	60 (24-82)	I-II	NSCLC	S	3.3	OS, DFS	R	MV/UV	(27)
Choi	2015	2004-2010	USA	NR	102	1,139	602/537	64.73[a]	I-III	NSCLC	S	5	OS, RFS	R	MV/UV	(28)
Mitchell	2015	2007-2011	33 countries	NR	58.7	1,239	846/393	61 (19-89)	III	NSCLC	C+R+T+I	5	OS	P	UV	(29)
Shao	2015	2000-2009	China	Asian	68.5	112	98/14	62 (45-82)	L+E	SCLC	C+R	4.15	OS, PFS	R	MV/UV	(30)
Shimizu	2015	2007-2012	Japan	Asian	32.0 (3-72)	334	219/115	69.3 (46-88)[a]	I-III	NSCLC	S	2.5	OS, DFS	R	MV/UV	(31)
Takahashi	2015	2000-2008	Japan	Asian	73.5 (15-159)	342	167/175	68 (25-87)	I	NSCLC	S	2.50	OS, RFS	R	MV/UV	(32)
Zhang	2015	2005-2009	China	Asian	45.0 (2-96)	1,238	812/426	60 (24-82)	I-IIIA	NSCLC	S	2.3	OS, DFS	R	MV/UV	(33)
Berardi	2016	2009-2014	Italy, UK	Caucasian	19.6 (16.5-28.6)	401	275/126	68 (25-86)	III-IV	NSCLC	C or T	3.7	OS, PFS	R	MV/UV	(34)

[a]Mean age. SD, standard deviation; NR, not reported; M, male; F, female; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; L, limited; E, extensive; S, surgery; C, chemotherapy; R, radiotherapy; T, targeted therapy; I, immunotherapy; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; RFS, recurrence-free survival; R, retrospective; P, prospective; MV, multivariate; UV, univariate.

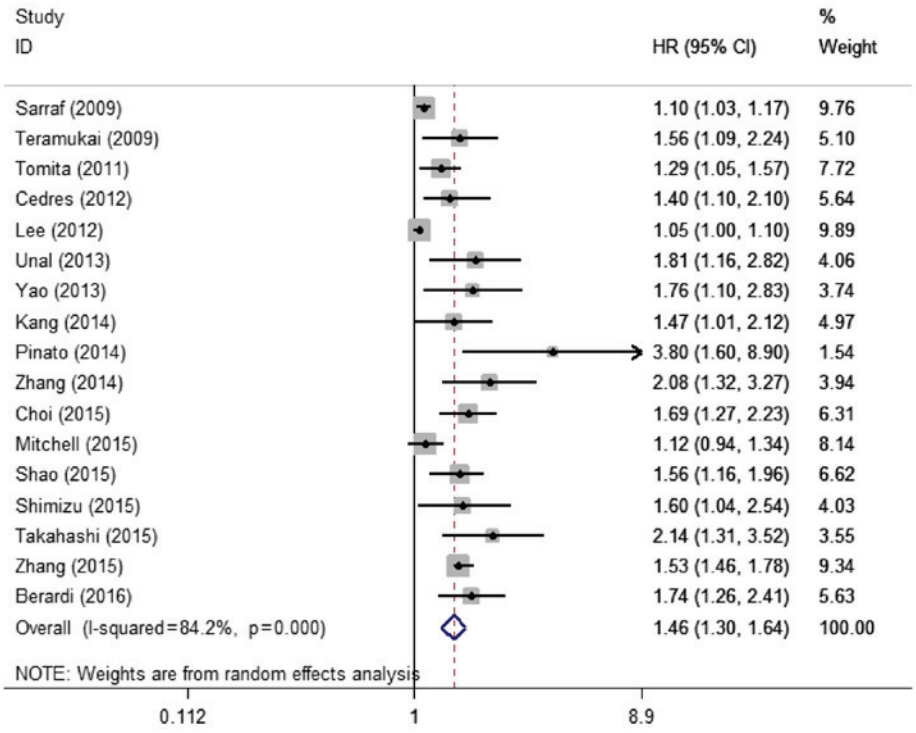

Figure 2. Forest plot of the association between elevated pretreatment neutrophil-to-lymphocyte ratio and overall survival among patients with lung cancer. HR, hazard ratio; CI, confidence interval.

