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Prognostic value of derived neutrophil-to-lymphocyte ratio (dNLR) in non-small cell lung cancer patients receiving immune checkpoint inhibitors: what should we expect from a meta-analysis?

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Abstract

Objectives: Derived neutrophil-to-lymphocytes ratio (dNLR) has recently been reported as a novel potential biomarker in predicting the prognosis of non-small cell lung cancer (NSCLC). However, evidence for the prognostic utility of dNLR in NSCLC patients treated with immune checkpoint inhibitors (ICIs) remains inconsistent. The objective of our meta-analysis was to assess the association of pretreatment dNLR and prognosis of NSCLC patients who were treated with ICIs.

Design: This study followed the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines (supplementary file 1).

Methods: We searched published articles from PubMed, Web of Science, EMBASE, and the Cochrane Library database. The meta-analysis of the chosen studies was conducted using STATA statistical software version 12.0.

Results: This analysis included 8 studies (2,456 cases) of the prognostic utility of dNLR in ICI therapy for NSCLC. The results indicate that elevated dNLR significantly predicted poor overall survival (OS) (hazard ratio [HR] = 1.65, 95% confidence interval [CI] 1.45–1.87; $P < 0.001$) and progression-free survival (PFS) (HR = 1.51, 95% CI 1.24–1.85; $P < 0.001$). 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.

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

PROSPERO registration number: CRD42021214034

Keywords: derived neutrophil-to-lymphocyte ratio, immune checkpoint inhibitors, non-small cell lung cancer, meta-analysis

Strengths and limitations of this study

- ▶ This is the first study to evaluate the prognostic value of pretreatment dNLR in

NSCLC patients who treated with ICIs.

- This meta-analysis may provide novel prognostic guidance for NSCLC patients 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.

Introduction

Global cancer statistics have shown that there are 1.24 million new cases and 1.09 million deaths from lung cancer each year.[1] Non-small cell lung cancer (NSCLC) accounts for about 85% of primary lung cancers and includes 3 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 five-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 ten years, the application of immune checkpoint inhibitors (ICIs) in the treatment of NSCLC has improved the therapeutic landscape for this intractable disease. Some patients with advanced NSCLC have shown overall survival (OS) or progression-free survival (PFS) benefits from ICI treatment after chemoradiotherapy.[4 5] Despite significant clinical improvements, not all ICI treatments are effective in NSCLC patients. Some valuable biomarkers that predict ICI response, such as programmed cell death-ligand 1 (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.[6] 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

cancer patients which can promote tumour growth and invasion and activate carcinogenic signalling pathways.[7] In 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.[8 9] 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.[10] DNLR has been used to assess response to immunotherapy in various cancers, including NSCLC.[11-13] Recent studies showed the predictive utility of pretreatment dNLR in urological cancer and breast cancer.[14 15] 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 NSCLC patients 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.

Search strategy and study inclusion

Our meta-analysis was conducted to explore the association between dNLR and prognosis of NSCLC patients 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. (supplementary 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) hazard ratio (HR) and 95% confidence interval (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; (3) duplicate publications; (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),[16] which assesses three aspects of the studies: selection, comparability, and outcome. Each study could be given a maximum of 9 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 NSCLC patients 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 utilised. 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 version 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 2,456 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 2 studies were Asian[17 18] and in the other 6 were European or American.[13 19-23] HRs and 95% CIs were reported exactly in 7 studies,[17-23] while the remaining study[13] reported only HR and P-value; we then estimated 95% CI for that study based on HR and P value.[24] This study[13] computed HRs using univariable analysis and the other 7 studies applied multivariable analysis.[17-23] Four of the study cohorts[13 19-21] enrolled <200 patients and 4 cohorts[17 18 22 23] 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 2 studies did not clearly report stage.[13 17] All studies investigated the associations of dNLR and OS, and 7 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.

Figure 1. Flow chart of the eligible studies

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 A[13]	2018	Italy	European	69(47-78)	28	Nivo	3	NA	U	17
Mezquita L	2018	France	European	NA	305	NA	3	IV	M	12
Prelaj A[19]	2019	Italy	European	67(31-86)	154	Nivo/Pembro	2.2	IIIb-IV	M	NA
Kazandjian D[23]	2019	USA	America	NA	1368	NA	3	IV	M	NA
Seban R[20]	2020	France	European	65(37-86)	63	Pembro	3	IIIb-IV	M	13.4
Seban R[21]	2020	France	European	61.9(34.2-84.8)	109	Nivo/Pembro/Atezo	3	III-IV	M	11.6
Yuan S[18]	2020	China	Asian	66(57-69)	203	Pembro/Nivo/Tori/Sinti/Cam/Tis	2.35	IIIb-IV	M	NA
Takada K[17]	2020	Japan	Asian	66(31-88)	226	Nivo/Pembro	2.79	NA	M	13.8

NA: not available; Nivo: nivolumab; Pembro: pembrolizumab; Atezo: atezolizumab; Crizo: crizotinib; Sinti: sintilizumab; Tori: toripalimab; Cam: camrelizumab; Tis: tislelizumab; U: univariable; M: multivariable

Table 2. Quality assessment of included studies

Studies	Representativeness of population	Non-respondents	Ascertainment of the 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 A 2018	☆	☆	☆	☆	☆–	☆	☆	☆	8
Mezquita L 2018	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Prelaj A 2019	☆	☆	☆	☆	☆☆	☆	–	☆	8
Kazandjian D 2019	☆	☆	☆	☆	☆☆	☆	–	☆	8
Seban R 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Seban R 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Yuan S 2020	☆	☆	☆	☆	☆☆	☆	–	☆	8
Takada K 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9

☆represents the score of the study in this item. –, no star in this item.

Association between pretreatment dNLR and OS in NSCLC

Eight studies with 2,456 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=20.6%, P = 0.266). Our pooled result indicated that elevated pretreatment dNLR predicted a worse outcome for OS (HR = 1.65, 95% CI 1.45–1.87; 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 1.18–1.98; P = 0.001) for Asian patients and 1.69 (95% CI 1.46–1.94; 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 1.42–1.85; P < 0.001) and the small sample size group (HR: 1.90, 95% CI 1.28–2.82; P < 0.001). In subgroup analyses by cut-off value =3 and cut-off value < 3, the data showed that the pooled HR was 1.60 (95% CI 1.41–1.82, P < 0.001) for cut-off value = 3 and 2.28 (95%CI 1.54-3.99, P < 0.001) for cut-off value < 3. Subgroup analysis was conducted using univariable and multivariable analysis (Table 3).

Figure 2. Forest plot of the association between pretreatment dNLR and OS

Association between pretreatment dNLR and PFS in NSCLC

Seven studies including 2,151 patients were finally selected for analysis of the association between pretreatment dNLR and PFS. A random effects model was adopted due to I^2=50.5% and P=0.059. The results demonstrated that high pretreatment dNLR was significantly associated with poorer PFS (HR = 1.51, 95% CI 1.24–1.85; 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 both in Asian (HR = 1.57, 95% CI 0.97–2.54; P = 0.068) and European or American patients (HR = 1.45, 95% CI 1.15–1.84; P = 0.002). In the small sample size group, the pooled HR was 1.80 (95% CI 1.28–2.53; P = 0.001), and in the large sample size group the HR was 1.35 (95% CI 1.20–1.53; P < 0.001). Subgroup analyses by cut-off value of dNLR

showed that the pooled HR was 1.47 (95% CI 1.15-1.88, P < 0.001) for cutoff value = 3 and 1.75 (95% CI 1.19-2.56, P = 0.004) 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).

Figure 3. Forest plot of the association between pretreatment dNLR and PFS

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

Variables	OS					PFS				
	Number of studies	Pooled HR (95% CI)	P	I2	Ph	Number of studies	Pooled HR (95% CI)	P	I2	Ph
Ethnicity										
Asian	2	1.53 (1.18,1.98)	0.001	0.00%	0.56	2	1.57 (0.97,2.54)	0.068	85.30%	0.009
European/American	6	1.69 (1.46,1.94)	0	37.90%	0.154	5	1.45 (1.15,1.84)	0.002	19.10%	0.293
Sample size										
≤200	4	1.90 (1.28,2.82)	0	60.50%	0.055	4	1.80 (1.28,2.53)	0.001	0.00%	0.669
> 200	4	1.62 (1.42,1.85)	0	0.00%	0.883	3	1.35 (1.20,1.53)	0.007	75.40%	0.017
Type of analysis										
Univariable	1	-	-	-	-	1	-	-	-	-
Multivariable	7	1.66 (1.46,1.88)	0	26.60%	0.226	6	1.40 (1.25,1.57)	0	57.40%	0.038
dNLR cut-off value										
<3	3	2.28 (1.54,3.99)	0	48.60%	0.143	3	1.75 (1.19,2.56)	0.004	0.00%	0.487
=3	5	1.60 (141,1.82)	0	0.00%	0.751	4	1.47 (1.15,1.88)	0.002	67.40%	0.027

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|=0.623 for Egger's test); publication bias was also not detected for PFS (Pr>|z|=1.0 and P>|t|=0.198, respectively). The plots of Begg's test and Egger's test are shown in Figure 4.

Figure 4. Funnel plot for analysis of publication bias. (A) Funnel plot established using Begg's test for studies with OS; (B) funnel plot utilising Egger's test for studies with OS. (C) Funnel plot established utilising Begg's test for studies with PFS; (D) funnel plot utilising Egger's test for studies with PFS.

Discussion

This meta-analysis evaluated the results of 2,456 NSCLC patients in 8 studies. The results showed that high level dNLR was a significant predictor of worse OS (HR = 1.65, 95% CI 1.45–1.87; P < 0.001) and PFS (HR = 1.51, 95% CI 1.24–1.85; P < 0.001) of NSCLC patients 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 showed that there was no significant difference in the Asian sample group. We conclude that pretreatment dNLR may be an important biomarker of the prognosis of NSCLC patients treated with ICIs.

