Original Article

Prognostic role of pretreatment neutrophil-to-lymphocyte ratio in non-small cell lung cancer patients treated with systemic therapy: a meta-analysis

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Background: Neutrophil-to-lymphocyte ratio (NLR) is related to prognosis in non-small cell lung cancer (NSCLC). However, no consensus on the relationship of pretreatment NLR and survival outcomes of systemic therapy in NSCLC exists. This meta-analysis investigated the prognostic role of pretreatment NLR during systemic therapy for NSCLC, including chemotherapy, immunotherapy and targeted therapy.

Methods: PubMed, Web of Science and Cochrane Library databases were systematically searched up to April 09, 2019. Hazard ratios (HRs) with their 95% confidence intervals (CIs) were pooled to investigate the association of pretreatment NLR with progression-free survival (PFS) and overall survival (OS).

Results: In total, 27 articles with 4,298 participants were selected. The pooled results showed that elevated pretreatment NLR was associated with inferior PFS (HR, 1.45, 95% CI, 1.28–1.66) and OS (HR, 1.63, 95% CI, 1.43–1.84) during systemic therapy. Subgroup analyses according to the treatment strategy suggested that higher pretreatment NLR was significantly associated with shorter survival in all therapies, including chemotherapy (PFS HR, 1.74, 95% CI, 1.39–2.17; OS HR, 1.73, 95% CI, 1.26–2.36), immunotherapy (PFS HR, 1.53, 95% CI, 1.27–1.84; OS HR, 2.50, 95% CI, 1.60–3.89) and targeted therapy (PFS HR, 1.53, 95% CI, 1.04–2.25; OS HR, 1.92, 95% CI, 1.14–3.24).

Conclusions: Pretreatment NLR is a promising prognostic indicator for NSCLC patients receiving systemic therapy, including chemotherapy, immunotherapy and targeted therapy.

Keywords: Chemotherapy; immunotherapy; lung neoplasms; molecular targeted therapy; neutrophil-to-lymphocyte ratio (NLR)

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Introduction

Lung cancer is the most commonly diagnosed cancer and a leading cause of cancer death (1). Surgical treatment can be curative, but efficacy is limited to early stage lung cancer (2). The majority of patients are diagnosed with metastatic diseases at the initial visit, which highlights the importance of effective systemic therapies (3). The traditional therapy is chemotherapy, and certain gene expression patterns (4,5) and liquid biomarkers (6,7) serve as predictors of chemotherapy outcomes. Targeted therapy with small molecule tyrosine

kinase inhibitors and immunotherapy with immune checkpoint inhibitors has improved patient survival and transformed the treatment paradigm of non-small cell lung cancer (NSCLC). According to the National Comprehensive Cancer Network guideline of NSCLC (Version 3. 2019), targeted therapy is the standard front-line treatment for advanced NSCLC patients with driver mutations, and pembrolizumab is the preferred first-line treatment for programmed cell death protein 1 ligand (PD-L1) expressing advanced NSCLC patients harboring negative driver mutations. The identification of targetable gene alterations can help select patients who may benefit from targeted therapy, whilst PD-L1 expression (8,9) and the tumor mutational burden (TMB) (10-12) are proposed biomarkers for both the response and outcome of immunotherapy.

Neutrophil-to-lymphocyte ratios (NLR), defined as the absolute neutrophil count (ANC) divided by the absolute lymphocyte count (ALC) from whole blood, can be easily and inexpensively accessed from regular blood tests and are associated with the prognosis of various cancers (13,14), including lung cancer (15,16). Our previous study indicated that elevated pretreatment NLR is an independent predictor of inferior survival for NSCLC patients receiving chemotherapy (17), which has been conflicted (18-20) and supported (21-24) by other studies. To our knowledge, no consensus on this relationship has been reached and there are a lack of recent meta-analyses (MAs) that comprehensively assess the relationship between pretreatment NLR and systemic treatment outcomes for NSCLC. We therefore performed an MA by referring to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, to investigate the prognostic role of pretreatment NLR from whole blood during lung cancer systemic therapy, including chemotherapy, immunotherapy and targeted therapy.

Methods

Search strategy and study selection

PubMed, Web of Science and Cochrane Library databases were systematically searched for published studies from the inception of each database to April 09, 2019. No language restrictions were applied. Search terms included "neutrophil", "lymphocyte", "ratio", "NLR", "dNLR" and "lung cancer". Reference lists of selected articles were manually explored to ensure a complete literature search.

