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Prognostic value of derived neutrophil-to-lymphocyte ratio (dNLR) in patients with non-small cell lung cancer receiving immune checkpoint inhibitors: a meta-analysis

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ABSTRACT

Objectives Derived neutrophil-to-lymphocytes ratio (dNLR) has recently been reported as a novel potential biomarker associated with prognosis of non-small cell lung cancer (NSCLC). However, evidence for the prognostic utility of dNLR in patients with NSCLC treated with immune checkpoint inhibitors (ICIs) remains inconsistent. The objective of this work was to evaluate the association between pretreatment dNLR and prognosis of patients with NSCLC treated with ICIs.

Design This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Data sources PubMed, EMBASE, Web of Science and the Cochrane Library were searched for eligible studies up to 16 October 2020.

Eligibility criteria (1) Human subjects receiving ICIs therapy and who had been diagnosed with NSCLC; (2) the baseline values of dNLR were obtained; (3) the objective of the study was to investigate the relationships between dNLR and overall survival (OS) or progression-free survival (PFS) in NSCLC and (4) HR and 95% CI were displayed in the original article or could be extracted from Kaplan-Meier curves.

Data extraction and synthesis Two investigators extracted data independently. Data synthesis was performed via systematic review and meta-analysis of eligible cohort studies. Meta-analysis was performed with Cochran's Q test and I^2 statistics. Publication bias of studies was assessed by Begg's test and Egger's test. We used V.12.0 of the Stata statistical software.

Results This analysis included eight studies (2456 cases) on the prognostic utility of dNLR in ICI therapy for NSCLC. The results indicate that higher dNLR significantly predicted poor OS (HR=1.65, 95% CI 1.46 to 1.88; p<0.001) and PFS (HR=1.38, 95% CI 1.23 to 1.55; p<0.001). Subgroup analyses of OS-related studies indicated that there were similar results in stratifications by ethnicity, sample size, type of HR and dNLR cut-off value. As for PFS-related studies, subgroup analyses showed no significant difference in Asian populations. Publication biases were not detected using Begg's test and Egger's linear regression test.
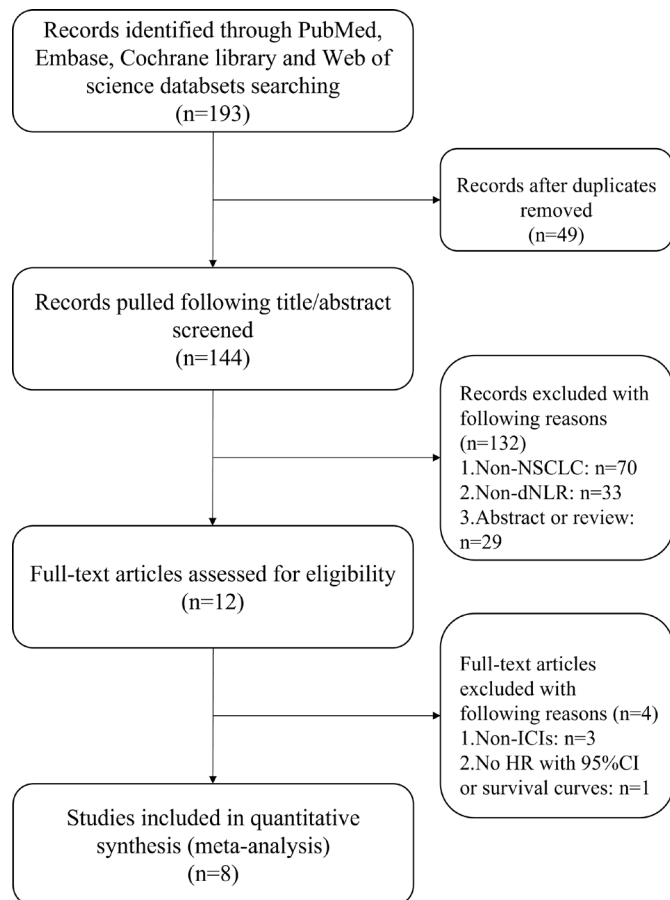
Strengths and limitations of this study

► This is the first study to evaluate the prognostic value of pretreatment derived neutrophil-to-lymphocyte ratio in patients with non-small cell lung cancer (NSCLC) who treated with immune checkpoint inhibitors (ICIs).

