Prognostic role of neutrophil to lymphocyte ratio in lung cancers: a meta-analysis including 7,054 patients

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Background: Neutrophil to lymphocyte ratio (NLR) has recently been reported to be a poor prognostic indicator in lung cancer. However, the prognostic value of the NLR in patients with lung cancer still remains controversial. We performed a meta-analysis to evaluate the prognostic value of NLR in patients with lung cancer.

Methods: We performed a comprehensive literature search in PubMed, Ovid, the Cochrane Library, and Web of Science databases in May 2015. Studies were assessed for quality using the Newcastle–Ottawa Scale.

Results: Twenty-two studies with a total of 7,054 patients were included in this meta-analysis. The meta-analysis was performed to generate combined hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS). Our analysis results indicated that high NLR predicted poorer OS (HR, 1.51; 95% confidence interval [CI], 1.33–1.71; P<0.001) and PFS (HR, 1.33; 95% CI, 1.07–1.67; P=0.002) in patients with lung cancer. High NLR was also associated with poor OS in lung cancer treated by surgical resection (HR, 1.59; 95% CI, 1.26–1.99; P<0.001) and chemotherapy (HR, 1.15; 95% CI, 1.08–1.22; P<0.001). In addition, NLR cut-off value <5 (HR, 1.57; 95% CI, 1.16–2.12; P=0.003) and NLR cut-off value <15 (HR, 1.47; 95% CI, 1.28–1.69; P<0.001).

Conclusion: This meta-analysis result suggested that NLR should have significant predictive ability for estimating OS and PFS in patients with lung cancer and may be as a significant biomarker in the prognosis of lung cancer.

Keywords: NLR, lung cancer, prognosis, meta-analysis

Introduction
As the second leading cancer type for the estimated new cancer cases, lung cancer represents the major cause of cancer death in both females and males.¹ Despite research on the diagnosis of lung cancer and the use of increasingly advanced technology in its treatment, the prognosis of lung cancer is still poor. Thus, there is an urgent need for development of prognostic serum biomarkers for the prognosis of lung cancer, which would help clinicians to adopt preventive and personalized medicine for patients with lung cancer.

In recent years, accumulating evidence shown that increased systemic inflammation is associated with poor overall survival (OS) in numerous cancers.² ³ Inflammation is a crucial component of tumor microenvironment.⁴ Inflammatory cells in the tumor microenvironment have important effects on tumor development, and markers of systemic inflammation may provide significant information for prognostication.⁵ ⁶ Neutrophil to lymphocyte ratio (NLR), calculated as a simple ratio between neutrophil and lymphocyte...
counts, an index of systemic inflammation, has been related to poor survival for a variety of malignant tumors.8–12

Several meta-analyses have showed that NLR has been linked to tumor progression and clinical outcome in many cancers besides lung cancer.13–15 Nevertheless, conflicting results have emerged regarding the use of NLR to predict disease progression-free survival (PFS) and OS in lung cancer.16,17 Therefore, it is necessary to perform a systemic review and meta-analysis to comprehensively and systematically evaluate the prognostic value of NLR in lung cancer. This study sought to assess and explore the prognostics of NLR for OS and PFS in patients with lung cancer by pooling outcomes from the available data.

Methods

Search strategy
We performed a comprehensive literature search of articles through the following databases without date limitation: PubMed, Ovid, the Cochrane Library, and Web of Science databases. The search was updated to May 2015. The main search terms included (NLR or neutrophil to lymphocyte ratio or neutrophil lymphocyte ratio or neutrophil-to-lymphocyte ratio) and (lung cancer or lung carcinoma or NSCLC or SCLC). A manual search of reference lists and potential related articles was also performed.

Data extraction
All candidate studies were evaluated and extracted by two independent investigators (Qing-Tao Zhao and Yong Yang). The articles, which could not be excluded on the basis of title and abstract, were retrieved for full-text review. If disagreement occurred, two investigators discussed and arrived at consensus with the third investigator (Shun Xu).

Inclusion criteria
Studies were included in this meta-analysis if they met the following criteria: 1) Patients with lung cancer in the studies were confirmed by pathological examination, 2) all evaluation indicators were derived from NLR in serum, 3) correlation of NLR with OS and/or PFS of patients with lung cancer was reported, and 4) articles that were not directly recording hazard ratios (HRs) and 95% confidence interval (CI) were allowed if we could rebuild them by P-values and other data reported.18

Exclusion criteria
We excluded articles with any of the following characteristics: 1) abstracts, letters, reviews, expert opinions, case reports, or nonclinical studies; 2) no access to the studies with sufficient data for estimating HR and 95% CI; 3) studies had duplicate or overlapping data; and 4) studies were not written in English.

