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The prediction potential of neutrophil-to-lymphocyte ratio for the therapeutic outcomes of programmed death receptor-1/programmed death ligand 1 inhibitors in non-small cell lung cancer patients

A meta-analysis

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Abstract

Background: Programmed death receptor-1 (PD-1)/programmed death ligand 1 (PD-L1) inhibitors have been demonstrated to improve the prognosis of patients with advanced non-small cell lung cancer (NSCLC) compared with chemotherapy. However, there were still some non-responders. Thus, how to effectively screen the responder may be an important issue. Recent studies revealed the immune-related indicator, neutrophil-lymphocyte ratio (NLR), may predict the therapeutic effects of anti-PD1/PD-L1 antibodies; however, the results were controversial. This study was to re-evaluate the prognostic potential of NLR for NSCLC patients receiving PD1/PD-L1 inhibitors by performing a meta-analysis.

Methods: Eligible studies were identified by searching online databases of PubMed, EMBASE and Cochrane Library. The predictive values of NLR for overall survival, (OS), progression free survival (PFS) and overall response rate (ORR) were estimated by hazard ratio (HR) with 95% confidence interval (CI).

Results: Twenty-four studies involving 2196 patients were included. The pooled analysis demonstrated that elevated NLR before PD-1/PD-L1 inhibitor treatment was a predictor of poor OS (HR = 2.17; 95% CI: 1.64 – 2.87, $P < .001$), PFS (HR = 1.54; 95% CI: 1.34 – 1.78, $P < .001$) and low ORR (HR = 0.64; 95% CI: 0.44 – 0.95, $P = .027$) in NSCLC patients. Subgroup analysis revealed the predictive ability of NLR for OS and PFS was not changed by ethnicity, sample size, cut-off, HR source, study design or inhibitor type (except the combined anti-PD-L1 group); while its association with ORR was only significant when the cut-off value was less than 5 and the studies were prospectively designed.

Conclusion: Our findings suggest patients with lower NLR may benefit from the use of PD-1/PD-L1 inhibitors to prolong their survival period.

Abbreviations: CI = confidence interval, HR = hazard ratios, NLR = neutrophil-lymphocyte ratio, NSCLC = non-small cell lung cancer, OS = overall survival, ORR = overall response rate, PD-1 = programmed death receptor-1, PD-L1 = programmed death ligand 1, PFS = progression free survival.

Keywords: non-small cell lung cancer, programmed death receptor-1, programmed death ligand 1, neutrophil-lymphocyte ratio, prognosis, response rate

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All data generated or analyzed during this study are included in this published article [and its supplementary information files.

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1. Introduction

Lung cancer is one of the most frequently seen malignant tumors worldwide, with an estimated 228,150 new cases diagnosed and causing 142,670 deaths in 2019 in the USA.[1] Non-small cell lung cancer (NSCLC) is the major subtype of lung cancer, which accounts for approximately 80% of all lung cancer patients. Clinically, chemotherapy is recommended as the first-line treatment option for patients with advanced inoperable NSCLC. However, both of the response rate (less than 50%)[2] and the 5-year overall survival (OS) rate (approximately 5%)[3] of patients undergoing chemotherapy seem to be relatively low, indicating more effective drugs are necessary to be developed.

Recently, there is increasing evidence to indicate that immune evasion is a central hallmark of lung cancer.[4,5] Activation of the program death-1 (PD-1)/program death-ligand 1 (PD-L1) pathway is an important mechanism to evade immune elimination of tumor cells.[4,5] The binding of PD-1 with its ligand PD-L1 transmits a co-inhibitory signal for activated T-cells and then promotes T-cell exhaustion, ultimately preventing T-cell-mediated cellular cytotoxicity.[4,5] NSCLC patients with high expression of PD-L1 and PD-1 were observed to have a tendency for shorter survival.[4–7] These findings suggest inhibition of the expressions of PD-1 and PD-L1 may be potentially important approaches for the treatment of NSCLC.[8] This theory has been demonstrated by some scholars via the use of monoclonal antibodies against PD-1 (nivolumab and pembrolizumab) or PD-L1 (atezolizumab, durvalumab and avelumab), with the response rate and OS respectively improving to 75%[9] and 25%.[10] However, there were still some patients who could not benefit from the use of PD-1/PD-L1 inhibitors.[11] Therefore, it is indispensable to distinguish the responders from the non-responders to schedule cost-effective treatment strategy for them, in which identification of appropriate biomarkers may be the first problem required to be resolved.

Assay of peripheral blood counts (including neutrophils and lymphocytes) is the routine examination in clinic to assess the inflammatory and immune status of cancer patients before treatment. The elevated neutrophil-lymphocyte ratio (NLR) representing systemic inflammation was shown to be associated with poor prognosis in NSCLC patients,[12] suggesting NLR may serve as a potential biomarker to predict the therapy outcomes of PD1/PD-L1 inhibitors for NSCLC patients. This hypothesis has been proved by a meta-analysis performed by Cao et al., which showed that higher baseline NLR was associated with poor progression free survival (PFS) [10 studies: hazard ratios (HR) = 1.44; 95% confidence interval (CI) = 1.18 – 1.77; $P < .05$] and OS (8 studies: HR = 1.75; 95% CI: 1.33 – 2.30; $P < .05$) in patients with NSCLC after nivolumab treatment.[13] The similar conclusion was also verified in NSCLC stratification of meta-analysis studies focusing on all cancer types (Tan et al[14]: 4 articles; Sacdalan et al[15]: 3 articles; Xie et al[16]: 6 articles). However, the literature size in these meta-analyses seemed to be small and abundant negative associations of NLR with OS or PFS were observed in the recent studies[17–20] published in 2019 which were not included previously. Hereby, the prediction ability of NLR for the therapeutic effects of anti-PD1/PD-L1 antibodies in NSCLC patients remains inconclusive.

The objective of this meta-analysis was to re-evaluate the significance of NLR as a predictive factor in NSCLC patients receiving PD1/PD-L1 inhibitors based on 24 published evidences.

