CLINICS

REVIEW

Prognostic value of the neutrophil to lymphocyte ratio in lung cancer: A meta-analysis

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Recently, a series of studies explored the correlation between the neutrophil to lymphocyte ratio and the prognosis of lung cancer. However, the current opinion regarding the prognostic role of the neutrophil to lymphocyte ratio in lung cancer is inconsistent.

We performed a meta-analysis of published articles to investigate the prognostic value of the neutrophil to lymphocyte ratio in lung cancer. The hazard ratio (HR) and its 95% confidence interval (CI) were calculated.

An elevated neutrophil to lymphocyte ratio predicted worse overall survival, with a pooled HR of 1.243 (95%CI: 1.106-1.397; $P_{heterogeneity}$=0.001) from multivariate studies and 1.867 (95%CI: 1.487-2.344; $P_{heterogeneity}$=0.047) from univariate studies. Subgroup analysis showed that a high neutrophil to lymphocyte ratio yielded worse overall survival in non-small cell lung cancer (NSCLC) (HR=1.192, 95%CI: 1.061-1.399; $P_{heterogeneity}$=0.003) as well as small cell lung cancer (SCLC) (HR=1.550, 95% CI: 1.156-2.077; $P_{heterogeneity}$=0.625) in multivariate studies.

The synthesized evidence from this meta-analysis of published articles demonstrated that an elevated neutrophil to lymphocyte ratio was a predictor of poor overall survival in patients with lung cancer.

KEYWORDS: NLR; Lung Cancer; Overall Survival; Meta-Analysis.

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INTRODUCTION

Lung cancer is one of the leading causes of cancer-related deaths (1,2). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer cases, and small-cell lung cancer (SCLC) accounts for nearly 13% of overall lung cancer cases. Despite continue efforts and progress in diagnosis and treatment, the overall survival (OS) for lung cancer patients remains poor (1,2). Prognostic factors influencing survival have been previously identified, including tumor stage, performance status, weight loss, age, sex, histopathology, and plasma lactate dehydrogenase (LDH) and carcinoembryonic antigen (CEA) levels (3-7). Although novel immunological and histological biomarkers such as intercellular adhesion molecule-1 (IDM-1) and epidermal growth factor receptor (EGFR) have been identified (8,9), these marks are expensive and often time-consuming to measure. Thus, there remains no promising prognostic factor that can be easily detected and closely linked to clinical outcomes for lung cancer patients (10).

The tumor immune environment plays an important role in tumor progression by promoting tumor angiogenesis, tumor metastasis, and cancer cell proliferation and by interfering with the response to systemic treatment (11,12). Neutrophils and T and B lymphocytes have been suggested to play vital roles in tumor inflammation (13,14), and the imbalance between neutrophils and lymphocytes is thought to be secondary to tumor hypoxia or necrosis and associated with anti-apoptotic effects (15). The neutrophil to lymphocyte ratio (NLR), representing a combination of circulating neutrophil and lymphocyte counts, can reflect the imbalance between neutrophils and lymphocytes in patients with tumors and serves as a representative index of systemic inflammation.

Recently, an elevated preoperative or pretreatment NLR, calculated from peripheral blood tests, was identified as an independent and readily available prognostic biomarker related to poor survival in numerous cancers, including colorectal cancer, breast cancer, gastric cancer and esophageal cancer (16-19). Additionally, a series of studies have explored the correlation between the NLR and the prognosis of lung cancer. However, according to their results, the

No potential conflict of interest was reported.

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current opinion on the prognostic role of the NLR in lung cancer is inconsistent and inconclusive. Thus, we performed this meta-analysis, which is the first systematic study on the subject, to investigate the prognostic value of the NLR in lung cancer.

