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*Review Article*

# Prognostic role of neutrophil/lymphocyte ratio (NLR) in patients with non-small-cell lung cancer treated with PD-1/PD-L1 inhibitors: a meta-analysis

Yu Zhang[1], Wei Wang[2], Lan LYu[3]

*[1]Department of Thoracic Surgery, [2]Expert's Outpatient, [3]Plastic Surgery, Feicheng Hospital Affiliated to Shandong First Medical University, Feicheng County, Taian 271600, Shandong Province, China*

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**Abstract:** Background: Emerging evidence shows that NLR is associated with the prognosis of multiple tumors including NSCLC. PD-1 and PD-L1 inhibitors have been widely used in the therapy of advanced NSCLC in recent years. However, the relationship between NLR and the prognosis of patients receiving immunotherapy has not been confirmed. We summarized the relevant literature to confirm whether NLR can predict the prognosis of such patients. Methods: Pubmed, EMBASE, WEB of SCI and Cochrane were searched to obtain as many appropriate literature as possible. After HR and 95% CI were extracted from the included literature, STATA was used to conduct effect size consolidation and other relevant tests to explore the effect of NLR on prognosis. Results: Twenty-seven cohort studies including 2286 patients were incorporated in our meta-analysis. This study revealed that the level of NLR was negatively correlated with OS and PFS in NSCLC patients. Subgroup analysis results show that a high level of NLR in a study with multivariate analysis, prospective study design, NOS score ≥7 is significantly correlated with a shorter OS. In addition, in the subgroup of squamous cell carcinoma patients with the proportion ≤0.4 and follow-up time ≤1 year, high NLR was significantly correlated with shorter PFS. Conclusion: Our results indicate that NLR is a simple and easily available prognostic indicator with broad application prospects in the immunotherapy of NSCLC, especially for the short-term progression-free survival of NSCLC patients with non-squamous carcinoma.

**Keywords:** NLR, non-small-cell lung cancer, meta-analysis

## Introduction

Lung cancer is the malignant tumor with one of the worst prognoses, with 1.6 million new cases diagnosed and 1.4 million deaths per year [1]. Numerous studies have shown that the generation and development of tumors is not only dependent on the characteristics of cancer cells, but also related to the interaction of the immune system [2]. The immune response mediated by T cells is regulated by stimulus signals and suppression signals. In tumor cells, dysfunction of regulator proteins leads to immune tolerance, which results in immune escape.

In immunotherapy for tumors, programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors have been immediate areas of research focus. PD-1 is a member of CD28/CTLA-4 T-cell regulator and protein family, mainly expressed in mature T cells [3], and its ligands include PD-L1 and PD-L2. PD-L1 is mainly expressed in tumor cells [4]. Since 2014, when the US FDA approved anti-PD-1 antibodies for the treatment of advanced melanoma, including Pembrolizumab and Nivolumab, the indications have expanded to a variety of different solid tumors. However, the overall response rate (ORR) for immunotherapy remains relatively low, particularly in non-selected lung cancer patients, where the average ORR is less than 20 percent, and the cost of these medicines is high. Therefore, it is particularly important to explore the predictors of the effectiveness of PD-1/PD-L1 inhibitors treatment to accurately identify the patients who may benefit.

Approximately 27% of patients have positive expression of PD-L1, which is mainly expressed

in the cell membrane or cytoplasm [5-7]. Many studies have shown that its expression is associated with the efficacy of immunotherapy. In a study on Pembrolizumab involving 194 patients with advanced NSCLC [8], ORR was 20% in patients with unscreened PD-L1 status, 23% in PD-L1 positive patients and 9% in PD-L1 negative patients. Expression of PD-L1 seems to predict treatment response, but in many other studies, patients who had PD-L1 positive tumors do not respond to treatment, while some PD-L1 negative tumor patients show clinical response to treatment [9, 10].

Neutroohil-lymphocyte ratio (NLR) is a simple indicator, which is easy to obtain from routine blood examination. A great deal of recent studies have linked it to the effectiveness of immunotherapy for lung cancer. However, this opinion remains controversial, because some articles do not support this conclusion. In view of this, we conducted this meta-analysis to further clarify whether NLR has prognostic value in NSCLC patients treated with PD-1/PD-L1 inhibitors.

This meta-analysis has been registered on the prospero website with a registration ID of CRD42020167137.

## Methods

### *Search strategy*

Pubmed, Embase, Web of SCI, and Cochrane library were searched, with a deadline of 1 August 2019. In order to prevent omissions, we also searched the references of included articles, relevant literature reviews and systematic reviews. The language of literature retrieval is limited to English. The formula for retrieval is [(neutrophil to lymphocyte ratio) OR (neutrophil-to-lymphocyte ratio) OR (neutrophil lymphocyte ratio) OR (neutrophil-lymphocyte ratio) OR (NLR)] AND [(Lung Neoplasms) OR (Pulmonary Neoplasms) OR (Lung Neoplasm) OR (Pulmonary Neoplasm) OR (Lung Cancer) OR (Lung Cancers) OR (Pulmonary Cancer) OR (Pulmonary Cancers) OR (Cancer of Lung) OR (NSCLC) OR (non-small-cell lung cancer) OR (non small cell lung cancer) OR (small cell lung cancer) OR (lung carcinoma)].