Inflammation tends to lead to the development of cancer and stimulates all stages of tumourigenesis through multiple mechanisms.[25] Induction of inflammation can bring increased mutagenesis, leading to collection of mutations in normal tissue that can further cause tumour formation.[26 27] Unlike in earlier stages of oncogenesis, cancer-related inflammation plays a crucial role in regulation of metastasis and leads to worse mortality.[28] 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 anti-tumour agents.[29] Moreover, a peripheral pro-inflammatory condition has been linked to poor prognosis in patients with cancer[7]. 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.[30-32] Novel biomarkers such as NLR, lymphocyte-monocyte ratio (LMR), and lymphocyte-platelet ratio (PLR) have also been used to assess inflammatory status in several cancer types, including NSCLCs.[33-35] In particular, NLR is a well-studied prognostic predictor in NSCLC patients, and some meta-analyses have confirmed the predictive value of NLR in patients with NSCLC.[36 37]

Recent studies indicated that dNLR is a novel serum marker of inflammatory in NSCLC patients treated with ICIs.[13 38] Although some studies have suggested relationships between NLR and survival and therapeutic outcomes in NSCLC patients treated with anti-PD-1 inhibitors,[8 39 40] dNLR may be more strongly linked because it includes monocytes and other granulocytes. Immature or poorly differentiated neutrophils can be released in a pro-inflammatory 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 NSCLC patients with ICIs. A larger sample study is needed to verify our results.

Most studies have chosen a dNLR cut-off value of 3 to distinguish the prognosis of NSCLC patients treated with ICIs. It is also probably necessary to use receiver operating characteristic (ROC) curves to determine the best cut-off value of dNLR based on large sample data, so that dNLR can be better applied to clinical practice.

Several limitations of our meta-analysis require careful consideration. First, the eligible studies were all retrospective, so retrospective biases may influence the accuracy of results. 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 NSCLC patients treated with ICIs. Future well-designed and large-scale studies are needed to validate the result.

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None.

Author contributions

ZL and SQ put forward the idea of research. The search strategy was developed and conducted by TY, LH, and XY. LH and XY independently screened the titles and abstracts of all included studies. Data extraction was performed by LH, XY, CL, and GW. TY and LH conducted the meta-analysis. Manuscript was written by TY and CLC.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no competing interests.

Ethical approval

Not applicable.

Patient consent for publication

Not applicable.

Data availability

No additional data available.

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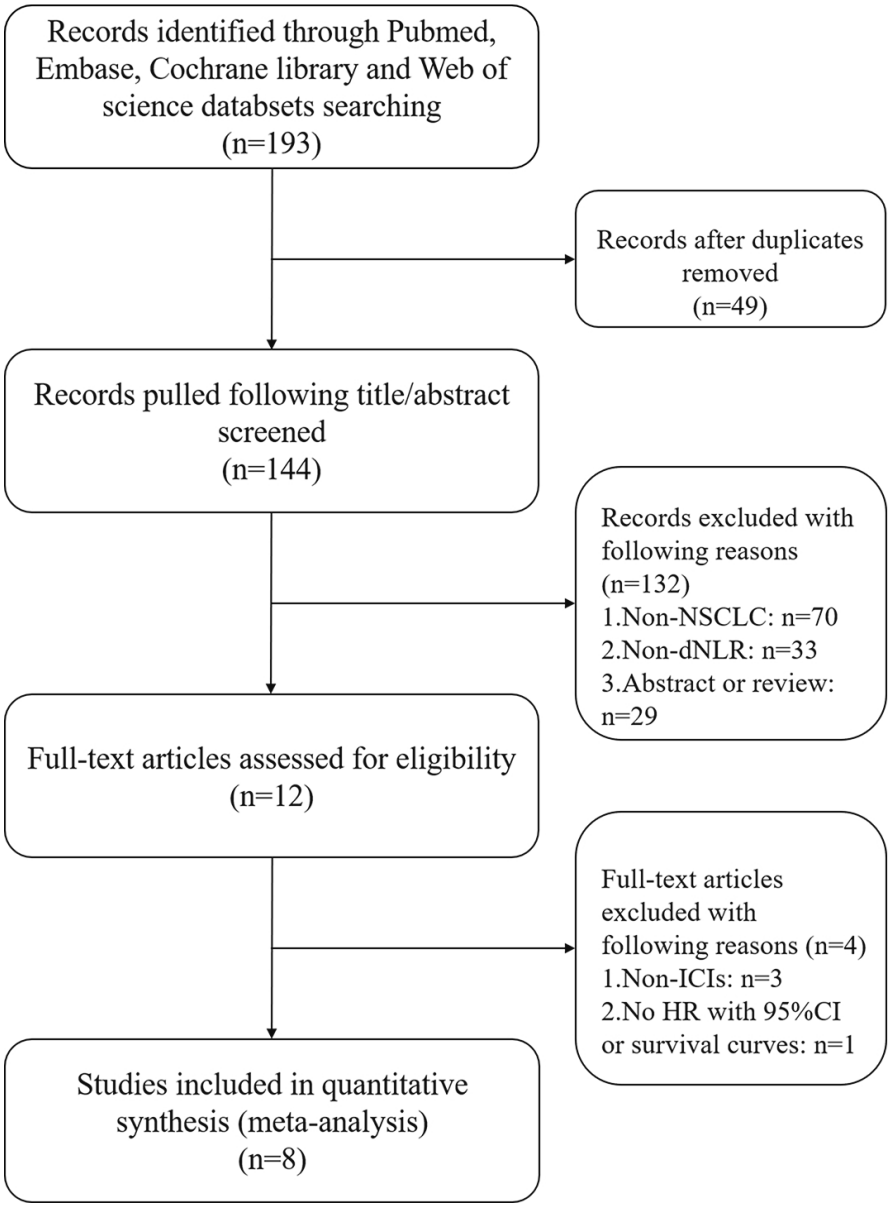
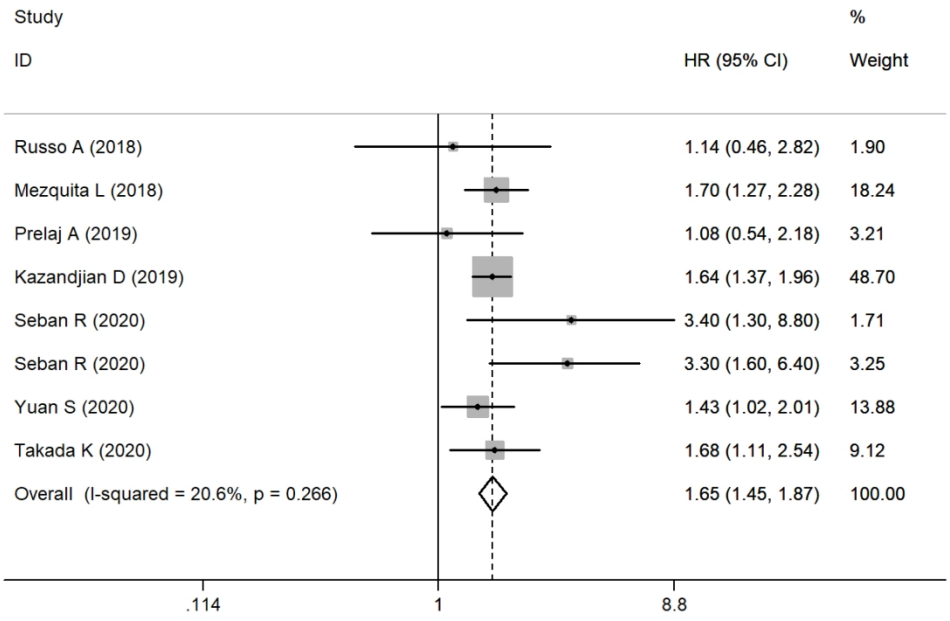


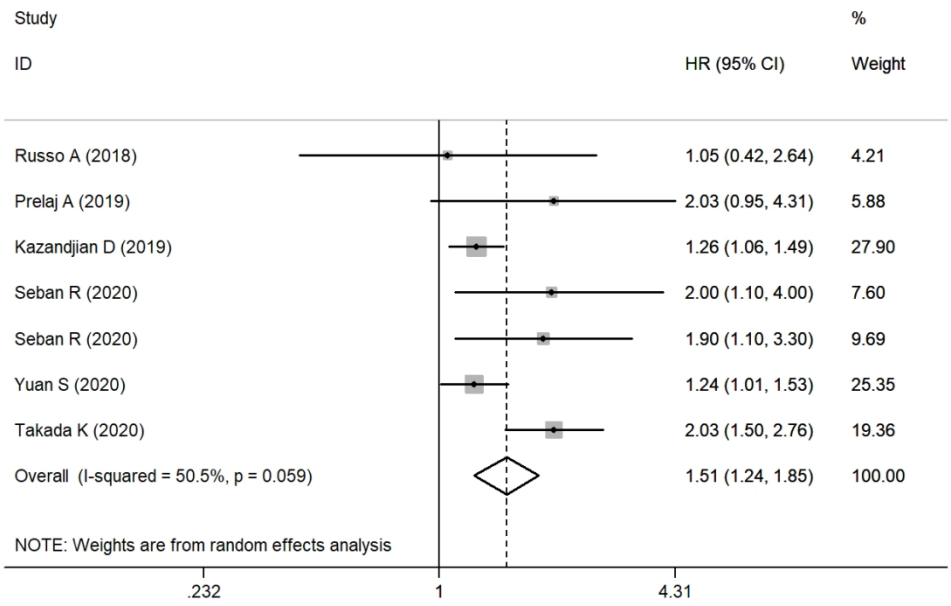
Flow chart of the eligible studies

181x245mm (150 x 150 DPI)