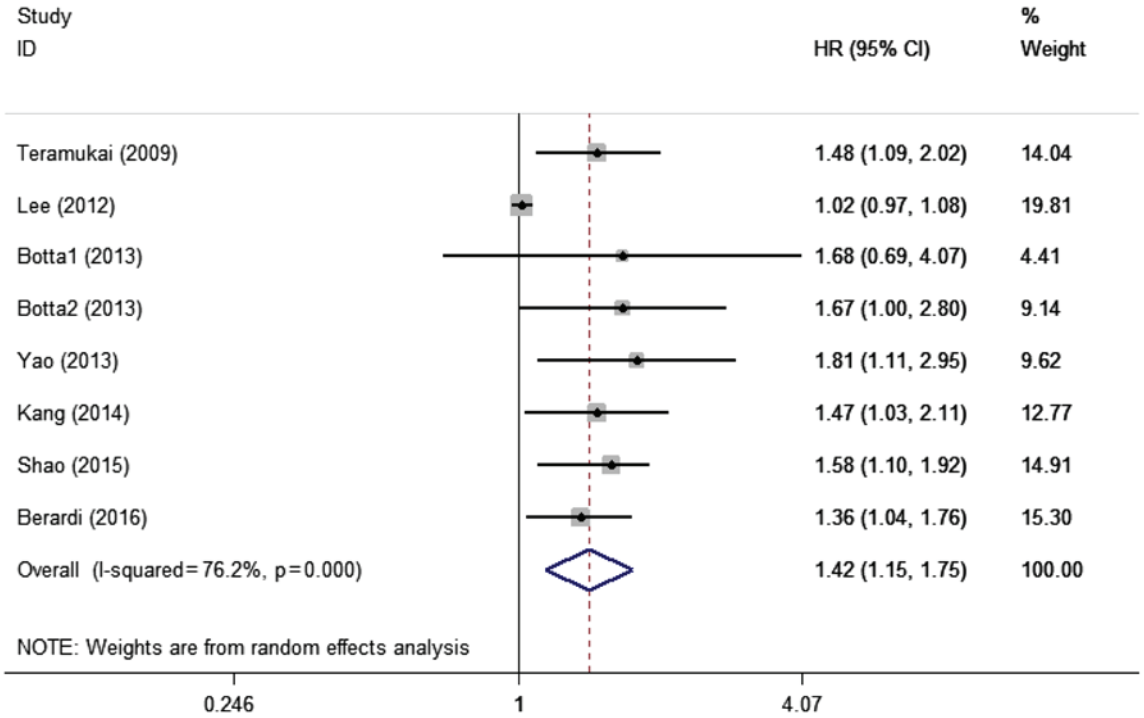

Figure 3. Forest plot of the association between elevated pretreatment neutrophil-to-lymphocyte ratio and progression-free survival among patients with lung cancer. HR, hazard ratio; CI, confidence interval.

composite index, compared with white blood cell count (40). By contrast, elevated levels of tumor-infiltrating lymphocytes are considered to be associated with a better prognosis (41), and decreasing levels of tumor-infiltrating lymphocytes are associated with a poor prognosis in lung cancer (42). Thus, the balance between the conflicting inflammatory responses in tumors is likely an effective predictor of prognosis (43), and NLR appears to be a superior index of the balance between the inflammatory response and tumor immune status, compared with individual neutrophil or lymphocyte counts.

The present study revealed significant heterogeneity in the available data, which was not explained by the subgroup

Table II. Summary of the meta-analysis results.

