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The Prognostic Significance of Baseline Neutrophil-to-Lymphocyte Ratio in Melanoma Patients Receiving Immunotherapy

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Summary: Immunotherapy has revolutionized the treatment in metastatic melanoma, but alternative biomarkers that are economical, simple and reliable still need to be clarified. In this study, we aimed to comprehensively analyze the prognostic significance of baseline neutrophil-to-lymphocyte ratio (NLR) in melanoma patients with immunotherapy. We searched PubMed, Embase, and Cochrane Library until September 16, 2020. Hazard ratio (HR) and 95% confidence intervals (CIs) were pooled to investigate the association of baseline NLR with overall survival (OS) and progression-free survival (PFS). Sensitivity analysis, subgroup analyses, publication bias assessment, and the Duval and Tweedie trim-and-fill method were used to evaluate the stability of results. A total of 18 studies including 2054 patients were included in our analysis. Pooled data demonstrated that higher baseline NLR was associated with a poorer OS (HR = 2.46, 95% CI = 1.77, 3.43) and PFS (HR = 2.38, 95% CI = 1.95, 2.89) of melanoma patients receiving immunotherapy. Subgroup analysis according to immunotherapy type showed that the prognostic effects of baseline NLR existed in all the subtypes of immunotherapy, including anticytotoxic T lymphocyte-associated protein 4 therapy (OS HR = 2.26, 95% CI = 1.43, 3.59; PFS HR = 2.68, 95% CI = 1.79, 4.02), antiprogrammed cell death-1 therapy (OS HR = 3.08, 95% CI = 2.21, 4.27; PFS HR = 2.01, 95% CI = 1.64, 2.47), and combination therapy (OS HR = 1.75, 95% CI = 1.13, 2.72; PFS HR = 3.13, 95% CI = 1.63, 6.03). Conclusions were still consistent in subgroup analyses stratified by study year, region, study type, sample size, analysis of HR and cuttoff of baseline NLR. Altogether, baseline NLR is a promising prognostic biomarker for melanoma patients receiving immunotherapy.

Key Words: neutrophil-to-lymphocyte ratio, melanoma, immunotherapy, biomarker, prognosis

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Immunotherapy with antibodies targeting the programmed cell death-1 receptor (PD-1) or its ligand or the cytotoxic T lymphocyte-associated protein 4 (CTLA4) has revolutionized the treatment in metastatic melanoma.[1] Recently, immunotherapy has been recommended as first-line treatment for advanced cutaneous melanoma.[2] Clinical trials showed that 5-year overall survival was 44% in the nivolumab group and even 52% in the nivolumab-plus-ipilimumab group.[3] However, some patients still have no response, and a subset of responding patients eventually deteriorate.[4,5] Moreover, relative long response time for immunotherapy could cause patients with no clinical response to miss the optimal treatment window.[6–8] Thus, it is imperative to investigate reliable markers to select the most suitable melanoma patients for immunotherapy.

Extensive research efforts have been undertaken to identify predictive biomarkers for the prognosis of melanoma patients receiving immunotherapy. Our team previously showed that some biomarkers, such as ADORA1 and P62, could be used to assess the clinical response of immunotherapy in melanoma.[9,10] Other groups highlighted that the tumor programmed cell death ligand-1 expression level was an important biomarker for evaluating the efficacy of immunotherapy.[11–13] Others markers like mutational burden and microsatellite instability, were also characterized in clinical practice.[14–16] In addition, several clinical scoring systems have been proposed to predict the outcome of immunotherapy in melanoma patients.[17–21] For example, Weide et al[17] reported that a combination model including visceral involvement, lactate dehydrogenase-ratio, relative lymphocyte count and relative eosinophil count, could identify melanoma patients receiving immunotherapy with excellent prognosis. Berry et al[18] developed the Astropath platform via the analysis of multispectral imaging to predict the outcome and response of immunotherapy. However, these markers and clinical systems had limitations like high costs, complex procedures, and great heterogeneity.[6] Therefore, alternative biomarkers that are economical, simple and reliable still need to be clarified.