2. Materials and methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis. Patient consent and ethical approval were waived since the present study only used published studies.

2.1. Search strategies

A systematic electronic search was conducted in the databases of PubMed, Embase and the Cochrane library on December 1, 2019. The following search terms were used: ("programmed death-1 receptor" OR "programmed death ligand-1" OR "PD-1 inhibitor" OR "PD-L1 inhibitor" OR "anti-PD-1 antibodies" OR "immune checkpoint inhibitors" OR "immunotherapy" OR "nivolumab" OR "pembrolizumab" OR "atezolizumab" "avelumab" OR "durvalumab") AND ("neutrophil-to-lymphocyte ratio" OR "NLR" OR "neutrophil to lymphocyte ratio"). Furthermore, the references of eligible studies and previous reviews were hand-checked for additional articles.

2.2. Inclusion and exclusion criteria

Studies were considered eligible if they met the following inclusion criteria:

(1) enrolled patients were histologically diagnosed with lung cancer;
(2) patient received the PD1/PD-L1 inhibitor monotherapy;
(3) the associations between NLR and therapeutic outcomes [such as OS, PFS and overall response rate (ORR)] were evaluated;
(4) NLR was measured before PD1/PD-L1 inhibitor; and
(5) HRs with corresponding 95% CIs could be directly collected or indirectly calculated from original data or Kaplan–Meier curves.

The exclusion criteria were as follows:

(1) duplicate publication;
(2) studies included the patients who received immune checkpoint inhibitors targeting cytotoxic T-lymphocyte–associated antigen 4 or underwent other therapeutic strategies concurrently;
(3) studies focused on mixed cancer types;
(4) studies did not analyze NLR value, but the derived or $\log_e$-transformed NLR;
(5) studies were not related to our topics;
(6) case reports, reviews and non-human studies;
(7) lack of sufficient data to estimate HRs and 95%CIs; and
(8) non-English publications.

2.3. Data extraction and quality assessment

Two researchers independently extracted the following data from each study: first author's name, publication year, country of origin, sample size, PD-1/PD-L1 inhibitor, study design, follow-up, NLR cut-off, the outcome measures, HR with 95% CI and their source. HRs and 95%CIs were preferentially extracted from the multivariable analysis if available. The survival probabilities were read from Kaplan-Meier curves using a digitizing software-Engauge Digitizer (version 4.1; Available at: http://digitizer.sourceforge.net/). Any discrepancies were resolved by discussion.

The quality of included studies was assessed according to Newcastle-Ottawa Scale.[21] Studies with a Newcastle-Ottawa Scale score greater than 7 were considered as the high-quality literatures.

2.4. Statistical analysis

All statistical analyses were carried out using STATA 13.0 (STATA Corporation, College Station, TX). The prediction potential of NLR for therapeutic outcomes of PD-1/PD-L1 inhibitors in NSCLC patients was evaluated by pooled HR and 95%CI. HR > 1 indicated poor OS, PFS and ORR in patients with a higher pretreatment NLR; HR < 1 implied high NLR predicted favorable therapeutic outcomes. Statistical difference was determined by using z test. Heterogeneity across studies was assessed by Cochrane Q and I^2 statistic tests. A random-effects model was adopted if significant heterogeneity was observed ($P < .10$ and $I^2 > 50\%$); otherwise, a fixed-effects model was chosen. Subgroup analyses were performed by country, sample size, cut-off of NLR, HR source, study design and PD-1/PD-L1 inhibitors. Publication bias was examined using Egger linear regression test,[22] followed by adjustment with the "trim and fill" algorithm.[23] Sensitivity analysis was performed by omitting one study at a time to assess the robustness of the results. Significance levels were set at $P < .05$.

3. Results

3.1. Literature search and study characteristics

A flowchart of the study inclusion process is shown in Figure 1. A total of 814 records were initially identified through electronic databases searching. Then, 314 studies were screened after the removal of duplicates. After reading titles and abstracts, 282