Subgroup	Number	Random-effects model HR (95% CI)	Random-effects model P-value	Fixed-effects model HR (95% CI)	Fixed-effects model P-value	Heterogeneity I^2 (%)	Heterogeneity P_h
A, Overall survival							
Treatment							
Surgery	7	1.57 (1.21-1.95)	<0.001	1.25 (1.19-1.31)	<0.001	88.3	<0.001
Non-surgery	10	1.42 (1.21-1.68)	<0.001	1.11 (1.06-1.16)	<0.001	75.9	<0.001
Ethnicity							
Caucasian	5	1.58 (1.15-2.17)	0.005	1.14 (1.08-1.22)	<0.001	80.9	<0.001
Asian	10	1.51 (1.26-1.81)	<0.001	1.17 (1.12-1.21)	<0.001	87.7	<0.001
Tumor stage							
Late	5	1.43 (1.09-1.87)	0.1	1.08 (1.03-1.13)	0.001	80.2	<0.001
Early	8	1.64 (1.37-1.97)	<0.001	1.50 (1.39-1.62)	<0.001	65.9	0.005
Sample size, n							
<200	7	1.25 (1.11-1.41)	<0.001	1.09 (1.05-1.13)	<0.001	74.1	0.001
≥200	10	1.56 (1.35-1.79)	<0.001	1.48 (1.38-1.59)	<0.001	60.3	0.007
Cut-off value							
<4	10	1.44 (1.24-1.66)	<0.001	1.14 (1.10-1.18)	<0.001	88.2	<0.001
≥4	5	1.56 (1.31-1.85)	<0.001	1.55 (1.32-1.81)	<0.001	14.3	0.323
Type							
NSCLC	15	1.45 (1.28-1.64)	<0.001	1.16 (1.12-1.20)	<0.001	85.2	<0.001
SCLC	2	1.53 (1.23-1.89)	<0.001	1.53 (1.23-1.89)	<0.001	0	0.792
Method							
Multivariate	16	1.50 (1.32-1.70)	<0.001	1.17 (1.13-1.21)	<0.001	85.2	<0.001
Univariate	12	1.51 (1.28-1.78)	<0.001	1.17 (1.13-1.22)	<0.001	87.4	<0.001
B, Progression-free survival							
Ethnicity							
Caucasian	3	1.43 (1.14-1.80)	0.002	1.43 (1.14-1.80)	0.002	0	0.735
Asian	5	1.40 (1.07-1.83)	0.015	1.06 (1.01-1.12)	0.024	82.1	<0.001
Sample size, n							
<200	6	1.44 (1.09-1.90)	0.1	1.06 (1.00-1.11)	0.034	77.1	0.001
≥200	2	1.41 (1.15-1.72)	0.001	1.41 (1.15-1.72)	0.001	0	0.683
Cut-off value							
<4	3	1.27 (0.93-1.72)	0.128	1.04 (0.99-1.09)	0.158	88.2	<0.001
≥4	5	1.54 (1.13-1.82)	<0.001	1.54 (1.30-1.82)	<0.001	57.2	0.029
Type							
NSCLC	6	1.38 (1.08-1.75)	0.1	1.06 (1.00-1.11)	0.4	72.9	0.002
SCLC	2	1.54 (1.24-1.92)	<0.001	1.54 (1.24-1.92)	<0.001	0	0.761
Method							
Multivariate	6	1.38 (1.10-1.74)	0.027	1.07 (1.02-1.13)	0.008	80.5	<0.001
Univariate	5	1.35 (1.03-1.75)	0.002	1.05 (1.00-1.11)	0.046	77	0.002

OS, overall survival; PFS, progression-free survival; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; HR, hazard ratio; CI, confidence interval; P_h, P-value of Q-test for heterogeneity.

analysis. Thus, we hypothesized that the heterogeneity may be associated with confounding or unconsidered factors. In this context, a number of traditional factors may be of value for predicting prognosis in lung cancer cases, and some of these factors may exert synergistic effects, particularly factors that are associated with host status. However, the studies in the