► This meta-analysis may provide novel prognostic guidance for patients with NSCLC treated with ICIs.

► All the studies included in this meta-analysis were retrospective cohort studies, and the number of eligible studies was <10, so there may be some retrospective bias and publication bias.

Conclusions This meta-analysis indicated that elevated pretreatment dNLR may be a negative prognostic predictor for patients with NSCLC treated with ICIs. More large-sample and higher-quality studies are warranted to support our findings.

PROSPERO registration number CRD42021214034.

INTRODUCTION

Worldwide, lung cancer remains the leading cause of cancer death, with an estimated 2.2 million new cases and 1.8 million deaths in 2020.[1] Non-small cell lung cancer (NSCLC) accounts for about 85% of primary lung cancers and includes three main pathological types: squamous cell carcinoma, adenocarcinoma and large cell lung cancer.[2] The treatment strategy for NSCLC depends on the stage of the cancer. Early-stage patients should be treated with surgical resection, while advanced-stage patients are mainly treated with systematic therapy. The 5-year survival rates for NSCLC range from 14% to 49% for stage I–IIIA patients, and are less than 5% for stage IIIB–IV disease.[3] In the past 10 years, the application of immune checkpoint inhibitors (ICIs) in the treatment of NSCLC

Records identified through PubMed, Embase, Cochrane library and Web of science databsets searching (n=193)

Records after duplicates removed (n=49)

Records pulled following title/abstract screened (n=144)

Records excluded with following reasons (n=132)
1.Non-NSCLC: n=70
2.Non-dNLR: n=33
3.Abstract or review: n=29

Full-text articles assessed for eligibility (n=12)

Full-text articles excluded with following reasons (n=4)
1.Non-ICIs: n=3
2.No HR with 95%CI or survival curves: n=1

Studies included in quantitative synthesis (meta-analysis) (n=8)

Figure 1 Flow chart of the eligible studies. dNLR, derived neutrophil-to-lymphocyte ratio; ICIs, immune checkpoint inhibitors; NSCLC, non-small cell lung cancer.

has improved the therapeutic landscape for this intractable disease. PD-1 and programmed cell death-ligand 1 (PD-L1) inhibitors have shown encouraging results in NSCLC (pembrolizumab and nivolumab, eg) and they have been approved by the US Food and Drug Administration for the treatment of advanced NSCLC.[4 5] The latest phase 3 study showed that nivolumab was demonstrated a superior overall survival (OS) versus docetaxel at 2 years in NSCLC.[6] And a real-life cohort of patients with advanced NSCLC treated with pembrolizumab demonstrated similar progression-free survival (PFS) to the pivotal clinical trial.[7] Some patients with advanced NSCLC have shown OS or PFS benefits from ICI treatment after chemoradiotherapy.[8 9]

Despite significant clinical improvements, not all ICI treatments are effective in patients with NSCLC. Some valuable biomarkers that predict ICI response, such as PD-L1, tumour mutational burden and tumour-infiltrating lymphocytes which could indicate the status of the tumour immune microenvironment have led to more effective application of ICIs.[10] However, most of these biomarkers are detected in an invasive manner, which depends heavily on sufficient tumour tissue. Thus, there is an urgent need to explore and evaluate better biomarkers for selecting patients suitable for ICI treatment.

Inflammation processes have been proven to be mechanisms of immune resistance in patients with cancer which can promote tumour growth and invasion and activate carcinogenic signalling pathways.[11] In the clinical practice, peripheral serum indicators are used to evaluate systemic inflammation, and some of them are associated with prognosis and therapeutic response of patients with cancer.[12 13] The common haematological inflammatory indicators include white blood cells (WBC), lymphocytes and C reactive protein (CRP). Derived neutrophil-to-lymphocyte ratio (dNLR) is a novel potential biomarker for systemic inflammation, which can be calculated by absolute value of neutrophils and value of leucocyte count.[14] DNLR has been used to assess response to immunotherapy in various cancers, including NSCLC.[15–17] Recent studies showed the predictive utility of pretreatment dNLR in urological cancer and breast cancer.[18 19] However, evidence of the association between the prognosis of NSCLC and dNLR remains mixed. Therefore, the objective of our study was to explore the relationship between pretreatment dNLR and survival in patients with NSCLC treated with ICIs.

METHODS
Patient and public involvement
It was not appropriate or possible to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research.