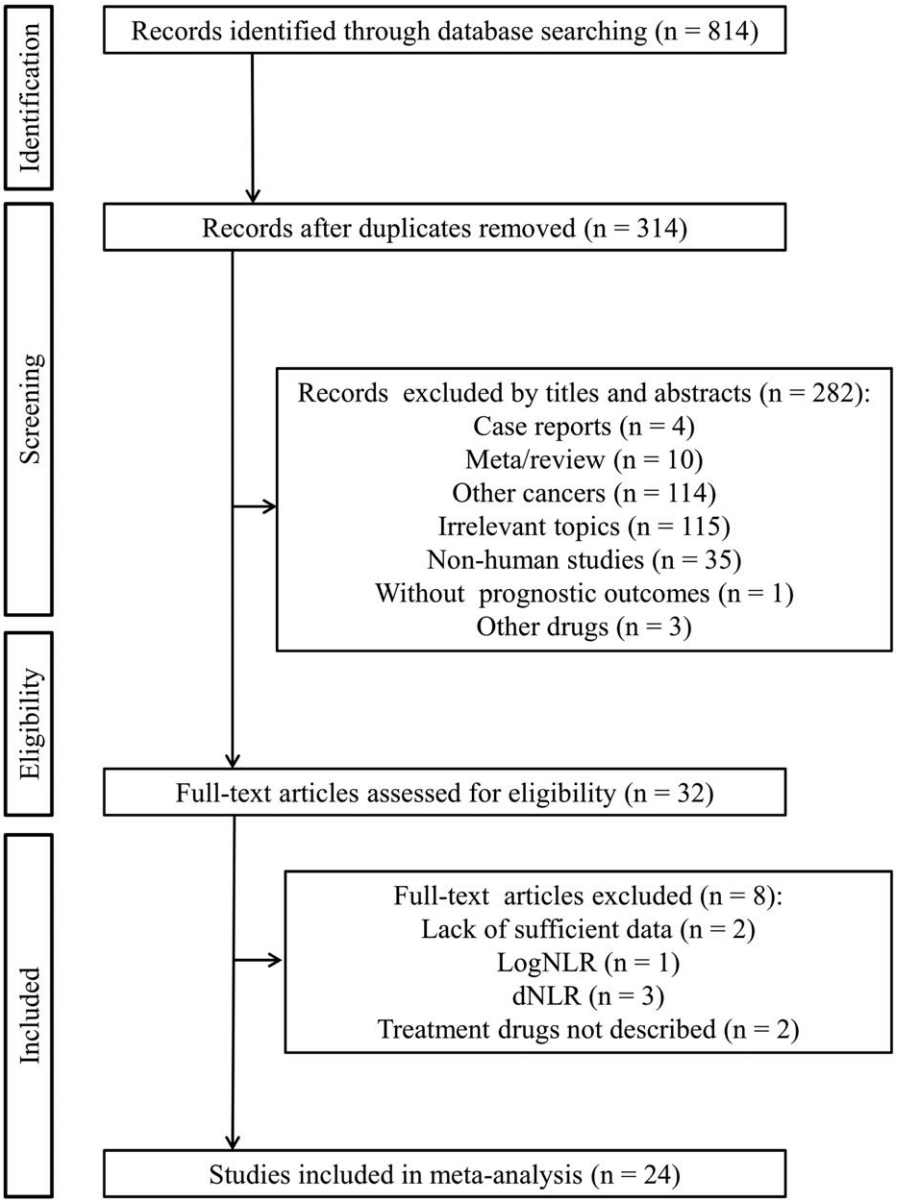

Figure 1. Flowchart of the study inclusion process.

Table 1

Characteristics of included studies.

Study	Year	Country	No.	Age (yr)	Male sex	PD-1/PD-L1 inhibitor	Design	Follow-up	Cut-off	Outcome	HR/95%CI source	NOS
Bagley SJ	2017	USA	175	68 (70–84)	80	Nivolumab	R	Unclear	5	OS, PFS (significant), ORR (non-significant)	OS, PFS (M), ORR (U)	8
Rogado J	2017	Spain	40	67	Unclear	Nivolumab	R	Unclear	5	OS, PFS (significant)	U	8
Galetta D	2017	Italy	47	47 (40–83)	41	Nivolumab	R	Unclear	4	PFS	U	8
Suh KJ	2018	Korea	54	Unclear	42	Nivolumab, pembrolizumab	R	26.2 mo	5	OS, PFS, ORR (non-significant)	U (K-M estimated)	8
Shiroyama T	2018	Japan	201	68 (27–87)	135	Nivolumab	R	12.4 mo	4	PFS, ORR (significant)	U	8
Khunger M	2018	USA	109	67 (45–90)	56	Nivolumab	R	30 mo	5	OS (non-significant)	U (K-M estimated)	8
Kiriu T	2018	Japan	19	71 (41–83)	19	Nivolumab	R	Unclear	5	OS (significant), PFS (non-significant)	U (K-M, estimated)	8
Takeda T	2018	Japan	30	71 (54–83)	19	Nivolumab	R	28 d	5	PFS (non-significant)	U (K-M, estimated)	8
Nakaya A	2018	Japan	101	69 (45–84)	77	Nivolumab	R	8.9 mo	3	PFS (non-significant)	U (K-M, estimated)	8
Facchinetti F	2018	Italy	54	69 (43–85)	45	Nivolumab	P	12.6 mo	4	OS (significant), ORR (significant)	OS (M), ORR (U)	8
Zer A	2018	Canada	88	64 (31–81)	43	No detail (mixed)	P	5.3 mo	4	OS (significant), PFS, ORR (non-significant)	OS, PFS (U; K-M, directly obtained), ORR (M)	9
Park W	2018	USA	159	68 (41–91)	82	Nivolumab	R	11.5 mo	5	OS, PFS (significant)	U	8
Svaton M	2018	Czech	120	Unclear	71	Nivolumab	R	Unclear	3.8	OS (significant)	U (K-M estimated)	8
Shiroyama T	2018	Japan	201	Unclear	135	Nivolumab	R	Unclear	5	PFS (non-significant)	M	8
Soyano AE	2018	USA	157	66 (27–87)	83	Nivolumab, pembrolizumab	P	20.0 mo	5.9	OS, PFS (significant)	M	8
Fukui T	2019	Japan	52	69 (46–83)	37	Nivolumab	P	10.9 mo	5	OS, PFS (significant)	OS (M), PFS (U)	8
Ichiki Y	2019	Japan	44	71 (42–91)	38	Nivolumab, pembrolizumab	R	145 d	Unclear	OS (significant)	M	8
Minami S	2019	Japan	76	Unclear	49	Nivolumab, vpembrolizumab, atezolizumab	R	Unclear	6	OS, PFS (non-significant)	M	8
Dusselier M	2019	France	59	60 (30–87)	44	Nivolumab	R	Unclear	5	OS (non-significant), ORR (significant)	U	8
Passiglia F	2019	Italy	45	66 (51–80)	32	Nivolumab	R	9.1 mo	3.3	PFS (non-significant)	PFS (M)	8
Liu J	2019	China	44	60 (43–74)	33	Nivolumab	R	6.9 mo	3.07	OS, PFS (significant)	OS, PFS (M)	8
Shoji F	2019	Japan	102	69 (42–86)	73	Nivolumab, pembrolizumab, atezolizumab	R	201 d	3.88	OS (non-significant), PFS (significant)	M	8
Pavan A	2019	Italy	184	67 (37–83)	125	Pembrolizumab, nivolumab, atezolizumab	R	56.3 mo	3	OS, PFS (significant)	M	8
Möller M	2020	Germany	35	65 (24–85)	19	Pembrolizumab, nivolumab	P	9.7 mo	5.2	OS, PFS (significant)	OS (U), PFS (K-M estimated)	8

CI = confidence intervals, HR = hazard ratio, K-M = Kaplan-Meier curve, M = multivariate analysis, NOS = Newcastle-Ottawa Scale, OS = overall survival, ORR = overall response rate, P = prospective, PD-1 = programmed death-1, PD-L1 = programmed death ligand 1, PFS = progression-free survival, R = retrospective, U = univariate analysis.