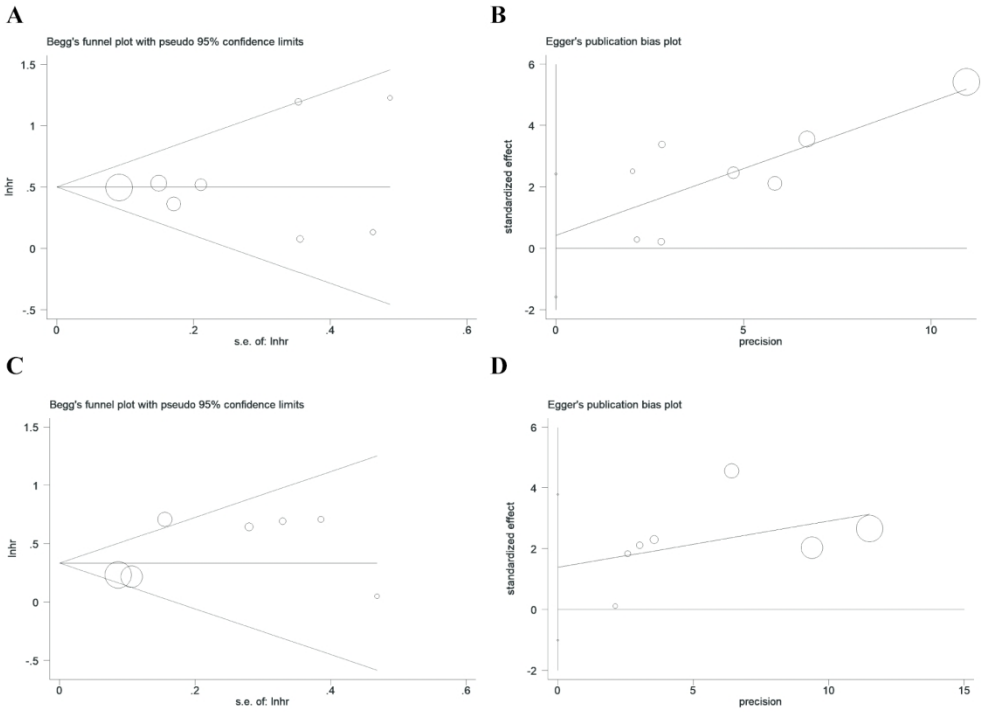
Forest plot of the association between pretreatment dNLR and OS

456x326mm (72 x 72 DPI)



Forest plot of the association between pretreatment dNLR and PFS

464x327mm (72 x 72 DPI)



Funnel plot for analysis of publication bias. (A) Funnel plot established using Begg's test for studies with OS; (B) funnel plot utilising Egger's test for studies with OS. (C) Funnel plot established utilising Begg's test for studies with PFS; (D) funnel plot utilising Egger's test for studies with PFS.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary Table 1 Search strategies for PubMed, Embase, Cochrane Library and Web of science

Database	Keywords
PubMed	
#1	"Carcinoma, Non-Small-Cell Lung"[Mesh]
#2	(Carcinoma, Non Small Cell Lung[Title/Abstract]) OR (Carcinomas, Non-Small-Cell Lung[Title/Abstract])) OR (Lung Carcinoma, Non-Small-Cell[Title/Abstract])) OR (Lung Carcinomas, Non-Small-Cell[Title/Abstract])) OR (Non-Small-Cell Lung Carcinomas[Title/Abstract])) OR (Nonsmall Cell Lung Cancer[Title/Abstract])) OR (Non-Small-Cell Lung Carcinoma[Title/Abstract])) OR (Non Small Cell Lung Carcinoma[Title/Abstract])) OR (Carcinoma, Non-Small Cell Lung[Title/Abstract])) OR (Non-Small Cell Lung Cancer[Title/Abstract])
#3	#1 OR #2
#4	(checkpoint*[Title/Abstract]) OR ("checkpoint inhibitor"[Title/Abstract])) OR (CTLA-4[Title/Abstract])) OR (PD-1[Title/Abstract])) OR (PD-L1[Title/Abstract])) OR (ipilimumab[Title/Abstract])) OR (atezolizumab[Title/Abstract])) OR (durvalumab[Title/Abstract])) OR (pembrolizumab[Title/Abstract])) OR (nivolumab[Title/Abstract])) OR (avelumab[Title/Abstract])) OR (tremelimumab[Title/Abstract])
#5	(derived neutrophil-lymphocyte ratio[Title/Abstract]) OR (dNLR[Title/Abstract])) OR (derived neutrophil lymphocyte ratio[Title/Abstract])) OR (derived neutrophil to lymphocyte ratio[Title/Abstract]))
#6	#3 AND #4 AND #5
Embase	
#1	'non small cell lung cancer'/exp
#2	'carcinoma, non small cell lung':ab,ti OR 'carcinomas, non-small-cell lung':ab,ti OR 'lung carcinoma, non-small-cell':ab,ti OR 'lung carcinomas, non-small-cell':ab,ti OR 'non-small-cell lung carcinomas ':ab,ti OR 'non small cell lung cancer:ab,ti OR 'non-small-cell lung carcinoma':ab,ti OR 'non small cell lung carcinoma ':ab,ti OR 'carcinoma, non-small cell lung':ab,ti OR 'non-small cell lung cancer':ab,ti
#3	#1 OR #2
#4	'checkpoint*':ab,ti OR 'checkpoint inhibitor':ab,ti OR 'ctla-4':ab,ti OR 'pd-1':ab,ti OR 'pd-l1':ab,ti OR 'ipilimumab':ab,ti OR 'atezolizumab':ab,ti OR 'durvalumab':ab,ti OR 'pembrolizumab':ab,ti OR 'nivolumab':ab,ti OR 'avelumab':ab,ti OR 'tremelimumab':ab,ti
#5	'derived neutrophil-lymphocyte ratio':ab,ti OR 'dnlr':ab,ti OR 'derived neutrophil lymphocyte ratio':ab,ti OR 'derived neutrophil to lymphocyte ratio':ab,ti
#6	#3 AND #4 AND #5
Cochrane Library	
#1	MeSH: Carcinoma, Non-Small-Cell Lung

#2	(Carcinoma, Non Small Cell Lung):ti,ab,kw OR (Carcinomas, Non-Small-Cell Lung):ti,ab,kw OR (Lung Carcinoma, Non-Small-Cell):ti,ab,kw OR (Lung Carcinomas, Non-Small-Cell):ti,ab,kw OR (Non-Small-Cell Lung Carcinomas):ti,ab,kw OR (Non small Cell Lung Cancer):ti,ab,kw OR (Non-Small-Cell Lung Carcinoma):ti,ab,kw OR (Non Small Cell Lung Carcinoma):ti,ab,kw OR (Carcinoma, Non-Small Cell Lung):ti,ab,kw OR (Non-Small Cell Lung Cancer):ti,ab,kw
#3	#1 OR #2
#4	(checkpoint*):ti,ab,kw OR (checkpoint inhibitor):ti,ab,kw OR (CTLA-4):ti,ab,kw OR (PD-1):ti,ab,kw OR (PD-L1):ti,ab,kw OR (ipilimumab):ti,ab,kw OR (atezolizumab):ti,ab,kw OR (durvalumab):ti,ab,kw OR (pembrolizumab):ti,ab,kw OR (nivolumab):ti,ab,kw OR (avelumab):ti,ab,kw OR (tremelimumab):ti,ab,kw
#5	(derived neutrophil-lymphocyte ratio):ti,ab,kw OR (dNLR):ti,ab,kw OR (derived neutrophil lymphocyte ratio):ti,ab,kw OR (derived neutrophil to lymphocyte ratio):ti,ab,kw
#6	#3 AND #4 AND #5
Web of science	
#1	TS=(Carcinoma, Non-Small-Cell Lung OR Carcinoma, Non Small Cell Lung OR Carcinomas, Non-Small-Cell Lung OR Lung Carcinoma, Non-Small-Cell OR Lung Carcinomas, Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma OR Carcinoma, Non-Small Cell Lung OR Non-Small Cell Lung Cancer)
#2	TS=(checkpoint* OR checkpoint inhibitor OR CTLA-4 OR PD-1 OR PD-L1 OR ipilimumab OR atezolizumab OR durvalumab OR pembrolizumab OR nivolumab OR avelumab OR tremelimumab)
#3	TS=(derived neutrophil-lymphocyte ratio OR Dnlr OR derived neutrophil lymphocyte ratio OR derived neutrophil to lymphocyte ratio)
#4	#1 AND #2 AND #3

BMJ Open

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

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Prognostic value of derived neutrophil-to-lymphocyte ratio (dNLR) in non-small cell lung cancer patients 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 in predicting the prognosis of non-small cell lung cancer (NSCLC). However, evidence for the prognostic utility of dNLR in NSCLC patients treated with immune checkpoint inhibitors (ICIs) remains inconsistent. The objective of our meta-analysis was to assess the association of pretreatment dNLR and prognosis of NSCLC patients who were treated with ICIs.

Design: This study followed the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) 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 OS or PFS in NSCLC; 4) hazard ratio (HR) and 95% confidence interval (CI) were displayed in the original article or could be extracted from Kaplan-Meier curves.

Data extraction and synthesis:

Two investigators independently extracted data. 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. The STATA statistical software version we used was 12.0.

Results: This analysis included 8 studies (2,456 cases) of the prognostic utility of dNLR in ICI therapy for NSCLC. The results indicate that higher dNLR significantly predicted poor overall survival (OS) (hazard ratio [HR] = 1.65, 95% confidence interval [CI] 1.46–1.88; $P < 0.001$) and progression-free survival (PFS) (HR = 1.38, 95% CI 1.23–1.55; $P < 0.001$). 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.

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

PROSPERO registration number: CRD42021214034

Keywords: derived neutrophil-to-lymphocyte ratio, immune checkpoint inhibitors, non-small cell lung cancer, meta-analysis

Strengths and limitations of this study

- This is the first study to evaluate the prognostic value of pretreatment dNLR in NSCLC patients who treated with ICIs.
- This meta-analysis may provide novel prognostic guidance for NSCLC patients 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.

Introduction

Global cancer statistics have shown that there are 1.24 million new cases and 1.09 million deaths from lung cancer each year.[1] Non-small cell lung cancer (NSCLC) accounts for about 85% of primary lung cancers and includes 3 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 five-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 ten years, the application of immune checkpoint inhibitors (ICIs) in the treatment of NSCLC has improved the therapeutic landscape for this intractable disease. PD-1 and PD-L1 inhibitors have shown encouraging results in NSCLC (Pembrolizumab and

Nivolumab, for instance) and they have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced NSCLC[4 5]. The latest phase 3 study showed that nivolumab was demonstrated a superior OS versus docetaxel at 2 years in NSCLC[6]. And a real-life cohort of advanced NSCLC patients treated with pembrolizumab demonstrated similar PFS to the pivotal clinical trial[7]. Some patients with advanced NSCLC have shown overall survival (OS) or progression-free survival (PFS) benefits from ICI treatment after chemoradiotherapy.[8 9]

Despite significant clinical improvements, not all ICI treatments are effective in NSCLC patients. Some valuable biomarkers that predict ICI response, such as programmed cell death-ligand 1 (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 cancer patients which can promote tumour growth and invasion and activate carcinogenic signalling pathways.[11] In 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 NSCLC patients 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 review and Meta-Analyses (PRISMA) guidelines (supplementary file 1). The protocol is registered at PROSPERO (CRD42021214034).