Reports were considered eligible if they met the following criteria: (I) studies involving NSCLC patients treated with chemotherapy, immunotherapy, targeted therapy, or their combination; (II) studies providing multivariable-adjusted hazard ratios (HR) with 95% confidence intervals (CI) for progression-free survival (PFS) or overall survival (OS), calculated using Cox proportional hazard analyses; and (III) studies assessing NLR at the time before the initiation of systemic therapy.

Exclusion criteria were: (I) studies including patients with other tumor types and in which subgroup analysis according to tumor type was not performed; (II) studies not specifying treatment strategies; (III) studies including patients receiving other types of treatment and subgroup analysis according to treatment strategy was not performed; (IV) studies published as review articles, letters, editorials, comments, or meeting abstracts; or (V) studies containing repeated data and not with the largest sample size or latest information.

Quality assessment

Study quality was assessed using the Newcastle-Ottawa Scale, which evaluated three aspects of the selected studies: selection, comparability and outcome. A maximum of 9 stars could be given for each study. A higher number of stars indicated better study quality.

Data extraction

Data were extracted from reports containing first author's name, year of publication, region, study design, numbers of enrolled patients, treatment type, NLR cut-off values and length of follow-up. Multivariable-adjusted HRs of each study and corresponding 95% CIs for PFS or OS according to pretreatment NLR were also retrieved.

Statistical analysis

To investigate the relationship between pretreatment NLR and survival outcomes of the NSCLC patients receiving systemic therapy, HRs with 95% CI were pooled to give the effective value. Since the HRs extracted from included studies were estimates of the ratio for higher NLR over lower NLR, a pooled HR >1 indicated inferior survival for the group with elevated pretreatment NLR.

The heterogeneity of the studies was assessed through the Cochrane Q test and I^2 statistics. A $P<0.05$ in the Cochrane Q test and $I^2>50$ % were interpreted as significant heterogeneity. A random effects model was used if

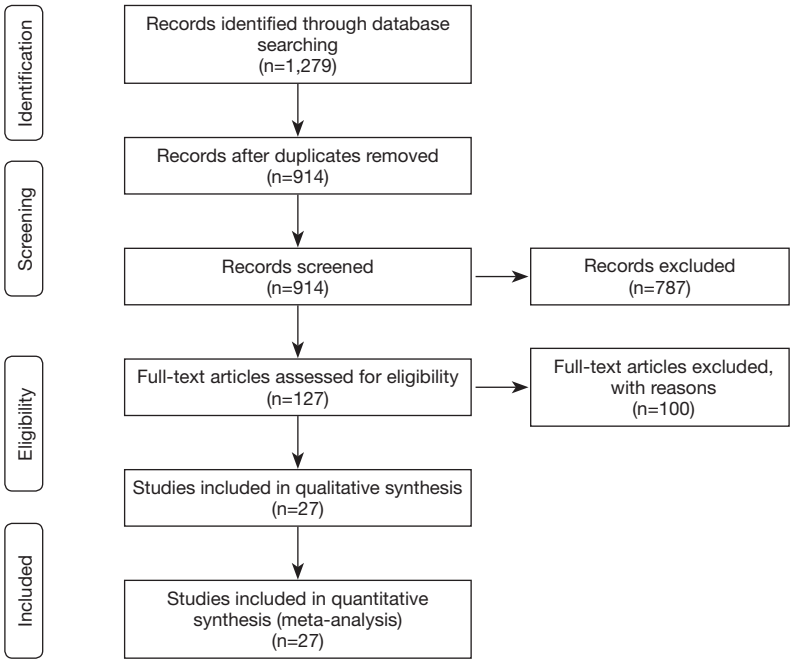

Figure 1 Flow diagram of study identification and selection.

statistically significant heterogeneity was indicated. A fixed effects model was otherwise applied.

Subgroup analysis stratified by treatment strategy was performed to test if pretreatment NLR could predict survival outcomes in each type of treatment. Subgroup analysis according to NLR cut-off values were also conducted, as various levels of NLR cut-off values were employed. In the study by Maymani *et al.* (25), the lower level of NLR cut-off failed to predict survival, whilst the higher NLR value could. Studies were allocated into two groups according to median NLR cut-off values of PFS and OS. Subgroup analyses according to study design, region, sample size and methods of cut-off determination were also performed. Publication bias was assessed using funnel plots, Begg's test and Egger's test. All calculations were performed by STATA version 12.0 (Stata Corporation, College Station, TX, USA). P values were two-sided and statistical significance was taken as a $P<0.05$.

