Prognostic significance of neutrophil-to-lymphocyte ratio in non-small cell lung cancer: a meta-analysis

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Published data on the prognostic significance of neutrophil-to-lymphocyte ratio (NLR) in non-small cell lung cancer (NSCLC) are controversial. We performed a meta-analysis to more accurately assess its prognostic value. The analysis was performed based on the data from 14 studies with 3,656 patients to estimate the correlation between NLR and overall survival (OS) and progression-free survival (PFS) in NSCLC. Hazard ratio (HR) with 95% confidence interval (CI) were calculated to estimate the effect. We also conducted subgroup analysis and meta-regression analysis. The results demonstrated that elevated pretreatment NLR predicted poorer OS (HR: 1.70, 95% CI: 1.39–2.09) and PFS (HR: 1.63, 95% CI: 1.27–2.09) in patients with NSCLC. Subgroup analysis indicated that cut-off value of 5 showed consistently prognostic value. There was no significant heterogeneity or publication bias for OS and PFS for included studies. This meta-analysis revealed that elevated pretreatment NLR might be a predicitve factor of poor prognosis for NSCLC patients.
studies suggest a potential prognostic role of NLR in NSCLC patients, however, the majority of the studies had relatively limited sample sizes. Furthermore, some authors presented conflicting data regarding the prognostic significance of NLR in NSCLC. We thus conducted this meta-analysis to systematically clarify the prognostic value of NLR in NSCLC patients.

**Results**

**Study selection and characteristics.** The flow chart of the literature selection was shown in Fig. 1. The initial search strategies retrieved a total of 195 studies. After screening the titles or abstracts, 170 studies were excluded as they were either duplicate reports, conference abstracts, reviews, case reports, reports in language other than English or studies irrelevant to the current analysis. Then, 25 identified studies concerning NLR and the prognosis of NSCLC were further evaluated. Eleven reports of them were discarded because of the following reasons: eight did not provide specific NLR data for OS or PFS, two failed to define cut-off value of “elevated NLR”, two reported on NLR and small cell lung cancer, we also added one article by manual search. Therefore, 14 studies with 3656 patients published between 2009 and 2015 were included in our meta-analysis finally. As the study by Botta et al. included two cohorts and reported the HR and 95%CI respectively, we marked them as Botta1 and Botta2. The main characteristics of these studies are shown in Table 1. Three studies were conducted in USA, two in Japan, China and Turkey, respectively, one in Spain, Italy, Korea, Belgium, and UK, respectively. One study involved all disease stages, six studies included only early stage disease (I/I-II/I-III/I-III) and seven studies included only late disease stages.
stage disease (IIIB-IV). Thirteen studies\(^1\)\(^{9-12,25-28}\) with 3,544 patients reported the correlations of NLR and OS, while nine studies\(^2\)\(^{20,21,24,25,28-32}\) (ten cohorts) with 2,623 patients reported the correlations of NLR and PFS. NOS scores of the studies ranged from 5 to 8, with a mean value of 6.64.

**NLR and OS in NSCLC.** Thirteen cohorts presented the data of pretreatment NLR and OS in NSCLC patients. Meta-analysis of these 13 cohorts showed that patients with elevated NLR were associated with shorter OS (HR obtained from DerSimonian–Laird random-effects model: 1.70 (95% CI: 1.39–2.09, \(p < 0.001\); Fig. 2), although there was heterogeneity between studies (\(I^2 = 83.1\%, Ph < 0.001\)). Then we conducted subgroup analyses according to confounders such as treatment method, study location, tumor stage, sample size, cut-off value defining “elevated NLR” and NOS score.

Stratification by treatment methods, we found the pooled HRs were 1.70 (95%CI: 1.39–2.10) for patients treated by surgery and 1.76 (95%CI: 1.30–2.39) for patients treated by non-surgery methods. Subgroup analyses by countries indicated that elevated NLR predicted poor prognosis for patients both in western countries (HR\(^2\) = 1.74, 95%CI: 1.44–2.12) and in eastern countries (HR\(^2\) = 1.58, 95%CI: 1.22–2.04). Stratification by cutoff value = 5 and cut-off value ≠ 5, the data showed that the pooled HR was 1.67 (95%CI:1.44–1.94) for cutoff value = 5 and 1.67 (95%CI:1.26–2.23) for cut-off value ≠ 5. Notably, when cut-off value = 5 was used, there was no heterogeneity (\(I^2 = 0, Ph = 0.506\), which may indicate NLR = 5 is more stable in prognosis prediction. In addition, subgroup analyses showed the elevated NLR predicted prognosis for NSCLC regardless of tumor stage (early stage vs. late stage), sample size(\(\geq 200\) vs. \(< 200\)) and NOS score(\(\geq 7\) vs. \(< 7\)) (Table 2).