### *Inclusion criteria*

The inclusion criteria were defined as: (1) The subject of the literature was the relationship between the blood NLR ratio and the prognosis of NSCLC patients treated with PD-1/PD-L1, not the variation in NLR. The time point of NLR can be before or after treatment. (2) The diagnosis of the patient is based on pathological or cytological diagnosis. (3) the types of studies included in the literature were prospective or retrospective cohort studies or randomized controlled trials, and the full text was available. (4) The outcome indicators of the literature include OS or PFS, and their HR and 95% CI can be directly extracted or calculated. (5) For studies using the same population sample, we only use the latest and most comprehensive studies.

### *Exclusion criteria*

The exclusion criteria for literature are: (1) the types of literature are abstract, review, systematic evaluation, expert consensus, case analysis or meeting minutes. (2) Studies with a sample size of less than 20 patients.

### *Data extraction*

The following data will be extracted: title of paper, journal name, name of the primary author, duration of study, year of publication, country or region, research method (prospective or retrospective), characteristics of study cohorts (sample size, age, sex), smoking history, target mutation, metastatic sites, PS scale, PD-1 expression, types of drugs, neutrophil-lymphocyte ratio (NLR) and its time, pathological type and malignant stage, outcome measures (OS and PFS; HRs and 95% CIs and/or *P* values), model of survival statistics analysis (multivariable analysis and/or univariable analysis), follow-up time.

### *Quality assessment*

NOS scores (Newcastle-Ottawa Scale) were used to evaluate the quality of studies. In order to ensure the accuracy of the evaluation, two independent researchers (Yu Zhang and Wei Wang) independently scored the results, and the disputes were solved through group discussion. Literature with NOS score greater than 7 is considered to be of high quality.

### *Statistical analysis*

HR and 95% CI of OS and PFS included in the studies have been combined to determine the prognostic value of NLR. HR greater than 1 and