articles were excluded because they were either case reports (n = 4), meta/review (n = 10), studies investigating other cancers (n = 114), other drugs (n = 3), irrelevant topics (n = 115), without prognostic outcomes (n = 1) or non-human studies (n = 35). Full-text review further eliminated 8 studies since they did not report detailed data (n = 2), treatment drugs (n = 2) or directly analyze NLR (n = 4). Finally, 24 studies were included in this meta-analysis.[17–20,24–43]

The detailed characteristics of these 24 studies are presented in Table 1. These included studies were published from 2017 to 2020 and analyzed the treatment effects for advanced NSCLC patients from Japan (n = 9), USA (n = 4), Korea (n = 1), France (n = 1), Italy (n = 4), Canada (n = 1), Germany (n = 1), Czech (n = 1), Spain (n = 1) and China (n = 1). The immunotherapy agent was nivolumab in 16 studies; while in the remaining 8 studies, patients treated with pembrolizumab, atezolizumab or atezolizumab were enrolled as the whole. Five studies were prospectively designed, while the other 19 studies retrospectively reviewed the records of patients. The associations of NLR with primary endpoints (ORR, OS and PFS) were obtained from univariate analysis, multivariate analysis or Kaplan-Meier curve. The cut-off value of NLR was reported in most of the studies (23/24, 95.8%), with the range from 3 to 6. The quality assessment result suggested that all the included studies were of high quality (Table 1).

3.2. The association between NLR and OS

Eighteen studies reported the association between pretreatment NLR and OS in NSCLC patients receiving PD-1/PD-L1 inhibitors. The heterogeneity test revealed significant heterogeneity existed among these studies ($I^2 = 79.2\%$, $P < .001$), so a random-effect model was used (Table 2). The pooled meta-analysis demonstrated that patients with an elevated NLR were associated with shorter OS after treatment with PD-1/PD-L1 inhibitor (HR = 2.17; 95% CI: 1.64 – 2.87, $P < .001$; Fig. 2). This conclusion was similar after stratified analyses, irrespective of ethnicity, sample size, cut-off, HR source, study design or PD-1/PD-L1 inhibitor type (Table 2).

3.3. The association between NLR and PFS

Nineteen studies investigated the association between baseline NLR and PFS in NSCLC patients treated with anti-PD-1/PD-L1 antibodies. A random-effect model was chosen due to obvious heterogeneity present among the included studies ($I^2 = 78.7\%$, $P < .001$) (Table 3). The pooled meta-analysis implied that NSCLC patients with high pretreatment NLR had a 1.54-fold higher risk of poor PFS (95% CI: 1.34 – 1.78, $P < .001$; Fig. 3). Moreover, this significant prognostic value of NLR for PFS was not changed after subgroup analyses according to ethnicity, sample size, cut-off, HR source, study design or PD-1/PD-L1 inhibitor type except the combined anti-PD-L1 group (Table 3).

Table 2

The association between NLR and OS in NSCLC patients receiving PD-1/PD-L1 inhibitors.

Comparison		Studies	HR (95%CI)	P_Z-value	I^2	P_H-value	Model
Overall		18	2.17 (1.64,2.87)	<.001	79.2	<.001	R
Subgroup							
Country	Asian	7	2.45 (1.83,3.28)	<.001	14.7	.318	F
	Non-Asian	11	1.95 (1.40,2.71)	<.001	80.5	<.001	R
Sample size	<100	11	2.63 (2.05,3.39)	<.001	27.9	.179	F
	>100	7	1.72 (1.24,2.39)	.001	78.7	<.001	R
Cut-off	<5	6	1.89 (1.22,2.92)	.004	75.8	.001	R
	≥ 5	11	2.21 (1.80,2.69)	<.001	34.4	.123	F
	No	1	3.02 (1.49,6.13)	.002	-	-	R
HR source [1]	M	9	2.11 (1.44,3.09)	<.001	79.0	<.001	R
	U	9	2.22 (1.77,2.79)	<.001	41.8	.089	F
HR source[2]	K-M estimated	4	2.07 (1.50,2.84)	<.001	1.0	.387	F
	Directly obtained	14	2.19 (1.57,3.05)	<.001	80.7	<.001	R
Study design	Retrospective	13	2.06 (1.48,2.87)	<.001	80.8	<.001	R
	Prospective	5	2.30 (1.68,3.16)	<.001	0.0	.669	F
PD-1/PD-L1 inhibitor[1]	Single type	10	2.33 (1.88,2.88)	<.001	48.5	.042	F
	Mixed	8	1.83 (1.30,2.59)	.001	71.6	.001	R
PD-1/PD-L1 inhibitor[2]	Anti-PD-1	15	2.30 (1.93,2.73)	<.001	25.7	.171	F
	Combined anti- PD-L1	3	1.11 (1.04,1.18)	.001	37.0	.204	F

CI = confidence interval, F = fixed-effects, HR = hazard ratio, M = multivariate analysis, NLR = neutrophil-lymphocyte ratio, NSCLC = non-small cell lung cancer, OS = overall survival, PD-1 = programmed death-1, PD-L1 = programmed death ligand 1, P_H = p-value for heterogeneity, P_Z = p-value for association, R = random-effects, U = univariate analysis.