Design
This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (online supplemental file 1).

Search strategy and study inclusion
Our meta-analysis was conducted to explore the association between dNLR and prognosis of patients with NSCLC treated with ICIs. We conducted a search of four electronic journal databases: PubMed, EMBASE, Web of Science and the Cochrane Library. The search consisted of three parts: (1) the subject words (Emtree in EMBASE and MeSH in other databases) and free words of NSCLC were searched respectively, (2) the abbreviations and specific names of ICIs were searched, (3) dNLR and its full name were also searched. The last search was updated on 16 October 2020 (online supplemental file 2).

The inclusion criteria were as follows: (1) human subjects receiving ICIs therapy and who had been diagnosed with NSCLC; (2) the baseline values of dNLR were obtained; (3) the objective of the study was to investigate the relationships between dNLR and OS or PFS in NSCLC; (4) HR and 95% CI were displayed in the original article or could be extracted from Kaplan-Meier curves.

The exclusion criteria were as follows: (1) studies including subjects with other diseases; (2) case reports, reviews, meta-analyses, conference abstracts and letters;

Table 1 Main characteristics of all the eligible studies in the meta-analysis

Author	Year	Country	Ethnicity	Age (median and range)	Sample size	ICIs	Cut-off value	Stage	Variable	Median follow-up time (months)
Russo[17]	2018	Italy	European	69 (47–78)	28	Nivo	3	NA	U	17
Mezquita[11]	2018	France	European	NA	305	NA	3	IV	M	12
Prelaj[23]	2019	Italy	European	67 (31–86)	154	Nivo/Pembro	2.2	IIIb–IV	M	NA
Kazandjian[26]	2019	USA	America	NA	1368	NA	3	IV	M	NA
Seban[24]	2020	France	European	65 (37–86)	63	Pembro	3	IIIb–IV	M	13.4
Seban[25]	2020	France	European	61.9 (34.2–84.8)	109	Nivo/Pembro/Atezo	3	III–IV	M	11.6
Yuan[22]	2020	China	Asian	66 (57–69)	203	Pembro/Nivo/Tori/Sinti/Cam/Tis	2.35	IIIb–IV	M	NA
Takada[21]	2020	Japan	Asian	66 (31–88)	226	Nivo/Pembro	2.79	NA	M	13.8

Atezo, atezolizumab; Cam, camrelizumab; Crizo, crizotinib; ICIs, immune checkpoint inhibitors; M, multivariable; NA, not available; Nivo, nivolumab; Pembro, pembrolizumab; Sinti, sintilizumab; Tis, tislelizumab; Tori, toripalimab; U, univariable.

(3) duplicate publications and (4) we were unable to acquire the full text or data from the text.

Quality assessment

We evaluated the quality of the included studies using the Newcastle-Ottawa Scale (NOS),[20] which assesses three aspects of the studies: selection, comparability and outcome. Each study could be given a maximum of nine stars. A higher number of stars indicated better study quality.

Data extraction

Two investigators independently extracted data. Any disagreement was settled by discussion until agreement was reached or by consulting a third investigator. Data extracted were author, year of publication, study districts, age, sample size, type of ICIs, median follow-up time, cut-off value of dNLR and clinical stage. As for quantitative data, HRs with 95% CI of OS and PFS were also acquired from the included studies.

Statistical analysis

To evaluate the association between pretreatment dNLR and survival outcomes of the patients with NSCLC treated with ICIs, HRs with 95% CI were gathered to give the effective value. We assessed the heterogeneity of the eligible studies by using Cochran's Q test and I^2 statistics. $I^2 > 50\%$ and $p < 0.05$ in the Cochran's Q test were considered to indicate significant heterogeneity, and the random effects model was applied to calculate the pooled HRs. If heterogeneity was not significant, the fixed effects model was used. Subgroup analysis was conducted to assess heterogeneity among the results of different studies and explore the stability of results in different stratifications. Publication bias of studies was assessed by Begg's test and Egger's test. All p values were two sided, and $p < 0.05$ was considered statistically significant. STATA statistical software V.12.0 was used for all statistical analysis in this study.