MATERIALS AND METHODS

Search strategy and study selection

To identify eligible studies regarding the NLR for predicting the prognosis of lung cancer, a systematic review was conducted. Relevant studies were identified by searching the PubMed and Web of Science databases using the following search terms: NLR, neutrophil-to-lymphocyte ratio, neutrophil lymphocyte ratio or neutrophil-lymphocyte ratio with lung cancer, carcinoma of the lung, pulmonary carcinoma and prognosis, prognostic, survival or outcome. The last search was updated on October 31, 2014. Both Medical subheadings (MeSH) and free text terms were used as keywords. The reference lists of papers of interest and published review articles were also explored to potentially retrieve additional studies. The inclusion criteria for the studies were as follows: (a) provided clear information on lung cancer confirmation and the included patients; (b) investigated the association of the pre-treatment NLR with OS; and (c) full text articles in English. The exclusion criteria were as follows: (a) letters, reviews, expert opinions, case reports or laboratory studies; (b) studies with overlapping or duplicate data; and (c) a lack of key information for evaluating the hazard ratio (HR) for further analysis.

Data extraction

All searches were conducted independently by two investigators. The same two authors independently extracted data on the name of the first author, the year of publication, the country of origin, ethnicity, the total number of cases, cancer types, stages, cut-off values, follow ups and HRs of the NLR for OS with 95% confidence intervals (CIs). Any discrepancy was resolved by consensus and, if needed, by consultation with the third author.

Statistical analysis

OS results were evaluated as HRs for each included study. HRs and 95% CIs were obtained directly from each publication. If not available, the necessary data were extracted to calculate the HR using the method reported by Tierney et al. (20). The heterogeneity of pooled results was estimated using Cochran's Q test and Higgins' I-squared statistic. A p-value <0.10 for the Q-test indicated significant heterogeneity, and a random-effects model (DerSimonian-Laird method) was used to calculate the pooled HRs (21). Otherwise, a fixed-effects model (Mantel-Haenszel method) was applied (22). Egger's linear regression and Begg's funnel plot test were applied to evaluate publication bias in the literature, and a p-value <0.05 was considered significant. A trim and fill method was performed to estimate asymmetry in the funnel plot. Meta-regression was performed to explore the potential source of heterogeneity using variables such as the year of publication, ethnicity, cancer type, cutoff value and sample size. To validate the credibility of outcomes in this meta-analysis, sensitivity analysis was performed by sequential omission of each individual study using the ''metainf'' STATA command. All statistical analyses were conducted with STATA software version 12.0 (STATA Corporation, College Station, TX, USA), and all p-values were two-sided.

RESULTS

Study characteristics

We identified fourteen studies according to the inclusion and exclusion criteria (23-36). The detailed screening process is shown in Figure 1. All of these articles were published in English. The characteristics of the included studies are shown in Table 1. Three studies were performed in China and Japan, whereas two each were performed in the USA, UK and Turkey and one each in Spain and Korea. Among the included studies, participants were Asian in seven studies and Caucasian in the other seven studies. A total of twelve studies explored the NLR in the prognosis of NSCLC, and two studies explored the NLR in SCLC. The cut-off value used in each study was not consistent, ranging from 2.5 to 5.0. The number of patients in each study ranged from 59 to 388. Six studies calculated HRs by multivariate analysis, five studies calculated HRs by univariate analysis, and the other three studies calculated HRs by both multivariate and univariate analyses. In total, nine studies contained HRs calculated from multivariate analysis, and eight studies contained HRs calculated from univariate analysis.

Outcome from eligible studies

As shown in Table 2, fourteen studies evaluating OS were classified into two groups: nine multivariate studies with HRs and 95% CIs acquired from multivariate analysis, and eight univariate studies with data from univariate analysis. In both the multivariate and univariate analysis groups, an elevated NLR predicted a worse outcome of OS, with a pooled HR of 1.243 (95%CI: 1.106-1.397; $P_{heterogeneity}=0.001$) and 1.867 (95% CI: 1.487-2.344; $P_{heterogeneity}=0.047$), respectively (Figure 2).

Subgroup analysis by cancer type in the multivariate studies showed that a high NLR yielded worse OS in NSCLC (HR=1.192, 95%CI: 1.061-1.399; $P_{heterogeneity}=0.003$) and SCLC (HR=1.550, 95%CI: 1.156-2.077; $P_{heterogeneity}=0.625$). The cancer type in the univariate studies was NSCLC only.