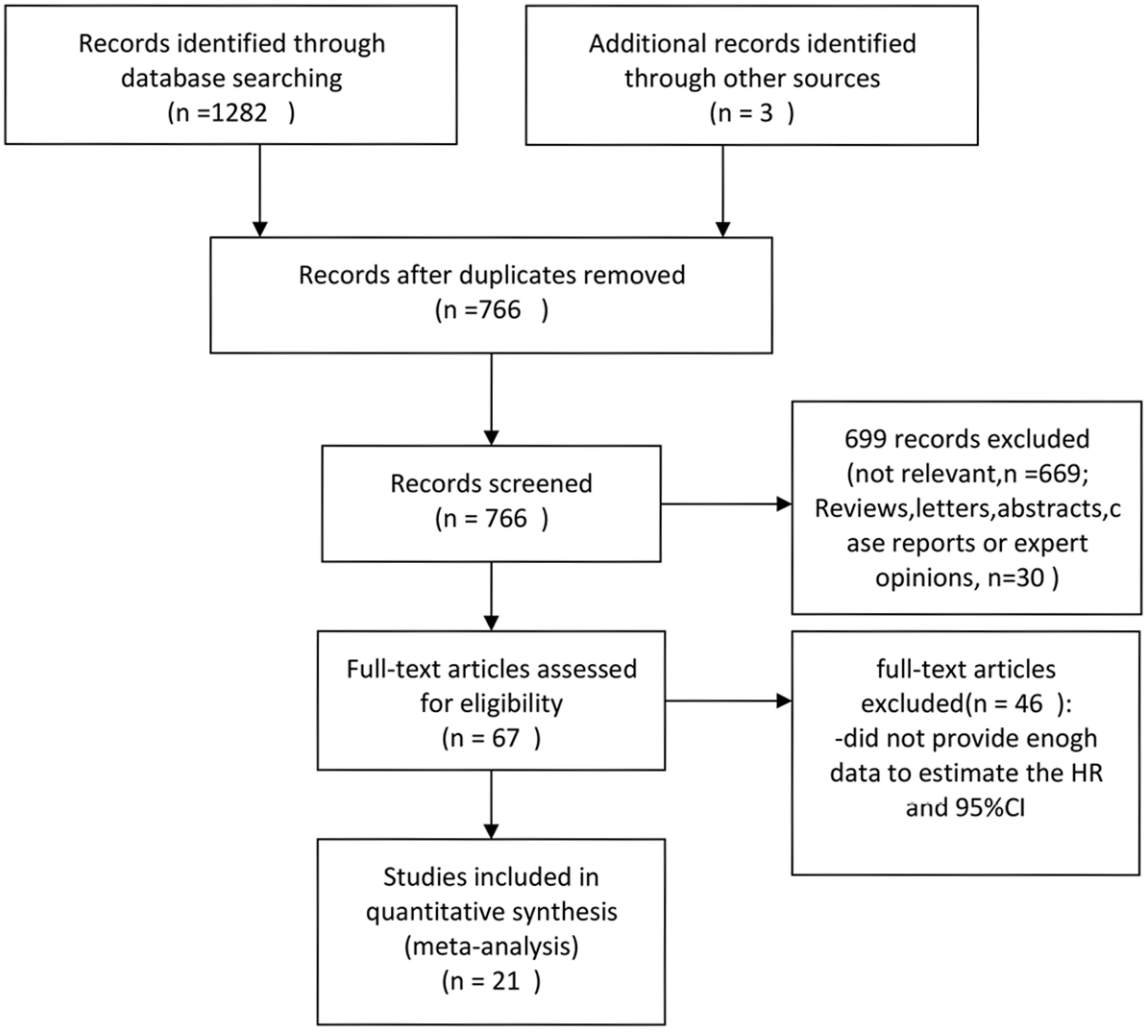


**Figure 1.** Flow chart of the included studies.

95% CI excluding 1 are considered to be associated with poor prognosis. The Q test and the $I^2$ statistical test were used to test the heterogeneity between included studies. If there was no obvious heterogeneity, the fixed effect model was used for effect size consolidation, and the random effect model was used for the other. In order to evaluate the sensitivity of our research results and reflect the stability of our research results, we performed a new meta-analysis of the merger effect size after successively excluding each included study and compared the new merger results with the previous one. In addition, we performed meta-regression analysis and subgroup analysis to find the factors causing heterogeneity. Since statistically significant studies are more likely to be published, a publication bias test is necessary. Due to the limitations of each publication bias test method, we used Begg method, Egger's method and trim and fill method to test the publication bias to verify the reliability of the results. All of the above tests and the combination of effect sizes were implemented using the STATA 12.0 software.

## Result

### *Study characteristics*

The literature selection process was illustrated in **Figure 1**. A total of 21 original studies [11-31] involving 2286 patients met the inclusion criteria. Nine of the studies were from Eastern countries and 12 were from Western countries. Two were prospective studies and 19 were retrospective. Twenty studies focused on OS, and another nineteen studied the relationship

between NLR and PFS. PD-1 expression rate was reported in 9 studies, gene mutation targeted detection results were reported in 13 studies, the condition of distant metastasis was available in 9 studies, and PS scores of patients were reported in 18 studies. The therapeutic drugs in 13 studies included only nivolumab, 5 were nivolumab or pembrolizumab, and 3 were nivolumab, pembrolizumab, or other drugs (atezolizumab or durvalumab). Twenty studies were about pre-immunotherapy NLR, and the other five were on post-treatment. In the study of Khunger, Suh, Takeda and Park, NLR before and after immunotherapy were studied simultaneously, so we labeled them as Khunger1, Khunger2, Suh1, Suh2, Takeda1, Takeda2, Park1 and Park2. NOS scores were distributed from 6 to 9 in all studies, 11 of which were high scores greater than or equal to 7. All the main information included in the study is listed in **Table 1**.

*NLR and OS in NSCLC*

We performed effect size combination of 20 studies including 2240 patients on relationships between NLR and OS, and the combination results showed that elevated NLR was associated with poor outcomes (HR: 2.71; 95% CI: 1.90-3.89) (**Figure 2**). Due to the obvious inter-study heterogeneity (Q H=3.7, $I^2$=93%), we adopted the random effect model for effect-size combination.

*NLR and PFS in NSCLC*

In our original study of 19 studies on NLR and PFS in 2,286 patients, we performed effect-volume consolidation, which showed that elevated NLR was associated with poor outcomes (HR: 1.77; 95% CI: 1.43-2.19) (**Figure 3**). Because of the obvious inter-study heterogeneity (Q H=2.4, $I^2$=83%), we adopted the random effect model for effect-size combination.

*Heterogeneity and subgroup analyses*

In order to explore the causes of heterogeneity, meta regression analysis was conducted, and according to the results, the time of NLR (P=0.488), country (P=0.982), medicine (P=0.823), data analysis method (P=0.304), study design (P=0.79), NOS score (P=0.849), sample size (P=0.342) were not the sources of heterogeneity in OS group. Sample size (P=0.045), cut-off value (P=0.017) and NOS score (P=0.013) may be the reason for heterogeneity in PFS group, but the time of NLR (pre-treatment or post-treatment) (P=0.639), country (P=0.209), histological type (P=0.183), Medicine (P=0.267), study Design (P=0.103) were not.

Further subgroup study of the sources of heterogeneity was conducted and the results are listed in **Table 2**. The results showed that increased NLR levels in subgroups of using multivariate analysis, prospective study methods, and NOS scores higher than 7 were associated with shorter OS, and that inter-study heterogeneity was not statistically significant. The proportion of squamous cell carcinoma was less than 0.4 and follow-up time ≤12 months was associated with shorter PFS, and the inter-study heterogeneity was not statistically significant. This indicates that NLR has a higher predictive value for the prognosis of patients in the above subgroups.

*Sensitivity analysis*

The sensitivity analysis of the meta-analysis results showed that the combined effect size did not affect the statistical significance of the combined effect size results was less affected by exclusion of any of the included studies. This indicates that our results are highly reliable, which means that new related studies will not affect the combined results in the future. The results of sensitivity study are shown in **Figures 4** and **5**.

*Publication bias*

Begg's test was used to detect publication bias in OS (P=0.87) (**Figure 6**) and PFS (P=0.889) (**Figure 7**). The results showed no publication bias. The results of trim and till method showed that the comprehensive HR (OS: HR=1.252, 95% CI: 0.898-1.747; PFS: HR=1.141, 95% CI: 0.936-1.391) was significantly different from previous studies, indicating a publication bias.

