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Clinical value of neutrophil-to-lymphocyte ratio in patients with non-small-cell lung cancer treated with PD-1/PD-L1 inhibitors

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ABSTRACT

Introduction: There is unmet need to explore the predictive biomarkers of PD-1/PD-L1 inhibitors in patients with non-small-cell lung cancer (NSCLC). Here, we aimed to investigate the predictive and prognostic value of blood neutrophil-to-lymphocyte ratio (NLR) in NSCLC patients treated with PD-1/PD-L1 inhibitors.

Methods: We performed a comprehensive online search to explore the association between blood NLR and overall survival (OS) or progression-free survival (PFS) in NSCLC patients received PD-1/PD-L1 inhibitors. Published data including hazard ratios (HRs) and 95% confidence interval (CI) were eligible. Pooled estimates of treatment outcomes were calculated using Stata/MP 14.1.

Results: 1700 patients from sixteen studies were included. The pooled results suggested that high blood NLR was correlated with significantly shorter OS (HR = 2.07, $P < 0.001$) and PFS (HR = 1.59, $P < 0.001$). The predictive and prognostic significance of blood NLR were observed consistently across most subgroups including publication year, study design, research region, PD-L1 expression detection, sample size, NLR cutoff, median follow-up time and study quality score. Additionally, there was a significant correlation between elevated NLR cutoff values and OS benefit ($r = 0.585$, $P = 0.036$) but not for PFS benefit ($r = 0.198$, $P = 0.496$). Notably, HRs of PFS showed significant correlation with HRs of OS ($r = 0.686$, $P = 0.041$).

Conclusion: Elevated blood NLR was associated with shorter PFS and OS in NSCLC patients treated with PD-1/PD-L1 inhibitors, suggesting its potential predictive and prognostic value in this clinical scenario.

1. Introduction

Immunotherapy targeting programmed cell death 1 (PD-1) and its ligand (PD-L1) has revolutionized the treatment landscape and therapeutic paradigms of advanced or metastatic non-small-cell lung cancer (NSCLC) [1,2]. Durable responses can be observed in these populations though the percentage was often found lower than 20% [3,4]. Currently, there are several promising biomarkers including PD-L1 expression, tumor mutational burden (TMB), gene expression signatures, and so on [5], in advanced or metastatic NSCLC. For patients with tumor proportion score (TPS) of PD-L1 expression $> 50\%$, pembrolizumab monotherapy showed the significantly longer progression-

free survival (PFS) and higher objective response rate (ORR) than platinum-doublet chemotherapy, which has been recommended in the first-line setting [6,7]. However, the proportion of these patients was only found at around 30% [8]. Additionally, another significant biomarker, named TMB, has shown to be associated with PFS benefit in patients with stage IV or recurrent NSCLC received nivolumab plus ipilimumab [9]. However, a recent updated descriptive analysis suggested that patients with high TMB received nivolumab plus ipilimumab did not have the significant overall survival (OS) benefit than those received chemotherapy. Collectively, these results suggest that there is unmet need to investigate the predictive biomarkers of PD-1/PD-L1 inhibitors to optimize patient benefit.

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Accumulating evidence indicated that tumor-associated inflammation plays a critical role in the host immune response to malignancies and could be applied to cancer immunotherapy [10–12]. Several inflammatory mediators and the measurable parameters of systemic inflammatory response including neutrophil-to-lymphocyte ratio (NLR), albumin, and C-reactive protein (CRP) were used to predict the therapeutic effect or outcomes in patients with various solid tumors. NLR, defined as neutrophil counts divided by lymphocyte counts, is a marker for the general immune response to distinct stress stimuli [13]. Recent publications reported that peripheral neutrophil counts measured by the NLR has been found to be directly associated with the intratumor neutrophil population, which could impair the antitumor immune response [14,15]. Theoretically, lymphopenia reflects the impaired cell-mediated immunity, whereas neutrophilia represents the response to systematic inflammation [16]. Therefore, elevated NLR would be associated with poor response to immunotherapy including PD-1/PD-L1 inhibitors in patients with advanced cancers. Although several studies investigated the predictive value of blood NLR in patients with NSCLC treated with PD-1/PD-L1 inhibitors, the inconsistent results together with retrospective design and small sample size could not provide the reliable evidence to the predictive and prognostic significance of NLR in this clinical scenario.

Considering the heterogeneous results and potential value of NLR detection, we conducted this meta-analysis to systematically and comprehensively investigate the predictive and prognostic significance of blood NLR for NSCLC patients received PD-1/PD-L1 inhibitors. The pooled results would be useful on daily clinical practice and help physicians to stratify patients in future clinical trials of anti-PD-1/PD-L1 treatment.