RESULTS

Study characteristics

A total of 193 articles were retrieved using the initial search strategies. After multiple screening processes, 8 studies with a total of 2456 patients, published between 2018 and 2020, were finally included in our meta-analysis. The flow chart of study inclusion is shown in figure 1. Among all studies, participants in two studies were Asian[21 22] and in the other six were European or American.[11 17 23–26] HRs and 95% CIs were reported exactly in seven studies,[11 21–26] while the remaining study[17] reported only HR and p value; we then estimated 95% CI for that study based on HR and p value.[27] The calculation formula is as follows:

$$SE = \frac{log(HR)}{-0.862 + \sqrt{2.404 \times log(P)}}$$

$$\text{Lower } 95\% = e^{log(HR) - 1.96 \times SE}$$

$$\text{Upper } 95\% = e^{log(HR) + 1.96 \times SE}$$

Table 2 Quality assessment of included studies

Studies	Representativeness of population	Non-respondents	Ascertainment of exposure	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 stars
Russo et al[17] 2018	☆	☆	☆	☆	☆ –	☆	☆	☆	8
Mezquita et al[11] 2018	☆	☆	☆	☆	☆☆	☆	☆	☆☆	9
Prelaj et al[23] 2019	☆	☆	☆	☆	☆☆	☆	–	☆☆	8
Kazandjian et al[26] 2019	☆	☆	☆	☆	☆☆	☆	–	☆☆	8
Seban et al[24] 2020	☆	☆	☆	☆	☆☆	☆	☆	☆☆	9
Seban et al[25] 2020	☆	☆	☆	☆	☆☆	☆	☆	☆☆	9
Yuan et al[22] 2020	☆	☆	☆	☆	☆☆	☆	–	☆☆	8
Takada et al[21] 2020	☆	☆	☆	☆	☆☆	☆	☆	☆☆	9

☆ represents the score of the study in this item. – no star in this item.
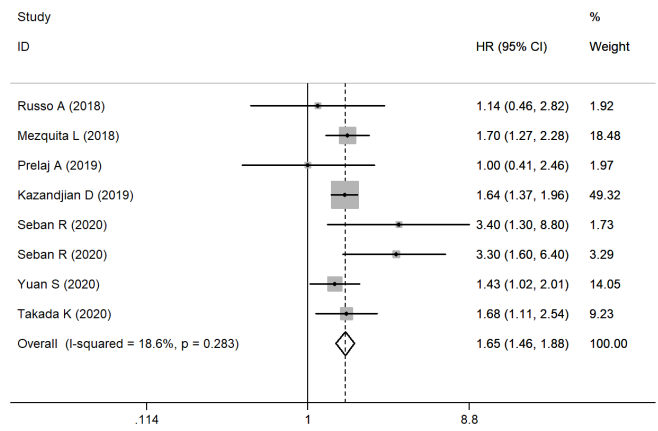
Figure 2 Forest plot of the association between pretreatment dNLR and OS. dNLR, derived neutrophil-to-lymphocyte ratio; OS, overall survival.

This study[17] computed HRs using univariable analysis and the other seven studies applied multivariable analysis.[11 21–26] Four of the study cohorts[17 23–25] enrolled <200 patients and four cohorts[11 21 22 26] had >200 patients. The cut-off values of NLR applied in the studies were not consistent, ranging from 2.2 to 3.0. Six studies involved stage III–IV/IIIb–IV cancer, and two studies did not clearly report stage.[17 21] All studies investigated the associations of dNLR and OS, and seven studies reported the associations of dNLR and PFS. The attributes of the eligible studies are shown in table 1, and the NOS score of included studies is shown in table 2.