## Discussion

Higher NLR was associated with shorter OS and PFS, according to the combined effect size, although there was significant heterogeneity between studies. In order to explore the causes of heterogeneity, we conducted multiple meta-

**Table 1.** Main characteristics and result of the eligible studies

| Study | Year | Country | Sample size | Gender (M/F) | Age (year) (median) | NLR (pre/post) | Smoking history (smoker:never) | Histology (SCC/non-SCC) | Medicine | Median Follow-up (month) | Cut-off value | Survival analysis | Method | NOS score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bagley | 2017 | USA | 175 | 80/95 | 68 | pre | 147/28 | 42/133 | Nivo | NA | 5 | OS, PFS | MV | 6 |
| Diem | 2017 | Switzerland | 52 | 29/23 | 66 | pre | 48/4 | 18/34 | Nivo | 0-14 | 5 | OS, PFS | MV | 7 |
| Facchinetti | 2018 | Italy | 54 | 45/9 | 69 (43-85) | pre | 50/4 | 26/28 | Nivo | 12.6 | 4 | OS | MV | 6 |
| Ichiki | 2019 | Japan | 44 | 38/6 | 71 | pre | 8/36 | NA | Niv, Pem | 4.8 | NA | OS | MV, UV | 6 |
| Fukui | 2018 | Japan | 52 | 37/15 | 69 | pre | 42/10 | 16/36 | Nivo | 10.9 | 5 | OS | MV, UV | 7 |
| Inomata | 2018 | Japan | 36 | 27/9 | NA | pre | 31/5 | 16/20 | Nivo, Pem | NA | 5 | PFS | UV | 7 |
| Khunger | 2018 | USA | 109 | 56/53 | 67 | pre+post | 92/17 | 26/83 | Nivo | 30 | 5 | OS | UV | 6 |
| Nakaya | 2018 | Japan | 101 | 23/78 | 69 | post | 85/16 | 37/64 | Nivo | NA | 3 | PFS | MV | 5 |
| Passaro | 2019 | Italy | 53 | 33/20 | 64 | pre | NA | 13/40 | Nivo | 19 | 3 | OS, PFS | MV | 5 |
| Passiglia | 2019 | Italy | 45 | 32/13 | 66 | pre | 38/7 | 20/25 | Nivo | 9.1 | 3.3 | OS | UV | 7 |
| Pavan | 2019 | Italy | 184 | 125/59 | 67 | pre | 160/24 | 59/125 | Nivo, Pem, Atezu | 56.3 | 3 | OS, PFS | UV | 6 |
| Ren | 2019 | China | 147 | 94/53 | 57 | pre | 91/56 | 62/85 | Nivo, Pem | 31.2 | 2.5 | OS | UV | 5 |
| Minami | 2019 | Japan | 76 | 49/27 | 69 | pre | 60/16 | 18/58 | Nivo, Pem, Atezu | NA | 6 | OS, PFS | UV | 5 |
| Shiroyama | 2017 | Japan | 201 | 135/66 | 68 | pre | 157/44 | 41/160 | Nivo | 12.4 | 4 | PFS | UV | 7 |
| Suh | 2017 | South Korea | 54 | 42/12 | 68 | pre+post | 39/15 | 17/37 | Nivo, Pem | 26.2 | 5 | OS, PFS | UV, MV | 5 |
| Svaton | 2018 | Czech Republic | 120 | 71/49 | NA | pre | 98/22 | 40/80 | Nivo | NA | 3.8 | OS, PFS | UV | 6 |
| Takeda | 2018 | Japan | 30 | 19/11 | 71 | pre+post | 26/4 | 9/21 | Nivo | NA | 5 | PFS | UV | 7 |
| Zer | 2018 | Canada | 88 | 43/45 | 64 | pre | 67/21 | 15/73 | Nivo, Pem | 5.3 | 4 | OS, PFS | UV | 6 |
| Park | 2017 | USA | 159 | 82/77 | 68 | pre+post | 133/24 | 39/120 | Nivo | 11.5 | 5 | PFS, OS | UV | 6 |
| Mezquita | 2018 | Europe | 466 | 301/165 | 62 | pre | 422/44 | 159/307 | Nivo, Pem, Atezu, Durvalu | 12 | 3 | OS, PFS | UV, MV | 6 |
| Rogado | 2017 | Spain | 40 | NA | 67 | pre | NA | NA | Nivo | NA | 5 | OS | UV, MV | 7 |

Pre: pretreatment; post: post-treatment; SCC: squamous carcinoma; Nivo: Nivolumab; Pem: Pembrolizumab; Atezu: Atezolizumab; Durvalu: Durvalumab; OS: overall survival; PFS: progression free survival; MV: Multivariate analysis; UV: Univariate analysis; NA: not available.