Data extraction and quality assessment
The following items were recorded: first author’s name, year of publication, country, total number of cases and sex, follow-ups, stage, cut-off value, cancer type, and HRs with 95% CIs. The Newcastle–Ottawa Scale (NOS) was used to assess each of the included studies’ quality by two independent investigators (Qing-Tao Zhao and Yong Yang).19 The NOS consists of three parts: selection (four points), comparability (two points), and outcome assessment (three points). Studies labeled with six or more points were considered to be of high quality.

Statistical analysis
HR and 95% CI were procured or estimated from each study according to the methods by Parmar et al.18 A HR >1 indicated a worse prognosis in patients with lung cancer with high expression of NLR. For each meta-analysis, the Cochrane’s Q statistic was undertaken to assess the heterogeneity of the included trials. F <50% represented acceptable no remarkable interstudy heterogeneity, and the fixed-effects (Mantel–Haenszel method) model was applied. Otherwise, the random-effects (DerSimonian–Laird method) model was used. Subgroup analysis and meta-regression analyses were conducted to explore and explain the diversity (heterogeneity) among the results of different studies. All P-values were two-sided, and P<0.05 was considered statistically significant. Publication bias was assessed by Begg’s rank correlation test and Egger’s regression asymmetry test.20 Trim and fill method was used to assess potential asymmetry in the funnel plot.21 Statistical analyses were performed using STATA statistical software version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Study characteristics
The flow chart of the study selection for the meta-analysis is shown in Figure 1. Twenty-two studies with a total of 7,054 patients16,17,22–41 were retrieved according to the inclusion and exclusion criteria after careful reading and selection. Of 22 articles, 21 articles investigated the prognostic role of NLR for OS and nine for PFS. Nine studies were from Western countries, including three studies from the US, two studies from the UK, one study from Italy, Spain, Belgium,
and Canada. Thirteen studies were from Eastern countries, including five from People’s Republic of China, four from Turkey, three from Korea, and one from Japan. All of the studies were retrospective cohort studies. All were reported within the past 5 years, and 82% were reported in 2013–2015. The characteristics of the included studies were summarized in Table 1.

**NLR and OS in lung cancer**

Twenty-one studies evaluated OS for NLR. Though with significant heterogeneity ($I^2 = 81.8\%$, $P<0.001$), therefore, a random-effects model was applied. The pooled HR of 1.51 (95% CI, 1.33–1.71; $P<0.001$; Figure 2) showed that patients with elevated NLR were expected to have shorter OS after the treatment.

**NLR and PFS in lung cancer**

Nine studies evaluated PFS for NLR. Meta-analysis using the random-effects model demonstrated that high NLR was significantly associated with shorter PFS (HR, 1.33; 95% CI, 1.07–1.67; $P=0.012$; Figure 3) with heterogeneity ($I^2 = 80.5\%$, $P<0.001$).

**Subgroup analyses**

We further explored potential causes of the heterogeneity in the meta-analysis. Regarding OS, subgroup analyses were also performed based on the treatment; NLR cut-off value and region are shown in Table 2. The pooled results were similar to those for OS. Majority of the subgroup analysis did not alter the prognostic role of NLR in OS/PFS substantially (Table 2).

**Publication bias**

Begg’s funnel plot and Egger’s test linear regression test were presented for the visual assessment of overt publication bias for the included cohorts in NLR. OS and PFS/disease-free survival (DFS) publication bias was not obvious, publication bias was detected for OS ($Pr>|z|=0.928$ for Begg’s test and $P>|t|=0.981$ for Egger’s test) and PFS/DFS ($Pr>|z|=0.64$ for Begg’s test and $P>|t|=0.994$ for Egger’s test).

**Discussion**

Inflammation plays an important role in tumor initiation and progression. The exact mechanism between inflammation and tumor in these patients with cancer was still undefined. Inflammation-related enhanced neutrophil response and/or suppression of lymphocyte leading to a high NLR participates in communication between the microenvironment and tumor cells. The high NLR potentially balances the functions of neutrophils and lymphocyte, making it a valuable prognostic role in gastric, hepatocellular, colorectal cancers, and so on. The mechanisms underlying the complex interplay between high NLR and poor outcome of numerous patients with cancers are poorly understood.