2. Methods

2.1. Search strategy

We conducted a comprehensive online search to screen the potential studies on PubMed, Embase, and Cochrane Library up to October 1st, 2018 without language restrictions. The main keywords used for the online search were “lung neoplasms”, “lung tumor,” “lung cancer,” “neutrophil,” “lymphocyte,” “neutrophil-to-lymphocyte ratio,” “neutrophil to lymphocyte ratio,” “checkpoint inhibitor,” “PD-1” and “PD-L1.” The full online search strategies were shown in Supplementary Text S1. Conference abstracts from annual meeting of the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the World Lung Cancer Conference (WCLC) were searched to screen unpublished studies. We also manually examined the references of the each screened study until no additional articles could be added.

2.2. Exclusion and inclusion criteria

The following items were the inclusion criteria for each eligible publication: (1) studies investigated the patients with NSCLC treated with PD-1/PD-L1 inhibitor (i.e. nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab); (2) studies reported the predictive and/or prognostic value of both pretreatment and posttreatment NLR; (3) data were reported for OS and/or PFS and related hazard ratio (HR) with 95% confidence interval (CI); (4) if two or more studies used the same population, only the study with the largest sample size and latest information was included; (5) if univariate and multivariate analysis results were simultaneously reported, only multivariate analysis results were extracted; (6) the full text was available. Publications were excluded if they were case reports, reviews or systematic reviews, comments, editorials, letters, cost effectiveness analyses, quality of life studies, early versions of data later published, or articles unrelated with our topics were excluded. Firstly, the titles and abstracts were screened to assess the eligibility and then the full text of articles were reviewed.

According to the inclusion and exclusion criteria, two reviewers carried out the selection of all included studies independently. Discrepancies were settled by discussion and consensus.

2.3. Quality assessment

According to the previous reports [17,18], two authors independently assessed the risk of bias of the each included study via using a set of modified predefined criteria (Supplemental Table S1): (1) Representativeness of population; (2) Non exposed cohort; (3) Ascertainment of exposure; (4) Outcome not present at beginning of study; (5) Appropriate confounding measurement and account; (6) Sufficient measurement of outcomes; (7) Completeness of follow-up. Publication with a quality score > 7 were considered as high quality and with a quality score of less than 7 defining low quality. Any disagreement was resolved by discussion and consensus.

2.4. Data extraction

Two authors independently conducted the data extraction on the basis of Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA) by using a standardized data collection form. The following items (Table 1) were extracted from each eligible study: first author's name, published year, inclusion period, study design, country of origin, total patients, median ages, number of female, number of ever/current smoker, number of Eastern Cooperative Oncology Group performance status (ECOG PS) < 2, number of squamous cell carcinoma, number of liver metastases, percentage of positive PD-L1 expression, cutoff value of NLR, time of NLR assessment, follow-up period and study quality score. Two authors also independently extracted the HRs and the related 95% CIs for OS and PFS outcomes to evaluated the therapeutic efficacy. Where available, we included the most updated survival data.

2.5. Statistical analysis

We tested the heterogeneity of different studies by using the Cochran's Q test. For time-to-event data, the HRs with 95% CIs were directly extracted from the research article or calculated using previously published methods proposed by Tierney et al. [19]. We calculated the I^2 to assess the extent of variability attributable to statistical heterogeneity across studies. $I^2 < 25\%$ and $P > 0.10$ were interpreted as signifying low-level heterogeneity. When there was no statistically significant heterogeneity, a pooled effect was calculated with a fixed-effects model; otherwise, a random-effect model was used. The heterogeneity between subgroup was calculated by using meta-regression analysis. OS was calculated from the date of initial diagnosis to the time of death from any cause or was censored at the last follow-up. PFS was defined as the time from the date of PD-1/PD-L1 inhibitors treatment initiation to the date of progression or death or was censored at the last tumor assessment. The pooled estimates of OS and PFS were calculated using effect variables. Publication bias was assessed by visual inspection of a funnel plot, Begg's and Egger's tests. A sensitivity analysis was conducted by excluding the studies with the low-quality score. Subgroup analysis was conducted to explore the effect of multiple factors on the predictive and prognostic value of NLR. The selected subgroups were publication year, study design research region, PD-L1 expression detection, sample size, NLR cutoff, median follow-up time and study quality score. P values were two-sided and considered significant if less than 0.05. All data were analyzed using the Statistical Package for Social Sciences (SPSS) software (version 20.0 for Windows). Meta-analyses were performed using Stata/MP 14.1.