In the subgroup analysis by ethnicity, regardless of whether the patients were Asian or Caucasian, an elevated NLR remained a poor predictor of OS in multivariate studies

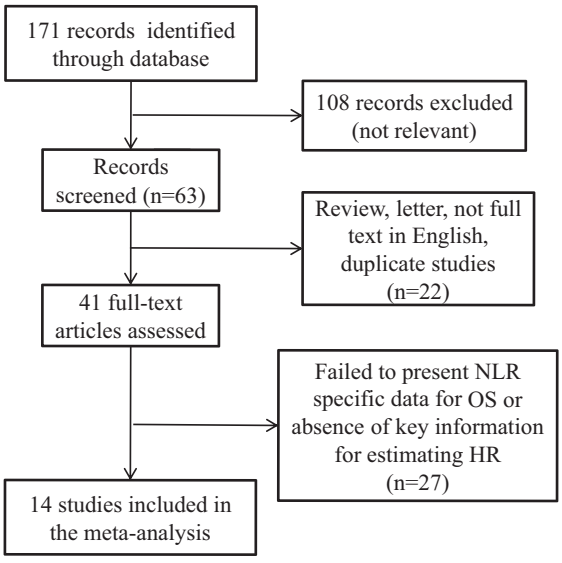

Figure 1 - Methodological flow diagram of the meta-analysis.

Table 1 - Characteristics of all included studies.

Study	Year	Country	Ethnicity	Number	Type	Method	Stage	Cut-off	Follow-up (months)
Teramukai (23)	2009	Japan	Asian	388	NSCLC	M	III/IV	4.744	18.9 (2.3-57.0)
Kacan (24)	2014	Turkey	Caucasian	299	NSCLC	M	I-IV	5	NA
Yao (25)	2013	China	Asian	182	NSCLC	U	III/IV	2.63	NA
Lee (26)	2012	Korea	Asian	199	NSCLC	M/U	III/IV	NA	36 (33.6-37.9)
Wang (27)	2014	China	Asian	114	SCLC	M	NA	3	NA
Cedrés (28)	2012	Spain	Caucasian	171	NSCLC	U	IV	5	9.1 (1-70.37)
Unal (29)	2013	Turkey	Caucasian	94	NSCLC	U	NA	3.44	NA
Pinato (30)	2014	UK	Caucasian	220	NSCLC	M/U	I-III	5	NA
Kang (31)	2014	USA	Caucasian	187	SCLC	M	NA	4	40.28 (2.60-89.26)
Cannon (32)	2014	USA	Caucasian	59	NSCLC	U	I1	2.98	17
Tomita (33)	2011	Japan	Asian	284	NSCLC	M/U	I-III	2.5	60.7-131.7
Sarraf (34)	2009	UK	Caucasian	177	NSCLC	M	I-IV	3.81	29 (8-56)
Liao (35)	2013	China	Asian	59	NSCLC	M	I-III	NA	30 (8-40)
Tomita (36)	2012	Japan	Asian	301	NSCLC	U	I-III	2.5	NA

NSCLC: non-small cell lung cancer; SCLC: small-cell lung cancer; M: multivariate; U: univariate.

(Caucasian: HR=1.545, 95%CI: 1.052-2.269; $P_{heterogeneity}$=0.005; Asian: HR=1.261, 95%CI: 1.092-1.547; $P_{heterogeneity}$=0.021) and univariate studies (Caucasian: HR=1.722, 95%CI: 1.360-2.179; $P_{heterogeneity}$=0.133; Asian: HR=1.661, 95%CI: 1.419-1.945; $P_{heterogeneity}$=0.036).

Considering different cut-off values, these studies used two subsets of NLR cut-offs and revealed similar results. The NLR was found to be a negative prognostic marker for the outcome of OS in multivariate studies (NLR$\geqslant$4: HR=1.646, 95%CI: 1.319-2.053; $P_{heterogeneity}$=0.247; NLR$<$4: HR=1.221, 95%CI: 1.016-1.468; $P_{heterogeneity}$=0.082) and univariate studies (NLR$\geqslant$4: HR=1.500, 95%CI: 1.111-2.025; $P_{heterogeneity}$=0.262; NLR$<$4: HR=2.043, 95%CI: 1.497-2.789; $P_{heterogeneity}$=0.017).