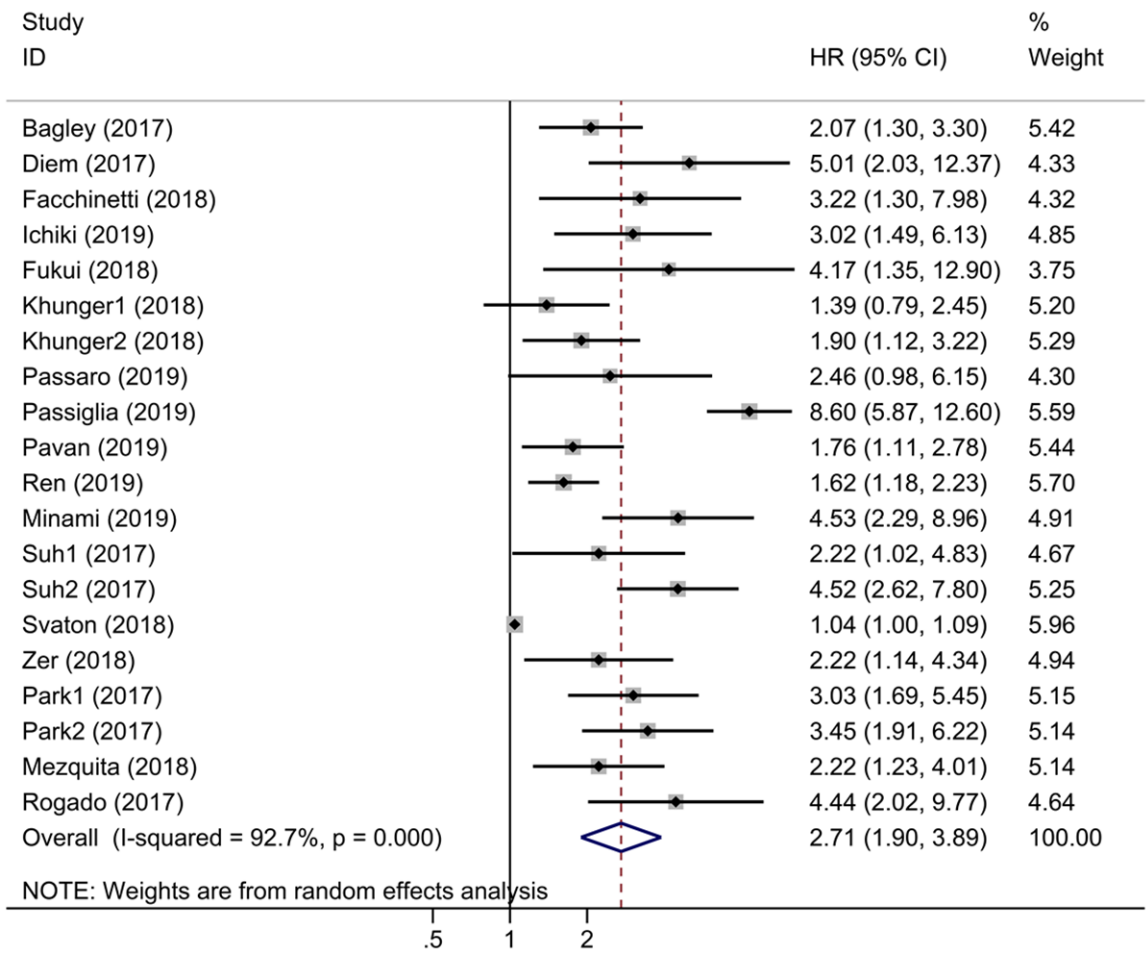


**Figure 2.** Forest plot of the association between NLR and OS of all patients.

regression analysis, and the results showed that none of the factors we consider was the source of OS heterogeneity, and sample size (P=0.045), cut-off value (P=0.017) and NOS score (P=0.013) may be the causes of heterogeneity. Furthermore, our subgroup analysis results show that a high level of NLR in the study with multi-factor analysis, prospective experimental design, NOS score ≥7 is significantly correlated with a shorter OS, and there is no significant heterogeneity within the group, indicating that elevated NLR, prospective study through multivariate analysis has higher OS predictive value. In addition, in the subgroup of squamous cell carcinoma patients with the proportion ≤0.4 and follow-up time ≤1 year, high NLR was significantly correlated with shorter PFS, and there was no significant heterogeneity within the group. This may mean that NLR has a high predictive value for short-term PFS in NSCLC other than squamous cell carcinoma.

The sensitivity analysis shows that our results are reliable, and removal of any study would have little effect on the current results. The results of Begg's test and trim and fill method are contradictory, which may be related to the low sensitivity of Begg's test. The selection bias may be another reason for the bias. Since our inclusion criteria restrict the language of articles to be English only, selection bias is inevitable. In view of the stability of Begg's method, we believe that publication bias is within the acceptable range, which show that our results are credible.

Inflammatory reaction is an important biological feature of tumors [2]. Uncontrolled inflammatory response is one of the main mechanisms of malignant tumor development. Long-term sustained chronic inflammatory response stimulation will result in accumulation of cell DNA damage, cell mutation and subsequent