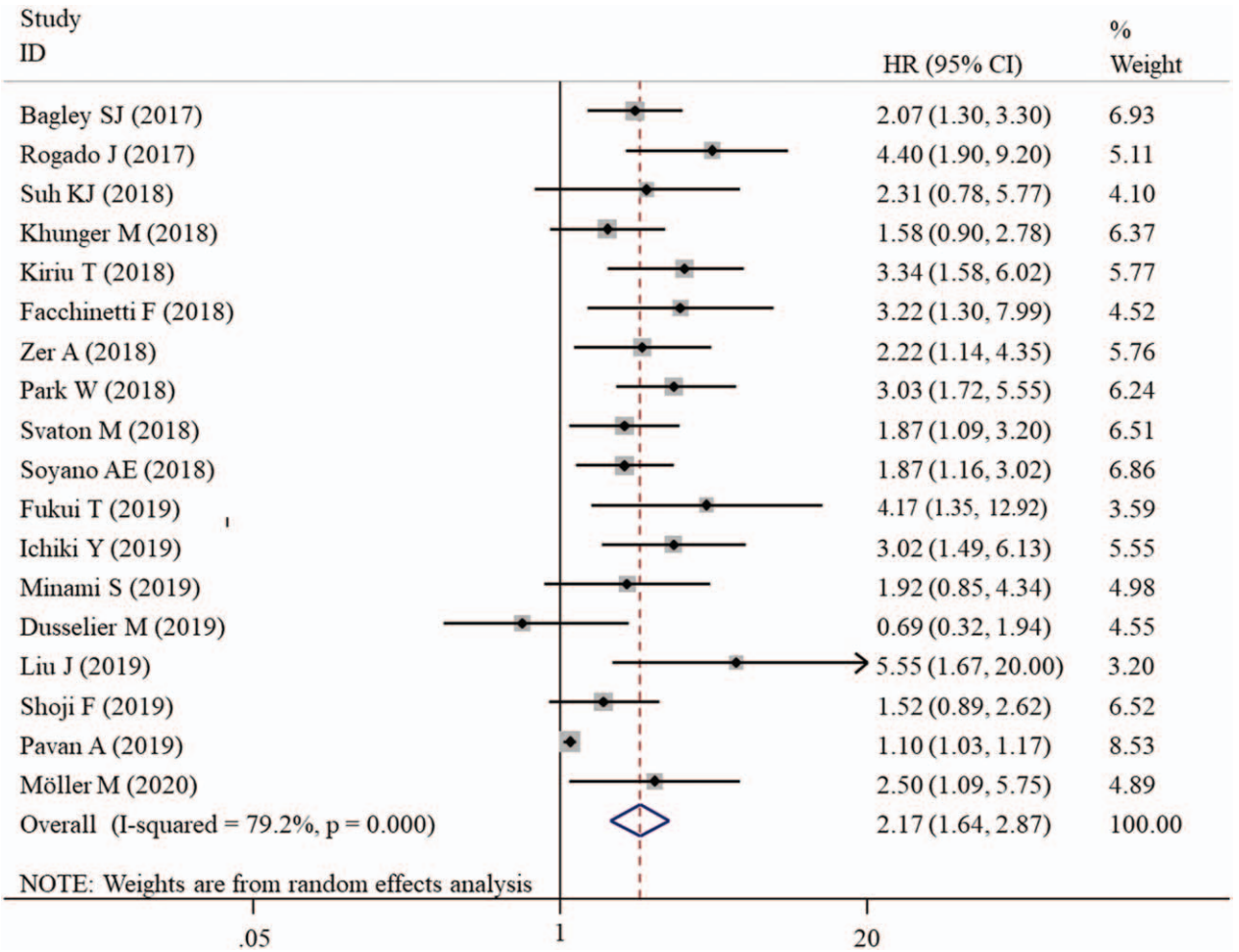

Figure 2. Forest plots showing the association between NLR and overall survival in non-small cell lung cancer patients receiving PD-1/PD-L1 inhibitors. HR, hazard ratio; CI, confidence interval; PD-1, programmed death receptor-1; PD-L1, programmed death ligand 1; NLR, neutrophil-lymphocyte ratio.

Table 3

The association between NLR and PFS in NSCLC patients receiving PD-1/PD-L1 inhibitors.

Comparison		Studies	HR (95%CI)	P_Z-value	I^2	P_H-value	Model
Overall		19	1.54 (1.34,1.78)	<.001	78.7	<.001	R
Subgroup							
Country	Asian	10	1.61 (1.39,1.85)	<.001	0.0	.706	F
	Non-Asian	9	1.45 (1.21,1.73)	<.001	84.1	<.001	R
Sample size	<100	11	1.85 (1.37,2.50)	<.001	75.4	<.001	R
	>100	8	1.45 (1.16,1.82)	.001	78.3	<.001	R
Cut-off	<5	8	1.30 (1.11,1.52)	.001	76.8	<.001	R
	≥ 5	11	1.65 (1.44,1.89)	<.001	43.8	.059	F
HR source [1]	M	9	1.45 (1.14,1.84)	.003	73.1	<.001	R
	U	10	1.80 (1.38,2.35)	<.001	77.2	<.001	R
HR source[2]	K-M estimated	4	2.22 (1.40,3.52)	.001	0.0	.848	F
	Directly obtained	15	1.49 (1.28,1.73)	<.001	81.3	<.001	R
Study design	Retrospective	15	1.45 (1.24,1.69)	<.001	76.2	<.001	R
	Prospective	4	1.73 (1.44,2.07)	<.001	0.0	.587	F
PD-1/PD-L1 inhibitor[1]	Single type	12	1.67 (1.35,2.06)	<.001	73.1	<.001	R
	Mixed	7	1.49 (1.08,2.05)	.015	74.1	.001	R
PD-1/PD-L1 inhibitor[2]	Anti-PD-1	16	1.71 (1.42,2.06)	<.001	69.8	<.001	R
	Combined anti-PD-L1	3	1.12 (0.81,1.54)	.486	48.5	.144	F

CI = confidence interval, F = fixed-effects, HR = hazard ratio, M = multivariate analysis, NLR = neutrophil-lymphocyte ratio, NSCLC = non-small cell lung cancer, PD-1, programmed death-1, PD-L1 = programmed death ligand 1, PFS = progression free survival, P_H = p-value for heterogeneity, P_Z = p-value for association, R = random-effects, U = univariate analysis.