Further analysis of studies evaluating OS by sample size (studies with more than 200 cases were classified as ''large'', and studies with less than 200 cases were classified as ''small'') also revealed that a high NLR remained a worse prognostic marker regardless of the sample size (large: HR=1.608, 95%CI: 1.186-2.179; $P_{heterogeneity}$=0.082; small: HR=1.090, 95%CI: 1.034-1.131; $P_{heterogeneity}$=0.103) in multivariate studies and (large: HR=2.018, 95%CI: 1.229-3.315; $P_{heterogeneity}$=0.016; small: HR=1.736, 95%CI: 1.403-2.148; $P_{heterogeneity}$=0.211) in univariate studies.

Heterogeneity

Meta-regression analysis was performed to explore the potential source of heterogeneity among multivariate and univariate studies for OS using variables such as the year of publication, ethnicity, cancer type, cut-off value and sample size. In multivariate studies, the results showed that year of publication (p=0.193), ethnicity (p=0.573), cancer type (p=0.407), cut-off value (0.116) and sample size (p=0.183) did not contribute to the source of heterogeneity. The same results were shown in the univariate studies; the year of publication (p=0.146), ethnicity (p=0.963), cut-off (0.457) and sample size (p=0.795) also did not contribute to the source of heterogeneity.

Table 2 - Meta-analysis results.

Outcome	Variable	Number of studies	Model	HR(95%CI)	$P_{heterogeneity}$
OS	**All**	14			
	MULTIVARIATE	9	Random	1.243 (1.106-1.397)	0.001
	Cancer type				
	NSCLC	7	Random	1.192 (1.061-1.339)	0.003
	SCLC	2	Fix	1.550 (1.156-2.077)	0.625
	Ethnicity				
	Asian	5	Random	1.261 (1.029-1.547)	0.021
	Caucasian	4	Random	1.545 (1.052-2.269)	0.005
	Cut-off				
	$\geqslant$4	4	Fix	1.646 (1.319-2.053)	0.247
	$<$4	3	Random	1.221 (1.016-1.468)	0.082
	Sample size				
	Large	4	Random	1.608 (1.186-2.179)	0.082
	Small	5	Fix	1.090 (1.034-1.131)	0.103
	UNIVARIATE	8	Random	1.867 (1.487-2.344)	0.047
	Ethnicity				
	Asian	4	Random	1.890 (1.301-2.744)	0.036
	Caucasian	4	Fix	1.722 (1.360-2.179)	0.133
	Cut-off				
	$\geqslant$4	2	Fix	1.500 (1.111-2.025)	0.262
	$<$4	5	Random	2.043 (1.497-2.789)	0.017
	Sample size				
	Large	3	Random	2.018 (1.229-3.315)	0.016
	Small	5	Fix	1.736 (1.403-2.148)	0.211

NSCLC: non-small cell lung cancer; SCLC: small-cell lung cancer.