**NLR and PFS in NSCLC.** Ten cohorts with 2,623 cases reported the data of pretreatment NLR and PFS in NSCLC patients. Combined data from the ten cohorts suggested that elevated pretreatment NLR were significantly correlated with PFS with a pooled HR estimate of 1.63 (95% CI: 1.27–2.09, \(p < 0.001\); Fig. 3), with heterogeneity (\(I^2 = 81.9\%, Ph < 0.001\)). Subgroup analysis indicated that elevated pretreatment NLR were significantly associated with PFS in western countries (HR\(^2\) = 1.56, 95% CI: 1.31–1.86, \(p < 0.001\)), without significant heterogeneity in the data (\(I^2 = 0, Ph = 0.791\)). We did not perform subgroup analysis for PFS based on treatment method as majority therapeutic regimen in the studies was chemotherapy. Moreover, elevated pretreatment NLR was also associated significantly with PFS in NSCLC patients with a cut-off value of 5 (HR: 1.54, 95% CI: 1.27–1.86, \(p < 0.001\)), without significant heterogeneity in the data (\(I^2 = 0, Ph = 0.453\)).

**Heterogeneity.** We conducted meta-regression analysis to investigate the potential source of heterogeneity among studies for OS and PFS. The results showed that treatment method (\(p = 0.891\)), study location (\(p = 0.387\)), tumor stage (\(p = 0.625\)), sample size (\(p = 0.97\)), cut-off value (\(p = 0.693\)) and NOS score (\(p = 0.084\)) did not contribute to the source of heterogeneity for OS. Moreover, the data demonstrated

| Study       | Year | Country | Duration | Sample size | Follow-up (m) | Stage | Treatment | Cut-off value | Survival analysis | Study design | NOS |
|-------------|------|---------|----------|-------------|---------------|-------|-----------|---------------|------------------|--------------|-----|
| Teramukai\(^2\)\(^5\) | 2009 | Japan   | 2001–2005| 388         | 18.9(2.3–57) | IIIB-IV| C         | 4.74          | OS,PFS           | P            | 8   |
| Tomita\(^2\)\(^6\) | 2011 | Japan   | 2000–2005| 284         | >60           | I-III | S         | 2.5           | OS              | R            | 8   |
| Cedres\(^7\) | 2012 | Spain   | 2004–2009| 171         | 9.1(1–70.4)  | IV    | C         | 5             | OS              | R            | 8   |
| Lee\(^8\) | 2012 | Korea   | 2005–2007| 199         | 36            | IIIB-IV| C         | 3.17          | OS,PFS           | P            | 7   |
| Botta\(^9\)\(^2\) | 2013 | Italy   | 2008–2011| 73          | 15            | IIIB-IV| C+T       | 4             | PFS             | R            | 7   |
| Botta\(^2\)\(^10\) | 2013 | Italy   | 2008–2011| 39          | 15            | IIIB-IV| C         | 4             | PFS             | R            | 7   |
| Forget\(^11\) | 2013 | Belgium | 1993–2004| 255         | 56.1          | I-II   | S         | 5             | OS,PFS           | R            | 8   |
| Jafri\(^12\) | 2013 | USA     | 2000–2011| 173         | NR            | IV     | C         | 5             | OS,PFS           | R            | 6   |
| Unal\(^13\) | 2013 | Turkey  | NR       | 94          | NR            | II-IIIB| C         | 3.44          | OS,PFS           | R            | 5   |
| Yao\(^14\) | 2013 | China   | 2007–2010| 182         | NR            | IIIB-IV| C         | 2.63          | OS,PFS           | R            | 6   |
| Kacan\(^15\) | 2014 | Turkey  | NR       | 299         | NR            | I-IV   | S         | 5             | OS              | R            | 5   |
| Pinato\(^16\) | 2014 | UK      | 2004–2011| 220         | 12            | I-III | S         | 5             | OS              | P            | 7   |
| Cannon\(^17\) | 2014 | USA     | 2009–2012| 59          | 17            | I      | R         | 2.98          | OS              | R            | 6   |
| Lin\(^18\) | 2014 | China   | 2009–2012| 81          | 13–40         | IV     | T         | 3.5           | OS,PFS           | R            | 6   |
| Choi\(^19\) | 2015 | USA     | 2004–2010| 1139        | NR            | I-III  | S         | 5             | OS,PFS           | R            | 6   |

Table 1. Characteristics of included studies. NR: not reported; Treatment describes whether the patients received surgery (S), chemotherapy (C), radiotherapy (R) or targeted therapy (T); OS: overall survival; PFS: progression-free survival; Study design describes the studies as either prospective (P) or retrospective (R) study.
that study location (p = 0.944), sample size (p = 0.733) and NOS score (p = 0.202) did not contribute to the source of heterogeneity for PFS. Sensitivity analysis indicated that removing any single study by turn did not significantly affect the pooled HRs for OS and PFS (Figs 4 and 5).