Table 1
Baseline features of included studies (N = 17).

Authors	Year	Inclusion period	Study design	Time of detection	Country of origin	Total cases	Age (years)	Female (%)	Ever/current smoker (%)	ECOG PS < 2 (%)	Squamous cell carcinoma (%)	Liver metastases (%)	PD-L1 expression (%)	NLR cutoff	Median Follow-up (months)	Drugs	Quality score
Soyano et al.	2017	NR	Retrospective	Pretreatment	USA	52	NR	NR	NR	NR	NR	NR	NR	4.59	13.6	Nivolumab or pembrolizumab	6
Rogado et al.	2017	2015–2017	Retrospective	Pretreatment	European	40	67	NR	NR	NR	NR	NR	NR	5	NR	Nivolumab	6
Bagley et al.	2017	2015–2016	Retrospective	Pretreatment	USA	175	68 (33–88)	95 (54)	147 (84)	129 (75)	42 (24)	41 (23)	NR	5	NR	Nivolumab	6
Diem et al.	2017	2015–2016	Retrospective	Pretreatment	European	52	66 (46–88)	23 (44)	48 (92)	36 (69)	18 (35)	17 (33)	13 (54)	5	NR	Nivolumab	6
Park et al. (1)	2017	2015–2017	Retrospective	Pretreatment	USA	159	68 (41–91)	77 (48)	133 (84)	125 (79)	39 (25)	NR	NR	5	11.5	Nivolumab	7
Park et al. (2)	2017	2015–2017	Retrospective	Post-treatment	USA	159	68 (41–91)	77 (48)	133 (84)	125 (79)	39 (25)	NR	NR	5	11.5	Nivolumab	7
Suh et al.	2018	2013–2016	Retrospective	Post-treatment	South Korea	54	68 (43–80)	12 (22)	39 (72)	54 (100)	17 (31)	10 (19)	11 (20)	5	26.2	Nivolumab or pembrolizumab	8
Nakaya et al.	2018	2015–2016	Retrospective	Post-treatment	Japan	101	69 (45–84)	78 (77)	85 (84)	85 (84)	37 (37)	NR	NR	3	NR	Nivolumab	6
Shirayama et al.	2018	2015–2016	Retrospective	Pretreatment	Japan	201	68 (27–87)	66 (33)	157 (78)	153 (76)	41 (20)	NR	NR	4	12.4	Nivolumab	7
Mezquita et al.	2018	2012–2017	Retrospective	Pretreatment	European	466	62 (29–86)	165 (35)	422 (90)	405 (87)	159 (34)	94 (20)	96 (74)	3	12.8	nivolumab, pembrolizumab, atezolizumab, durvalumab	9
Putzu et al.	2018	NR	Retrospective	Pretreatment	European	78	67	12 (15)	74 (95)	NR	69 (63)	NR	3/11 (27)	4.4	11	Nivolumab	7
Fukui et al.	2018	2016–2017	Prospective	Pretreatment	Japan	52	69 (46–83)	15 (29)	42 (81)	49 (94)	16 (31)	10 (19)	NR	5	10.9	Nivolumab	7
Zer et al.	2018	2013–2016	Retrospective	Pretreatment	European	88	64 (31–81)	45 (51)	67 (76)	NR	15 (17)	NR	34 (39)	4	5.3	Nivolumab or pembrolizumab	7
Facchinetti et al.	2018	2015–2017	Retrospective	Pretreatment	European	54	69 (43–85)	9 (17)	50 (92)	39 (72)	26 (48)	8 (15)	13/23 (67)	4	12.6	Nivolumab	8
Russo et al.	2018	2016–2017	Retrospective	Pretreatment	European	62	68 (45–82)	14 (23)	56 (90)	NR	25 (40)	NR	NR	3	17	Nivolumab	7
Inomata et al.	2018	2016–2018	Retrospective	Pretreatment	Japan	36	NR	9 (25)	31 (86)	23 (64)	16 (44)	NR	14 (39)	5	NR	Nivolumab or pembrolizumab	6
Takeda et al.	2018	2016–2017	Retrospective	Post-treatment	Japan	30	71 (54–83)	11 (37)	26 (87)	24 (80)	9 (30)	NR	10/17 (59)	5	NR	Nivolumab	6

NR, not reported; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death ligand 1; NLR, neutrophil to lymphocyte ratio.