Results

Literature search

A total of 1,279 records were identified in the literature research. After excluding duplicated records and screening titles and abstracts, 127 records were evaluated by full text and 27 articles (*Table 1*) with 4,298 patients were selected for final synthesis (*Figure 1*). One publication (46) was discarded as it included a redundant population (41).

Study characteristics

The major characteristics of the included studies are summarized in *Table 1*. Regarding treatment strategy, 9 articles assessed immunotherapy, 6 articles assessed targeted therapy, 9 articles assessed chemotherapy, 2 articles reported both targeted therapy and chemotherapy, and a single article presented data on targeted therapy and chemotherapy independently. Fifteen reports presented data related to PFS and 24 reports presented data on OS. Regarding study design, 23 reports were retrospective cohort studies, 2 reports were prospective cohort studies and 2 reports provided data from randomized controlled trials. One article (21) was published in Chinese and the rest were all published in English. The quality assessment of the selected studies is shown in *Table 2*.

Association between pretreatment NLR and PFS

Fifteen reports with 2,599 patients were chosen for the pooled analysis of the association between pretreatment NLR and PFS. The median value of the NLR cut-off was

Table 1 Characteristics of included studies

First author	Year	Study design	Sample size (L/H)	Region	Type of treatment	Methods of cut-off value determination	NLR cut-off value	Outcomes	Length of follow-up (months)
Bozkaya Y (26)	2019	Multi-center, retrospective cohort	153 (NA/NA)	Turkey	Chemotherapy	NA	4.3	OS	Median 6 (range, 0.7–32.7)
Kiriu T (27)	2019	Single-center, retrospective cohort	47 (33/14)	Japan	Immunotherapy	Previous literature	5	OS	Median 8.4 (range, 1.2–22.7)
Phan TT (28)	2018	Single-center, retrospective cohort	112 (36/76)	Vietnam	Targeted therapy	ROC curve analysis	2.96	PFS	NA
Aguiar-Bujanda D (29)	2018	Single-center, retrospective cohort	41 (30/11)	Spain	Targeted therapy	ROC curve analysis	4.39	OS	Median 54.5 (IQR, 36.1–75.2)
Guo D (30)	2019	Single-center, retrospective cohort	125 (58/67)	China	Chemotherapy	ROC curve analysis	2.37	PFS, OS	Median 15.5 (range, 9–36)
Soyano AE (31)	2018	Single-center, retrospective-prospective cohort	157 (NA/NA)	America	Immunotherapy	The method of Contal and O'Quigley	5.9	PFS, OS	Median 20 (range, 2.9–122.2)
Zhang Y (32)	2018	Single-center, retrospective cohort	127 (60/67)	China	Targeted therapy	ROC curve analysis	2.9	PFS, OS	Mean 28.12 (range, 3–49)
Yi F (21)	2018	Single-center, retrospective cohort	68 (13/55)	China	Chemotherapy	ROC curve analysis	2.16	OS	Range, 1.27–71.23
Shiroyama T (33)	2018	Multi-center, retrospective cohort	201 (NA/NA)	Japan	Immunotherapy	Previous literature	5	PFS	NA
Naqash AR (34)	2018	Single-center, retrospective cohort	87 (48/39)	America	Immunotherapy	Online tool	6.5	OS	NA
Minami S (19)	2018	Single-center, retrospective cohort	107 (82/25)	Japan	Chemotherapy	Online tool	5.28	OS	NA
Minami S (18)	2018	Single-center, retrospective cohort	159 (NA/NA)	Japan	Chemotherapy	Online tool	4.05	OS	NA
Fukui T (35)	2019	Single-center, prospective cohort	52 (34/18)	Japan	Immunotherapy	NA	5	OS	Median 10.9 (IQR, 5.6–16.4)
Facchinetti F (36)	2018	Multi-center, prospective cohort	54 (NA/NA)	Italy	Immunotherapy	Previous literature	4	OS	Median 12.6 (95% CI, 11.3–13.9)
Xiong Y (22)	2017	Single-center, retrospective cohort	78 (NA/NA)	China	Chemotherapy	ROC curve analysis	3.11	PFS, OS	NA
Shiran I (20)	2017	Single-center, retrospective cohort	79 (NA/NA)	Israel	Chemotherapy	NA	NA	OS	NA

