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ORIGINAL ARTICLE

Pretreatment neutrophil-to-lymphocyte ratio is associated with outcome of advanced-stage cancer patients treated with immunotherapy: a meta-analysis

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Abstract

Background To investigate the association between pretreatment blood neutrophil-to-lymphocyte ratio (NLR) and clinical outcomes for advanced-stage cancer patients treated with immunotherapy.

Methods We conducted a comprehensive literature search to assess the relationship between pretreatment blood NLR and overall survival (OS) or progression-free survival (PFS) in advanced-stage cancer patients treated with immunotherapy. Published data including hazard ratios (HRs) and related 95% confidence interval (CI) were extracted. Pooled estimates of treatment outcomes were calculated using RevMan 5.3.5.

Results Twenty-seven studies with 4647 patients were included in the current study. The pooled results suggested that high pretreatment blood NLR was correlated with significant shorter OS (HR = 1.98, 95% CI 1.66–2.36, $P < 0.001$) and PFS (HR = 1.78, 95% CI 1.48–2.15, $P < 0.001$). Subgroup analysis stratified by study targets revealed that anti-VEGF/VEGFR therapy (HR = 2.04, 95% CI 1.61–2.60, $P < 0.001$) and immune checkpoints blockade (HR = 2.16, 95% CI 1.86–2.51, $P < 0.001$) were significantly associated with inferior OS while other targets (HR = 1.63, 95% CI 0.89–2.99, $P = 0.120$) were not associated with OS. There was no correlation between distinct NLR cutoff values and OS ($r^{\text{Pearson}} = 0.218$, $P = 0.329$) or PFS benefit ($r^{\text{Pearson}} = -0.386$, $P = 0.140$). Of note, HRs of PFS showed significant correlation with HRs of OS ($r^{\text{Pearson}} = 0.656$, $P = 0.015$).

Conclusion Elevated pretreatment blood NLR was a promising prognostic and predictive biomarker for advanced-stage cancer patients treated with immunotherapy.

Keywords Cancer · Neutrophil-to-lymphocyte ratio · Immunotherapy · Biomarker · Immune microenvironment

Abbreviations

ASCO	American Society of Clinical Oncology
CI	Confidence interval
ESMO	European Society for Medical Oncology
HR	Hazard ratio
NLR	Neutrophil-to-lymphocyte ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses statement
SPSS	Statistical Package for Social Sciences
WCLC	World Lung Cancer Conference

Introduction

Cancer still remains the most threatening disease to human health worldwide [1]. Although we have a deeper understanding to cancer with the completion of genomic sequence, the effective therapeutic strategies are still limited and

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long-term survival rate remains disappointing. Recently, with the improvement in the understanding of the role of immune system in the tumor development, and immune response to cancer, immunotherapy has experienced a rapid development and plays a critical role in the current cancer therapy [2, 3]. The advent of cancer immunotherapy, especially the immune checkpoints blockade, has brought about a paradigm shift in the landscape of advanced-stage cancer treatment [4].

The ultimate aim of immunotherapy was to effectively establish or enhance the immune response to cancer, which can be achieved via distinct strategies including tumor vaccination, adoptive immune cells transfer, and blockade of inhibitory signal pathways in TME [5–7]. The most successful case refers to the immune checkpoints inhibitors anti-PD-1 and CTLA-4 that have recently obtained huge success in several types of solid tumors including melanoma, renal cell carcinoma, NSCLC, etc. [4, 6, 8, 9]. In addition, another effective strategy was against VEGF and its receptor, VEGFR. The activation of VEGF/VEGFR could promote the angiogenesis in TME, which is one of the significant hallmarks of cancers [10]. Blockade of VEGF/VEGFR via antibody or small-molecule kinase inhibitors also showed the encouraging anti-tumor effect in several solid tumors [11–15]. However, both blockade of immune checkpoints and VEGF/VEGFR were confronted with the same obstacle to further expand the survival benefit: lack of the reliable biomarkers. For immune checkpoints inhibitors, published data suggested that the response rate to anti-PD-1/PD-L1 monotherapy was approximately 30% [16, 17]. Although several factors including PD-L1 expression, tumor infiltrating lymphocytes, tumor mutation load, neoantigen and so on, showed the predictive value in preclinical or clinical studies [4, 18–20], the optimal predictive biomarkers still remain undetermined. For anti-VEGF/VEGFR, researchers have put so much effort into the exploration of predictive biomarkers to anti-VEGF/VEGFR over these years, but the results were disappointing [21, 22]. To date, there is no study to report the reliable biomarkers of anti-VEGF/VEGFR therapy in advanced cancers.