Increasing studies demonstrated that neutrophil-to-lymphocyte ratio (NLR), a biomarker of systemic inflammation,

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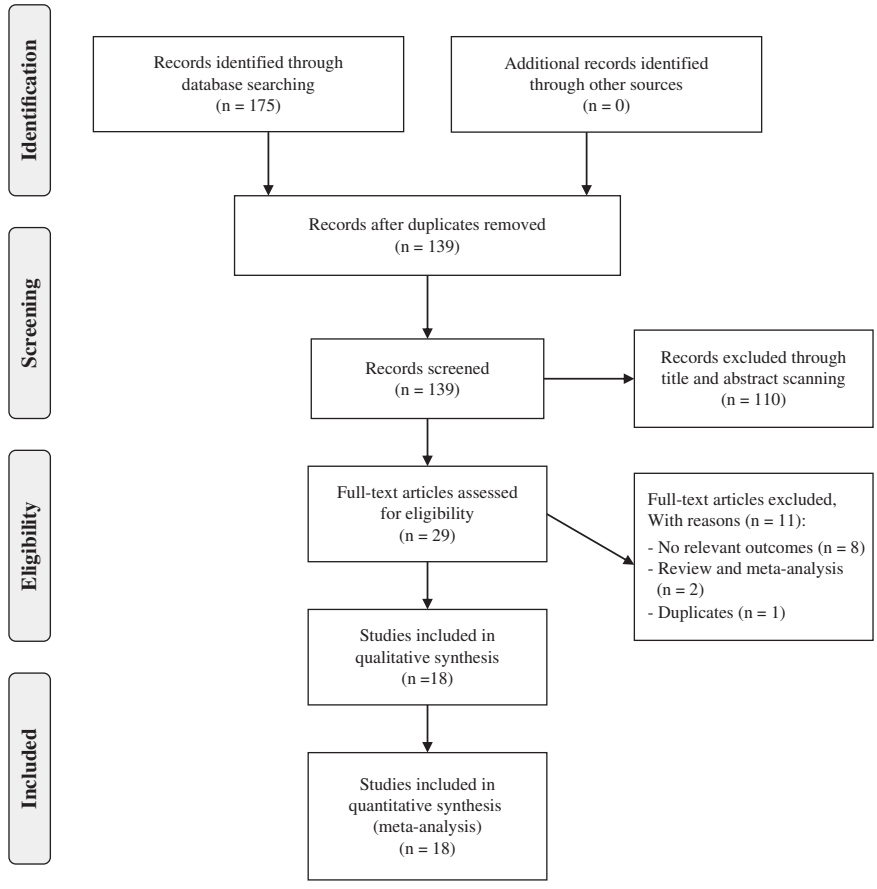

FIGURE 1. Flow diagram of study identification and selection.

was associated with poor clinical prognosis in melanoma, a tumor that is highly associated with inflammation.[6,22–25] Considering that tumor inflammation could predict the response of melanoma patients with immunotherapy,[26] we wondered whether baseline NLR could be used as a biomarker for the assessment of clinical response to immunotherapy. Studies reported the associations, but conclusions were inconsistent.[27–31] Therefore, in this study, we aimed to comprehensively analyze the prognostic significance of baseline NLR in melanoma patients with immunotherapy.

To our knowledge, this is the first meta-analysis to evaluate the association between baseline NLR and the prognosis of melanoma patients receiving immunotherapy. Our study will assist clinicians with patient counseling and clinical treatment guiding.

METHODS

Search Strategy

This meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[32,33] A systematic online search of PubMed, Embase, and Cochrane Library was performed to identify all relevant published literatures until September 16, 2020. Search strategies were as follows: ("Melanoma" OR "melanoma*") OR ("Skin Neoplasms" OR "malignant melanoma*" OR "skin cancer*" OR "skin neoplas*") AND ("Neutrophil-Lymphocyte ratio" OR "Neutrophil Lymphocyte ratio" OR "Neutrophil-to-Lymphocyte ratio" OR "Neutrophil to Lymphocyte ratio" OR "Neutrophil/Lymphocyte ratio" OR "NLR") AND ("CTLA4" OR "cytotoxic T-lymphocyte-associated protein 4" OR "PD-1" OR "programmed death receptor 1" OR "immune checkpoint inhibitor" OR "ipilimumab" OR "tremelimumab" OR "nivolumab" OR "pembrolizumab"). We did not apply any restriction on language or study design. The references of eligible articles and main reviews were searched for further potentially relevant articles. The identifier of systematic review registration was PROSPERO CRD42021223932.