Table 1 *(continued)*

Table 1 *(continued)*

First author	Year	Study design	Sample size (L/H)	Region	Type of treatment	Methods of cut-off value determination	NLR cut-off value	Outcomes	Length of follow-up (months)
Minami S (37)	2017	Single-center, retrospective cohort	152 (54/98)	Japan	Targeted therapy	ROC curve analysis	2.11	PFS, OS	NA
Meriggi F (38)	2017	Multi-center, retrospective cohort	63 (40/23)	Italy	Targeted therapy	Previous literature	3.5	PFS, OS	NA
Diem S (39)	2017	Single-center, retrospective cohort	52 (NA/NA)	Switzerland	Immunotherapy	NA	NA	PFS, OS	Range, 0–14
Bagley SJ (40)	2017	Single-center, retrospective cohort	175 (73/102)	America	Immunotherapy	Previous literature	5	PFS, OS	NA
Sim SH (23)	2016	Single-center, retrospective cohort	165 (NA/NA)	Korea	Chemotherapy	ROC curve analysis	3	PFS	NA
			85 (NA/NA)		Targeted therapy				
Liu ZL (41)	2016	Single-center, retrospective cohort	325 (172/153)	China	Chemotherapy	ROC curve analysis	3.19	PFS, OS	Median 16.7 (range, 0.3–75.4)
Chen YM (42)	2016	Single-center, retrospective cohort	80 (NA/NA)	Taiwan	Targeted therapy	ROC curve analysis	5.2	OS	Median 7.0 (the longest 20.4)
Berardi R (43)	2016	Multi-center, retrospective cohort	401 (137/264)	Italy, the UK	Chemotherapy or targeted therapy	ROC curve analysis	3.7	PFS, OS	NA
Mitchell P (44)	2015	Multi-center RCT	772 (395/377)	Several regions	Immunotherapy	Previous literature	5	OS	Median 58.7
Yao Y (17)	2013	Single-center, retrospective cohort	182 (81/101)	China	Chemotherapy	ROC curve analysis	2.63	PFS, OS	NA
Lee Y (45)	2012	Single-center data from a multi-center RCT	199 (NA/NA)	Korea	Chemotherapy or targeted therapy	ROC curve analysis	3.25	PFS, OS	Median 36.0 (95 % CI, 33.6–37.9)

L, below the cut-off value; H, above the cut-off value; NLR, neutrophil-to-lymphocyte ratio; NA, not available; OS, overall survival; PFS, progression-free survival; ROC, receiver operating characteristic; IQR, interquartile range; CI, confidence interval.

Table 2 Quality assessment of included studies

Author, year	Representativeness of the cohort with higher NLR	Selection of the cohort with lower NLR	Ascertainment of NLR measurement	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Enough follow-up period	Adequacy of follow up of cohorts	Total score
Bozkaya Y, 2019	★	★	★	★	★ -	★	-	★	7
Kiriu T, 2019	★	★	★	★	★★	★	★	★	9
Phan TT, 2018	★	★	★	★	★ -	★	-	★	7
Aguiar-Bujanda D, 2018	★	★	★	★	★★	★	★	★	9
Guo D, 2019	★	★	★	★	★★	★	★	★	9
Soyano AE, 2018	★	★	★	★	★ -	★	★	★	8
Zhang Y, 2018	★	★	★	★	★★	★	★	★	9
Yi F, 2018	★	★	★	★	★ -	★	★	★	8
Shiroyama T, 2018	★	★	★	★	★ -	★	-	★	7
Naqash AR, 2018	★	★	★	★	★ -	★	-	★	7
Minami S, 2018	★	★	★	★	★ -	★	-	★	7
Minami S, 2018	★	★	★	★	★ -	★	-	★	7
Fukui T, 2019	★	★	★	★	★ -	★	★	★	8
Facchinetti F, 2018	★	★	★	★	★ -	★	★	★	8
Xiong Y, 2017	★	★	★	★	★★	★	-	★	8
Shiran I, 2017	★	★	★	★	★ -	★	-	★	7
Minami S, 2017	★	★	★	★	★★	★	-	★	8
Meriggi F, 2017	★	★	★	★	★★	★	-	★	8
Diem S, 2017	★	★	★	★	★ -	★	★	★	8
Bagley SJ, 2017	★	★	★	★	★ -	★	-	★	7
Sim SH, 2016	★	★	★	★	★ -	★	-	★	7
Liu ZL, 2016	★	★	★	★	★★	★	★	★	9
Chen YM, 2016	★	★	★	★	★ -	★	-	★	7
Berardi R, 2016	★	★	★	★	★★	★	-	★	8
Mitchell P, 2015	★	★	★	★	★★	★	★	★	9
Yao Y, 2013	★	★	★	★	★★	★	-	★	8
Lee Y, 2012	★	★	★	★	★ -	★	★	★	8