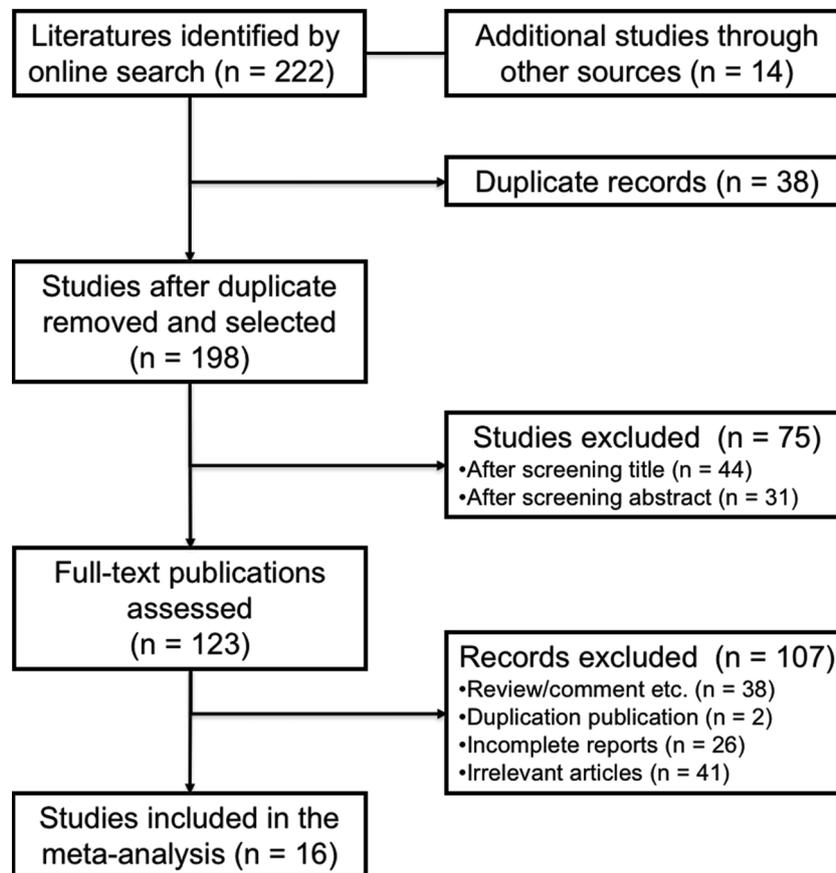


Fig. 1. Flow chart of the eligible studies selection.

3. Results

3.1. Studies online research

In total, we initially identified 236 publications that met the inclusion criteria after searching the online databases; 38 of them were excluded due to duplications. After eligibility screening of the titles and abstracts, we excluded 75 irrelevant articles. We then carefully reviewed the full texts of the remaining 123 papers and 107 articles were excluded due to the various reasons. Finally, 16 studies were chosen for the current meta-analysis [20–35]. Details of the eligible study selection were shown in Fig. 1.

3.2. Study characteristics and quality assessment

A total of 1700 patients with NSCLC treated with PD-1/PD-L1 inhibitors were included. The baseline characteristics of the eligible studies were listed in Table 1. In summary, fifteen recently published retrospective studies and one prospective observational study with different study populations were included. Six studies were conducted in Asia, 4 in America, and 6 in Europe. Nivolumab and pembrolizumab were the main study drugs. Eight studies reported the test results of positive PD-L1 expression with a median percentage 46.5%. Six studies showed the proportion of patients with liver metastases. The most common cut-off value of NLR was 5.0 and median cut-off value was also 5.0. Twelve studies investigated the association between blood NLR and OS for patients with NSCLC, and 12 studies reported PFS outcomes. Notably, two studies recorded the Kaplan-Meier curve of PFS and OS. To avoid the selection bias, we did not extract the HRs with 95% CIs from the reported curves. According to the items of quality assessment, we assessed the included studies using the aspects mentioned above [17]. The results of quality assessment are summarized in Supplemental

Table S1. Seven studies had quality scores of 7 or less, and nine studies had a score of more than 7.