Inclusion and Exclusion Criteria

Studies were considered eligible if they met the following inclusion criteria: (1) advanced or metastatic melanoma patients receiving immunotherapy; (2) accessible survival outcomes between high and low baseline NLR groups. Exclusion criteria were: (1) studies without specifying the treatments or receiving other types of treatments; (2) studies including other types of tumors without performing subgroup analysis of melanoma; (3) duplicated studies with small sample size in the same institute or hospital; (4) review, case reports or meta-analysis.

Data Extraction and Quality Assessment

Two authors (F.Z. and Y.L.) independently scanned the initial search to exclude any duplicate and irrelevant studies. The following data were extracted from eligible studies: first authors, published year, region of study, type of study, cases, age, sex, cutoff value of baseline NLR,

TABLE 1. Characteristics of Eligible Studies

References	Region	Study Type	Cases	Age (y)	Sex (Male, %)	Cutoff	Immunotherapy Type	Variables	NOS Scores
Ferrucci et al[42]	Italy	Multicenter	187	60.6 ± 40.9	152 (81.3)	5	Ipilimumab	OS*, PFS*	9
Khoja et al[45]	Canada	Single-center	183	56.9 ± 48.6	115 (62.8)	4	Ipilimumab	OS*	8
Zaragoza et al[50]	France	Multicenter	58	54.7 ± 15.6	33 (56.9)	4	Ipilimumab	OS*	8
Araujo et al[38]	Brazil	Single-center	74	—	—	5	Nivolumab	OS, PFS	7
Cassidy et al[40]	USA	Single-center	197	50.0 ± 60.6	125 (63)	5	Ipilimumab	OS*, PFS*	8
Chow et al[41]	England	Multicenter	86	—	—	3.1	Ipilimumab	PFS*	8
Jung et al[44]	Korea	Multicenter	104	58.0 ± 12.0	51 (49)	5	Ipilimumab	OS, PFS	7
Capone et al[39]	Italy	Single-center	97	55.4 ± 48.2	42 (43.2)	5	Nivolumab	OS*, PFS*	8
Garnier et al[43]	France	Multicenter	101	66.8 ± 11.1	50 (49.5)	5	Nivolumab/ pembrolizumab	OS*	8
Minowa et al[30]	Japan	Single-center	21	65.7 ± 45.3	11 (52.4)	3.4	PD-1 blockade	OS	7
Rosner et al[49]	American	Single-center	209	56.1 ± 48.1	124 (59.3)	4.73	Nivolumab/ipilimumab	OS*	8
Afzal et al[27]	Lebanon	Single-center	120	63.35 ± 13.46	76 (63.3)	5	Ipilimumab/nivolumab/ pembrolizumab	OS*, PFS*	9
Lee et al[46]	Korea	Single-center	152	54.3 ± 45.7	72 (47)	2.1	Nivolumab/ pembrolizumab	OS*, PFS*	8
Marconcini et al[47]	Italian	Multicenter	48	—	—	0.7	PD-1 blockade	OS, PFS	7
Martins et al[48]	Portugal	Multicenter	85	64.24 ± 45.7	—	3	PD1 blockade	PFS*	8
Tsutsumida et al[31]	Japan	Multicenter	61	64.4 ± 32.6	33 (54.1)	4	Ipilimumab/nivolumab	OS*, PFS*	8
Balatoni et al[28]	Hungary	Single-center	47	55.2 ± 43.6	27 (57)	4	Ipilimumab	OS	7
Bartlett et al[29]	USA	Single-center	224	61.0 ± 52.2	147(66)	5	Nivolumab/ pembrolizumab	OS*, PFS*	8

*Means their variables are calculated by multivariable analysis.
NOS indicates the Newcastle-Ottawa Scale; OS, overall survival; PD-1, programmed cell death-1; PFS, progression-free survival.

immunotherapy type, hazard ratio (HR) of each study and corresponding 95% confidence interval (CI) for overall survival (OS) and progression-free survival (PFS). HR from multivariable analyses was preferentially retrieved. If studies did not report specified HR, HR was estimated from Kaplan-Meier curves between high and low baseline NLR groups according the previous methods.[34,35] Studies quality was assessed using the Newcastle-Ottawa Scale with a total of 9 stars in 3 aspects: selection, comparability and outcome. Studies with >6 stars were recognized to be of high quality.