Search strategy and study inclusion

Our meta-analysis was conducted to explore the association between dNLR and prognosis of NSCLC patients 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. (supplementary 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) hazard ratio (HR) and 95% confidence interval (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; (3) duplicate publications; (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 9 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 NSCLC patients 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 utilised. 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 version 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 2,456 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 2 studies were Asian[21 22] and in the other 6 were European or American.[17 23-27] HRs and 95% CIs were reported exactly in 7 studies,[21-27] 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.[28] The calculation formula is as

follows:

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

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

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

This study[17] computed HRs using univariable analysis and the other 7 studies applied multivariable analysis.[21-27] Four of the study cohorts[17 23-25] enrolled <200 patients and 4 cohorts[21 22 26 27] 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 2 studies did not clearly report stage.[17 21] All studies investigated the associations of dNLR and OS, and 7 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.

Figure 1. Flow chart of the eligible studies

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 A[17]	2018	Italy	European	69(47-78)	28	Nivo	3	NA	U	17
Mezquita L	2018	France	European	NA	305	NA	3	IV	M	12
Prelaj A[23]	2019	Italy	European	67(31-86)	154	Nivo/Pembro	2.2	IIIb-IV	M	NA
Kazandjian D[27]	2019	USA	America	NA	1368	NA	3	IV	M	NA
Seban R[24]	2020	France	European	65(37-86)	63	Pembro	3	IIIb-IV	M	13.4
Seban R[25]	2020	France	European	61.9(34.2-84.8)	109	Nivo/Pembro/Atezo	3	III-IV	M	11.6
Yuan S[22]	2020	China	Asian	66(57-69)	203	Pembro/Nivo/Tori/Sinti/Cam/Tis	2.35	IIIb-IV	M	NA
Takada K[21]	2020	Japan	Asian	66(31-88)	226	Nivo/Pembro	2.79	NA	M	13.8

NA: not available; Nivo: nivolumab; Pembro: pembrolizumab; Atezo: atezolizumab; Crizo: crizotinib; Sinti: sintilizumab; Tori: toripalimab; Cam: camrelizumab; Tis: tislelizumab; U: univariable; M: multivariable

Table 2. Quality assessment of included studies

Studies	Representativeness of population	Non-respondents	Ascertainment of the 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 A 2018	☆	☆	☆	☆	☆–	☆	☆	☆	8
Mezquita L 2018	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Prelaj A 2019	☆	☆	☆	☆	☆☆	☆	–	☆	8
Kazandjian D 2019	☆	☆	☆	☆	☆☆	☆	–	☆	8
Seban R 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Seban R 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Yuan S 2020	☆	☆	☆	☆	☆☆	☆	–	☆	8
Takada K 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9

☆represents the score of the study in this item. –, no star in this item.

Association between pretreatment dNLR and OS in NSCLC

Eight studies with 2,456 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%-61.4%, P = 0.283). Our pooled result indicated that elevated pretreatment dNLR predicted a worse outcome for OS (HR = 1.65, 95% CI 1.46–1.88; 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 1.18–1.98; P = 0.001) for Asian patients and 1.70 (95% CI 1.47–1.96; 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 1.42–1.85; P < 0.001) and the small sample size group (HR: 2.03, 95% CI 1.33–3.09; 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 1.49–1.99, P < 0.001) for cut-off value ≥ 3 and 1.48 (95% CI 1.15-1.90, P = 0.002) for cut-off value < 3. Subgroup analysis was conducted using univariable and multivariable analysis (Table 3).

Figure 2. Forest plot of the association between pretreatment dNLR and OS

Association between pretreatment dNLR and PFS in NSCLC

Seven studies including 2,151 patients were finally selected for analysis of the association between pretreatment dNLR and PFS. A fixed effects model was adopted due to I^2=46.5% (95% CI -27.0%-77.4%)and P=0.082. The results demonstrated that high pretreatment dNLR was significantly associated with poorer PFS (HR = 1.38, 95% CI 1.23–1.55; 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 1.14–1.55; P < 0.001), but in Asian dNLR and PFS have no significant relationship (HR = 1.57, 95% CI 0.97–2.54; P = 0.068). In the small sample size group, the pooled HR was 1.67 (95% CI 1.17–2.37; P = 0.005), and in the large sample size group the HR was 1.43 (95% CI

1.10–1.85; P = 0.007). Subgroup analyses by cut-off value of dNLR showed that the pooled HR was 1.33 (95% CI 1.14-1.55, P < 0.001) for cutoff value ≥ 3 and 1.51 (95% CI 1.01-2.26, 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).

Figure 3. Forest plot of the association between pretreatment dNLR and PFS

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

Variables	OS					PFS				
	Number of studies	Pooled HR (95% CI)	P	I2	Ph	Number of studies	Pooled HR (95% CI)	P	I2	Ph
Ethnicity										
Asian	2	1.53(1.18,1.98)	0.001	0.00%	0.56	2	1.57(0.97,2.54)	0.068	85.30%	0.009
European/American	6	1.70(1.47,1.96)	0	35.80%	0.169	5	1.33(1.14,1.55)	0	0.00%	0.431
Sample size										
≤200	4	2.03(1.33,3.09)	0	56.90%	0.073	4	1.67(1.17,2.37)	0.005	0.00%	0.598
> 200	4	1.62(1.42,1.85)	0	0.00%	0.883	3	1.43(1.10,1.85)	0.007	75.40%	0.017
Type of analysis										
Univariable	1	-	-	-	-	1	-	-	-	-
Multivariable	7	1.66(1.46,1.88)	0	24.40%	0.243	6	1.39(1.24,1.56)	0	54.00%	0.054
dNLR cut-off value										
<3	3	1.48(1.15,1.90)	0.002	0.00%	0.568	3	1.51(1.01,2.26)	0.043	71.10%	0.031
≥3	5	1.72(1.49,1.99)	0	37.60%	0.17	4	1.33(1.14,1.55)	0	21.00%	0.284

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.

Figure 4. Funnel plot for analysis of publication bias. (A) Funnel plot established using Begg's test for studies with OS; (B) funnel plot utilising Egger's test for studies with OS. (C) Funnel plot established utilising Begg's test for studies with PFS; (D) funnel plot utilising Egger's test for studies with PFS.

Discussion

This meta-analysis evaluated the results of 2,456 NSCLC patients in 8 studies. The results showed that high level dNLR was a significant predictor of worse OS (HR = 1.65, 95% CI 1.46–1.88; P < 0.001) and PFS (HR = 1.38, 95% CI 1.23–1.55; P < 0.001) of NSCLC patients 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 showed that there was no significant difference in the Asian sample group, but Asian sample subgroup only included 2 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 NSCLC patients treated with ICIs.

Inflammation tends to lead to the development of cancer and stimulates all stages of tumourigenesis through multiple mechanisms.[29] Induction of inflammation can bring increased mutagenesis, leading to collection of mutations in normal tissue that can further cause tumour formation.[30 31] Unlike in earlier stages of oncogenesis, cancer-related inflammation plays a crucial role in regulation of metastasis and leads to worse mortality.[32] 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 anti-tumour agents.[33] Moreover, a peripheral pro-inflammatory 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.[34-36] Novel biomarkers such as NLR, lymphocyte-monocyte ratio (LMR), and lymphocyte-platelet ratio (PLR) have also been used to assess inflammatory status in several cancer types, including NSCLCs.[37-39] In particular, NLR is a well-studied prognostic predictor in NSCLC patients, and some meta-analyses have confirmed the predictive value of NLR in patients with NSCLC.[40 41]

Recent studies indicated that dNLR is a novel serum marker of inflammatory in NSCLC patients treated with ICIs.[17 42] Although some studies have suggested relationships between NLR and survival and therapeutic outcomes in NSCLC patients treated with anti-PD-1 inhibitors,[12 43 44] dNLR may be more strongly linked because it includes monocytes and other granulocytes. Immature or poorly differentiated neutrophils can be released in a pro-inflammatory 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 NSCLC patients 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 NSCLC patients 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 (ROC) 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.

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. 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 NSCLC patients treated with ICIs. Future well-designed and large-scale studies are needed to validate the result.

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None.

Author contributions

ZL and SQ put forward the idea of research. The search strategy was developed and conducted by TY, LH, and XY. LH and XY independently screened the titles and abstracts of all included studies. Data extraction was performed by LH, XY, CL, and GW. TY and LH conducted the meta-analysis. Manuscript was written by TY and CLC.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no competing interests.

Ethical approval

Not applicable.

Patient consent for publication

Not applicable.

Data availability

No additional data available.