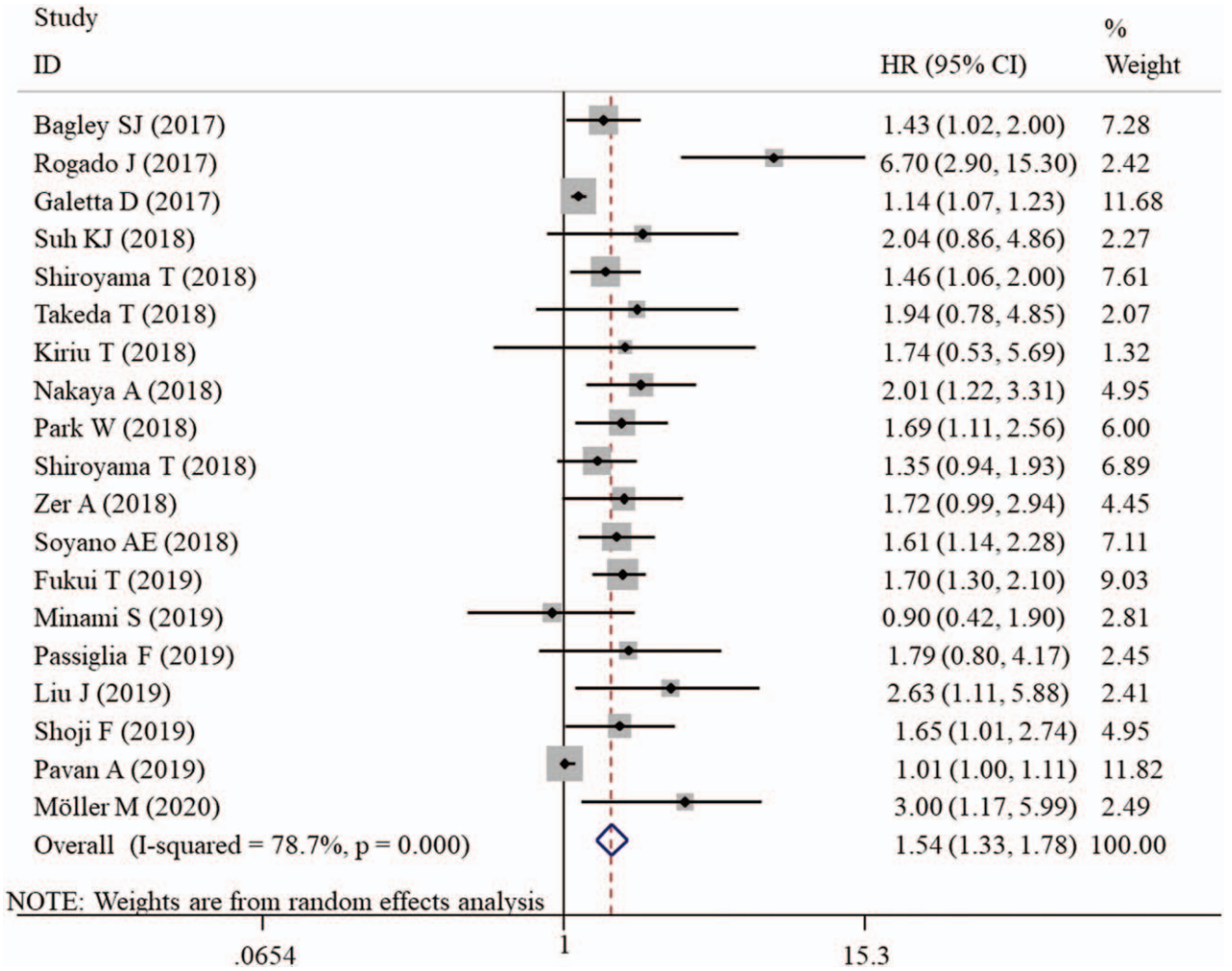

Figure 3. Forest plots showing the association between NLR and progression-free survival in non-small cell lung cancer patients receiving PD-1/PD-L1 inhibitors. HR, hazard ratio; CI, confidence interval; PD-1, programmed death receptor-1; PD-L1, programmed death ligand 1; NLR, neutrophil-lymphocyte ratio.

Table 4

The association between NLR and ORR in NSCLC patients receiving PD-1/PD-L1 inhibitors.

Comparison		Studies	HR (95%CI)	P_Z-value	I^2	P_H-value	Model
Overall		6	0.64 (0.44,0.95)	.027	67.6	.009	R
Subgroup							
Country	Asian	2	0.68 (0.32,1.48)	.332	83.7	.013	R
	Non-Asian	4	0.58 (0.32,1.07)	.079	64.3	.038	R
Sample size	<100	4	0.68 (0.41,1.07)	.092	71.9	.014	R
	>100	2	0.60 (0.30,1.17)	.136	50.8	.154	R
Cut-off							
	<5	3	0.38 (0.25,0.59)	<.001	0.0	.586	F
	≥ 5	3	0.95 (0.78,1.16)	.606	0.0	.952	F
HR source	M	1	0.40 (0.16,1.01)	.052	-	-	R
	U	5	0.68 (0.46,1.03)	.068	69.5	.011	R
Study design	Retrospective	4	0.81 (0.59,1.11)	.195	51.7	.102	F
	Prospective	2	0.32 (0.17,0.60)	<.001	0.0	.479	R
PD-1/PD-L1 inhibitor	Single type	4	0.58 (0.33,1.02)	.058	68.2	.024	R
	Mixed	2	0.70 (0.30,1.62)	.404	69.6	.070	R

CI = confidence interval, F = fixed-effects, HR = hazard ratio, M = multivariate analysis, NLR = neutrophil-lymphocyte ratio, NSCLC = non-small cell lung cancer, ORR = overall response rate, PD-1 = programmed death-1, PD-L1 = programmed death ligand 1, P_H = p-value for heterogeneity, P_Z = *P*-value for association, R = random-effects, U = univariate analysis.

3.4. The association between NLR and ORR

As shown in Table 4, the random-effect model was used for exploring the association between NLR and ORR because of significant heterogeneity among 6 included studies. Overall, the meta-analysis results showed elevated NLR contributed to a lower ORR for PD-1/PD-L1 inhibitors in NSCLC patients (HR = 0.64; 95% CI: 0.44 – 0.95, $P = .027$; Fig. 4). This significant result was only observed in subgroups with cut-off < 5 (HR = 0.38; 95% CI: 0.25 – 0.59, $P < .001$) and prospective design (HR = 0.32; 95% CI: 0.17 – 0.60, $P < .001$) (Table 4).