Statistical Analysis

All the statistical analyses were performed using STATA software (Version 12.0; STATA Corporation, College Station, TX). Statistical heterogeneity was assessed with I^2 and P-value. Random effect model was preferentially performed due to the heterogeneity in the comparisons. Fixed effect model was also adopted in all analyses to evaluate the stability of results. Sensitivity analysis was performed by omitting one study each time as previously described.[36,37] Subgroup analyses were stratified by study year, region, study type, sample size, analysis of HR, cutoff of baseline NLR and immunotherapy type to test whether baseline NLR could predict survival outcomes in these circumstances. Publication bias was assessed using funnel plots and Egger tests. If publication bias existed, the Duval and Tweedie trim-and-fill method was implemented to adjust for this bias. $P<0.05$ was considered statistically significant.

RESULTS

Literature Search and Studies Characteristics

The detailed flowchart of our literature search was shown in Figure 1. In summary, a total of 175 abstracts and titles were initially identified, in which 36 studies were removed due to duplication. After abstract and title reviewing, 29 articles remained for full-text scanning. Eleven studies were excluded due to no relevant outcomes (n = 8), review and meta-analyses (n = 2), and duplicates (n = 1). Finally, 18 studies including 2054 patients were included in the meta-analysis.[27–31,38–50]

The main characteristics of the included studies were summarized in Table 1. All the studies were published between 2015 and 2020, with 5 studies published before 2018. All the studies reported data related to OS and 12 studies presented data on PFS. About the regions, 8 studies were from Europe, 5 from America and 5 from Asia. As for study type and analysis of HR, 8 studies were multicenter and 13 studies were analyzed by multivariate analysis. Cutoffs of baseline NLR were not the same in these studies. Ten studies used 5 as cutoff to stratify high and low baseline NLR group. Regarding the immunotherapy types, 8 studies assessed anti-CTLA therapy, 7 studies evaluated anti-PD1 therapy, and 2 studies assessed combination therapy. The quality assessment of the selected studies was presented in Additional File 1 (Supplemental Digital Content 1, http://links.lww.com/JIT/A635).

Association Between Baseline NLR and OS

All the eligible studies with 2054 patients were chosen for the pooled analysis of the association between baseline NLR and OS. With great heterogeneity ($I^2=88.3\%$, $P<0.001$), random effect model was adopted and results showed that higher baseline NLR was associated with a poorer OS (HR = 2.46, 95% CI = 1.77, 3.43, $P<0.001$) (Fig. 2A). The fixed effect model and sensitivity analysis did not change the conclusion (Figs. 2A, B).