One reason of the prognostic impact of NLR may be an association of elevated levels of NLR with inflammation. Neutrophil restrain the immune system by suppressing the
### Table 1 Main characteristics of all the studies included in the meta-analysis

| Study cohort     | Year | Study region | No (M/F) | Follow-up (months) (median and range) | Treatment                          | Age (years) (median and range) | Cut-off | Outcome | Stage | Type | HR | NOS score |
|------------------|------|--------------|----------|---------------------------------------|------------------------------------|--------------------------------|---------|---------|-------|------|----|-----------|
| Cannon et al22    | 2015 | USA          | 59 (31/28) | 17                                    | Radiation                          | 70 (48–89)                     | 2.98    | OS      | I     | NSCLC | E(U) | 7         |
| Choi et al23      | 2015 | USA          | 1,139 (602/537) | 102                     | Surgery                           | 64.73                            | 5       | RFS/OS  | I/II/III | NSCLC | R(U/M) | 7       |
| Kos et al24       | 2015 | Turkey       | 138 (124/14) | NR                                   | NR                                | 57 (26–83)                      | 3.24    | OS      | I/II/IV | NSCLC | R(U/M) | 6       |
| Mitchell et al25   | 2015 | Canada       | 1,157 (797/360) | 58.7 | Chemotherapy radiotherapy            | Surgery                           | <60 years, n=666; ≥60 years, n=572 | 2.3     | DFS/OS  | I/II/III | NSCLC | R(U)   | 7       |
| Zhang et al26     | 2015 | People’s Republic of China | 1,238 (426/812) | 45 | Surgery                            | Radiation                         | 70 (48–89)                     | 2.98    | OS      | I     | NSCLC | E(U) | 7         |
| Go et al27        | 2014 | Korea        | 114 (87/27) | NR                                   | Chemotherapy                       | NLR<3.68 (44–80); NLR ≥3.69 (35–84) | 3       | OS      | I/II/IV | NSCLC/ SCLC | R(M) | 5       |
| Kang et al28      | 2014 | Korea        | 187 (162/65) | 40.28 (2.60–89.26) | Surgery                           | 68 (43–84)                      | 4       | PFS/OS  | NR     | SCLC  | R(M) | 6       |
| Kacan et al29     | 2014 | Turkey       | 299 (270/29) | 13 (1–24)                            | NR                                | 61 (31–82)                      | 5       | OS      | I/II/III | NSCLC | R(U/M) | 6       |
| Lin et al30       | 2014 | People’s Republic of China | 81 (47/34) | 12–51 | TKI treatment                       | Surgery                           | <65 years, n=46; ≥65 years, n=35 | 3.5     | PFs/OS  | NR     | NSCLC/ SCLC | R(U/M) | 7       |
| Pinato et al31    | 2014 | UK           | 220 (110/110) | 13 (1–87)                            | Surgery                           | 65                                | 5       | OS      | I/II/III | NSCLC | R(U/M) | 7       |
| Wang et al32      | 2014 | People’s Republic of China | 114 (89/25) | NR                                   | Surgery                           | 65                                | 5       | OS      | I/II/III | NSCLC | R(U/M) | 7       |
| Zhang et al33     | 2014 | People’s Republic of China | 400 (272/128) | 46 (1–78)                            | Surgery                           | 60.8 (27–84)                    | 3.3     | DFS/OS  | I/II    | NSCLC/ SCLC | R(U/M) | 7       |
| Botta et al34     | 2013 | Italy        | 112 (81/31) | 15                                    | Chemotherapy                       | 62±11                            | 4       | PFS     | III/IV  | NSCLC | R(U)  | 6       |
| Forget et al35    | 2013 | Belgium      | 255      | 60                                    | Surgery                           | NR                                | 5       | PFs/OS  | I/II    | NSCLC | R(M)  | 5       |
| Yao et al36       | 2013 | People’s Republic of China | 182 (119/63) | 7.3 (1–30)                            | Chemotherapy                       | 61 (28–79)                      | 2.63    | PFs/OS  | III/IV  | NSCLC | R(U/M) | 7       |
| Yildirim et al37  | 2013 | Turkey       | 95 (77/18) | 14±10.8                             | Chemotherapy                       | 59 (30–88)                      | 5       | OS      | III/IV  | NSCLC | R(E)  | 6       |
| Jafari et al38    | 2013 | USA          | 173      | 5                                     | Chemotherapy                       | 57 (34–88)                      | 5       | PFs/OS  | NR     | NSCLC | R(E)  | 5       |
| Kaya et al39      | 2013 | Turkey       | 156 (80/76) | 17.6 (1.41–21.1)                   | NR                                | 60 (30–88)                      | 5       | OS      | III/IV  | NSCLC | R(E)  | 5       |
| Cédrés et al40    | 2012 | Spain        | 171 (143/28) | 9.1 (1–70.37)                       | Chemotherapy                       | 63 (30–81)                      | 5       | PFs/OS  | IV     | NSCLC | R(U/M) | 7       |
| Lee et al41       | 2012 | Korea        | 199      | 36                                    | Chemotherapy                       | 57 (19–74)                      | 3.25    | PFs/OS  | III/IV  | NSCLC | R(U/M) | 6       |
| Sarraf et al42    | 2009 | UK           | 177 (104/73) | 29 (8–56)                            | Surgery                           | 63±10                            | 3.8     | OS      | I/II/III | NSCLC | R(U/M) | 7       |
| Teramukai et al43 | 2009 | Japan        | 388 (276/122) | 18.9 (2.3–57)                       | Chemotherapy                       | 65 (33–81)                      | 4.744   | PFs/OS  | III/IV  | NSCLC | R(M)  | 6       |