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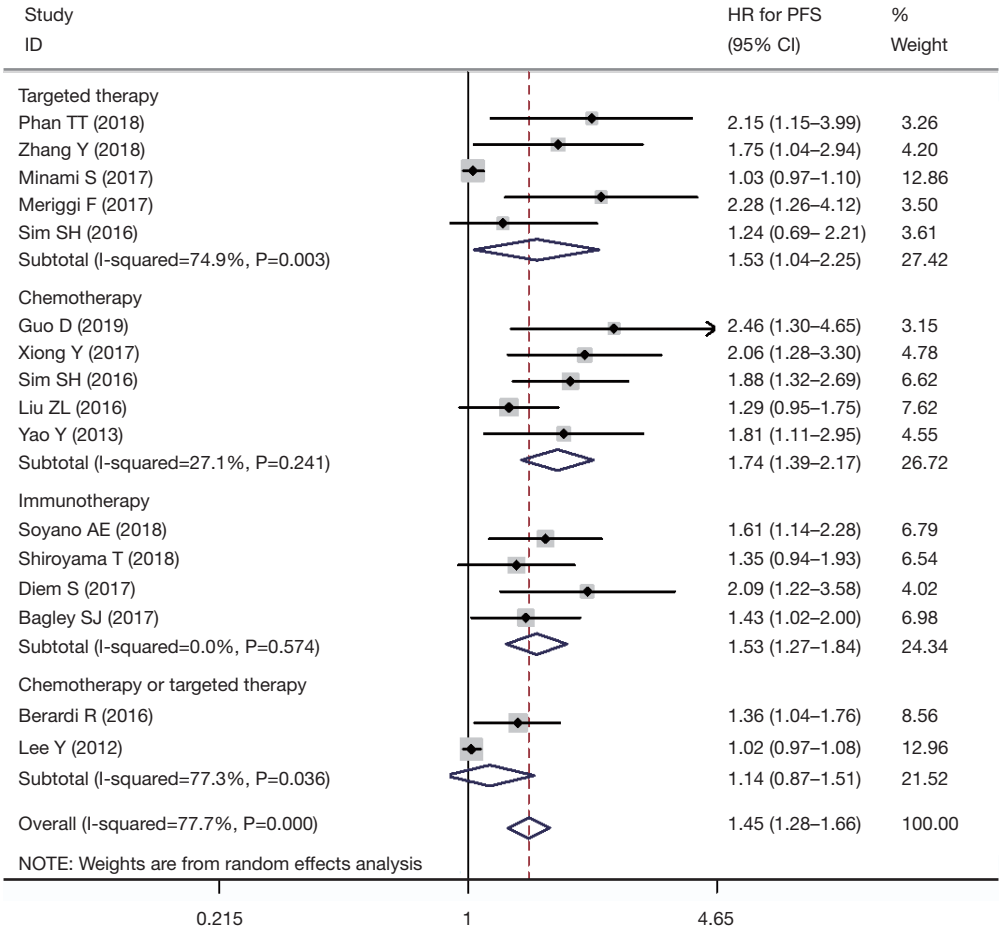

Figure 2 Forest plot of studies investigating the association of pretreatment NLR and PFS with subgroup analysis stratified by treatment strategy. HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival.

3.11 (range, 2.11–5.90). Since significant heterogeneity (I^2=77.7%, P=0.00) was indicated, a random effects model was applied. The pooled results (*Figure 2*) suggested that higher pretreatment NLR was associated with a poorer PFS (HR, 1.45, 95% CI, 1.28–1.66).

Subgroup analysis according to treatment strategy (*Figure 2*) showed that the prognostic effects of pretreatment NLR existed in all the systemic therapies, including chemotherapy (HR, 1.74, 95% CI, 1.39–2.17), immunotherapy (HR, 1.53, 95% CI, 1.27–1.84) and targeted therapy (HR, 1.53, 95% CI, 1.04–2.25). Subgroup analysis according to the NLR cut-off values suggested no significant differences between higher (HR, 1.42, 95% CI, 1.15–1.75) and lower NLR cut-off values (HR, 1.63, 95% CI, 1.17–2.27) existed for the prediction of PFS. Subgroup analyses stratified by the study design, region, sample size and methods of cut-off value determination are summarized in *Table 3*. Significant differences between subgroups were detected in the subgroup analysis of the sample size.