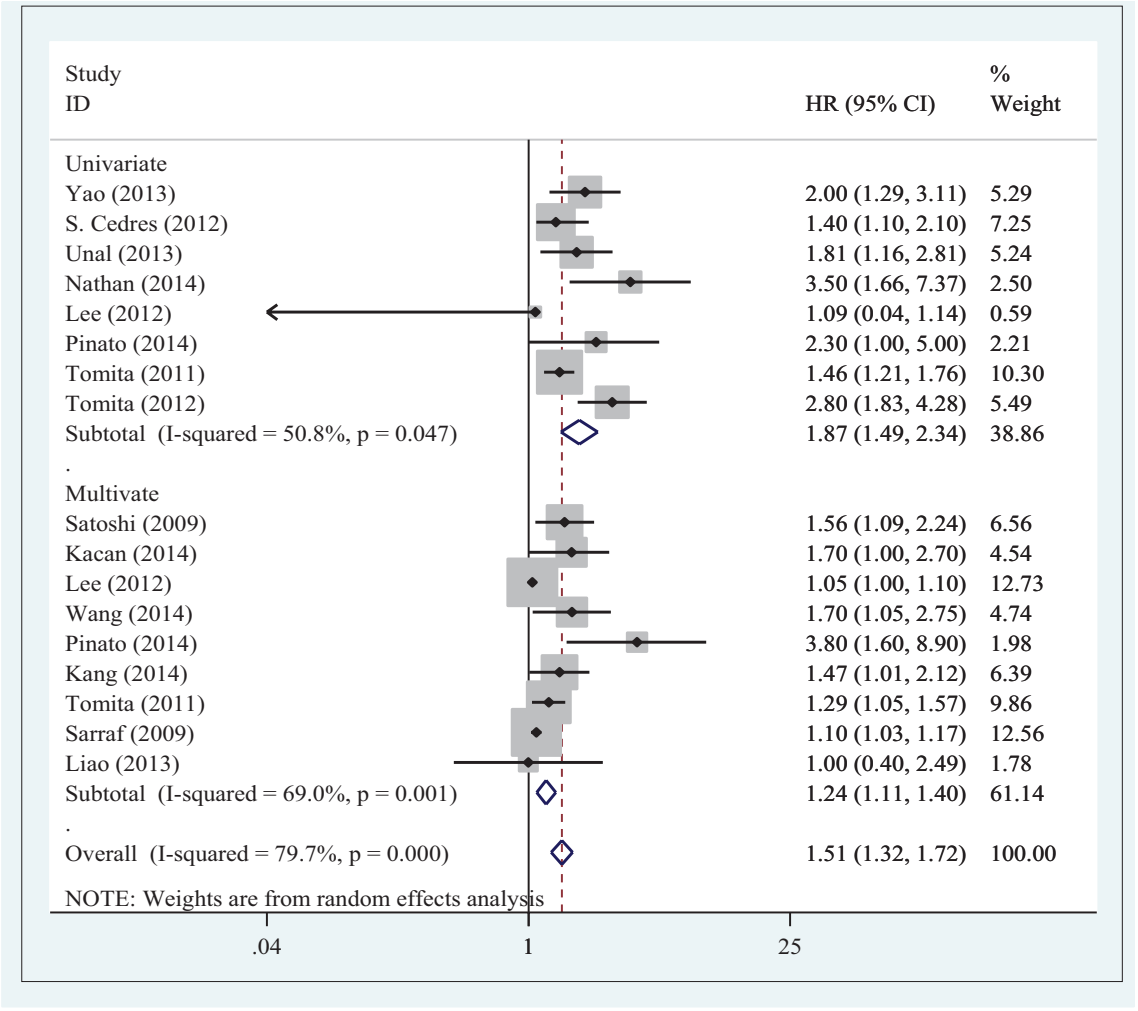

Figure 2 - Forrest plots of studies evaluating HRs of the NLR for OS.

Publication bias and sensitivity analysis

We conducted leave-one-out sensitivity analysis by removing one study per time to check if any individual study affected the results. The result patterns were not obviously affected by any single study in either the univariate or multivariate group (Figures 3, 4). Begg's funnel plot and Egger's linear regression tests were used to evaluate publication bias. In the univariate studies, the results did not show any evidence of publication bias (p=0.711 for Begg's test, and p=0.141 for Egger's test). However, publication bias was found in the multivariate studies (p=0.002 for Egger's test and p=0.251 for Begg's test and). Therefore, a trim and fill method was used to evaluate the asymmetry in the funnel plot. The recalculated pooled HRs with presumed missing studies did not significantly change for multivariate studies (HR=1.118, 95%CI: 1.002–1.233; $P_{heterogeneity=}$0.026; Figure 5), indicating the stability of the results.

DISCUSSION

Systemic inflammation appears to play a pivotal role in the progression of numerous cancers by promoting tumor angiogenesis, tumor metastasis and cancer cell proliferation and by affecting the tumor response to systemic treatment (11). The NLR, a combination of circulating neutrophil and lymphocyte counts, serves as a representative index of systemic inflammation. Moreover, because it is calculated from peripheral blood test results, the NLR is a readily available biomarker of systemic inflammation that may predict the prognostic outcome of patients. Indeed, recent studies have evaluated the predictive value of the NLR in various types of cancers (16-19). Our current study aimed to evaluate the role of the NLR in lung cancer, and to the best of our knowledge, it is the first meta-analysis to investigate the prognostic role of the NLR in lung cancer.