3.5. Publication bias and sensitivity analyses

Publication bias analysis showed that no evidence of publication bias was observed in the analysis of ORR, indicating the results were reliable ($P = .051$). There was significant publication bias for OS ($P < 0.001$) and PFS ($P < .001$), which were then corrected by the trim and fill method. However, the results still showed elevated NLR was a predictor for unfavorable OS (HR = 1.29; 95% CI: 1.00 – 1.68, $P < .001$) and PFS (HR = 1.19; 95% CI: 1.03 – 1.37, $P < .001$). The sensitivity analysis also proved that no individual study influenced the summary effects on OS and PFS, also suggesting the robustness of the results for these 2 prognostic outcomes (Fig. 5).

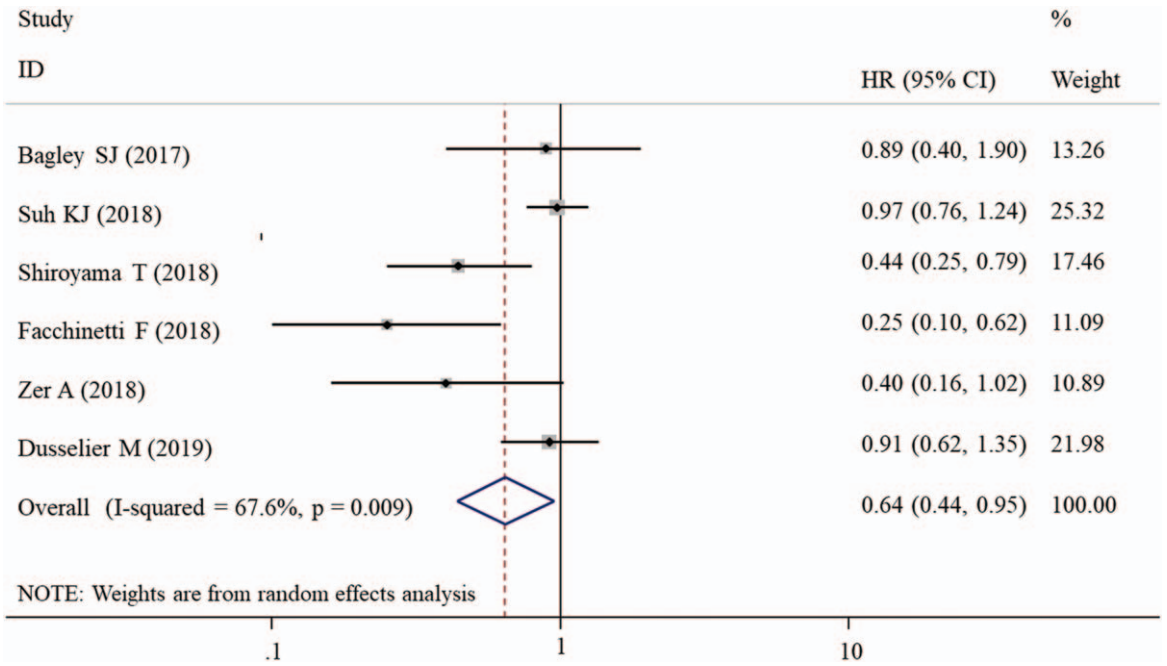

Figure 4. Forest plots showing the association between NLR and overall response rate in non-small cell lung cancer patients receiving PD-1/PD-L1 inhibitors. HR, hazard ratio; CI, confidence interval; PD-1, programmed death receptor-1; PD-L1, programmed death ligand 1; NLR, neutrophil-lymphocyte ratio.