The funnel plot was basically symmetrical (*Figure S1*) and the results of Begg's test (P=0.119) and Egger's test (P=0.149) indicated a lack of publication bias in our pooled analysis.

Association between pretreatment NLR and OS

Twenty-four reports with 3,735 patients were used to analyze the correlation of pretreatment NLR and OS. The median NLR cut-off value was 4.03 (range, 2.11–6.50). A random effects model was adopted due to significant heterogeneity (I^2=82.8%, P=0.000). The pooled result (*Figure 3*) suggested that elevated pretreatment NLR correlated with inferior OS (HR, 1.63, 95% CI, 1.43–1.84).

Table 3 Subgroup analyses for the meta-analysis of PFS and OS

Variables	PFS		OS	
	Number of studies	Pooled HR (95% CI)	Number of studies	Pooled HR (95% CI)
Type of treatment				
Chemotherapy	5	1.74 (1.39–2.17)	9	1.73 (1.26–2.36)
Targeted therapy	5	1.53 (1.04–2.25)	5	1.92 (1.14–3.24)
Immunotherapy	4	1.53 (1.27–1.84)	8	2.50 (1.60–3.89)
Chemotherapy or targeted therapy	2	1.14 (0.87–1.51)	2	1.32 (0.80–2.15)
Study design				
Single-center	13	1.44 (1.25–1.66)	19	1.65 (1.43–1.90)
Multi-center	3	1.46 (1.15–1.86)	5	1.59 (1.14–2.22)
Sample size				
<150	7	1.95 (1.58–2.41)	14	2.67 (1.78–4.01)
≥150	9	1.27 (1.12–1.43)	10	1.29 (1.15–1.46)
Region				
Asia	11	1.36 (1.18–1.57)	15	1.43 (1.25–1.63)
Europe and America	5	1.54 (1.31–1.82)	9	2.15 (1.55–2.99)
Methods of cut-off value determination				
ROC curve analysis	11	1.37 (1.19–1.57)	11	1.65 (1.39–1.98)
Previous literature	3	1.51 (1.18–1.93)	5	2.20 (1.27–3.82)
Others	1	1.61 (1.14–2.28)	4	1.66 (1.10–2.50)
NLR cut-off value[†]				
Lower	7	1.63 (1.17–2.27)	11	1.67 (1.39–2.00)
Higher	8	1.42 (1.15–1.75)	11	1.82 (1.38–2.40)

[†], the cut-off for PFS was 3.11 and that for OS was 4.03. PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ROC, receiver operating characteristic; NLR, neutrophil-to-lymphocyte ratio.

Subgroup analysis according to treatment strategy (*Figure 3*) indicated that the relationship didn't markedly change for chemotherapy (HR, 1.73, 95% CI, 1.26–2.36), immunotherapy (HR, 2.50, 95% CI, 1.60–3.89) or targeted therapy (HR, 1.92, 95% CI, 1.14–3.24). Subgroup analysis according to the NLR cut-off values showed that higher (HR 1.82, 95% CI, 1.38–2.40) and lower (HR 1.67, 95% CI, 1.39–2.00) values had a similar ability to predict OS. Subgroup analyses stratified by study design, region, sample size and the methods of cut-off value determination are summarized in *Table 3*. Similar to the PFS, studies with smaller sample sizes had higher HR values.

No publication bias was detected following pooled analysis by Begg's test (P=0.162) or Egger's test (P=0.056). The funnel plot was almost symmetrical (*Figure S2*).

Discussion

Inflammation plays an important role in tumorigenesis and development (47) and NLR as a biomarker of inflammation, is associated with treatment outcomes in various types of cancer (48-52). The current MA pooled the results from 27 studies consisting of 4,298 patients and indicated that for NSCLC patients treated with systemic therapy, elevated pretreatment NLR is associated with an inferior survival outcome. In addition, this MA highlighted for the first time that a higher level of pretreatment NLR predicts poorer survival for NSCLC patients receiving targeted therapy.