3.3. Overall survival

Twelve studies with 1471 cases were included to analyze the association between NLR and OS. The median OS was significantly longer in low blood NLR than high blood NLR group (16.0 vs. 4.7 months, $P < 0.001$). The pooled result showed that high blood NLR was correlated with significantly shorter OS (HR = 2.07, 95%CI 1.70–2.44, $P < 0.001$; Fig. 2A). Then, we carried out the subgroup analyses across the potential sources of heterogeneity among several clinical parameters (Fig. 3). The pooled results for most subgroups were not markedly changed by the study features together with low-level heterogeneity. However, stratified analysis by NLR cutoff value suggested that higher NLR cutoff seems to be associated with higher HR but it did not reach the statistical significance (NLR cutoff > 5: HR = 2.65, 95%CI 1.87–3.42, $P < 0.001$; NLR cutoff < 5: HR = 1.90, 95%CI 1.48–2.32, $P < 0.001$; $P_{\text{interaction}} = 0.083$), indicating the significantly inferior OS. Both of the pretreatment and posttreatment NLR could well predict the prognosis of NSCLC patients treated with PD-1 /PD-L1 inhibitors (pretreatment: HR = 2.01, 95%CI 1.64–2.39, $P < 0.001$; posttreatment: HR = 3.54, 95%CI 1.66–5.42, $P < 0.001$). Interestingly, there was a high level of statistical heterogeneity for studies with unclear follow-up information ($I^2 = 21.0\%$, $P = 0.283$).

3.4. Progression-free survival

Twelve studies with 1532 cases were included in the final analysis of blood NLR and PFS. Patients with high blood NLR had the significantly shorter PFS than those with low blood NLR than group (1.9 vs. 4.7 months, $P < 0.001$). The pooled result showed that high NLR

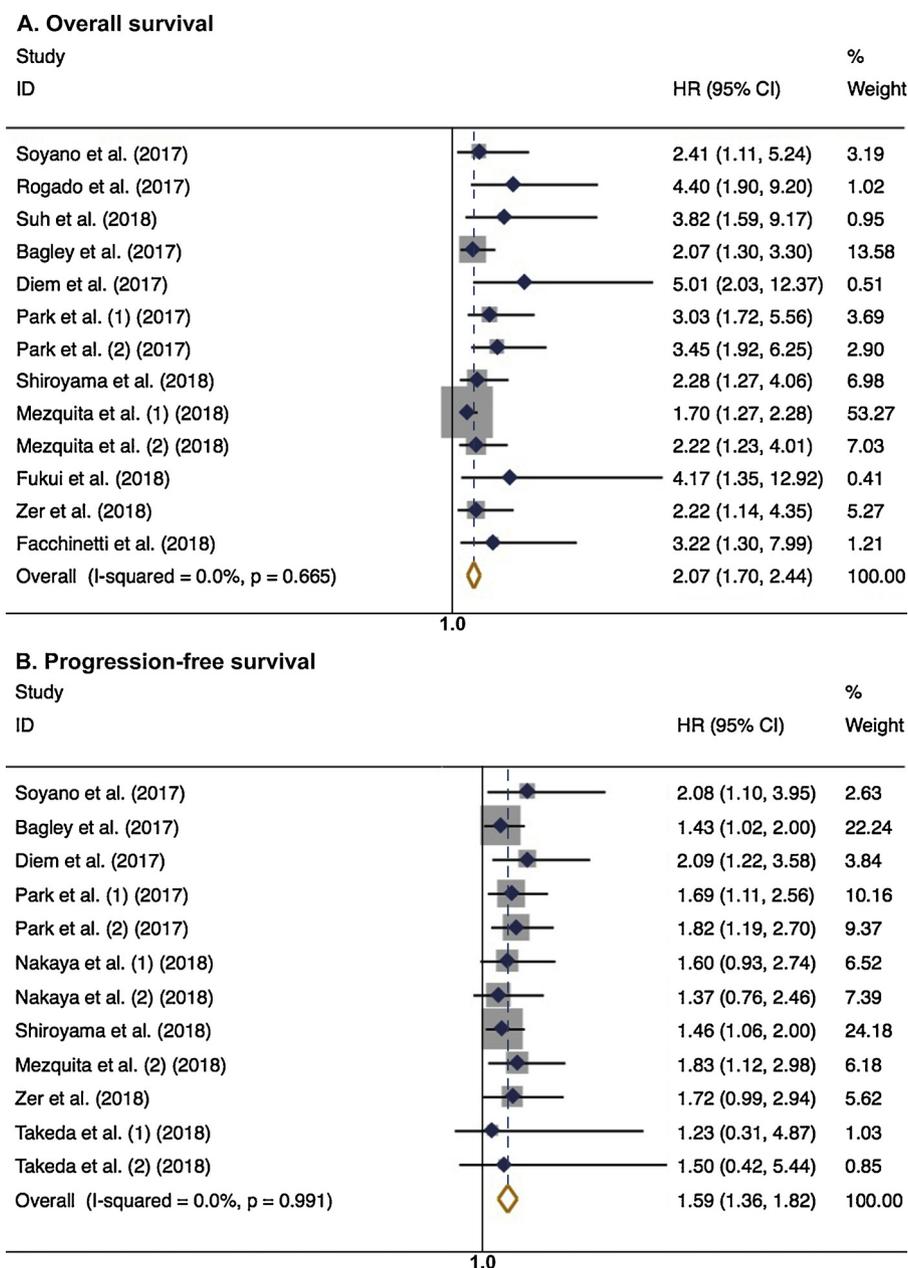


Fig. 2. Meta-analysis of the associations between blood neutrophil-to-lymphocyte ratio and (A) overall survival, (B) progression-free survival.