Association between pretreatment dNLR and OS in NSCLC

Eight studies with 2456 patients were finally included in our analysis of the association between pretreatment dNLR and OS. A fixed effects model was applied due to relatively satisfactory homogeneity (I^2=18.6%, (95% CI (−71.4% to 61.4%)), p=0.283). Our pooled result indicated that elevated pretreatment dNLR predicted a worse outcome for OS (HR=1.65, (95% CI (1.46 to 1.88)); p<0.001) (figure 2) compared with those with low pretreatment dNLR. In subgroup analyses by ethnicity, the pooled HR was 1.53 ((95% CI (1.18 to 1.98)); p=0.001) for Asian patients and 1.70 ((95% CI (1.47 to 1.96)); p<0.001) for European or American patients. Stratification by sample size found that dNLR was a negative predictor for OS in both the large sample size group (HR: 1.62, (95% CI (1.42 to 1.85)); p<0.001) and the small sample size group (HR: 2.03, 95% CI 1.33 to 3.09; p<0.001). In subgroup analyses by cut-off value ≥3 and cut-off value <3, the data showed that the pooled HR was 1.72 ((95% CI (1.49 to 1.99)), p<0.001) for cut-off value ≥3 and 1.48 ((95% CI (1.15 to 1.90)), p=0.002) for cut-off value <3. Subgroup analysis was conducted using univariable and multivariable analysis (table 3).
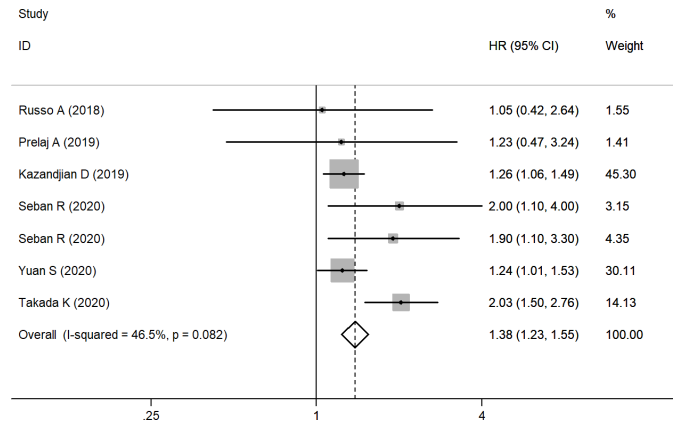
Association between pretreatment dNLR and PFS in NSCLC

Seven studies including 2151 patients were finally selected for analysis of the association between pretreatment dNLR and PFS. A fixed effects model was adopted due to

Table 3 Summary of the subgroup analysis results in studies with dNLR

Variables	OS					PFS				
	No of studies	Pooled HR (95% CI)	P value	I²	Ph	No of studies	Pooled HR (95% CI)	P value	I²	Ph
Ethnicity										
Asian	2	1.53 (1.18 to 1.98)	0.001	0.00%	0.56	2	1.57 (0.97 to 2.54)	0.068	85.30%	0.009
European/American	6	1.70 (1.47 to 1.96)	0	35.80%	0.169	5	1.33 (1.14 to 1.55)	0	0.00%	0.431
Sample size										
≤200	4	2.03 (1.33 to 3.09)	0	56.90%	0.073	4	1.67 (1.17 to 2.37)	0.005	0.00%	0.598
>200	4	1.62 (1.42 to 1.85)	0	0.00%	0.883	3	1.43 (1.10 to 1.85)	0.007	75.40%	0.017
Type of analysis										
Univariable	1	–	–	–	–	1	–	–	–	–
Multivariable	7	1.66 (1.46 to 1.88)	0	24.40%	0.243	6	1.39 (1.24 to 1.56)	0	54.00%	0.054
dNLR cut-off value										
<3	3	1.48 (1.15 to 1.90)	0.002	0.00%	0.568	3	1.51 (1.01 to 2.26)	0.043	71.10%	0.031
≥3	5	1.72 (1.49 to 1.99)	0	37.60%	0.17	4	1.33 (1.14 to 1.55)	0	21.00%	0.284

dNLR, derived neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

Figure 3 Forest plot of the association between pretreatment dNLR and PFS. dNLR, derived neutrophil-to-lymphocyte ratio; PFS, progression-free survival.

I^2=46.5% (95% CI (−27.0% to 77.4%)) and p=0.082. The results demonstrated that high pretreatment dNLR was significantly associated with poorer PFS (HR=1.38, (95% CI (1.23 to 1.55)); p<0.001) (figure 3) compared with low pretreatment dNLR. Subgroup analysis was performed by ethnicity; the results showed that dNLR was a negative predictor for NSCLC in European or American patients (HR=1.33, (95% CI (1.14 to 1.55)); p<0.001), but in Asian dNLR and PFS have no significant relationship (HR=1.57, (95% CI (0.97 to 2.54)); p=0.068). In the small sample size group, the pooled HR was 1.67 ((95% CI (1.17 to 2.37)); p=0.005), and in the large sample size group the HR was 1.43 ((95% CI (1.10 to 1.85)); p=0.007). Subgroup analyses by cut-off value of dNLR showed that the pooled HR was 1.33 ((95% CI (1.14 to 1.55)), p<0.001) for cut-off value≥3 and 1.51 ((95% CI (1.01 to 2.26)), p=0.043) for cut-off value<3. Furthermore, subgroup analysis was conducted using univariable and multivariable analysis, and the results also illustrated the interrelation between baseline dNLR and PFS (table 3).