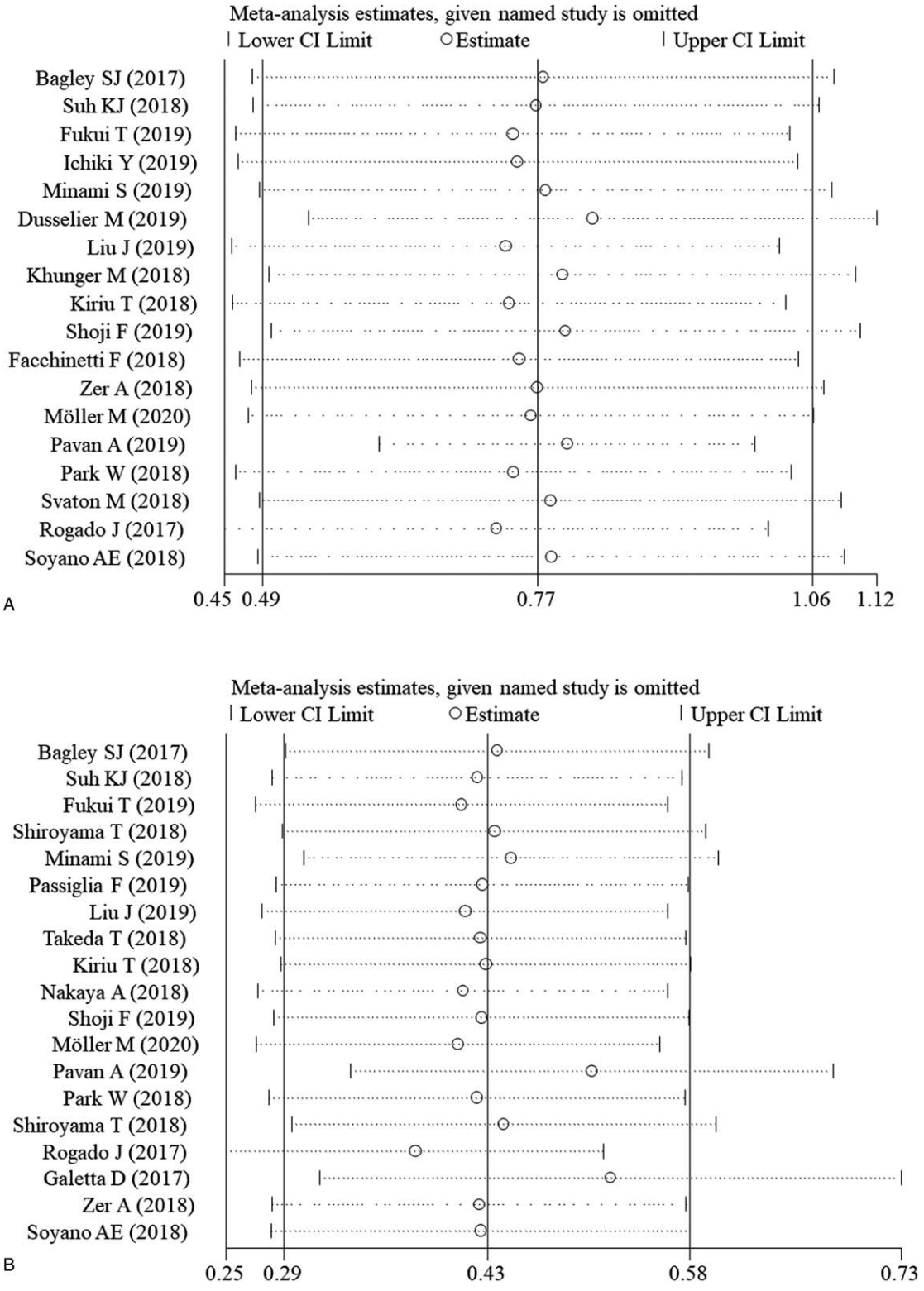

Figure 5. Sensitivity analysis. A, overall survival; B, progression-free survival. CI, confidence interval.

4. Discussion

Although there were meta-analyses to investigate the prognostic value of NLR for anti-PD-1/PD-L1 treatment in NSCLC patients,[13–16] their sample size was relatively small ($\leq$ 10). In the present study, a total of 24 publications involving 2196 patients were included to perform an updated meta-analysis. In line with previous meta-analyses, our pooled analysis validated that elevated NLR before PD-1/PD-L1 inhibitor treatment was a predictor of poor OS[13,14,16] and PFS[13–16] in NSCLC patients,

demonstrating NLR may be a promising biomarker to evaluate the prognostic outcome after anti-PD-1/PD-L1 antibody treatment. Furthermore, subgroup analysis was also conducted. However, different from the analysis results of Cao et al. in small sample size[13] which showed only NLR $\geq$ 5 could predict PFS and OS, but not NLR $<$ 5; NLR could predict PFS for American, not the Asian, our study indicated the associations of NLR for OS and PFS were still significant regardless of ethnicity or cut-off. These findings further reveal the necessity of our updated meta-analysis in order to achieve more reliable conclusions. Some subgroups were newly assessed for patients based on HR source, study design or inhibitor type. Most of them were also significant, except combined anti-PD-L1 (atezolizumab) subgroup for PFS. More interesting, high NLR was also proved to be associated with lower ORR, especially when the cut-off value was set to be less than 5 and the studies were prospectively designed. This conclusion was, for the first time, reported in our study, although the data were collected in the study of Cao et al.[13] These results may enrich the evidence to indicate the importance to detect NLR before the use of PD-1/PD-L1 inhibitors.

The prognostic potential of NLR for patients with PD-1/PD-L1 inhibitor treatment may be attributed to the correlation between neutrophil/lymphocyte and PD-1/PD-L1.[44] It was reported that patients with NSCLC showed a significantly higher neutrophil infiltration, but decreased $CD3^+CD8^+$ T-cell infiltration.[45] Tumour-derived granulocyte colony stimulating factor activated neutrophils[46–48] and induced PD-L1 expression on neutrophils.[49] The activated neutrophils could suppress T cell proliferation and cytotoxic activity via binding of PD-L1 on the surface of neutrophils to PD-1 on T cells,[49–52] which may be beneficial for tumor immune evasion and malignant growth, ultimately leading to reduced survival of cancer patients.[49] The combined application of cytotoxic T lymphocytes and PD-1 inhibitor significantly decreased tumor volume and tumor weight in model mice, but promoted tumor necrosis and apoptosis compared with PD-1 inhibitor alone and blank control groups.[53] Thus, the presence of high NLR in lung cancer antagonized the therapeutic effects of PD-1/PD-L1 antibodies and resulted in the treatment failure.[54] The fact that high NLR could not predict the poor PFS for some patients receiving atezolizumab may be ascribed to their low PD-L1 expression (possible having other ligands[55]) on neutrophils.[50]

Several limitations should be considered in this study. First, most of included studies were retrospective which may introduce unavoidable bias in patient selection and data collection. Second, although the scale of our included literatures has been relative large, some potential outcomes (such as adverse events[29,37,55]) related with PD-1/PD-L1 inhibitor treatment remains rarely reported and the meta-analysis for it could not been assessed; while the reducing the complications was also an important advantage of PD-1/PD-L1 inhibitor compared with chemotherapy.[56] Third, the cut-off value of NLR varied widely in different studies, which influenced the clinical generalization. Fourth, most of the studies focused on the prognostic ability of NLR for patients undergoing anti-PD-1 (nivolumab and pembrolizumab). The role of NLR in predicting outcomes for anti-PD-L1 (atezolizumab, durvalumab and avelumab) monotherapy needed further investigation because the therapeutic effects of anti-PD-L1 and anti-PD1 antibodies seemed to be different.[55,57] Fifth, the prognostic values of post-treatment NLR for NSCLC patients treated with PD-1/PD-L1 inhibitors were also worth investigating in the future, especially for PFS.[13,25,27]

5. Conclusion

This meta-analysis demonstrated that NLR may serve as a potential biomarker to predict the treatment outcomes of PD-1/PD-L1 inhibitors for NSCLC cancer patients. Only patients with lower NLR may benefit from the use of PD-1/PD-L1 inhibitors to prolong their survival period.

Author contributions

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Formal analysis: Ying Huang, Aizong Shen.
Methodology: Ying Huang.
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