was associated with significantly poorer PFS (HR = 1.59, 95%CI 1.36–1.82, $P < 0.001$; Fig. 2B). Fig. 4 showed the results of the subgroup analyses by stratifying several published features of the included studies for PFS. The pooled results for most subgroups were not changed by the study parameters together with low-level heterogeneity. There was no statistical significance of HR between distinct NLR cutoffs groups (NLR cutoff > 5 : HR = 1.63, 95%CI 1.29–1.96, $P < 0.001$; NLR cutoff < 5 : HR = 1.57, 95%CI 1.25–1.892, $P < 0.001$; $P_{\text{interaction}} = 0.803$). A similar pooled HR was observed in both the pretreatment and posttreatment NLR groups (pretreatment: HR = 1.60, 95%CI 1.33–1.86, $P < 0.001$; posttreatment: HR = 1.60, 95%CI 1.14–2.06, $P < 0.001$).

3.5. Association between distinct NLR cutoff values and clinical outcome

We then investigated the association between different NLR cutoff values and clinical outcome of those populations. As shown in Supplemental Figure S1, there was a significant association between

elevated NLR cutoff values and increased OS benefit ($r = 0.585$, $P = 0.036$). Although higher NLR cutoff value seemed to be associated with increased HRs of PFS, there was no statistical significance ($r = 0.198$, $P = 0.496$). Interestingly, HRs of PFS showed significant correlation with HRs of OS ($r = 0.686$, $P = 0.041$), suggesting PFS could be a potential surrogate for OS in these study designs (Supplemental Figure S2).

3.6. Publication bias

As shown in Supplemental Figure S3, the funnel plots were almost symmetrical and the test results indicated that no publication bias existed regarding the HRs of OS (Begg's test, $P = 0.067$; Egger's test, $P = 0.103$) or PFS (Begg's test, $P = 0.176$; Egger's test, $P = 0.329$).

4. Discussion

To our knowledge, this is the first meta-analysis to comprehensively

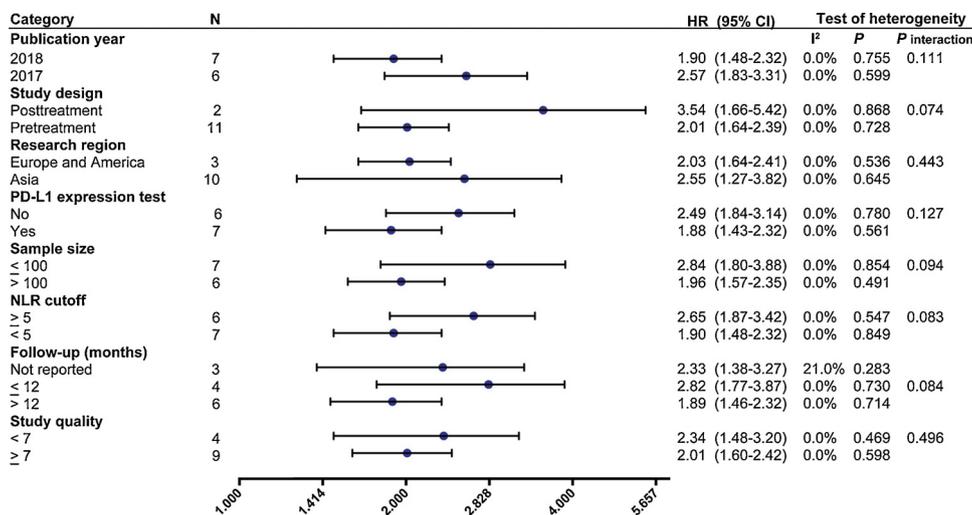


Fig. 3. Subgroup analyses by stratifying several published features of the included studies for overall survival. P for heterogeneity within each subgroup; Pinteraction for heterogeneity between subgroups with meta-regression analysis.