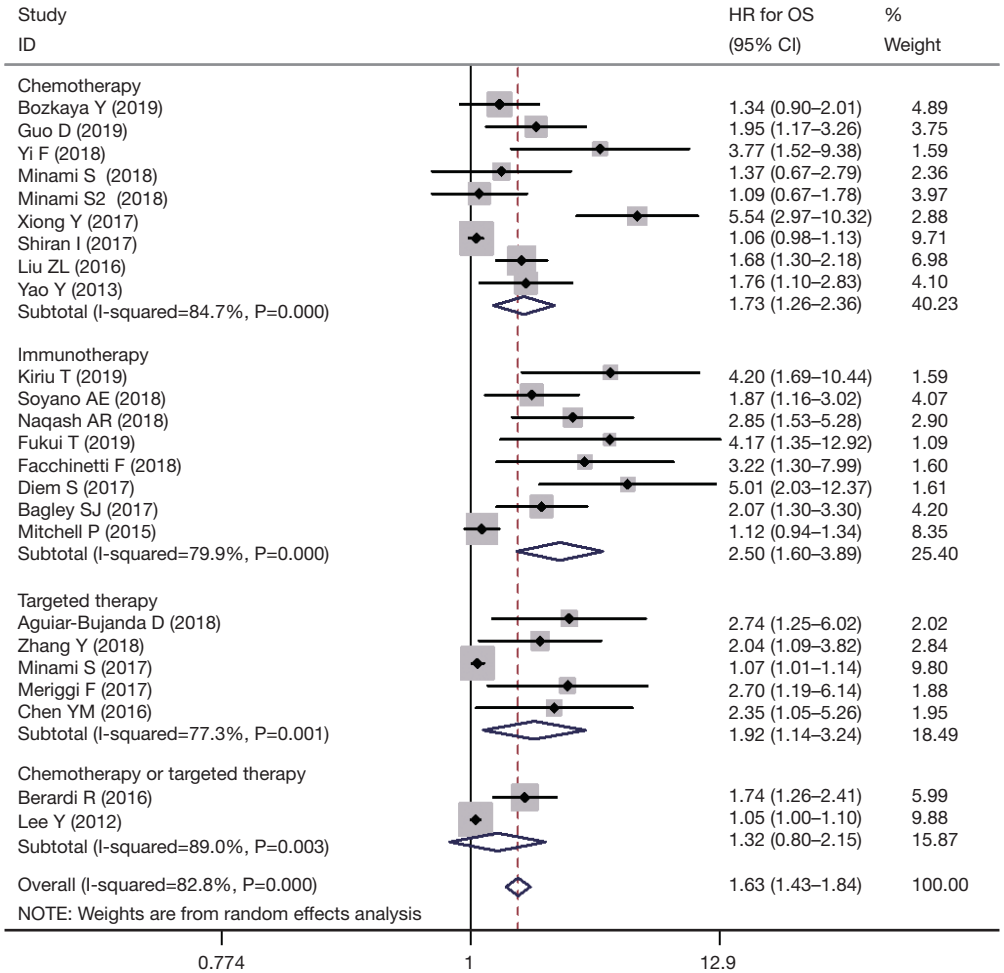

Figure 3 Forest plot of studies investigating the association of pretreatment NLR and OS with subgroup analysis stratified by treatment strategy. HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival.

Previous MAs published in the last years explored the role of pretreatment NLR in lung cancer, mainly focusing on prognosis as opposed to treatment strategy (15,16,53-56). Although subgroup analyses according to treatment strategy were performed in some of the MAs (16,53-56), only chemotherapy was investigated in terms of systemic therapy (15,53,55) and no consensus on the association of pretreatment NLR and the survival outcomes of chemotherapy were achieved. The validity of the results was limited as some of the patients were not solely administered chemotherapy. Our MA selected studies in which patients were treated with chemotherapy alone and only the results from multivariate analysis were included to reduce bias. Also, we added studies published in recent years and applied a more comprehensive search strategy to minimize the risk of missing relevant studies. Our results suggested that elevated pretreatment NLR correlated with inferior survival of NSCLC patients receiving chemotherapy.

Immunotherapy, mainly immune checkpoint inhibitors, leads to variable responses in an array of cancers, but only a minority of patients show benefits. Thus, predictors of the response to immunotherapy are urgently required to select appropriate patients that will benefit from this therapy. The levels of PD-L1 expression (9), TMB (10-12) and other markers (57) have been proposed for lung cancer, but no gold standard has been achieved. Several recent MAs assessed the prognostic role of pretreatment NLR in immunotherapy (48,51,58) and suggested that pretreatment NLR was a promising predictive biomarker for cancer patients treated with immunotherapy. When stratified by cancer type to

explore this relationship in lung cancer, the data was limited and the MAs failed to reach a consensus. A recent MA (59) focusing on lung cancer showed that higher pretreatment NLR was significantly associated with a poorer PFS and OS for lung cancer patients treated with nivolumab. In this MA, the treatments were not limited to nivolumab. Our results also favored the prognostic role of pretreatment NLR in immunotherapy, predominantly identified in studies that administered nivolumab. Future studies are required to validate our results in lung cancer patients receiving immunotherapy with nivolumab and other drugs.