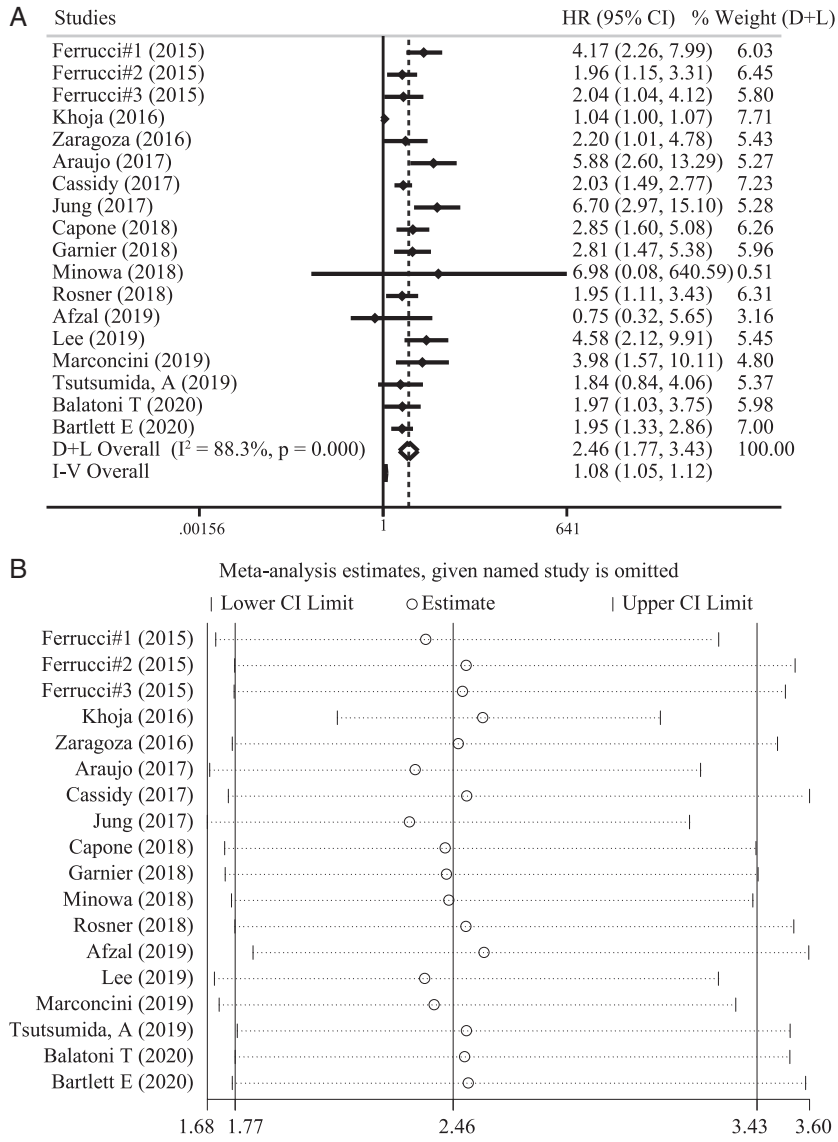

FIGURE 2. Forest plot (A) and sensitivity analysis (B) for the pooled hazard ratio (HR) of overall survival in melanoma patients receiving immunotherapy between high and low baseline neutrophil-to-lymphocyte ratio. Cutoff value was defined in each included study. CI indicates confidence interval.

To explore whether heterogeneity affected the stability of results, we did the subgroup analyses stratified by study year, region, study type, sample size, analysis of HR, cuttoff of baseline NLR and immunotherapy type. The conclusions were consistent in all the subgroup analyses (Table 2). Notably, subgroup analysis based on multivariate analysis demonstrated that elevated baseline NLR were correlated with inferior OS (HR = 2.13, 95% CI = 1.51, 2.99, $P < 0.001$). What's more, the baseline NLR showed prognostic value either in a cutoff of 5 (HR = 2.65, 95% CI = 2.01, 3.49, $P < 0.001$) or less than 5 (HR = 2.15, 95% CI = 1.31, 3.52, $P < 0.001$). In addition, subgroup analysis according to immunotherapy type showed that the prognostic effects of baseline NLR existed in all the subtypes of immunotherapy, including anti-CTLA4 therapy (HR = 2.26, 95% CI = 1.43, 3.59, $P < 0.001$), anti-PD1 therapy (HR = 3.08, 95% CI = 2.21, 4.27, $P < 0.001$), and combination therapy (HR = 1.75, 95% CI = 1.13, 2.72, $P < 0.001$) (Table 2).

Funnel plot identified most of studies over the pseudo 95% CI (Additional File 2, Supplemental Digital Content 1, http://links.lww.com/JIT/A635), and Egger test was used to further detect the presence of publication bias ($P < 0.001$) (Additional File 2, Supplemental Digital Content 1, http://links.lww.com/JIT/A635). Thus, we applied the Duval and Tweedie trim-and-fill method to adjust for this bias. The results showed that no studies were trilled and filled, suggesting that the conclusion was stable.

Association Between Baseline NLR and PFS

Twelve studies with 1435 patients were enrolled to analyze the correlation of baseline NLR and PFS. Due to significant heterogeneity ($I^2 = 37.5\%$, $P = 0.091$), we used random effect model to analyzed the pooled data and results suggested that higher baseline NLR was significantly