**Publication bias.** Publication bias estimate was mainly used to evaluate the reliability of meta-analysis results, especially which showed statistical significance. Assessment of publication bias by using Begg’s test (statistical significance was set at p < 0.05) suggested that there were no significant publication bias in OS and PFS studies (p = 0.2 and p = 0.721, respectively).

**Discussion**

This meta-analysis aimed to examine the associations between elevated pretreatment NLR and OS and PFS of NSCLC. Our analysis combined the outcomes of 3,656 NSCLC patients from 14 individual studies, demonstrating that elevated pretreatment NLR significantly predicted poor OS (HR: 1.70, 95% CI 1.39–2.09), and PFS (HR: 1.63, 95% CI 1.27–2.09) of NSCLC cancer patients. Although heterogeneity exists, most of the prognostic significance is not weakened by subgroup analysis stratified by treatment method, study location, tumor stage, sample size, cut-off value of NLR and NOS score. Furthermore, subgroup analysis indicated that NLR had consistent prognostic value for NSCLC populations of OS with a cut-off value of 5. Whereas, NLR could better predicted poor PFS for NSCLC patients in western countries with a cut-off value of 5. This finding suggested that dichotomized NLR cut-off value of 5 could help guide clinical decision-making in regard of therapeutic strategies and outcomes for NSCLC patients both for OS and PFS. To the best of our knowledge, this is the first meta-analysis on the association between elevated pretreatment NLR and clinical outcomes in NSCLC.

Accumulating evidence showed the connection between inflammation and cancer and mechanistic studies have presented solid evidence to support the biological and prognostic importance of a pro-inflammatory tumor microenvironment in cancer progression. An elevated NLR implies an increased neutrophil count and/or a decreased lymphocyte count, as well as a relative lymphopenia. Lymphocytes have an important role in tumor defence, which inhibits tumor cell proliferation and migration. However, a large amount of neutrophils had been indicated to influence cytolytic activity of lymphocytes or natural killer cells, as well as suppress T-cell proliferation. Thus, neutrophils in the tumor microenvironment could have negative impact on tumor growth. Therefore, NLR could concisely reflect the imbalance of pro-tumor and anti-tumor activity of the hosts in respect of inflammatory response. Thus, the relative value of a combined neutrophil and lymphocyte counts index in form of a neutrophil to lymphocyte (N/L) ratio can reflect the protumor efficacy and antitumor capacity of the host.
more accurately. IL-17 and peritumoral CD163 may exert important roles in the inflammatory tumor microenvironment and facilitate tumor progression and recurrence. Additionally, it is convenient and cost-effective to measure the parameter of NLR in clinical practice, which makes NLR an attractive biomarker for NSCLC prognostication.

More recently, several meta-analyses reported the prognostic value of NLR in a variety of cancers, including colorectal cancer, hepatocellular carcinoma, gastric cancer, renal cell carcinoma, pancreatic cancer and esophageal cancer. Our study was the first study investigating the prognostic significance of NLR for NSCLC patients and the results were in line with previous reports, indicating that elevated NLR gained prognostic values for solid tumors and NLR could be widely used in clinical settings, especially for cancer patients. In addition, the value of NLR was easy to obtain because it is a routine test and more importantly, it does not add extra cost. So NLR is a promising biomarker for clinical use.

In spite of the intrinsic defects associated with meta-analysis, there are a number of other limitations in our study. First, significant heterogeneity was observed in the results due to confounding factors, such as the baseline characteristics of the patients, treatment methods, follow-up period, sample size and cut-off value of NLR. However, subgroup analysis, meta-regression analysis and sensitivity analysis showed that none of the above-mentioned confounders could completely explain the heterogeneity.

Table 2. Summary of the meta-analysis results. Ph: p value of Q test for heterogeneity test; N: number of studies (cohorts); HR: hazard ratio; 95% CI: 95% confidence interval; For OS and PFS, subgroup analyses were performed by treatment (surgery vs. non-surgery), study location (Western vs. Eastern countries), sample size (≥200 vs. <200), cut-off value of NLR (5 vs. not 5) and NOS score (≥7 vs. <7).
Thus, we supposed that the heterogeneity could be a result of combined effect of the above-mentioned confounders and the genotypic diversity of lung cancer in these studies. Second, we did not analyze the correlation between the elevated NLR and clinicopathological parameters of patients, such as lymph node metastasis, grade of differentiation and tumor stage, because only two studies reported the relevant

Figure 3. Forrest plots of studies evaluating hazard ratio (HR) with 95% CI of NLR for progression-free survival (PFS).