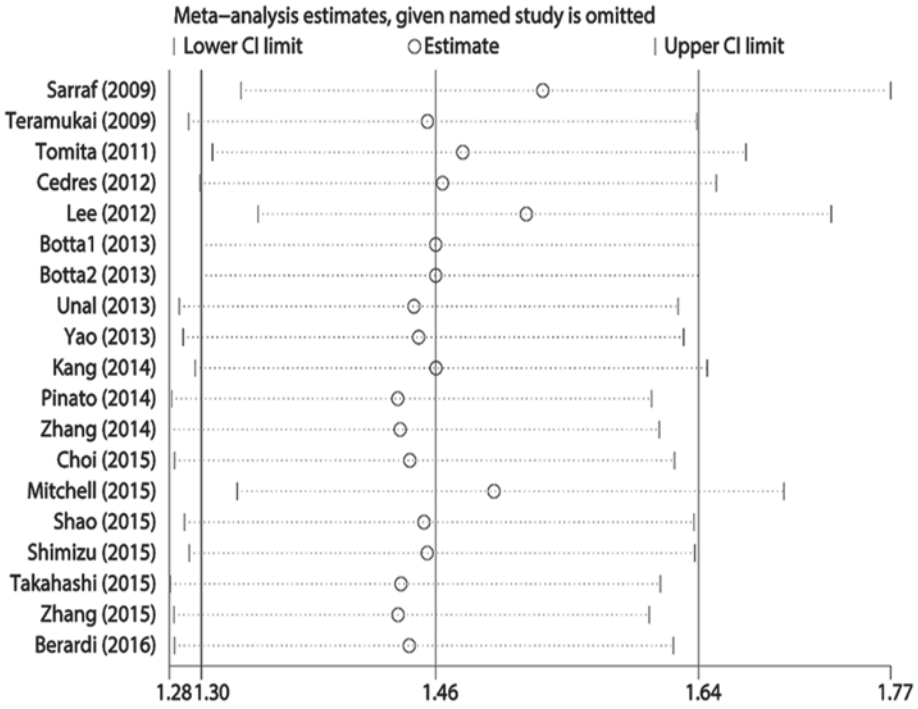

Figure 4. Sensitivity analysis of the included studies for the association of neutrophil-to-lymphocyte ratio and overall survival. CI, confidence interval.

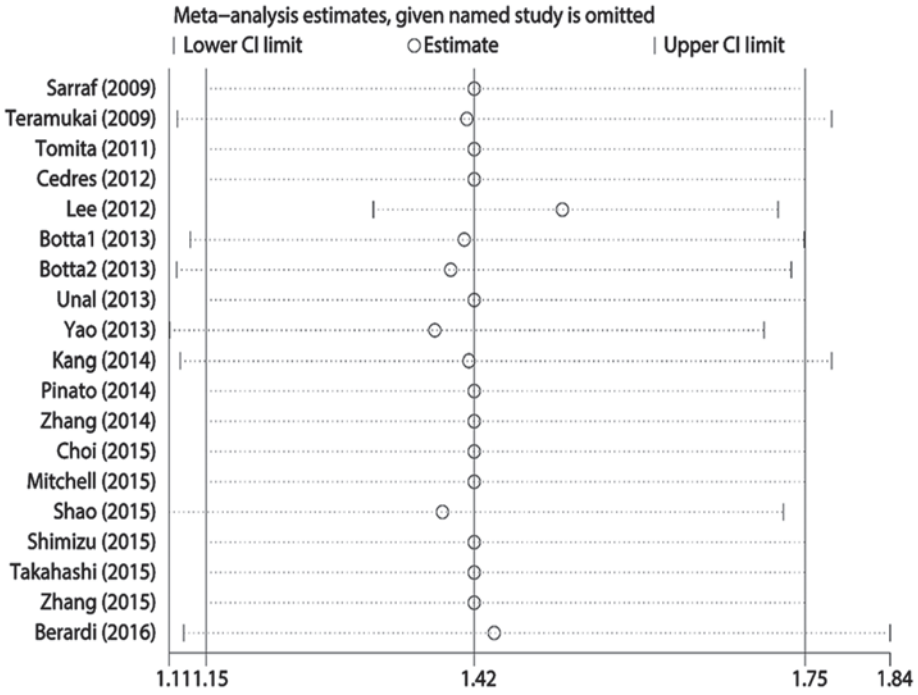

Figure 5. Sensitivity analysis of the included studies for the association of neutrophil-to-lymphocyte ratio and progression-free survival. CI, confidence interval.