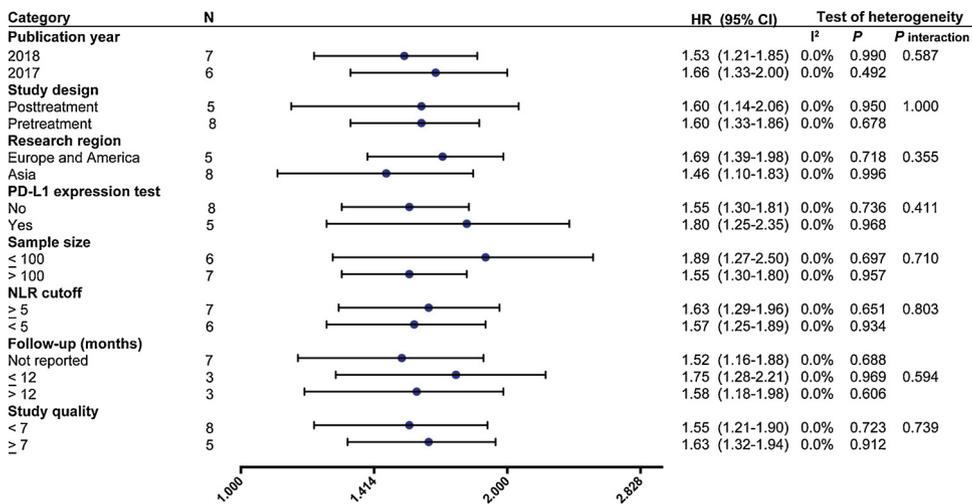


Fig. 4. Subgroup analyses by stratifying several published features of the included studies for progression-free survival.

investigate both predictive and prognostic significance of blood NLR in NSCLC patients treated with anti-PD-1/PD-L1 monotherapy. The current study summarized the published data from sixteen studies with 1700 cases and found that elevated blood NLR was associated with significantly shorter OS and PFS. Subgroup analyses stratified by publication year, study design, research region, PD-L1 expression detection, sample size, NLR cutoff, median follow-up time and study quality scores showed that the main findings remained unchanged. It is worthwhile to mention that higher NLR cutoff was correlated with markedly increased HR of OS. However, there was no correlation between distinct NLR cutoff values and PFS benefit. Intriguingly, HRs of PFS was significantly associated with HRs of OS, indicating PFS would be an alternative endpoint for OS in these trials' design.

To date, there were many studies to evaluate the predictive and prognostic value of blood NLR in patients with various solid tumors received immune checkpoints inhibitors (ICIs) [36–38]. In a recent study, Bilen et al. reported that high baseline NLR value was associated significantly with worse OS and PFS ($P < 0.05$) in 90 patients with advanced cancer who received treatment on phase 1 clinical trials of immunotherapy-based treatment regimens [38]. Moreover, increased NLR value 6 weeks after baseline was associated with shorter OS and PFS ($P < 0.052$). However, to date, there were only two meta-analyses and no one specifically focused on NSCLC. The first study included 17

studies incorporating a total of 2091 patients with different solid tumors [39]. Their results indicated that patients with high pretreatment NLR had significantly poorer OS (HR = 2.26, 95% CI: 1.68–3.03) and PFS (HR = 1.81, 95% CI: 1.36–2.41). Moreover, the results remained constant in sensitivity and subgroup analyses. Another study only included seven studies and 738 patients with four types of tumors (melanoma, NSCLC, renal cell carcinoma and urothelial carcinoma) [40]. Consistently, the pooled results showed high pretreatment NLR resulted in inferior OS (HR = 1.92, 95% CI: 1.29–2.87) and PFS (HR = 1.66, 95% CI: 1.38–2.01) across types of malignancies and all ICIs (ipilimumab, nivolumab and pembrolizumab). However, both studies just investigated the clinical value of pretreatment NLR in various cancers and included both CTLA-4 and PD-1/PD-L1 inhibitors. Whether both pretreatment and posttreatment NLR had the predictive value in NSCLC patients with treated with anti-PD-1/PD-L1 monotherapy remains unknown. In our study, we further demonstrated both the predictive and prognostic value of pretreatment and posttreatment blood NLR in NSCLC patients treated with PD-1/PD-L1 inhibitors. The pooled results suggested that elevated blood NLR was associated with significantly shorter OS and PFS in whole groups, indicating blood NLR was a promising predictive and prognostic biomarker in this clinical scenario. Taken together with previous meta-analyses, strict-designed and prospective clinical studies are needed to validate the prominent role of

blood NLR in NSCLC patients treated with anti-PD-1/PD-L1 monotherapy. Additionally, we conducted the correlation analysis between NLR cutoff value and OS/PFS benefit and found that higher NLR cutoff was correlated with less OS benefit but different NLR cutoffs were not associated with PFS benefit. Similarly, Mei et al. reported that higher cutoff value was associated with worse PFS [17] and our previous study also showed that stratified analysis by NLR cutoff value could significantly increase the HR for OS but not for PFS [41]. However, the optimal NLR cutoff value for patients' selection or stratification remains unknown and further large-scale prospective studies are still warranted.