**Abbreviations:** M, male; F, female; HR, hazard ratio; NOS, Newcastle-Ottawa Scale; OS, overall survival; NSCLC, non-small-cell lung cancer; E, estimating; R, reporting; M, multivariate; NR, not reported; NLR, neutrophil to lymphocyte ratio; PFs, progression-free survival; U, univariate analysis; RFS, recurrence-free survival; DFS, disease-free survival; TKI, tyrosine kinase inhibitor.
### Figure 2
Meta-analysis of the association between NLR and OS of lung cancer. Results are presented as individual and pooled hazard ratio (HR), and 95% confidence interval (CI).

**Note:** Weights are from random-effects analysis.

**Abbreviations:** NLR, neutrophil to lymphocyte ratio; OS, overall survival.

| Study ID       | HR (95% CI) | % weight |
|----------------|-------------|----------|
| Cannon et al22 |             |          |
| Choi et al23   | 1.92 (1.20, 3.08) | 3.86    |
| Kos et al24    | 1.69 (1.27, 2.23) | 6.02    |
| Mitchell et al25 |            |          |
| Zhang et al26  | 1.53 (1.46, 1.78) | 8.20    |
| Go et al27     | 1.32 (0.66, 2.65) | 2.34    |
| Kang et al28   | 1.47 (1.01, 2.12) | 4.91    |
| Kacar et al29  | 1.70 (1.00, 2.70) | 3.64    |
| Lin et al30    | 3.29 (1.62, 6.71) | 2.26    |
| Pinato et al31 | 3.80 (1.60, 8.90) | 1.69    |
| Wang et al32   | 1.70 (1.05, 2.75) | 3.77    |
| Zhang et al33  | 2.08 (1.32, 3.27) | 4.01    |
| Forget et al34 | 1.78 (1.00, 3.19) | 3.00    |
| Yao et al35    | 1.76 (1.10, 2.83) | 3.83    |
| Yildirim et al36 |          |          |
| Jafri et al37  | 0.57 (0.41, 0.79) | 5.41    |
| Kaya et al38   | 1.91 (1.32, 2.77) | 4.90    |
| Cedrés et al39 | 1.50 (1.10, 2.10) | 5.47    |
| Lee et al40    | 1.13 (1.06, 1.21) | 8.46    |
| Sarraf et al41 | 1.10 (1.03, 1.17) | 8.48    |
| Teramukai et al42 |       |          |
| Subtotal (I²=81.8%, P=0.000) | | 100     |
| Overall (I²=81.8%, P=0.000) | | 100     |

### Figure 3
Meta-analysis of the association between NLR and PFS of lung cancer. Results are presented as individual and pooled hazard ratio (HR), and 95% confidence interval (CI).