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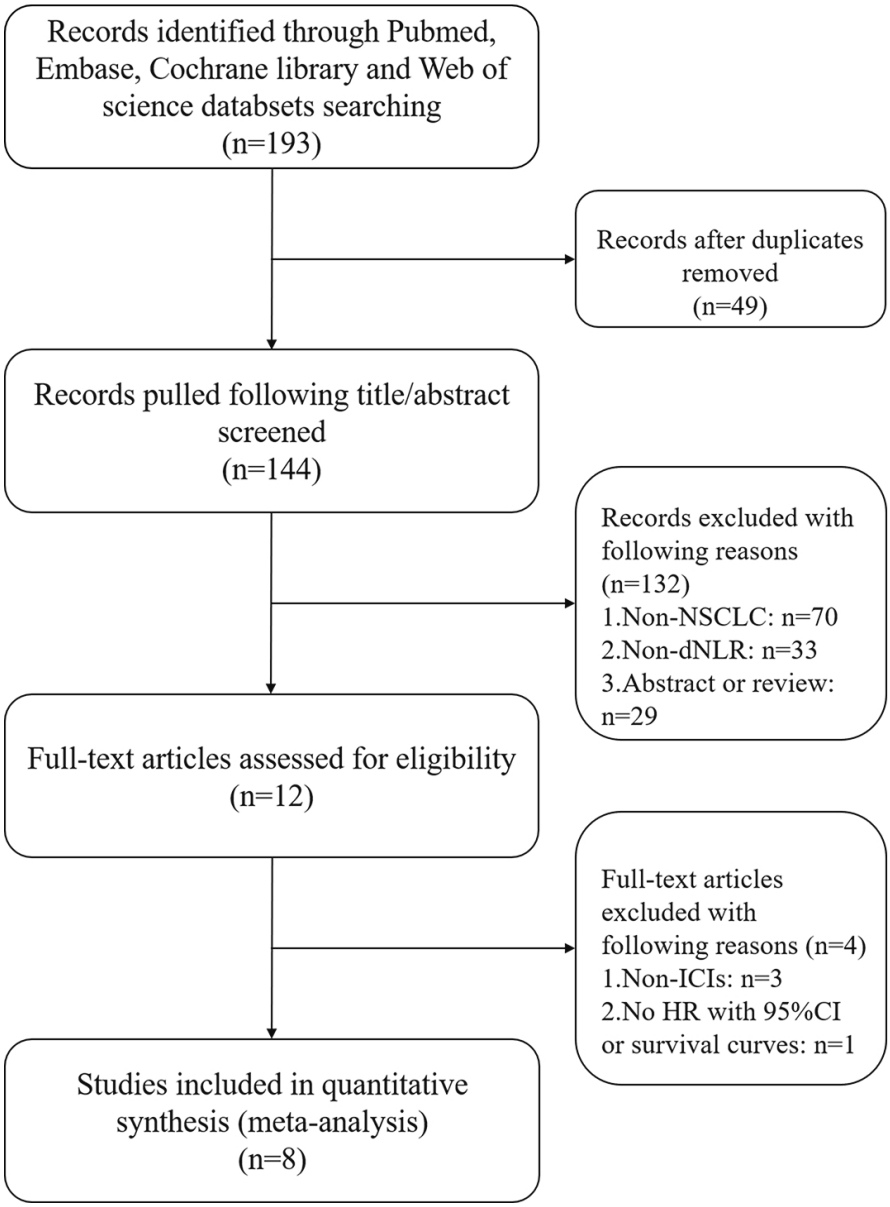

Flow chart of the eligible studies

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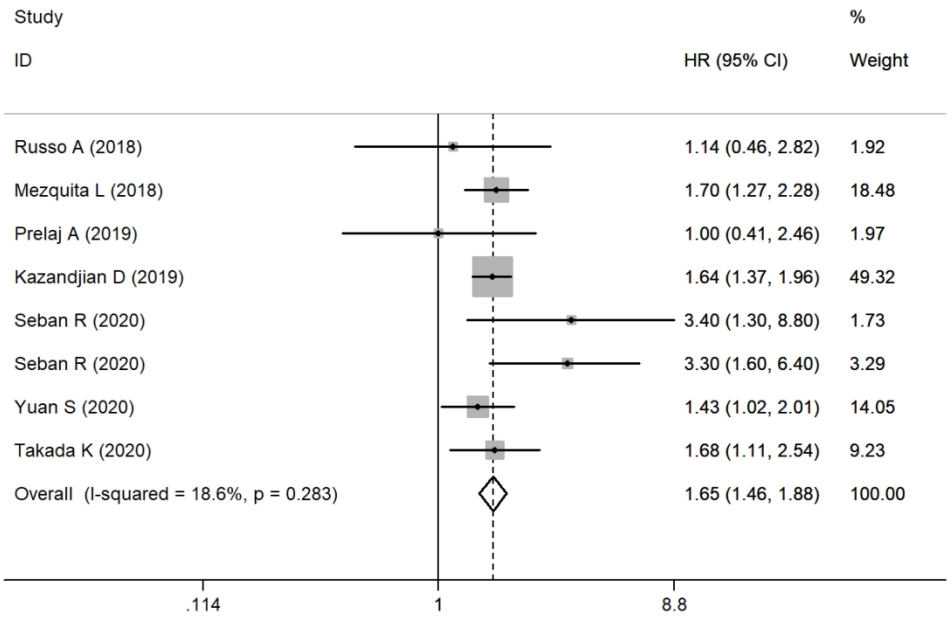

Forest plot of the association between pretreatment dNLR and OS

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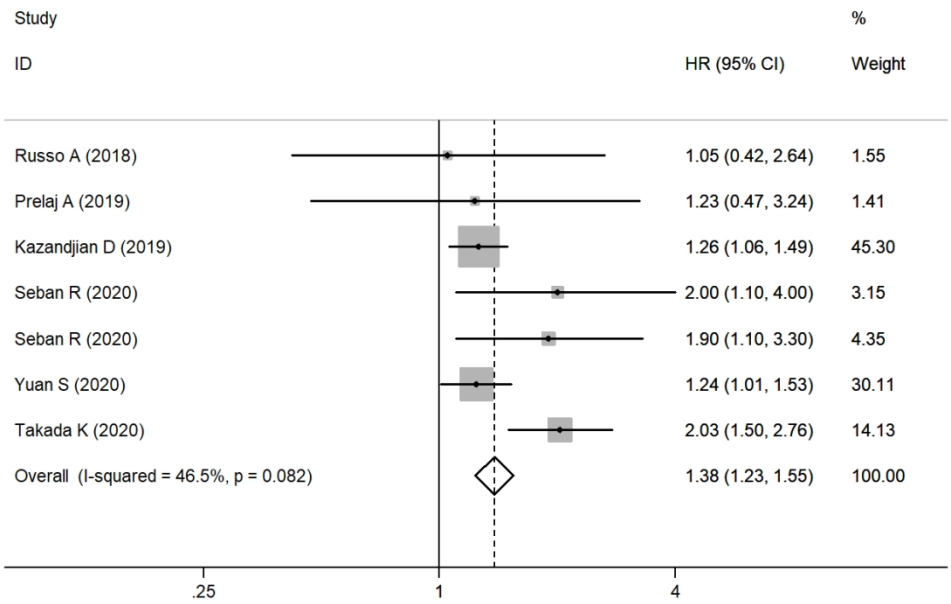

Forest plot of the association between pretreatment dNLR and PFS

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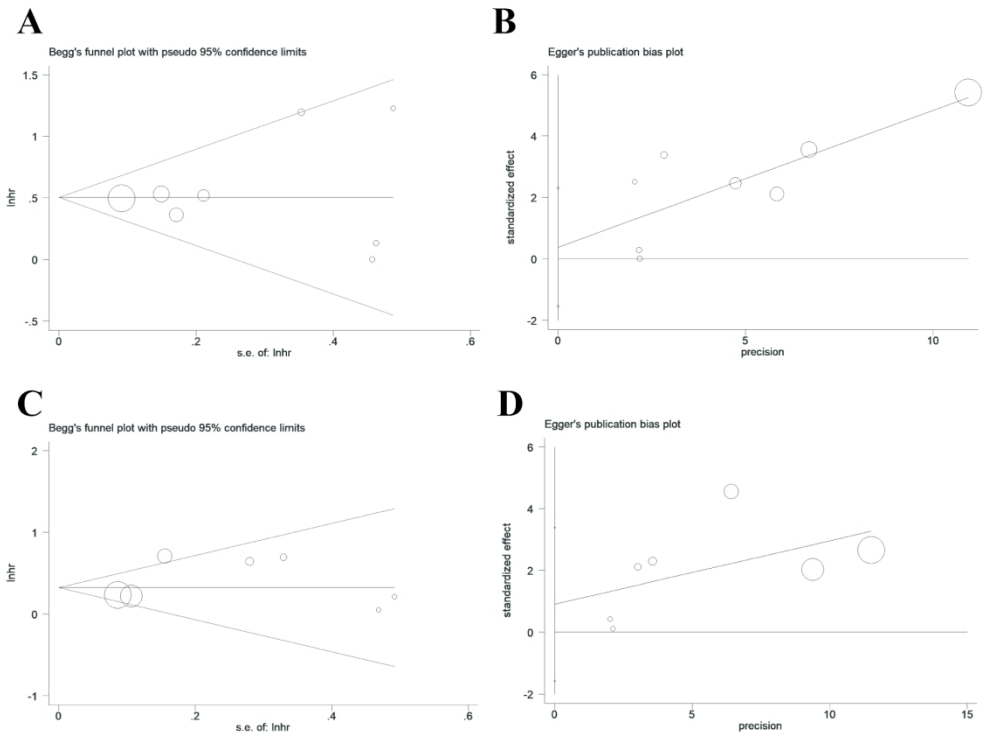

Funnel plot for analysis of publication bias

PRISMA 2020 for Abstracts Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2020 for Abstracts Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Supplementary Table 1 Search strategies for PubMed, Embase, Cochrane Library and Web of science

Database	**Keywords**
PubMed	
#1	"Carcinoma, Non-Small-Cell Lung"[Mesh]
#2	(Carcinoma, Non Small Cell Lung[Title/Abstract]) OR (Carcinomas, Non-Small-Cell Lung[Title/Abstract])) OR (Lung Carcinoma, Non-Small-Cell[Title/Abstract])) OR (Lung Carcinomas, Non-Small-Cell[Title/Abstract])) OR (Non-Small-Cell Lung Carcinomas[Title/Abstract])) OR (Nonsmall Cell Lung Cancer[Title/Abstract])) OR (Non-Small-Cell Lung Carcinoma[Title/Abstract])) OR (Non Small Cell Lung Carcinoma[Title/Abstract])) OR (Carcinoma, Non-Small Cell Lung[Title/Abstract])) OR (Non-Small Cell Lung Cancer[Title/Abstract])
#3	#1 OR #2
#4	(checkpoint*[Title/Abstract]) OR ("checkpoint inhibitor"[Title/Abstract])) OR (CTLA-4[Title/Abstract])) OR (PD-1[Title/Abstract])) OR (PD-L1[Title/Abstract])) OR (ipilimumab[Title/Abstract])) OR (atezolizumab[Title/Abstract])) OR (durvalumab[Title/Abstract])) OR (pembrolizumab[Title/Abstract])) OR (nivolumab[Title/Abstract])) OR (avelumab[Title/Abstract])) OR (tremelimumab[Title/Abstract])
#5	(derived neutrophil-lymphocyte ratio[Title/Abstract]) OR (dNLR[Title/Abstract])) OR (derived neutrophil lymphocyte ratio[Title/Abstract])) OR (derived neutrophil to lymphocyte ratio[Title/Abstract]))
#6	#3 AND #4 AND #5
Embase	
#1	'non small cell lung cancer'/exp
#2	'carcinoma, non small cell lung':ab,ti OR 'carcinomas, non-small-cell lung':ab,ti OR 'lung carcinoma, non-small-cell':ab,ti OR 'lung carcinomas, non-small-cell':ab,ti OR 'non-small-cell lung carcinomas ':ab,ti OR 'non small cell lung cancer:ab,ti OR 'non-small-cell lung carcinoma':ab,ti OR 'non small cell lung carcinoma ':ab,ti OR 'carcinoma, non-small cell lung':ab,ti OR 'non-small cell lung cancer':ab,ti
#3	#1 OR #2
#4	'checkpoint*':ab,ti OR 'checkpoint inhibitor':ab,ti OR 'ctla-4':ab,ti OR 'pd-1':ab,ti OR 'pd-l1':ab,ti OR 'ipilimumab':ab,ti OR 'atezolizumab':ab,ti OR 'durvalumab':ab,ti OR 'pembrolizumab':ab,ti OR 'nivolumab':ab,ti OR 'avelumab':ab,ti OR 'tremelimumab':ab,ti
#5	'derived neutrophil-lymphocyte ratio':ab,ti OR 'dnlr':ab,ti OR 'derived neutrophil lymphocyte ratio':ab,ti OR 'derived neutrophil to lymphocyte ratio':ab,ti
#6	#3 AND #4 AND #5
Cochrane Library	
#1	MeSH: Carcinoma, Non-Small-Cell Lung