This meta-analysis, including 14 studies with 2,734 lung cancer cases, showed that an elevated NLR indeed predicted worse OS, regardless of whether the HRs were calculated from multivariate or univariate analysis. Subgroup analysis showed that a high NLR yielded a worse OS in NSCLC and SCLC based on multivariate analysis. The cancer type of the studies using univariate analysis was NSCLC only. In the subgroup analyses by ethnicity, we found that regardless of whether patients were Asian or Caucasian, an elevated NLR was still a poor predictor of OS in both multivariate and univariate analyses. Considering different cut-off values, these studies using two subsets of NLR cut-offs revealed similar results, showing that the NLR was a negative

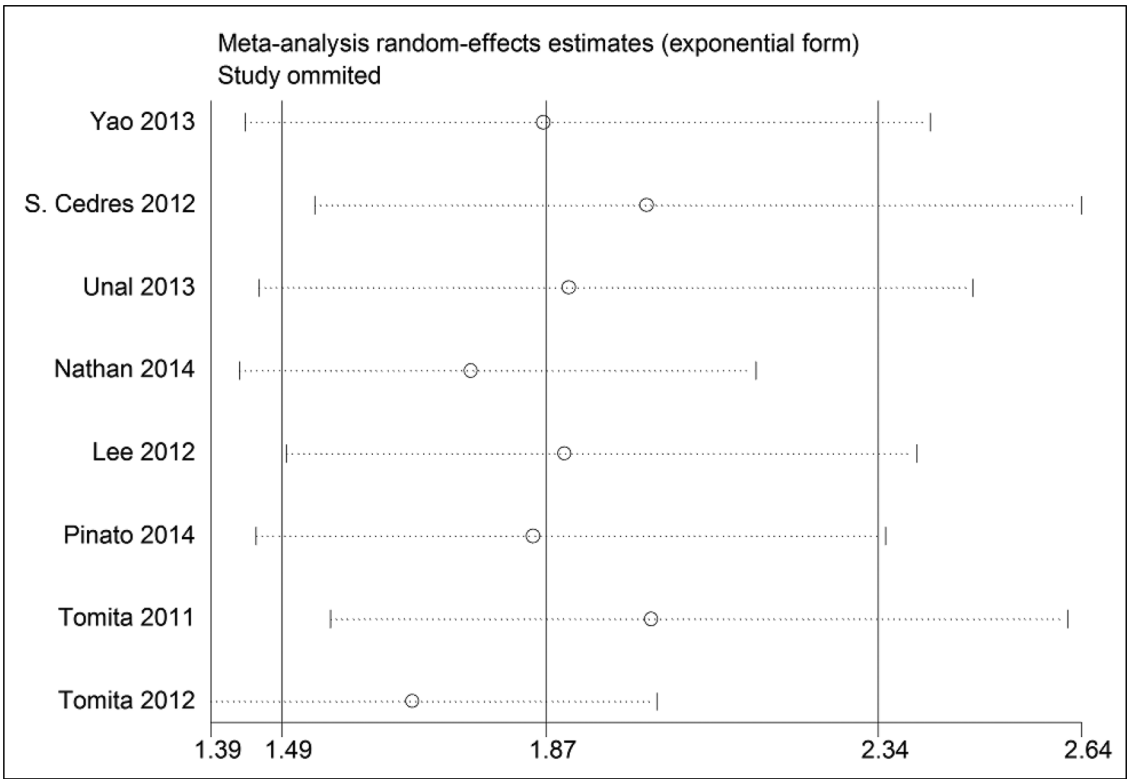

Figure 3 - Effect of univariate studies on the pooled HR for the NLR and OS of patients.