present meta-analysis did not take into consideration factors in combination with NLR, and there were insufficient data to perform additional subgroup analysis. Thus, we considered other studies' results to explore these potential factors and their prognostic value in lung cancer. For example, young Japanese patients (aged ≤50 years) exhibit better survival after surgery for lung cancer, compared with older patients, which may be associated with the significantly better performance status among younger patients (44). In addition, a study of two cohorts in Australia and America revealed that male sex was independently associated with poor prognosis in NSCLC (5). Furthermore, another meta-analysis suggested that smoking cessation improves prognosis for patients with early-stage lung cancer, and this result may also be associated with a poor prognosis among male patients, as they are relatively heavy smokers (45). Moreover, smoking may promote the progression

of both early- and late-stage lung cancer through DNA alterations and modified protein expression (6). According to Kanarek *et al* (46), patients may also achieve a rapid reduction in tumor burden if they have a short referral interval and pre-surgery delay, which may be associated with continued smoking. Thus, all these factors may be useful in predicting the prognosis of lung cancer, with the exception of histological classification after radiotherapy (47) or chemotherapy (48). In addition, there is a clear inverse correlation between NLR and nutritional status (31), which indicates that NLR in the inflammatory response may be a host-related prognostic factor. Therefore, as NLR may be affected by various factors and their combinations, large-scale studies are required to elucidate the mechanism(s) underlying the association between elevated NLR and prognosis after treatment for lung cancer.

Several recent meta-analyses have used NLR as an important prognostic factor for various cancer types with different but similar cut-off values, including esophageal cancer (2-5) (49), breast cancer (3) (50), gastric cancer (3) (51), hepatocellular carcinoma (3-4) (52), pancreatic cancer (2.3-5) (53), colorectal cancer (5) (54), renal cell carcinoma (3) (55) and prostate cancer (3) (56). All these studies have reported that NLR may be a promising prognostic factor for that specific cancer. Moreover, NLR may be associated with diseases other than cancer, such as diabetes mellitus and cardiovascular disease (57). Thus, NLR is likely of value for predicting prognosis in a wide range of inflammation-associated diseases.

There are certain limitations regarding the present meta-analysis that should be addressed. First, only 4 prospective studies were identified, whereas 13 studies (14 cohorts) used a retrospective design, which increases the risk of bias. Second, substantial heterogeneity was observed in the various studies, which was associated with various confounding factors, such as ethnicity, sex, treatment method, follow-up period, age distribution, and NLR cut-off value. However, this significant heterogeneity was not attributable to a single factor in the subgroup analysis, meta-regression, and sensitivity analysis, suggesting that the heterogeneity may be associated with the inter-related factors that were discussed in the previous paragraphs. Third, only 2 studies on SCLC were identified, and included a limited amount of data for the PFS-related analysis, which increases the risk of bias in our findings. Fourth, the association between the NLR and clinicopathological parameters (e.g., lymph node metastasis) or pathological patterns was not analyzed. Fifth, only 3 studies evaluated NLR using multivariate analysis, and the remaining studies either performed univariate analysis alone or a combination of multivariate and univariate analysis. Sixth, significant publication bias was identified, which was likely associated with the language restriction and the increased likelihood that reports with positive results would be published.

In conclusion, the present meta-analysis demonstrated that elevated pretreatment NLR was associated with prognosis among patients with lung cancer. Thus, NLR may be an easily accessible and effective prognostic biomarker in lung cancer, as it may be evaluated during routine blood tests. However, the specific mechanism underlying its prognostic value remains unclear, as significant heterogeneity was observed in the present meta-analysis. Therefore, additional well-designed large-scale studies are required to clearly determine the prognostic role of NLR in lung cancer.

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