#2	(Carcinoma, Non Small Cell Lung):ti,ab,kw OR (Carcinomas, Non-Small-Cell Lung):ti,ab,kw OR (Lung Carcinoma, Non-Small-Cell):ti,ab,kw OR (Lung Carcinomas, Non-Small-Cell):ti,ab,kw OR (Non-Small-Cell Lung Carcinomas):ti,ab,kw OR (Non small Cell Lung Cancer):ti,ab,kw OR (Non-Small-Cell Lung Carcinoma):ti,ab,kw OR (Non Small Cell Lung Carcinoma):ti,ab,kw OR (Carcinoma, Non-Small Cell Lung):ti,ab,kw OR (Non-Small Cell Lung Cancer):ti,ab,kw
#3	#1 OR #2
#4	(checkpoint*):ti,ab,kw OR (checkpoint inhibitor):ti,ab,kw OR (CTLA-4):ti,ab,kw OR (PD-1):ti,ab,kw OR (PD-L1):ti,ab,kw OR (ipilimumab):ti,ab,kw OR (atezolizumab):ti,ab,kw OR (durvalumab):ti,ab,kw OR (pembrolizumab):ti,ab,kw OR (nivolumab):ti,ab,kw OR (avelumab):ti,ab,kw OR (tremelimumab):ti,ab,kw
#5	(derived neutrophil-lymphocyte ratio):ti,ab,kw OR (dNLR):ti,ab,kw OR (derived neutrophil lymphocyte ratio):ti,ab,kw OR (derived neutrophil to lymphocyte ratio):ti,ab,kw
#6	#3 AND #4 AND #5
Web of science	
#1	TS=(Carcinoma, Non-Small-Cell Lung OR Carcinoma, Non Small Cell Lung OR Carcinomas, Non-Small-Cell Lung OR Lung Carcinoma, Non-Small-Cell OR Lung Carcinomas, Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma OR Carcinoma, Non-Small Cell Lung OR Non-Small Cell Lung Cancer)
#2	TS=(checkpoint* OR checkpoint inhibitor OR CTLA-4 OR PD-1 OR PD-L1 OR ipilimumab OR atezolizumab OR durvalumab OR pembrolizumab OR nivolumab OR avelumab OR tremelimumab)
#3	TS=(derived neutrophil-lymphocyte ratio OR Dnlr OR derived neutrophil lymphocyte ratio OR derived neutrophil to lymphocyte ratio)
#4	#1 AND #2 AND #3

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

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Prognostic value of derived neutrophil-to-lymphocyte ratio (dNLR) in non-small cell lung cancer patients 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 NSCLC patients treated with immune checkpoint inhibitors (ICIs) remains inconsistent. The objective of this work was to evaluate the association between pretreatment dNLR and prognosis of NSCLC patients treated with ICIs.

Design: This study followed the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines (supplementary file 1).

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 OS or PFS in NSCLC; 4) hazard ratio (HR) and 95% confidence interval (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 version 12.0 of the Stata statistical software.

Results: This analysis included 8 studies (2,456 cases) on the prognostic utility of dNLR in ICI therapy for NSCLC. The results indicate that higher dNLR significantly predicted poor overall survival (OS) (hazard ratio [HR] = 1.65, 95% confidence interval [CI] 1.46–1.88; $P < 0.001$) and progression-free survival (PFS) (HR = 1.38, 95% CI 1.23–1.55; $P < 0.001$). 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.

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

PROSPERO registration number: CRD42021214034

Keywords: derived neutrophil-to-lymphocyte ratio, immune checkpoint inhibitors, non-small cell lung cancer, meta-analysis

Strengths and limitations of this study

- This is the first study to evaluate the prognostic value of pretreatment dNLR in NSCLC patients who treated with ICIs.
- This meta-analysis may provide novel prognostic guidance for NSCLC patients 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.

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 3 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 five-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 ten years, the application of immune checkpoint inhibitors (ICIs) in the treatment of NSCLC has improved the therapeutic landscape for this intractable disease. PD-1 and PD-L1 inhibitors have shown encouraging results in NSCLC

(Pembrolizumab and Nivolumab, for instance) and they have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced NSCLC[4 5]. The latest phase 3 study showed that nivolumab was demonstrated a superior OS versus docetaxel at 2 years in NSCLC[6]. And a real-life cohort of advanced NSCLC patients treated with pembrolizumab demonstrated similar PFS to the pivotal clinical trial[7]. Some patients with advanced NSCLC have shown overall survival (OS) or progression-free survival (PFS) benefits from ICI treatment after chemoradiotherapy.[8 9]

Despite significant clinical improvements, not all ICI treatments are effective in NSCLC patients. Some valuable biomarkers that predict ICI response, such as programmed cell death-ligand 1 (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 cancer patients which can promote tumour growth and invasion and activate carcinogenic signalling pathways.[11] In 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 NSCLC patients 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 review and Meta-Analyses (PRISMA) guidelines (supplementary file 1). The protocol is registered at PROSPERO (CRD42021214034).

Search strategy and study inclusion

Our meta-analysis was conducted to explore the association between dNLR and prognosis of NSCLC patients 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. (supplementary 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) hazard ratio (HR) and 95% confidence interval (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; (3) duplicate publications; (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 9 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 NSCLC patients 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 utilised. 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 version 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 2,456 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 2 studies were Asian[21 22] and in the other 6 were European or American.[17 23-27] HRs and 95% CIs were reported exactly in 7 studies,[21-27] 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.[28] The calculation formula is as

follows:

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

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

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

This study[17] computed HRs using univariable analysis and the other 7 studies applied multivariable analysis.[21-27] Four of the study cohorts[17 23-25] enrolled <200 patients and 4 cohorts[21 22 26 27] 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 2 studies did not clearly report stage.[17 21] All studies investigated the associations of dNLR and OS, and 7 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.

Figure 1. Flow chart of the eligible studies

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 A[17]	2018	Italy	European	69(47-78)	28	Nivo	3	NA	U	17
Mezquita L	2018	France	European	NA	305	NA	3	IV	M	12
Prelaj A[23]	2019	Italy	European	67(31-86)	154	Nivo/Pembro	2.2	IIIb-IV	M	NA
Kazandjian D[27]	2019	USA	America	NA	1368	NA	3	IV	M	NA
Seban R[24]	2020	France	European	65(37-86)	63	Pembro	3	IIIb-IV	M	13.4
Seban R[25]	2020	France	European	61.9(34.2-84.8)	109	Nivo/Pembro/Atezo	3	III-IV	M	11.6
Yuan S[22]	2020	China	Asian	66(57-69)	203	Pembro/Nivo/Tori/Sinti/Cam/Tis	2.35	IIIb-IV	M	NA
Takada K[21]	2020	Japan	Asian	66(31-88)	226	Nivo/Pembro	2.79	NA	M	13.8

NA: not available; Nivo: nivolumab; Pembro: pembrolizumab; Atezo: atezolizumab; Crizo: crizotinib; Sinti: sintilizumab; Tori: toripalimab; Cam: camrelizumab; Tis: tislelizumab; U: univariable; M: multivariable

Table 2. Quality assessment of included studies

Studies	Representativeness of population	Non-respondents	Ascertainment of the 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 A 2018	☆	☆	☆	☆	☆–	☆	☆	☆	8
Mezquita L 2018	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Prelaj A 2019	☆	☆	☆	☆	☆☆	☆	–	☆	8
Kazandjian D 2019	☆	☆	☆	☆	☆☆	☆	–	☆	8
Seban R 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Seban R 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Yuan S 2020	☆	☆	☆	☆	☆☆	☆	–	☆	8
Takada K 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9

☆represents the score of the study in this item. –, no star in this item.

Association between pretreatment dNLR and OS in NSCLC

Eight studies with 2,456 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%~61.4%)], P = 0.283). Our pooled result indicated that elevated pretreatment dNLR predicted a worse outcome for OS (HR = 1.65, [95% CI (1.46~1.88)]; 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 (1.18~1.98)]; P = 0.001) for Asian patients and 1.70 ([95% CI (1.47~1.96)]; 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 (1.42~1.85)]; P < 0.001) and the small sample size group (HR: 2.03, 95% CI 1.33~3.09; 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 (1.49~1.99)], P < 0.001) for cut-off value ≥ 3 and 1.48 ([95% CI (1.15~1.90)], P = 0.002) for cut-off value < 3. Subgroup analysis was conducted using univariable and multivariable analysis (Table 3).