Emerging evidence suggested that tumor-associated inflammation plays a significant role in the distinct stages of cancer development, including initiation, promotion, invasion and distant metastasis [23, 24]. Inflammation could also influence the host immune response to cancers and could be applied to cancer immunotherapy [24–26]. Several studies attempted to utilize the inflammatory mediators and the measurable parameters of systemic inflammatory response to predict the therapeutic effect or survival in patients with advanced cancers. The latter category includes albumin, C-reactive protein and neutrophil-to-lymphocyte ratio (NLR) that have been incorporated in prognostic scores for different types of cancer [27]. NLR was defined as neutrophil counts divided by lymphocyte counts. Theoretically, lymphopenia reflects the impaired cell-mediated immunity, whereas neutrophilia represents the response to systematic inflammation [23]. Elevated NLR would be associated with poor response to immunotherapy in patients with advanced cancers. Recently, several studies investigated the predictive value of pretreatment blood NLR in advanced cancer patients treated with immunotherapy [28–31], but the results remain inconsistent. Therefore, we conducted this meta-analysis to systematically and comprehensively evaluate both the predictive and prognostic significance of pretreatment blood NLR for advanced-stage cancer patients treated with immunotherapy. The pooled results could be used on daily clinical practice and help physicians to stratify patients in future clinical trials of immunotherapy.

Methods

Search strategy

We carried out a comprehensive online search to select the potential studies on PubMed, Web of Science, EMBASE, and Cochrane Library up to May 2017 without language restrictions. The main keywords used for the online search were “neoplasms”, “tumor”, “cancer”, “neutrophil”, “lymphocyte”, “ratio”, “survival” and “prognosis”. The full search strategies are listed in Supplementary Table S1. Abstracts from conference proceedings 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 identify unpublished studies. We also manually searched the reference lists of the selected articles until no additional potential articles could be identified.

Inclusion criteria

The following items were the inclusion criteria for each eligible publication: (1) studies investigated the patients with advanced cancer treated with immunotherapy (targeting tumor immune microenvironment including VEGF, VEGFR, CTLA-4, PD-1, PD-L1, etc.); (2) studies reported the predictive and/or prognostic value of pretreatment NLR; (3) data were presented 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) the full text was available. Case report, reviews, comments, editorials, letters or articles unrelated with our topics were excluded. First, the titles and abstracts were screened to assess the eligibility and then the full text of articles were reviewed. According to the inclusion criteria, two reviewers

(Meng Qiao and Chunxia Su) conducted the selection of all included publications independently. The third reviewer resolved the discrepancy on whether an article should be included.

Data extraction

Two reviewers independently carried out the data extraction on the basis of Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA). The following items were extracted from each study: first author's name, published year, inclusion period, study design, tumor type and stage, country of origin study, number of patients, average ages, treatment, main targets, cut-off value of NLR, time of NLR assessment, follow-up period and study endpoints. Two researchers (Tao Jiang and Shengxiang Ren) also independently extracted the HRs and the associated 95% CIs for PFS and OS outcomes to assess the therapeutic efficacy. HRs from multivariate analyses were preferentially extracted. Where available, we included the most updated survival data.

Quality assessment

As the previous studies reported [32, 33], two reviewers independently investigated the risk of bias of the included studies using a set of modified predefined criteria: (1) Representativeness of population; (2) Non exposed cohort; (3) Ascertainment of exposure; (4) Outcome not present at start of study; (5) Appropriate confounding measurement and account; (6) Sufficient measurement of outcomes; (7) Completeness of follow-up. Studies with a score of 7 or higher were considered as high quality and with a score of less than 7 defining low quality. Any disagreement was resolved by discussion.