Of note, different NLR cut-off values were adopted and the selection and source of sources of the cut-off values varied, including receiver operating characteristic (ROC) curve analysis, previously published studies and website tools. The study by Maymani *et al.* (25) found that different cut-off values showed different efficacies of predicting the treatment outcome. However, our MA indicated that different cut-off values did not significantly alter the association between NLR and survival outcomes, which were consistent with previous MAs (13-16,48,53,54,56,58). The study by Cho *et al.* (60) showed that in head and neck squamous cell carcinoma, significant HR of OS could be produced by all NLR cut-off values from 2 to 6, suggesting a three-tier classification system (<2, 2 to 6, and ≥6). Similar studies are required to explore the association of pretreatment NLR cut-off values and their prognostic efficacy, and to determine the optimal pretreatment NLR cut-off value in NSCLC as a prognostic tool in clinical practice.

Other tools have been developed to predict the treatment outcomes of cancer patients. A derived NLR (dNLR), defined as the ANC divided by the difference between white blood cell (WBC) counts and ANC, was calculated since only ANC and WBC were recorded in some of the clinical studies. A similar prognostic value to the NLR was observed (61). The dNLR had been assessed as a predictor of treatment outcomes in other tumors receiving immunotherapy (62) or chemotherapy (63,64). In lung cancer, dNLR was a prognostic biomarker of the immunotherapy (65) and chemotherapy (22) outcome. Besides dNLR, prognostic tools integrating some items are also under investigation, including tumor immune dysfunction and exclusion (66), lung immune prognostic index (65), and the Glasgow prognostic score (67).

To our knowledge, this MA is the first to comprehensively assess the association of pretreatment NLR with systemic treatment outcomes for NSCLC. However, several limitations remain. Firstly, the observational design of the included studies may introduce bias to the MA, but we tried to reduce bias through the inclusion of multivariable results. Secondly, because studies on targeted therapy focused on tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR), we could not assess the relationship of NLR and targeted therapy for other driver mutations. Thirdly, the heterogeneity across studies which may have resulted from different baseline characteristics of the patients, may influence the interpretation of our results.

Conclusions

Elevated pretreatment NLR is associated with inferior survival for NSCLC patients treated with systemic therapy, including chemotherapy, immunotherapy and targeted therapy. Although higher and lower pretreatment NLR cut-off values have a similar ability to predict survival, further studies are required to determine the optimal cut-off values. Future clinical trials are warranted to decide whether pretreatment NLR should be incorporated into the prognostic tools of lung cancer patients, to identify those most likely to benefit from systemic therapies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

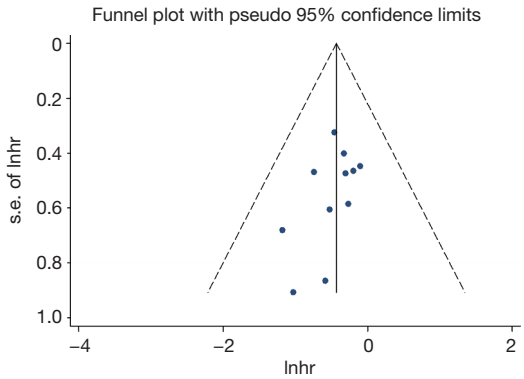

Figure S1 PFS funnel plot. PFS, progression-free survival.

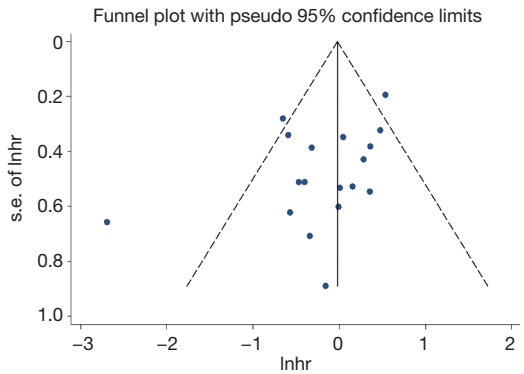

Figure S2 OS funnel plot. OS, overall survival.