Although the biological basis of these findings is not thoroughly clear, a series of recent studies give some suggestive explanations. Neutrophils play a significant role in tumor development, progression and metastasis via direct effect on tumor cells or indirect effect on other components of tumor microenvironment by secreting chemokines and cytokines including transforming growth factor-beta, vascular endothelial growth factor, interleukin-6 (IL-6), IL-8 and matrix metalloproteinases [42–44]. Neutrophils can be manipulated to develop different phenotypic and functional polarization states inducing antitumor or protumor effects [45]. Furthermore, a recent study reported that higher count of neutrophil was correlated with decreased CD8⁺ cellular content in NSCLC [46], indicating neutrophilia as an inflammatory response to suppress anti-tumor immune response by inhibiting the cytotoxic activity of immune cells especially activated CD8⁺ T cells [47]. In addition, lymphocytes play a critical role in the anti-tumor immunity and the increased infiltration of lymphocytes in the tumor region has been demonstrated to be associated with better responsiveness to treatment and prognosis in patients with solid tumors [48]. Theoretically, lymphopenia reflects the impaired cell-mediated immune response. NLR, as defined as neutrophil counts divided by lymphocyte counts, was not only an indicator of inflammatory and tumor immune response, but also reflects the extent of local neutrophil and lymphocytes infiltration. Collectively, elevated NLR would be associated with poor response to PD-1/PD-L1 inhibitors in patients with NSCLC due to the systematically impaired antitumor immunity.

Hematological biomarkers are promising predictors of response to ICIs due to its convenience to obtain and readily accessible in daily clinical practice. In addition to blood NLR, other markers from peripheral blood including serum albumin, CRP, lactate dehydrogenase (LDH), and specific subtype immune cells (e.g. frequency of CD14⁺CD16⁻HLA-DR^{hi} monocytes and Ki-67⁺PD-1⁺CD8⁺ T cells) also showed the potential predictive value to ICIs [27,31,49,50]. Importantly, when NLR combined with these peripheral blood markers including serum albumin, CRP and LDH, it shows a stronger prediction of treatment benefit and serves as a more comprehensive indicator of outcomes [27,31]. These results suggested that rational combinations of different hematological biomarkers could help to more precisely identify patients who could benefit from PD-1/PD-L1 inhibitors. Whether it could improve the predictive power when combined NLR with the significant biomarkers including PD-L1 expression, TMB and tumor infiltrating lymphocytes in NSCLC received anti-PD-1/PD-L1 treatment need further investigations.

The current meta-analysis has several limitations that should be acknowledged. Firstly, most of the included studies were retrospective studies together with small sample sizes. Hence the present findings must be interpreted with caution due to the overestimation of the treatment effect in retrospective and smaller studies. Secondly, the eligible studies used distinct values as NLR cutoffs that make direct comparisons difficult. For example, the cutoff value of NLR was 5 in most of studies while other studies utilized 3 or 4 as the cut-off values. Thirdly, although publication bias was not found in this study, we cannot ignore the fact that positive results are preferentially reported. In addition, we identified several meeting abstracts without further detailed publications; herein, we did not include these abstracts in this meta-analysis. Last but not least, the pooled results based on published data tend to overestimate treatment effects since it is not an individual

patient data meta-analysis. Therefore, physicians should interpret our findings with caution.

In summary, the current study suggested that elevated blood NLR was a promising predictive and prognostic biomarker for NSCLC patients received PD-1/PD-L1 inhibitors. Further large-scale and strict-designed studies are still warranted to validate its clinical value. In the future, clinical trials in patients with NSCLC are advocated to determine whether blood NLR could be selected as the stratification factors to help identify patients who could benefit more from PD-1/PD-L1 inhibitors.

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Disclosures

The authors declare that they have no competing interests.

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Tao Jiang, Xiaoxia Chen and Caicun Zhou designed this study; Tao Jiang, Yuchen Bai, Fei Zhou, Wei Li, Guanghui Gao, Chunxia Su and Shengxiang Ren collected the clinical data; X Fei Zhou, Wei Li, and Guanghui Gao performed the quality assessment; Tao Jiang, Yuchen Bai and Shengxiang Ren performed statistical analyses; Caicun Zhou gave critical comments and suggestions; Tao Jiang and Xiaoxia Chen drafted the manuscript; all authors approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.lungcan.2019.02.009>.

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