Statistical analysis

Pretreatment blood NLR was defined as the ratio of the number of neutrophils to the number of lymphocytes in the peripheral blood before any treatment. 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 first-line treatment initiation to the date of cancer progression or death or was censored at the last tumor assessment. Cochran's Q test and I^2 statistic were used to test the heterogeneity of different studies. 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. [34]. The I^2 test was used to test for statistical heterogeneity and the I^2 statistic was used to assess the extent of variability attributable to statistical heterogeneity across studies. $I^2 < 25\%$ was 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. PFS and OS were calculated using effect variables. Publication bias was assessed using funnel plots, Begg's and Egger's tests. A sensitivity analysis was conducted by excluding the studies with the low-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 RevMan 5.3.5 (http://tech.cochrane.org/revman).

Results

Selection of eligible studies

Totally, we identified 2054 studies that met the inclusion criteria after searching the relevant online databases; 428 of them were excluded due to duplicate records. By verifying related terms in the titles and abstracts, we excluded 1425 irrelevant articles, and another 190 articles were excluded after the assessment of full text. Finally, 27 studies were selected for the present meta-analysis [28–31, 35–57]. A flowchart describing the eligible study selection was shown in Fig. 1.

Characteristics of included studies and quality assessment

A total of 4647 patients with six different kinds of advanced cancers were included in the current study. The baseline characteristics of the included studies are summarized in Table 1. In summary, all studies were published between 2012 and 2017. 26 of the included studies were retrospective studies and only one was prospective study. Fifteen studies focused on metastatic renal cell carcinoma and 4 of them studied metastatic melanoma. Other types of cancer included advanced NSCLC, hepatocellular carcinoma, gastric cancer and metastatic colorectal cancer. Ten studies were conducted in Asia, 6 in America, 10 in Europe and one covered multiple countries. VEGF/VEGFR and CTLA-4 were the main targets. The most common cut-off value of NLR was 3 and median cut-off value was 3.02. Twenty-one studies investigated the association between pretreatment NLR and OS for patients with advanced cancer, whereas 15 studies reported PFS outcome. Of note, 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 published figures. According to the risk assessment scale, we evaluated the eligible studies using the aspects mentioned