Publication bias

We conducted Begg's and Egger's linear regression test to assess publication bias. OS publication bias was not discovered in studies with dNLR (Pr>|z|=0.902 for Begg's test and P>|t|=0.648 for Egger's test); publication bias was also not detected for PFS (Pr>|z|=0.764 and P>|t|=0.392, respectively). The plots of Begg's test and Egger's test are shown in figure 4.

DISCUSSION

This meta-analysis evaluated the results of 2456 patients with NSCLC in eight studies. The results showed that high level dNLR was a significant predictor of worse OS (HR=1.65, (95% CI (1.46 to 1.88)); p<0.001) and PFS (HR=1.38, (95% CI (1.23 to 1.55)); p<0.001) of patients with NSCLC treated with ICIs. Subgroup analyses of OS-related studies indicated similar results in stratifications by ethnicity, sample size, type of HR and dNLR cut-off value. In PFS-related studies, subgroup analyses
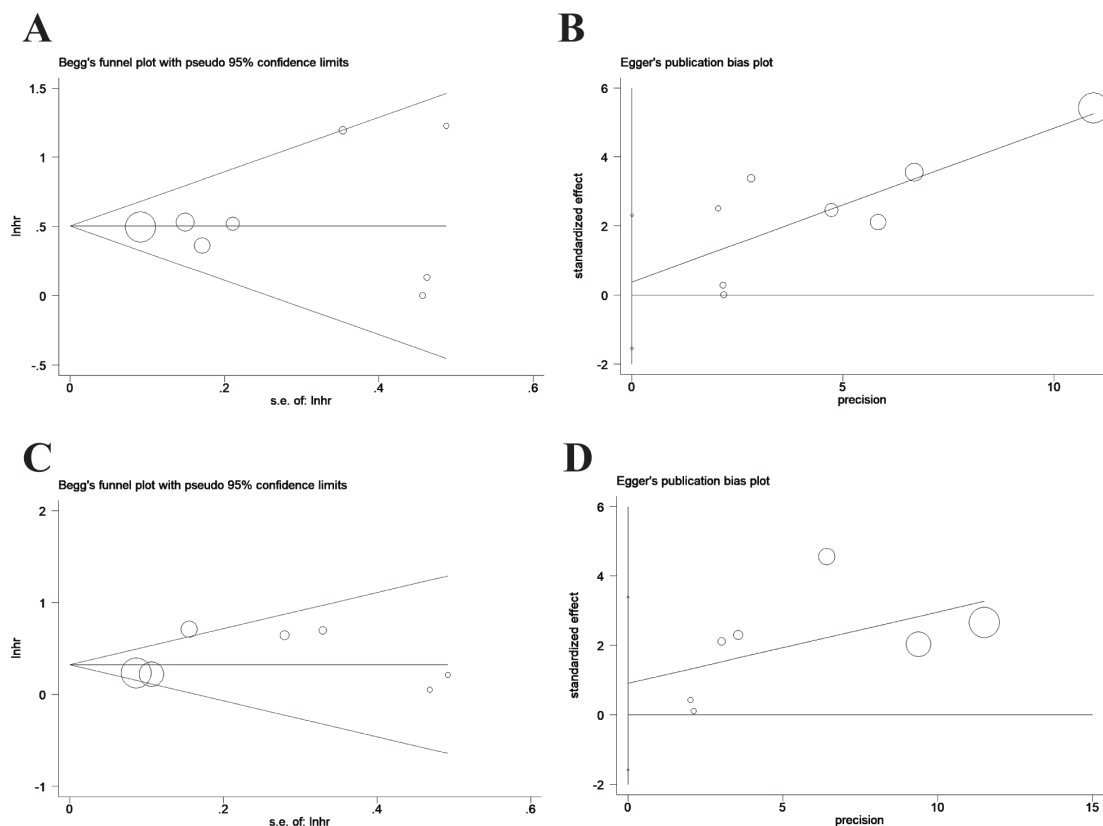
Figure 4 Funnel plot for analysis of publication bias. (A) Funnel plot established using Begg's test for studies with overall survival (OS) ; (B) funnel plot using Egger's test for studies with OS. (C) Funnel plot established utilising Begg's test for studies with progression-free survival (PFS); (D) funnel plot using Egger's test for studies with PFS.

showed that there was no significant difference in the Asian sample group, but Asian sample subgroup only included two studies, which might weaken the credibility of the results of subgroup analysis. We conclude that pretreatment dNLR may be an important biomarker of the prognosis of patients with NSCLC treated with ICIs.