Figure 2. Forest plot of the association between pretreatment dNLR and OS

Association between pretreatment dNLR and PFS in NSCLC

Seven studies including 2,151 patients were finally selected for analysis of the association between pretreatment dNLR and PFS. A fixed effects model was adopted due to I^2=46.5% [95% CI (-27.0%~77.4%)] and P=0.082. The results demonstrated that high pretreatment dNLR was significantly associated with poorer PFS (HR = 1.38, [95% CI (1.23~1.55)]; 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 (1.14~1.55)]; P < 0.001), but in Asian dNLR and PFS have no significant relationship (HR = 1.57, [95% CI (0.97~2.54)]; P = 0.068). In the small sample size group, the pooled HR

was 1.67 ([95% CI (1.17~2.37)]; P = 0.005), and in the large sample size group the HR was 1.43 ([95% CI (1.10~1.85)]; P = 0.007). Subgroup analyses by cut-off value of dNLR showed that the pooled HR was 1.33 ([95% CI (1.14~1.55)], P < 0.001) for cutoff value ≥ 3 and 1.51 ([95% CI (1.01~2.26)], 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).

Figure 3. Forest plot of the association between pretreatment dNLR and PFS

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

Variables	OS					PFS				
	Number of studies	Pooled HR (95% CI)	P	I2	Ph	Number of studies	Pooled HR (95% CI)	P	I2	Ph
Ethnicity										
Asian	2	1.53(1.18,1.98)	0.001	0.00%	0.56	2	1.57(0.97,2.54)	0.068	85.30%	0.009
European/American	6	1.70(1.47,1.96)	0	35.80%	0.169	5	1.33(1.14,1.55)	0	0.00%	0.431
Sample size										
≤200	4	2.03(1.33,3.09)	0	56.90%	0.073	4	1.67(1.17,2.37)	0.005	0.00%	0.598
> 200	4	1.62(1.42,1.85)	0	0.00%	0.883	3	1.43(1.10,1.85)	0.007	75.40%	0.017
Type of analysis										
Univariable	1	-	-	-	-	1	-	-	-	-
Multivariable	7	1.66(1.46,1.88)	0	24.40%	0.243	6	1.39(1.24,1.56)	0	54.00%	0.054
dNLR cut-off value										
<3	3	1.48(1.15,1.90)	0.002	0.00%	0.568	3	1.51(1.01,2.26)	0.043	71.10%	0.031
≥3	5	1.72(1.49,1.99)	0	37.60%	0.17	4	1.33(1.14,1.55)	0	21.00%	0.284

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.

Figure 4. Funnel plot for analysis of publication bias. (A) Funnel plot established using Begg's test for studies with OS; (B) funnel plot utilising Egger's test for studies with OS. (C) Funnel plot established utilising Begg's test for studies with PFS; (D) funnel plot utilising Egger's test for studies with PFS.

Discussion

This meta-analysis evaluated the results of 2,456 NSCLC patients in 8 studies. The results showed that high level dNLR was a significant predictor of worse OS (HR = 1.65, [95% CI (1.46~1.88)]; P < 0.001) and PFS (HR = 1.38, [95% CI (1.23~1.55)]; P < 0.001) of NSCLC patients 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 showed that there was no significant difference in the Asian sample group, but Asian sample subgroup only included 2 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 NSCLC patients treated with ICIs.

Inflammation tends to lead to the development of cancer and stimulates all stages of tumourigenesis through multiple mechanisms.[29] Induction of inflammation can bring increased mutagenesis, leading to collection of mutations in normal tissue that can further cause tumour formation.[30 31] Unlike in earlier stages of oncogenesis, cancer-related inflammation plays a crucial role in regulation of metastasis and leads to worse mortality.[32] 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 anti-tumour agents.[33] Moreover, a peripheral pro-inflammatory 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.[34-36] Novel biomarkers such as NLR, lymphocyte-monocyte ratio (LMR), and lymphocyte-platelet ratio (PLR) have also been used to assess inflammatory status in several cancer types, including NSCLCs.[37-39] In particular, NLR is a well-studied prognostic predictor in NSCLC patients, and some meta-analyses have confirmed the predictive value of NLR in patients with NSCLC.[40 41]

Recent studies indicated that dNLR is a novel serum marker of inflammatory in NSCLC patients treated with ICIs.[17 42] Although some studies have suggested relationships between NLR and survival and therapeutic outcomes in NSCLC patients treated with anti-PD-1 inhibitors,[12 43 44] dNLR may be more strongly linked because it includes monocytes and other granulocytes. Immature or poorly differentiated neutrophils can be released in a pro-inflammatory 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 NSCLC patients 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 NSCLC patients 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 (ROC) 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 NSCLC patients treated with ICIs. Future well-designed and large-scale studies are needed to validate the result.

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None.

Author contributions

ZL and SQ put forward the idea of research. The search strategy was developed and conducted by TY, LH, and XY. LH and XY independently screened the titles and abstracts of all included studies. Data extraction was performed by LH, XY, CL, and

GW. TY and LH conducted the meta-analysis. Manuscript was written by TY and CLC.

Funding

None.

Compliance with ethical standards

Conflict of interest

The authors declare that they have no competing interests.

Ethical approval

Not applicable.

Patient consent for publication

Not applicable.

Data availability

No additional data available.

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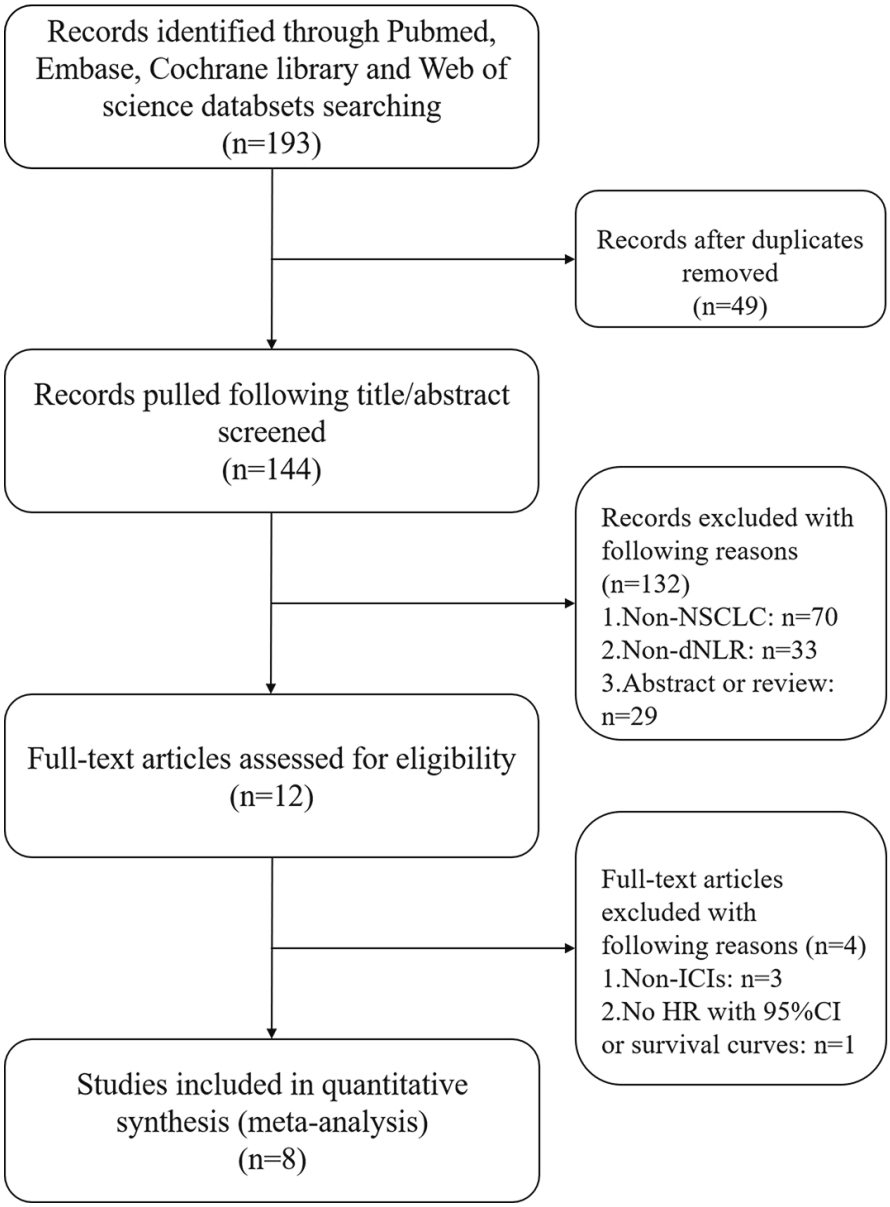

Flow chart of the eligible studies

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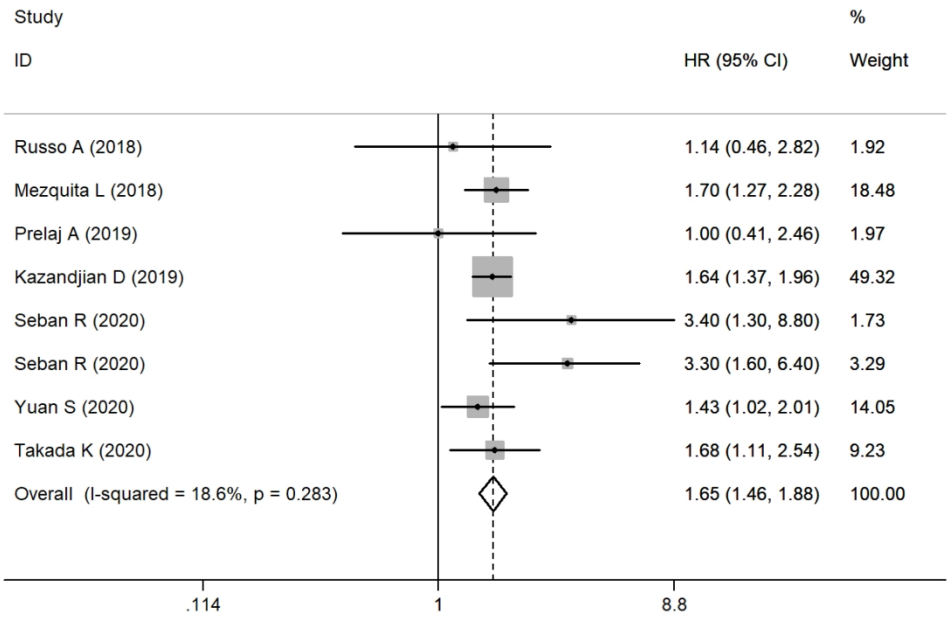