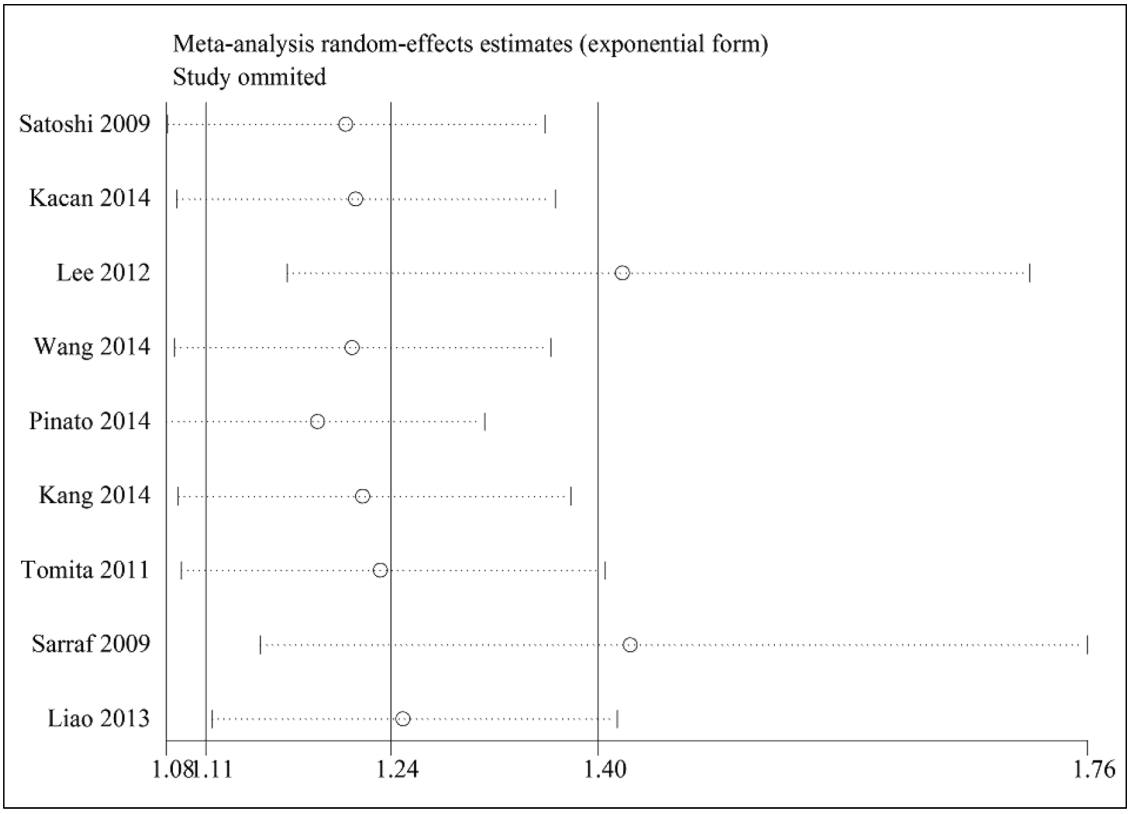

Figure 4 - Effect of multivariate studies on the pooled HR for the NLR and OS of patients.