Figure 4. Sensitivity analysis on the relationship between NLR and OS in NSCLC.

Thus, we supposed that the heterogeneity could be a result of combined effect of the above-mentioned confounders and the genotypic diversity of lung cancer in these studies. Second, we did not analyze the correlation between the elevated NLR and clinicopathological parameters of patients, such as lymph node metastasis, grade of differentiation and tumor stage, because only two studies reported the relevant
information. The data is insufficient to analyze. Third, some primary studies evaluated the prognostic role of NLR in univariate analysis, whereas others used multivariate analysis, which may contribute to some bias when the data were pooled. Forth, most of the original studies showed that high NLR predicted poor prognosis due to positive results tend to be published, although two studies\textsuperscript{24,28} gained negative results for PFS, more controversial papers could not be searched.

Despite several limitations, our meta-analysis also had some advantages. First, we got similar results when the data were analyzed neither in random-effects model nor in fixed-effects model, which indicated that robustness of the statistic results. Second, the results of sensitivity analysis did not significantly altered, indicating that our results were stable. At last, all the scores of study quality assessed by NOS were ≥5, which demonstrated the creditability of our meta-analysis results.

In conclusion, our results indicated that elevated pretreatment NLR might be an unfavorable prognostic factor for patients with NSCLC, which could be useful in stratifying patients and in determining individual treatment plans. However, these findings need to be interpreted cautiously when used in clinical practice because of the limitations listed above. More well-designed and large-scale investigations are warranted to better understand the value of NLR in the prognosis of NSCLC.

**Methods**

**Publication search.** A literature search was conducted via Pubmed, Embase, and Web of Science databases for articles that assessed NLR as a prognostic factor for survival of patients with NSCLC (last search was updated on May 6, 2015). The search strategy used key words such as "neutrophil-to-lymphocyte ratio", "neutrophil lymphocyte ratio", "NLR", "lung cancer", "lung carcinoma", "NSCLC", "non small cell lung cancer", "non-small cell lung cancer", "prognosis", "prognostic" and "survival". Article language was restrained to English. The references in the identified articles were also retrieved to find other relevant studies.

**Study selection criteria.** Two reviewers (X.B.G. and X.J.T.) reviewed all candidate articles independently. Discrepancies were resolved by discussion. Studies were eligible for inclusion in the meta-analysis if they met the following criteria: (a) patients with NSCLC in the studies were confirmed histopathologically; (b) investigated the association of pre-treatment NLR with overall survival (OS) or progression-free survival (PFS); (c) reported a hazard ratio (HR) and 95% confidence intervals (CIs) or the data sufficient to estimate the HR and 95% CIs; (d) to be published as full texts in the English language. Small-cell lung cancer was not included in our study because it is a highly undifferentiated cancer with distinct biological behaviors from NSCLC.
Data extraction and quality assessment. Two investigators (X.B.G. and T.T.) reviewed each eligible study and extracted data. The extracted data including: first author's name, study location, publication year, duration of the studies, follow-up period, sample size, tumor stage, predominant treatment methods, study design, cut-off value of “elevated NLR” and HRs with 95% CIs. If not available, data were extracted to calculate HR by the method of Tierney et al.42. Quality assessment was independently conducted in all the included studies by three investigators (X.B.G., X.J.Z. and X.J.T.) using the Newcastle–Ottawa Quality Assessment Scale (NOS). Disagreements were resolved by discussion. The NOS comprised of three parameters of quality: selection (0–4 points), comparability (0–2 points), and outcome assessment (0–3 points). The maximum possible score is 9 points and NOS scores ≥7 are considered as high-quality studies.

Statistical analysis. We directly obtained hazard ratio (HR) and 95% confidence intervals (95% CI) from each article or estimated these data according to the methods illustrated by Tierney et al.42. A test of heterogeneity of pooled results was performed using Cochran's Q test and Higgins I-squared statistic. I² > 50% is considered as a measure of significant heterogeneity. Both random effects (DerSimonian–Laird method) and fixed-effects (Mantel–Haenszel method) models were used to generate the pooled HRs and 95% CIs. Owing to a tendency of possible heterogeneity between primary studies, the random-effects model was chosen because it was usually more conservative. We also investigated reasons for inter-study heterogeneity using subgroup analysis and meta-regression analysis. Sensitivity analyses were conducted to evaluate the stability of the results. Publication bias of literatures was evaluated using Begg's funnel plot. All statistical tests were two sided and the significance level was set at 5%. All analyses were carried out using STATA 12.0 software (STATA, College Station, TX).

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