Inflammation tends to lead to the development of cancer and stimulates all stages of tumourigenesis through multiple mechanisms.[28] Induction of inflammation can bring increased mutagenesis, leading to collection of mutations in normal tissue that can further cause tumour formation.[29 30] Unlike in earlier stages of oncogenesis, cancer-related inflammation plays a crucial role in regulation of metastasis and leads to worse mortality.[31] Additionally, the inflammation process has been suggested as a reason for immune resistance in cancer patients. The cellular effectors of inflammation are significant elements of the tumour microenvironment that break down adaptive immune responses and impede responses to antitumour agents.[32] Moreover, a peripheral proinflammatory condition has been linked to poor prognosis in patients with cancer.[11] Many routine blood indices including WBC, CRP, absolute neutrophil count and lactate dehydrogenase level have been evaluated as potential inflammatory biomarkers, which are associated with worse survival in various types of cancer.[33–35] Novel biomarkers such as NLR, lymphocyte-monocyte ratio and lymphocyte-platelet ratio have also been used to assess

inflammatory status in several cancer types, including NSCLCs.[36–38] In particular, NLR is a well-studied prognostic predictor in patients with NSCLC, and some meta-analyses have confirmed the predictive value of NLR in patients with NSCLC.[39 40]

Recent studies indicated that dNLR is a novel serum marker of inflammatory in patients with NSCLC treated with ICIs.[17 41] Although some studies have suggested relationships between NLR and survival and therapeutic outcomes in patients with NSCLC treated with anti-PD-1 inhibitors,[12 42 43] dNLR may be more strongly linked because it includes monocytes and other granulocytes. Immature or poorly differentiated neutrophils can be released in a proinflammatory environment, which increases neutrophil generation rapidly. dNLR seems to reflect this negative inflammation more comprehensively. Our study demonstrated that dNLR may be a valuable prognostic serum biomarker for clinicians' decision making in NSCLC ICIs treatment. Future studies should pay more attentions to the prognostic effect of dNLR on the patients with NSCLC with ICIs. A larger sample study is needed to verify our results.

In our study, most included studies have chosen a dNLR cut-off value of 3 to distinguish the prognosis of patients with NSCLC treated with ICIs, however, the selection and source of dNLR cut-off values were rarely mentioned in original studies. We performed subgroup analysis according to different dNLR cut-off levels, the

results show that significant HR of OS and PFS could be produced by all subgroups. It is also probably necessary to use receiver operating characteristic curves or other tools to determine the optimal pretreatment dNLR cut-off value based on large sample data, so that dNLR can be better applied to clinical practice. In addition, the included original studies did not provide information that might affect dNLR, such as related diseases, previous treatment, etc. These factors may lead to differences in the baseline characteristics of the patients, which may influence the interpretation of our results. In the future study, we will pay more attention to this aspect, and more comprehensive original studies should be used to obtain more reliable results.

Several limitations of our meta-analysis require careful consideration. First, the eligible studies were all retrospective, retrospective study is more prone to several bias including selection, recall and measurement biases, so these retrospective biases may influence the accuracy of results. Although recall bias was not explicit mentioned in the original studies, the systematic error between the accuracy or integrity and the real situation is often the result of the memory distortion or incomplete recall of the research object when collecting the information. In addition, most of the included studies were retrospective and single institution case series, and as mentioned above, the original study did not provide more information such as other diseases and previous treatment and so on, which may lead to selection bias. Second, although neither Begg's test nor Egger's test showed publication bias in this study, the effectiveness of the two tests was low when the number of meta-analyses was <10. In addition, our study mainly searched English-language databases. Hence, publication bias should also be considered.

In conclusion, this meta-analysis revealed that elevated pretreatment dNLR may be a negative prognostic index for patients with NSCLC treated with ICIs. Future well-designed and large-scale studies are needed to validate the result.

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