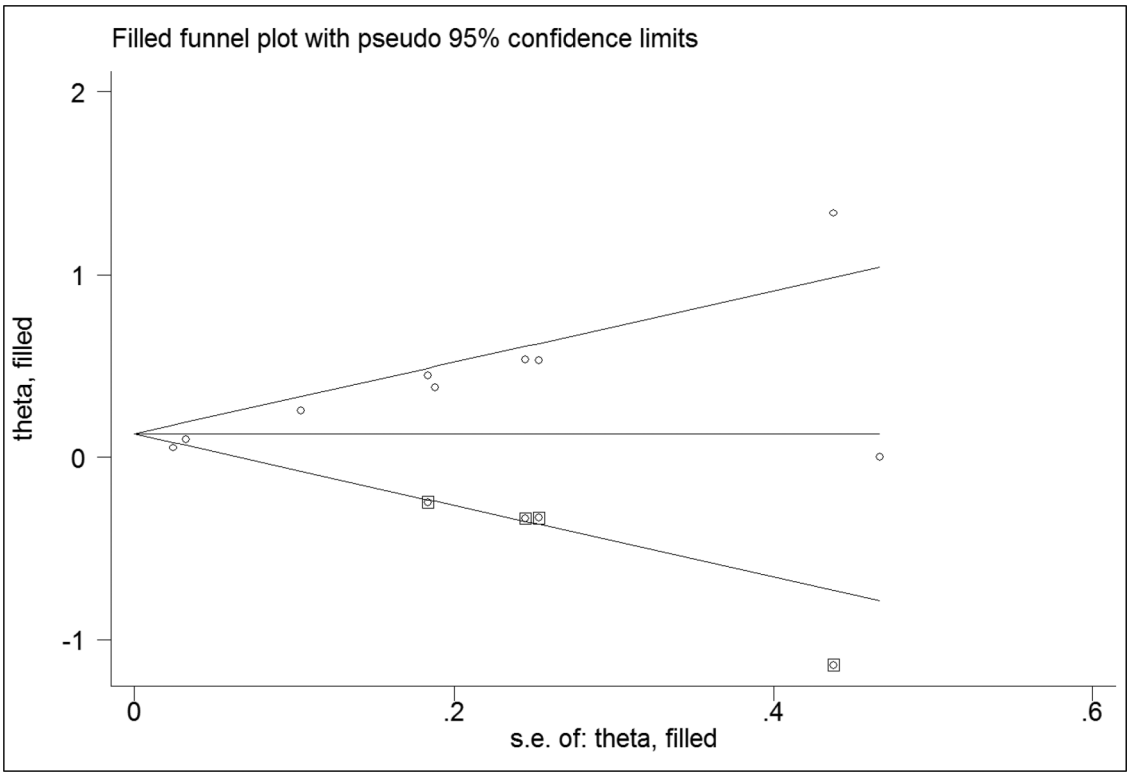

Figure 5 - Funnel plots adjusted with the trim and fill method for OS. Circles: included studies. Diamonds: presumed missing studies.

prognostic marker for the outcome of OS regardless of the analysis method. Further analysis by sample size also revealed the same results. Meta-regression analysis was performed using variables such as the year of publication, ethnicity, cancer type, cut-off value and sample size; however, none of these variables contributed to heterogeneity.

The NLR has been related to patient prognosis in numerous cancers, although the specific mechanism for this relationship remains incompletely understood. Myeloid cells are known to play a critical role in tumor pathogenesis by promoting cancer cell proliferation, tumor angiogenesis, cell invasion, and metastasis (37). In particular, tumor-derived inflammation can increase myelopoiesis with defective myeloid cell differentiation and proliferation by regulating the bone marrow and spleen, leading to the accumulation of immature myeloid cells in the peripheral circulation (38). In the context of cancer-mediated myelopoiesis, the neutrophil precursors myelocytes and promyelocytes proliferate and are released into the peripheral blood. Neutrophils are the most abundant granulocytes, which account for most peripheral white blood cells (37). Thus, the prognostic and predictive value of peripheral neutrophils as an independent index or as part of the NLR in cancers is apparent, and enhanced neutrophil responses and/or lymphocyte suppression, leading to a high NLR, might promote tumor progression and inhibit the antitumor immune response.

Our study has several limitations that should be carefully considered. First, the studies included in the analysis were full texts in English and were identified by searching the PubMed and Web of Science databases. Thus, publication bias cannot be excluded, although it did not affect the results according to the trim and fill method. In addition, marked heterogeneity of the studies was found; this may have been caused by the year of publication, ethnicity, cancer type, cut-off value and sample size. However, no variables listed above that were analyzed in the meta-regression analysis contributed to the observed heterogeneity. In fact, the existence of heterogeneity may have resulted from a variety of other factors. Due to the lack of detailed data, we could not use other clinical parameters in the meta-regression analysis. Additionally, the number of included studies was not large enough for part of the subgroup analysis; for example, only two studies investigated the NLR for OS in SCLC, and only two univariate studies with a small sample size (less than 100 cases was classified as "small") yielded a trend of a poor prognostic role of the NLR for OS. In the future, more well-designed studies are needed to present more reliable results.

In conclusion, despite the limitations listed above, the synthesized evidence from published articles revealed that elevated NLR was a poor predictor of survival in patients with lung cancer. The NLR is an easily available blood test and may serve as a useful prognostic biomarker in lung cancer that does not require any additional resources for routine use. Nevertheless, the clinical utility of the NLR must still be confirmed in future analyses.

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■ AUTHOR CONTRIBUTIONS

Wang J conceived and designed the experiments. Wang J, Yin YM, Wang XD, Kuai SG and Shang ZB performed the experiments. JW, YMY,

Wang XD, Gu L, Pei H and Zhang YY analyzed the data. The first three authors contributed equally to this article.

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