TABLE 2. Subgroup Analysis of OS

Subgroup	Cases	Effect Model	HR	Lower CI Limit	Upper CI Limit
Study year					
Before 2018	8	Random	2.58	1.55	4.29
		Fixed	1.06	1.03	1.1
2018 and beyond	10	Random	2.32	1.86	2.88
		Fixed	2.3	1.87	2.84
Region					
Europe	8	Random	2.55	2.03	3.22
		Fixed	2.55	2.03	3.22
America	5	Random	1.99	1.2	3.29
		Fixed	1.06	1.02	1.09
Asia	5	Random	2.99	1.39	6.41
		Fixed	3.3	2.14	5.1
Study type					
Single-center	10	Random	2.16	1.42	3.29
		Fixed	1.07	1.03	1.1
Multicenter	8	Random	2.8	2.06	3.81
		Fixed	2.75	2.15	3.52
Cases					
<100	10	Random	2.59	2.02	3.31
		Fixed	2.52	2.04	3.1
≥ 100	8	Random	2.2	1.37	3.54
		Fixed	1.06	1.03	1.1
Analysis of HR					
Univariate	5	Random	4.05	2.32	7.07
		Fixed	3.81	2.58	5.61
Multivariate	13	Random	2.13	1.51	2.99
		Fixed	1.08	1.04	1.11
Cutoff of NLR					
<5	8	Random	2.15	1.31	3.52
		Fixed	1.05	1.02	1.09
5	10	Random	2.65	2.01	3.49
		Fixed	2.43	2.05	2.88
Immunotherapy type					
Anti-CTLA4	8	Random	2.26	1.43	3.59
		Fixed	1.06	1.03	1.1
Anti-PD1	7	Random	3.08	2.21	4.27
		Fixed	2.8	2.19	3.58
Combination	3	Random	1.75	1.13	2.72
		Fixed	1.75	1.13	2.72

CI indicates confidence interval; CTLA4, cytotoxic T lymphocyte-associated protein 4; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PD-1, programmed cell death-1.

associated with poorer PFS (HR = 2.38, 95% CI = 1.95, 2.89, $P < 0.001$) (Fig. 3A). The fixed effect model and sensitivity analysis did not change the conclusion (Figs. 3A, B).

Subgroup analyses were used to evaluate the stability of results based on study year, region, study type, sample size, analysis of HR, cutoff of baseline NLR and immunotherapy type. The results showed that the trend of the pooled HR for all the subgroups were not changed. Noteworthily, stratified analysis by multivariate analysis suggested worse PFS in the low baseline NLR group (HR = 2.02, 95% CI = 1.73, 2.36, $P < 0.001$). Subgroup analysis according to baseline NLR cutoff showed that worse PFS was noted in high baseline NLR group with 5 as cutoff (HR = 2.32, 95% CI = 1.79, 3.01, $P < 0.001$) or cutoff less than 5 (HR = 2.44, 95% CI = 1.82, 3.27, $P < 0.001$). Moreover, subgroup analysis based on immunotherapy type demonstrated a consistent conclusion in anti-CTLA4 therapy (HR = 2.68, 95% CI = 1.79, 4.02, $P < 0.001$), anti-PD1 therapy (HR = 2.01, 95% CI = 1.64, 2.47, $P < 0.001$), and combination therapy (HR = 3.13, 95% CI = 1.63, 6.03, $P < 0.001$) (Table 3).

The funnel plot was not symmetrical and Egger test detected the presence of publication bias ($P = 0.012$) (Additional File 3, Supplemental Digital Content 1, http://links.lww.com/JIT/A635). The Duval and Tweedie trim-and-fill method were then applied to adjust for this bias and 5 studies was filled, but the conclusion was consistent in both fixed effect model (HR = 1.97, 95% CI = 1.72, 2.25) and random effect model (HR = 2.01, 95% CI = 1.62, 2.51).

DISCUSSION

Malignant melanoma is one of the most common, aggressive and lethal form of skin cancers.[7] Its incidence has steadily increased by about 6.8% annually in the past 5 years, and the number of deaths has decreased from 10,130 to 6850 in 2016 to 2020.[51–55] Notably, that decline reversed in 2021, with 7180 deaths in the United States.[56] Immunotherapy plays a critical role in reducing mortality. However, a significant proportion of patients do not benefit from immunotherapy, which requires biomarkers to predict treatment outcomes and select the most appropriate patients.

NLR is a reflection of the alteration in peripheral blood cell composition, which is associated with systemic inflammation. Inflammation-induced cancer dedifferentiation has been reported to be highly associated with the acquired resistance to cancer immunotherapy.[57] Increasing studies have reported the prognostic value of baseline NLR in melanoma patients receiving immunotherapy.[28,29,46,47] However, a comprehensive analysis is lacking and stronger evidence is needed to highlight the association between baseline NLR and the prognosis of melanoma patients receiving immunotherapy.

Through searching all the relevant studies, 18 studies including 2054 patients were finally enrolled in our study. Pooled data of these studies showed that higher baseline NLR was associated with a poorer OS and PFS. The conclusion was consistent in the fixed effect model, sensitivity analysis and subgroup analysis. Therefore, we concluded that higher baseline NLR is a poor prognostic biomarker for melanoma patients receiving immunotherapy.