**Note:** Weights are from random-effects analysis.

**Abbreviations:** NLR, neutrophil to lymphocyte ratio; PFS, progression-free survival.

| Study ID       | HR (95% CI) | % weight |
|----------------|-------------|----------|
| Kang et al23   | 1.47 (1.03, 2.11) | 11.39   |
| Lin et al24    | 3.89 (1.98, 7.68) | 6.50    |
| Botta et al25  | 1.67 (1.00, 2.80) | 8.68    |
| Forget et al26 | 1.45 (1.02, 2.06) | 11.48   |
| Yao et al27    | 1.81 (1.11, 2.95) | 9.06    |
| Jafri et al28  | 0.58 (0.42, 0.80) | 12.02   |
| Cedrés et al29 | 1.00 (1.00, 1.74) | 12.85   |
| Lee et al30    | 1.23 (1.15, 1.31) | 15.76   |
| Teramukai et al31 |       |          |
| Subtotal (I²=80.5%, P<0.000) | | 100     |
| Overall (I²=80.5%, P<0.000) | | 100     |
Table 2 Summary of the meta-analysis results

| Analysis | N | References | Random-effects model | Fixed-effects model | Heterogeneity |
|----------|---|------------|----------------------|--------------------|---------------|
| Overall survival (OS) | 21 | 16,17,22–32,34–41 | HR (95% CI) | P | HR (95% CI) | P | I² (%) | Ph |
| Subgroup 1 | | | 1.506 (1.330, 1.706) | 0 | 1.229 (1.182, 1.276) | 0 | 81.8 | 0 |
| Surgery | 7 | 16,23,26,28,32,34,40 | 1.587 (1.264, 1.992) | 0 | 1.245 (1.182, 1.311) | 0 | 87.7 | 0 |
| Chemotherapy | 7 | 17,23,33,35,36,38,41 | 1.305 (0.983, 1.733) | 0 | 1.148 (1.080, 1.221) | 0 | 82.5 | 0.066 |
| Subgroup 2 | | | | | | | | |
| Eastern countries | 13 | 24,26–32,35–37,39,41 | 1.638 (1.390, 1.931) | 0 | 1.302 (1.236, 1.370) | 0 | 77.5 | 0 |
| Western countries | 8 | 16,17,22,23,25,34,38,40 | 1.380 (1.067, 1.784) | 0.014 | 1.143 (1.079, 1.210) | 0 | 84.6 | 0 |
| Subgroup 3 | | | | | | | | |
| Cut-off value =5 | 9 | 16,17,23,25,29,34,36–38 | 1.570 (1.164, 2.116) | 0.003 | 1.434 (1.270, 1.618) | 0 | 81.7 | 0.405 |
| Cut-off value <5 | 12 | 22,24,26–28,30–32,35,39–41 | 1.472 (1.280, 1.693) | 0 | 1.208 (1.160, 1.257) | 0 | 81.4 | 0 |
| Subgroup 4 | | | | | | | | |
| NSCLC | 16 | 16,17,22–26,29,34–41 | 1.447 (1.266, 1.654) | 0 | 1.215 (1.169, 1.263) | 0 | 84.1 | 0 |
| SCLC | 2 | 28,31 | 1.549 (1.156, 2.077) | 0.003 | 1.549 (1.156, 2.077) | 0.003 | 0.0 | 0.626 |
| NSCLC/SCLC | 3 | 27,30,32 | 2.073 (1.329, 3.234) | 0.001 | 2.070 (1.480, 2.895) | 0 | 38 | 0.199 |
| Subgroup 5 | | | | | | | | |
| I/III/IV | 5 | 24,25,27,29,40 | 1.295 (1.073, 1.563) | 0.007 | 1.131 (1.065, 1.202) | 0 | 50.3 | 0.090 |
| Advanced: III/IV | 6 | 33,35–37,39,41 | 1.583 (1.222, 2.051) | 0.001 | 1.193 (1.121, 1.269) | 0.001 | 77 | 0 |
| Subgroup 6 | | | | | | | | |
| Sample size ≥200 | 8 | 16,23,25,26,29,32,34,41 | 1.576 (1.433, 1.733) | 0 | 1.565 (1.441, 1.699) | 0 | 5.9 | 0.385 |
| Sample size <200 | 13 | 17,22,24,27,28,30,31,35–40 | 1.395 (1.202, 1.619) | 0 | 1.149 (1.101, 1.200) | 0 | 79 | 0 |
| Subgroup 7 | | | | | | | | |
| Univariate analysis | 13 | 16,17,22–26,30,32,35,38–40 | 1.420 (1.242, 1.623) | 0 | 1.200 (1.160, 1.241) | 0 | 88.2 | 0.001 |
| Multivariate analysis | 17 | 16,23,24–27,32–34,41 | 1.581 (1.386, 1.803) | 0 | 1.189 (1.139, 1.240) | 0 | 74.9 | 0 |
| Progression-free survival (PFS) | 9 | 17,28,30,33–35,38,39,41 | 1.334 (1.066, 1.670) | 0.012 | 1.230 (1.161, 1.304) | 0 | 80.5 | 0 |
| Subgroup 8 | | | | | | | | |
| Surgery | 2 | 28,34 | 1.462 (1.138, 1.877) | 0.003 | 1.462 (1.138, 1.877) | 0.003 | 0.0 | 0.949 |
| Chemotherapy | 6 | 17,33,35,38,941 | 1.173 (0.901, 1.527) | 0.235 | 1.207 (1.137, 1.282) | 0 | 82 | 0 |
| Subgroup 9 | | | | | | | | |
| Eastern countries | 5 | 28,30,35,39,41 | 1.598 (1.216, 2.099) | 0.001 | 1.266 (1.190, 1.347) | 0 | 73.3 | 0.005 |
| Western countries | 4 | 17,33,34,38 | 1.065 (0.683, 1.660) | 0.782 | 0.991 (0.836, 1.175) | 0.919 | 84.3 | 0 |
| Subgroup 10 | | | | | | | | |
| Cut-off value =5 | 3 | 17,34,38 | 0.941 (0.575, 1.541) | 0.809 | 0.930 (0.776, 1.113) | 0.429 | 86.3 | 0.001 |
| Cut-off value <5 | 6 | 28,30,33,35,39,41 | 1.596 (1.250, 2.037) | 0 | 1.271 (1.195, 1.351) | 0 | 68.9 | 0.007 |
| Subgroup 11 | | | | | | | | |
| Univariate analysis | 6 | 17,30,33,35,38,39 | 1.361 (0.956, 1.938) | 0.087 | 1.227 (1.159, 1.299) | 0 | 88.5 | 0 |
| Multivariate analysis | 6 | 28,30,34,35,39,41 | 1.547 (1.237, 1.935) | 0 | 1.271 (1.196, 1.351) | 0 | 67.9 | 0.008 |
| NSCLC | 7 | 17,33–35,38,39,41 | 1.205 (0.958, 1.517) | 0.112 | 1.213 (1.143, 1.287) | 0 | 79.2 | 0 |