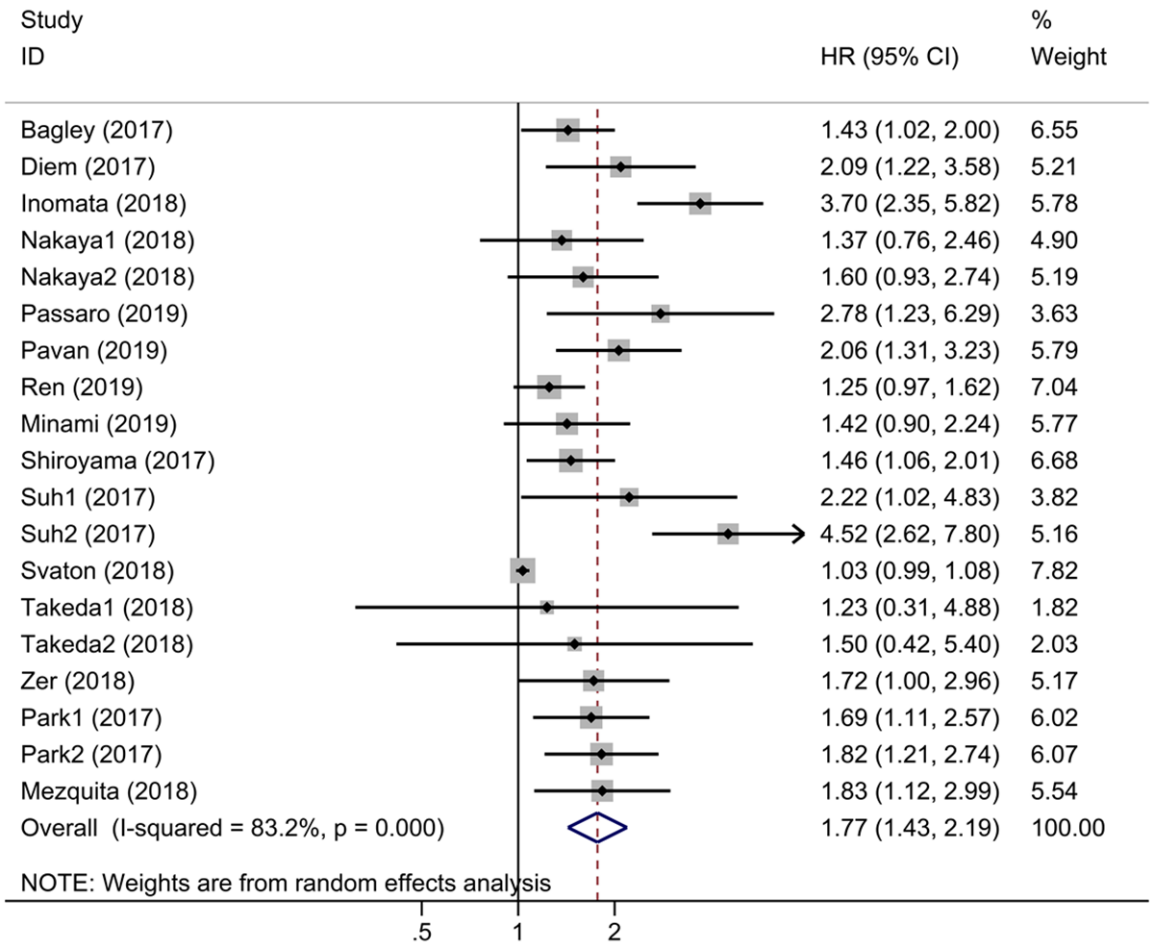


**Figure 3.** Forest plot of the association between NLR and PFS of all patients.

tumor occurrence [32, 33]. When pulmonary epithelial cells proliferate excessively, they can promote their proliferation and renewal by secreting various inflammatory cytokines, chemokines and enzymes [34, 35]. At the same time, the product of proto-oncogenes can activate inflammatory reaction pathways [36], and accumulation of a large number of DNA damage and cell aging in the environment [37] further aggravates inflammatory reactions of tumor, which will overthrow the differentiation and development of the body's immune cells, resulting in a large number of immunosuppressive cells, which can promote the development and metastasis of tumors. Therefore, it can be seen that the inflammatory reaction is closely related to the occurrence and development of tumors.

NLR can be calculated from routine blood tests through dividing neutrophils by lymphocytes, which can reflect the immune status of the body and play a certain indicator role in judging the disease progression and prognosis of tumor patients.

Elevated NLR may indicate the angiogenesis or pro-inflammatory status of tumor tissues [38], which reflects the balance between neutrophils and lymphocytes and the immune status of patients. High NLR may be associated with increased neutrophils or decreased lymphocytes. After the occurrence of tumor, the tumor area of the body is in a region of immunosuppression with low lymphocyte levels. The increase of NLR can reflect the low lymphocyte mediated immune function, which leads to poor prognosis.

In recent years, many studies have suggested that NLR is associated with the prognosis of various solid tumors, including colon cancer [39], gastric cancer [40], liver cancer [41] and breast cancer [42]. A meta-analysis which

**Table 2.** Table of subgroup analysis results

| Outcome | Grouping strategy | No of studies | Random-effect | | Fixed-effect | | Heterogeneity | |
|---|---|---|---|---|---|---|---|---|
| | | | HR (95% CI) | P | HR (95% CI) | P | $I^2$ (%) | Ph |
| OS | Method | | | | | | | |
| | MV | 8 | 2.778 2.154-3.581 | 0 | 2.778 2.154-3.581 | 0 | 0 | 0.56 |
| | UV | 12 | 3.450 1.912-6.224 | 0 | 1.117 1.073-1.163 | 0 | 94.7 | 0 |
| | Study method | | | | | | | |
| | Retro | 18 | 2.680 1.840-3.905 | 0 | 1.139 1.094-1.185 | 0 | 93.3 | 0 |
| | Pro | 2 | 3.033 1.489-6.179 | 0.002 | 3.033 1.498-6.179 | 0.002 | 0 | 0.477 |
| | NOS score | | | | | | | |
| | ≥7 | 13 | 2.343 1.896-2.897 | 0 | 2.213 1.894-2.586 | 0 | 40.1 | 0.067 |
| | <7 | 7 | 3.294 1.407-7.714 | 0.006 | 1.091 1.047-1.137 | 0 | 96.4 | 0 |
| PFS | SCC% | | | | | | | |
| | ≥0.4 | 13 | 1.807 1.360-2.402 | 0 | 1.095 1.047-1.145 | 0 | 86.1 | 0 |
| | <0.4 | 6 | 1.634 1.367-1.954 | 0 | 1.634 1.367-1.954 | 0 | 0 | 0.73 |
| | Follow-up | | | | | | | |
| | ≥12 months | 7 | 1.991 1.435-2.762 | 0 | 1.680 1.437-1.964 | 0 | 0 | 0.640 |
| | ≤12 months | 4 | 1.807 1.432-2.279 | 0 | 1.807 1.432-2.279 | 0 | 63.3 | 0.066 |