The mechanisms underlying the association between high baseline NLR and poor prognosis of melanoma patients receiving immunotherapy are poorly known. Neutrophils have direct and indirect protumor and antitumor effects during the process of tumor initiation and growth. The phenotypic heterogeneity of neutrophils depends on the spatial-specific, temporal-specific, and disease-specific parameters.[58] Moreover, several studies have identified several neutrophils subtypes associated with the protumor or antitumor function.[59–64] It should be highlighted that Zhu and colleagues identified and characterized 7 blood neutrophils clusters through CYTOF mass cytometry in blood from melanoma patients. Among them, cneut2 and cneu5 subtypes displayed the highest ability to produce ROS, which amplify DNA damage and promote tumorigeneses.[64] We could reasonably speculate that these 2 types of neutrophils were increased in the melanoma patients with poor prognosis after receiving immunotherapy. Lymphocytes are considered as the primary effector cell in the immunotherapy, and tumor-infiltrating lymphocytes are prognostic as well as predictive of response to immunotherapy in multiple cancer types.[65] Besides, less blood lymphocytes were reported to be associated with poor prognosis of melanoma patients receiving immunotherapy,[17] because functional lymphocytes remain critically important for antitumor activity.[66]

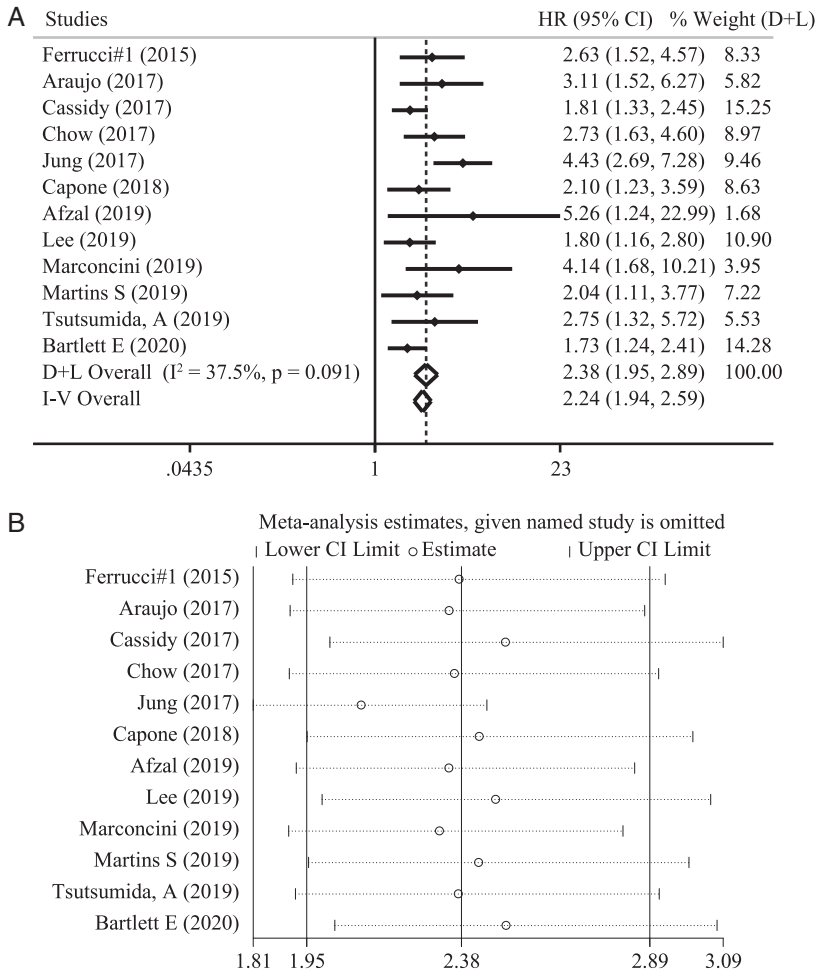

FIGURE 3. Forest plot (A) and sensitivity analysis (B) for the pooled hazard ratio (HR) of progression-free survival in melanoma patients receiving immunotherapy between high and low baseline neutrophil-to-lymphocyte ratio. Cutoff value was defined in each included study. CI indicates confidence interval.