Note: Meta-regression analysis was applied only if the pooled cohorts exceeded 10.
Abbreviations: N, number of studies; HR, hazard ratio; CI, confidence interval; Ph, P-value of Q-test for heterogeneity test; NSCLC, non-small-cell lung cancer.

cytolytic activity of activated T-cells, lymphocytes, and natural killer cells. However, the significance of lymphocytes has been highlighted in some studies in which increasing infiltration of tumors with lymphocytes may play a key role in cytotoxic treatment and prognosis in patients with cancer.

NLR was frequently used as an inflammatory marker, while its prognostic role in lung cancer was revealed just during the recent years. The present meta-analysis demonstrated that the elevated level of NLR is associated with the poor survival of lung cancer. A prognostic role was demonstrated for both OS and PFS of patients with lung cancer. Similar to our study, two recent meta-analyses confirmed the prognostic value of the NLR in colorectal cancer and hepatocellular carcinoma. Though with heterogeneity, subgroup estimation in the present study showed that high NLR was an effective prognostic factor for poor OS of patients with lung cancer who received various types of treatment including surgical resection and chemotherapy. There was also a significant association between NLR and therapeutic and cut-off value NLR =5/<5. Taking all these into consideration, NLR is a promising prognostic inflammation marker helpful for the clinical decision-making process regarding lung cancer treatment and outcomes.
Limitations of this meta-analysis deserve comment. First, the majority of the enrolled studies were retrospective, which was more susceptible to some biases. Second, heterogeneity is a potential problem that may affect the interpretation of the results of all meta-analyses. The presence of heterogeneity may result from many other factors, including age distribution, sex, NLR cut-off value, and so on. Third, NLR was not included in the multivariate analysis because it failed to gain statistical significance in the univariate analysis. The corresponding HR and 95% CI could only be retrieved from univariate analysis. The accuracy of the pooled estimates may thus be impaired. Fourth, publication bias inevitably hides in meta-analysis since positive results were more likely to be published than negative ones. A tendency for journals to only publish positive results leads to a larger magnitude of an association in pooled analysis than the actual value.

In conclusion, this meta-analysis demonstrated that the high NLR is associated with worse prognosis for patients with lung cancer. NLR seems to be a convenient, repeated, inexpensive, widely available, and reliable to predict the survival and treatment response of patients with lung cancer. In future, more research with better design to test this hypothesis is necessary.

Disclosure
The authors declare that they have no conflicts of interest in this work.

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