Random-effect: random-effect models; Fixed-effect: fixed-effect models; HR: hazard ratio; 95% CI: 95% confidence interval; Ph: *P* value of Q test for heterogeneity test; OS: Overall survival; PFS: Progression free survival; Retro: Retrospective study; Pro: Prospective study; MV: multivariate analysis; UV: univariate analysis; SCC: squamous-cell carcinoma.

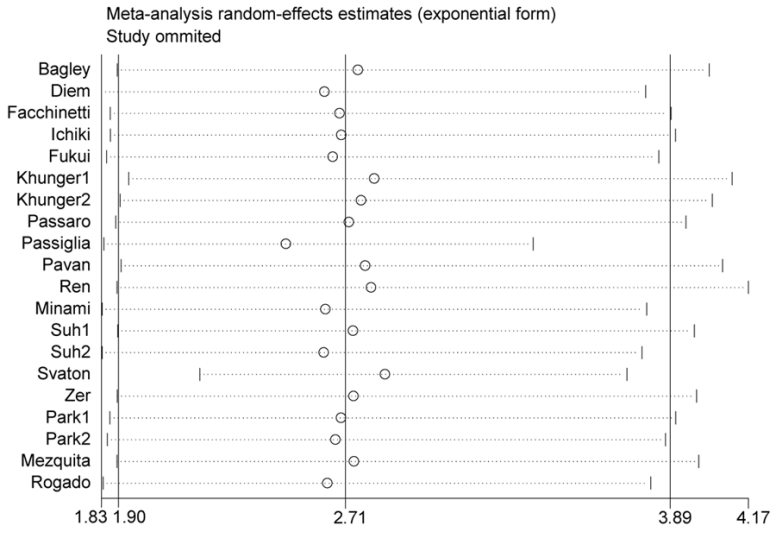


**Figure 4.** Sensitivity analysis of the publication in the OS group.

included more than 10 clinical studies on the correlation between NLR and lung cancer prognosis [43] showed that high NLR levels indicated poor prognosis (HR=1.18; 95% CI: 1.08-1.29, P<0.0002).

In addition, many other factors have also been claimed to be related to the efficacy of immunotherapy.

PD-L1 expression is the preferred efficacy predictor in most studies on PD1/PD-L1, and multiple studies on NSCLC treated with PD-1/PD-L1 inhibitor have revealed that patients with high expression of PD-L1 have significant advantage with PFS, OS or ORR compared to those with low expression [44-50]. However, the cut-off value of PD-L1 expression was set differ-