Nonetheless, lymphopenia still could not dampen the prognostic value of neutrophils for melanoma patients receiving immunotherapy,[67] which highlights the better prognostic value of the combined indictor, NLR. NLR is calculated as the counts of neutrophil dividing by lymphocyte, which amplify their effects alone.[37] As a systemic inflammation marker, NLR reflects the balance between the immunosuppressive protumor neutrophils and the adaptive antitumor lymphocytes.[68] Therefore, NLR could be the prognostic biomarker for melanoma patients receiving immunotherapy, and more studies are needed to investigate the underlying mechanisms.

To the best of our knowledge, we are the first to comprehensively analyze the association between baseline NLR and the prognosis of melanoma patients receiving immunotherapy. Some other important strengths of our meta-analysis should be also addressed. For example, appropriate subgroup analyses were performed across studies, and almost consistent findings were obtained, despite the inter-study heterogeneity. Besides, multiple approaches, such as Duval and Tweedie trim-and-fill method, were applied to adjusted for the publication bias, further confirming the robustness of the results.

Admittedly, there are several limitations of our study. First, we found that considerable heterogeneity existed in the meta-analysis, though sensitivity analysis and subgroup analysis did not change the conclusion. Second, funnel plot asymmetry indicated the occurrence of publication bias for both OS and PFS, although the Duval and Tweedie trim-and-fill method indicated the same trend of the results. Third, some of the HRs were extracted from Kaplan-Meier curves for the unavailability of original data, which could lead to the imprecision of the HR. Fourth, we only validated the association between higher baseline NLR and poorer prognosis in melanoma patients receiving immunotherapy without exploring the detailed mechanism. Finally, NLR alone is insufficient to determine which patients are suitable for immunotherapy as it may exclude those patients with high baseline NLR who still benefit from immunotherapy, while our study provided a useful clinical prognostic indicator for the construction of other combined prognostic models for evaluating the efficacy of immunotherapy.

In conclusion, baseline NLR was identified as an independent predictor for the prognosis of melanoma patients receiving immunotherapy. Baseline NLR is a simple, cost-efficient and readily available biomarker that could be used to help predict response to immunotherapy in patients with metastatic or advanced melanoma. Future clinical trials are advocated to determine the association

TABLE 3. Subgroup Analysis of PFS

Subgroup	Cases	Effect Model	HR	Lower CI Limit	Upper CI Limit
Study year					
Before 2018	5	Random	2.72	1.92	3.85
		Fixed	2.48	2.02	3.04
2018 and beyond	7	Random	2.03	1.65	2.49
		Fixed	2.03	1.65	2.49
Region					
Europe	5	Random	2.49	1.92	3.25
		Fixed	2.49	1.92	3.25
America	3	Random	1.88	1.49	2.37
		Fixed	1.87	1.51	2.31
Asia	4	Random	2.96	1.74	5.05
		Fixed	2.76	2.06	3.71
Study type					
Single-center	6	Random	1.91	1.6	2.29
		Fixed	1.91	1.6	2.29
Multicenter	6	Random	3	2.35	3.83
		Fixed	3	2.35	3.83
Cases					
<100	8	Random	2.26	1.87	2.74
		Fixed	2.26	1.87	2.74
≥ 100	4	Random	2.55	1.55	4.22
		Fixed	2.21	1.77	2.76
Analysis of HR					
Univariate	3	Random	3.97	2.74	5.76
		Fixed	3.97	2.74	5.76
Multivariate	9	Random	2.02	1.73	2.36
		Fixed	2.02	1.73	2.36
Cutoff of NLR					
<5	5	Random	2.32	1.79	3.01
		Fixed	2.32	1.79	3.01
5	7	Random	2.44	1.82	3.27
		Fixed	2.21	1.85	2.62
Immunotherapy type					
Anti-CTLA4	4	Random	2.68	1.79	4.02
		Fixed	2.43	1.96	3.01
Anti-PD1	6	Random	2.01	1.64	2.47
		Fixed	2.01	1.64	2.47
Combination	2	Random	3.13	1.63	6.03
		Fixed	3.13	1.63	6.03

CI indicates confidence interval; CTLA4, cytotoxic T lymphocyte-associated protein 4; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; PD-1, programmed cell death-1; PFS, progression-free survival.

between baseline NLR and the outcomes of immunotherapy, as well as the optimal cutoff of baseline NLR, to select the suitable population for immunotherapy.

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Conflicts of Interest/Financial Disclosures

None reported. All authors have declared there are no financial conflicts of interest with regard to this work.

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