Forest plot of the association between pretreatment dNLR and OS

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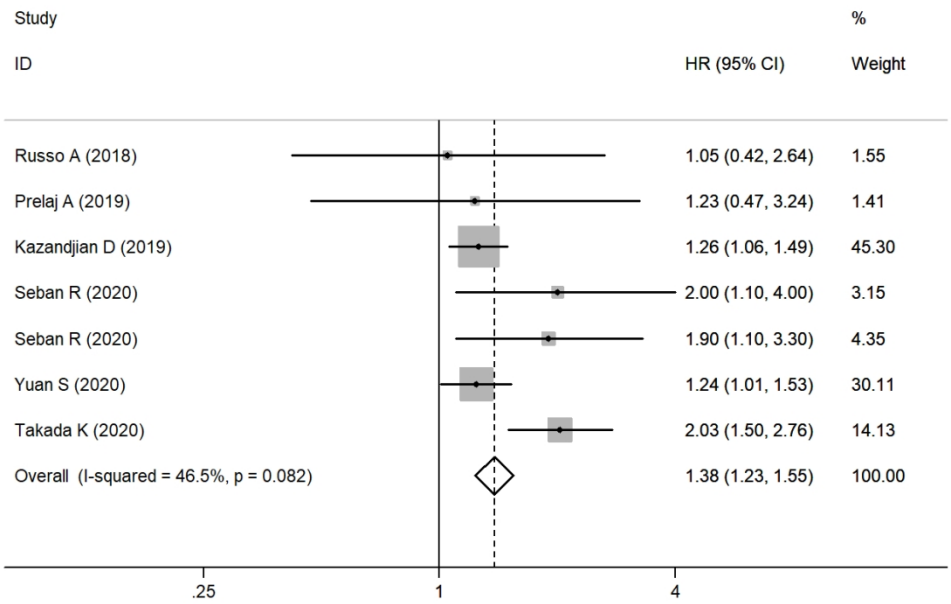

Forest plot of the association between pretreatment dNLR and PFS

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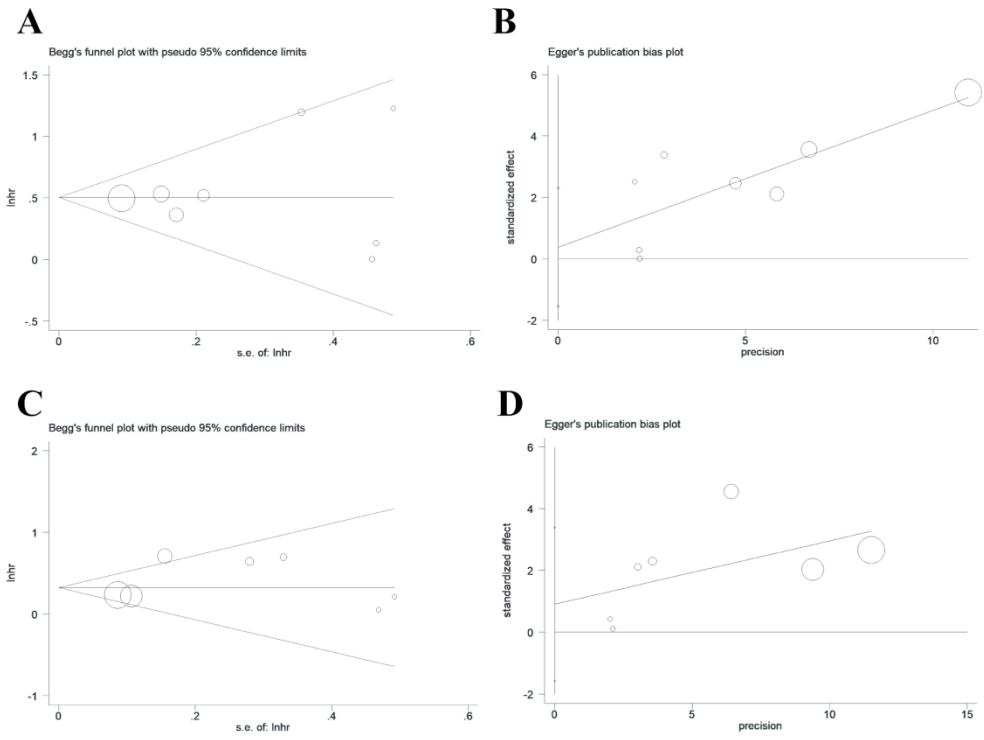

Funnel plot for analysis of publication bias

PRISMA 2020 for Abstracts Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2020 for Abstracts Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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Supplementary Table 1 Search strategies for PubMed, Embase, Cochrane Library and Web of science

Database	**Keywords**
PubMed	
#1	"Carcinoma, Non-Small-Cell Lung"[Mesh]
#2	(Carcinoma, Non Small Cell Lung[Title/Abstract]) OR (Carcinomas, Non-Small-Cell Lung[Title/Abstract])) OR (Lung Carcinoma, Non-Small-Cell[Title/Abstract])) OR (Lung Carcinomas, Non-Small-Cell[Title/Abstract])) OR (Non-Small-Cell Lung Carcinomas[Title/Abstract])) OR (Nonsmall Cell Lung Cancer[Title/Abstract])) OR (Non-Small-Cell Lung Carcinoma[Title/Abstract])) OR (Non Small Cell Lung Carcinoma[Title/Abstract])) OR (Carcinoma, Non-Small Cell Lung[Title/Abstract])) OR (Non-Small Cell Lung Cancer[Title/Abstract])
#3	#1 OR #2
#4	(checkpoint*[Title/Abstract]) OR ("checkpoint inhibitor"[Title/Abstract])) OR (CTLA-4[Title/Abstract])) OR (PD-1[Title/Abstract])) OR (PD-L1[Title/Abstract])) OR (ipilimumab[Title/Abstract])) OR (atezolizumab[Title/Abstract])) OR (durvalumab[Title/Abstract])) OR (pembrolizumab[Title/Abstract])) OR (nivolumab[Title/Abstract])) OR (avelumab[Title/Abstract])) OR (tremelimumab[Title/Abstract])
#5	(derived neutrophil-lymphocyte ratio[Title/Abstract]) OR (dNLR[Title/Abstract])) OR (derived neutrophil lymphocyte ratio[Title/Abstract])) OR (derived neutrophil to lymphocyte ratio[Title/Abstract]))
#6	#3 AND #4 AND #5
Embase	
#1	'non small cell lung cancer'/exp
#2	'carcinoma, non small cell lung':ab,ti OR 'carcinomas, non-small-cell lung':ab,ti OR 'lung carcinoma, non-small-cell':ab,ti OR 'lung carcinomas, non-small-cell':ab,ti OR 'non-small-cell lung carcinomas ':ab,ti OR 'non small cell lung cancer:ab,ti OR 'non-small-cell lung carcinoma':ab,ti OR 'non small cell lung carcinoma ':ab,ti OR 'carcinoma, non-small cell lung':ab,ti OR 'non-small cell lung cancer':ab,ti
#3	#1 OR #2
#4	'checkpoint*':ab,ti OR 'checkpoint inhibitor':ab,ti OR 'ctla-4':ab,ti OR 'pd-1':ab,ti OR 'pd-l1':ab,ti OR 'ipilimumab':ab,ti OR 'atezolizumab':ab,ti OR 'durvalumab':ab,ti OR 'pembrolizumab':ab,ti OR 'nivolumab':ab,ti OR 'avelumab':ab,ti OR 'tremelimumab':ab,ti
#5	'derived neutrophil-lymphocyte ratio':ab,ti OR 'dnlr':ab,ti OR 'derived neutrophil lymphocyte ratio':ab,ti OR 'derived neutrophil to lymphocyte ratio':ab,ti
#6	#3 AND #4 AND #5
Cochrane Library	
#1	MeSH: Carcinoma, Non-Small-Cell Lung

#2	(Carcinoma, Non Small Cell Lung):ti,ab,kw OR (Carcinomas, Non-Small-Cell Lung):ti,ab,kw OR (Lung Carcinoma, Non-Small-Cell):ti,ab,kw OR (Lung Carcinomas, Non-Small-Cell):ti,ab,kw OR (Non-Small-Cell Lung Carcinomas):ti,ab,kw OR (Non small Cell Lung Cancer):ti,ab,kw OR (Non-Small-Cell Lung Carcinoma):ti,ab,kw OR (Non Small Cell Lung Carcinoma):ti,ab,kw OR (Carcinoma, Non-Small Cell Lung):ti,ab,kw OR (Non-Small Cell Lung Cancer):ti,ab,kw
#3	#1 OR #2
#4	(checkpoint*):ti,ab,kw OR (checkpoint inhibitor):ti,ab,kw OR (CTLA-4):ti,ab,kw OR (PD-1):ti,ab,kw OR (PD-L1):ti,ab,kw OR (ipilimumab):ti,ab,kw OR (atezolizumab):ti,ab,kw OR (durvalumab):ti,ab,kw OR (pembrolizumab):ti,ab,kw OR (nivolumab):ti,ab,kw OR (avelumab):ti,ab,kw OR (tremelimumab):ti,ab,kw
#5	(derived neutrophil-lymphocyte ratio):ti,ab,kw OR (dNLR):ti,ab,kw OR (derived neutrophil lymphocyte ratio):ti,ab,kw OR (derived neutrophil to lymphocyte ratio):ti,ab,kw
#6	#3 AND #4 AND #5
Web of science	
#1	TS=(Carcinoma, Non-Small-Cell Lung OR Carcinoma, Non Small Cell Lung OR Carcinomas, Non-Small-Cell Lung OR Lung Carcinoma, Non-Small-Cell OR Lung Carcinomas, Non-Small-Cell OR Non-Small-Cell Lung Carcinomas OR Non small Cell Lung Cancer OR Non-Small-Cell Lung Carcinoma OR Non Small Cell Lung Carcinoma OR Carcinoma, Non-Small Cell Lung OR Non-Small Cell Lung Cancer)
#2	TS=(checkpoint* OR checkpoint inhibitor OR CTLA-4 OR PD-1 OR PD-L1 OR ipilimumab OR atezolizumab OR durvalumab OR pembrolizumab OR nivolumab OR avelumab OR tremelimumab)
#3	TS=(derived neutrophil-lymphocyte ratio OR Dnlr OR derived neutrophil lymphocyte ratio OR derived neutrophil to lymphocyte ratio)
#4	#1 AND #2 AND #3