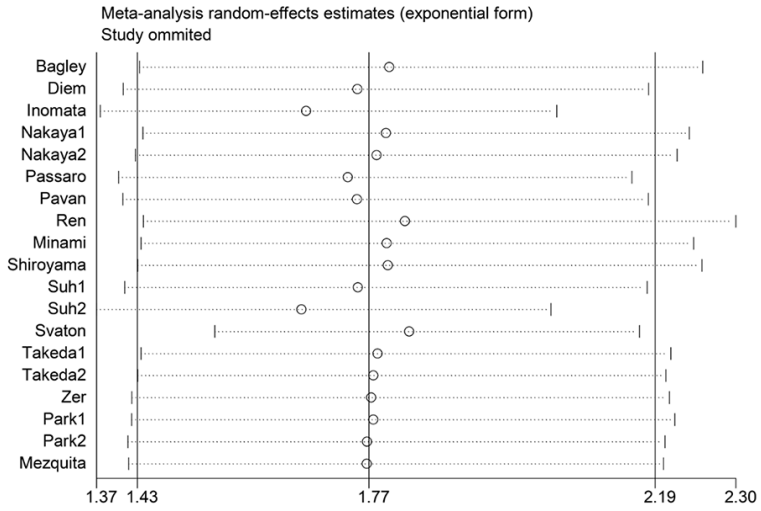


**Figure 5.** Sensitivity analysis of the publication in the PFS group.

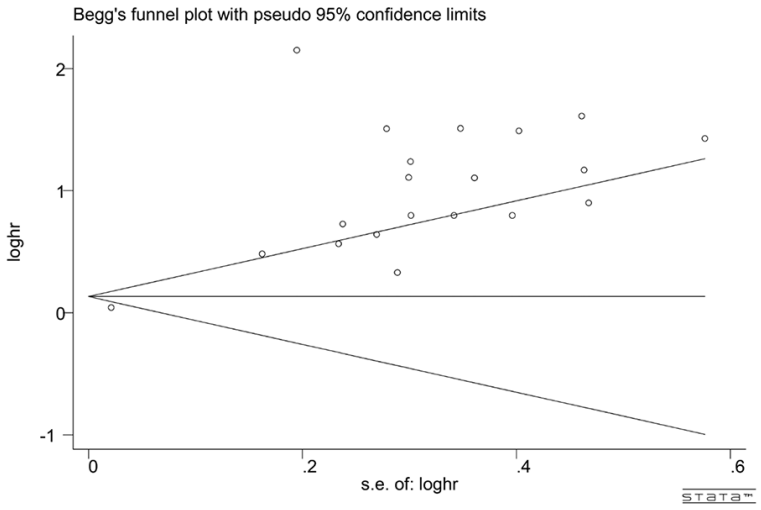


**Figure 6.** Begg's funnel plot estimating the publication bias of the included studies in the OS group.

ently in various tests. There were no recognized standards of positive or high expression of PD-L1, and the efficacy was not strictly related to the expression. Patients with low or negative expression in some trials also showed clinical benefits [51]. In addition, some factors, including differences in medicine, drug regimen, initial treatment, and the pathological acquisition mode and time, which could potentially affect the expression of PD-L1 in tumor cells, should be further studied.

Checkmate 026 [52] and Checkmate 227 [53] studied the correlation between TMB and the clinical efficacy of Navumab. Patients with high TMB received antibody therapy for prolonged survival benefit, and no correlation between TMB and PD-L1 expression was found. A lung adenocarcinoma study [54] found that EMT is independent of TMB, and tumor cells with EMT characteristics, such as PD-1, PD-L1, PD-L2, CTLA-4, IFN, IDO, have higher expression levels of immune checkpoints and immune molecules, which is a potential predictor. Studies [55] have found that EGFR mutations can increase the expression level of PD-L1, so blocking EGFR can reduce PD-L1 expression and indirectly enhance body immunity. Poplar test [48] detected the expression level of PD-L1 in the enrolled patients. The mOS of the IC group with high expression of PD-L1 was longer than those with low expression. IMpower 150 [50] analyzed the prognosis of patients with high Teff expression, and found that these patients received antibody combination therapy for longer mPFS and mOS. It has been suggested that the number of CD8 T cells can be used as an indirect predictor of immunoantibody therapy [56]. Multiple clinical trials of PD-1/PD-L1 inhibitor [53, 57] have found that patients with a history of smoking have a better prognosis with antibody treatment than non-smokers.

There are still some flaws in our research. First, despite the high quality of the studies included, most of the studies adopted a retrospective, with a non-blind approach, which may increase the risk of bias and reduce the reliability of the evidence. Secondly, the sample size of some included studies is small, and the results of randomized controlled trials with large samples are lacking, which inevitably affects the conclusion. Thirdly, some conclusions of this study are difficult to explain the heterogeneity. Although the random effect model was adopted for

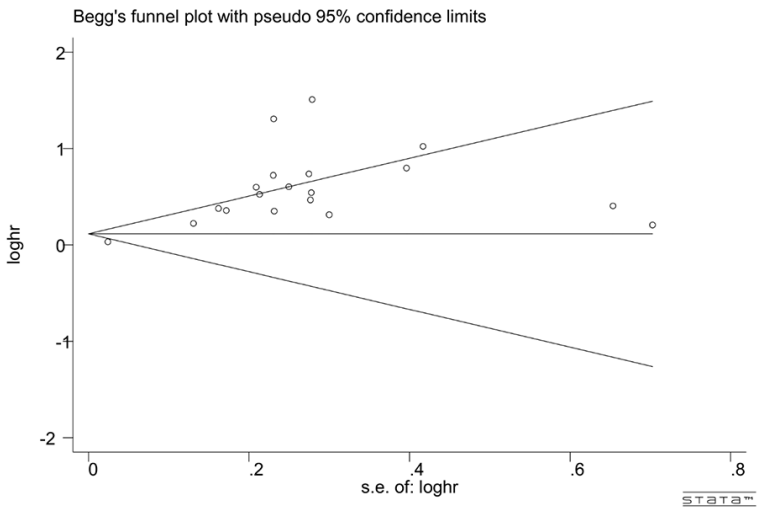


**Figure 7.** Begg's funnel plot estimating the publication bias of the included studies in the PFS group.

effect size combination, and the sensitivity analysis showed that the results were stable and reliable, this could not completely eliminate the influence of heterogeneity in the results. In addition, the included studies were inconsistent in the lines of PD-1/PD-L1 therapy, initial treatment and follow-up methods, which affected the reliability of the results. Finally, since most papers have tendency to publish the positive results, meta-analysis may magnify the correlation between NLR and prognosis, and may lead to unreliable results. Therefore, more large-scale, rigorously designed clinical trials are still needed to confirmed the prognostic value of NLR in immunotherapy for NSCLC.

In conclusion, we believe that NLR is a simple and easily available prognostic indicator with broad application prospect in the immunotherapy of NSCLC, especially for the short-term progression-free survival of NSCLC patients with non-squamous carcinoma. In our opinion, the combined application of multiple indicators, including NLR, or further basic research may help us to make a more accurate judgment on the efficacy of PD-1/PD-L1 treatment, so that we can more accurately identify whether the treatment is effective for specific patients.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Yu Zhang, Department of Thoracic Surgery, Feicheng Hospital Affiliated to Shandong First Medical University, No. 108, Xincheng Road, Feicheng County, Taian 271600, Shandong Province, China. Tel: +86-17864871727; E-mail: zyalmxm@163.com

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