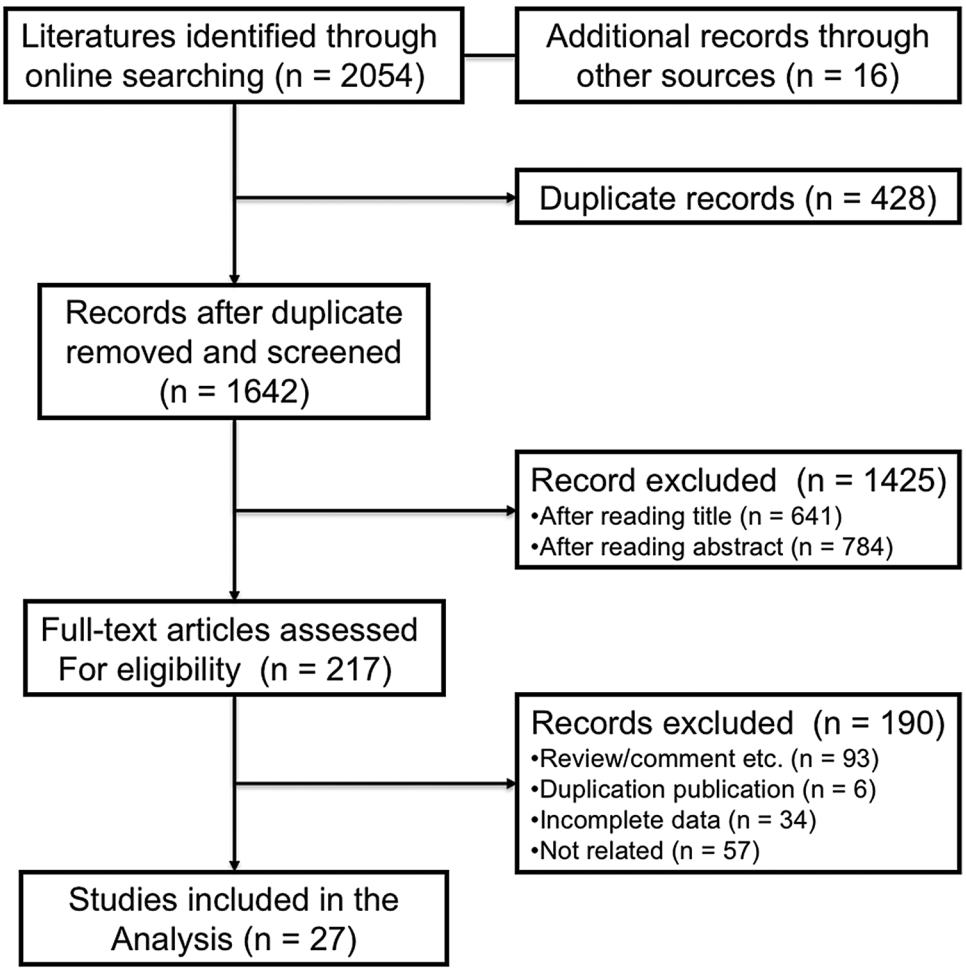

Fig. 1 Flow chart of the eligible studies in the current meta-analysis

above [32]. The results of quality assessment are listed in Supplemental Table S2. Twelve studies had quality scores of 7 or less, and 15 studies had a score of more than 7.

Association between pretreatment NLR and overall survival

Twenty-one studies with 3891 cases were included in the final analysis of pretreatment NLR and OS. The pooled result showed that high pretreatment NLR was correlated with significantly poorer OS (HR = 1.98, 95% CI 1.66–2.36, $P < 0.001$; Fig. 2a), among which metastatic renal cell carcinoma ($n = 11$, HR = 2.18, 95% CI 1.63–2.92, $P < 0.001$) and metastatic melanoma ($n = 3$, HR = 2.17, 95% CI 1.85–2.55, $P < 0.001$) were two common types of cancer involved. We summarized the results of the subgroup analyses by the potential sources of heterogeneity among several related clinical parameters of the included studies for OS in Table 2. The pooled results for most subgroups were not markedly changed by the study features. However, there was only marginally statistical significance in patients with hepatocellular carcinoma when we pooled three studies (HR = 1.72, 95% CI 1.00–2.96, $P = 0.050$; $I^2 = 82\%$, $P = 0.004$). Significant difference was not indicated in patients with gastric cancer (HR = 1.28, 95% CI 0.73–2.25, $P = 0.368$). Of note, stratified analysis by study targets of TME suggested that anti-VEGF/VEGFR ($n = 14$; HR = 2.04, 95% CI 1.61–2.60, $P < 0.001$; $I^2 = 84\%$, $P < 0.001$) and immune checkpoints blockade ($n = 4$; HR = 2.16, 95% CI 1.86–2.51, $P < 0.001$; $I^2 = 0\%$, $P = 0.960$) were significantly correlated with inferior OS while other targets (including IL-2 receptor and oncolytic viruses) ($n = 2$; HR = 1.63, 95% CI 0.89–2.99, $P = 0.120$; $I^2 = 34\%$, $P = 0.220$) were not associated with OS, indicating the prognostic value of pretreatment NLR in these studies. Interestingly, the pooled HRs did not significantly alter by pretreatment NLR cutoff value but it can reduce the level of statistical heterogeneity (NLR > 3, $I^2 = 79\%$; NLR > 4, $I^2 = 0\%$; NLR > 5, $I^2 = 0\%$;). We also noted the significant reduction of statistical heterogeneity by median age (≤ 60, $I^2 = 7\%$) and main target of immune checkpoints ($I^2 = 0\%$).

Table 1 Baseline characteristics of included studies ($n=27$)

Authors	Year	Inclusion period	Study design	Tumor type and stage	Country of origin	Number of cases	Age (years)	Treatment	Main targets	NLR cutoff	Time of assessment	Follow-up period (months)	Study endpoints	Quality score
Keizman et al.	2012	2004–2011	Retrospective	Metastatic renal cell carcinoma	USA	133	61 (24–85)	Sunitinib	VEGFR, PDGFR	> 3	Pretreatment	37 (5–85)	RR, PFS, OS	8
Botta et al.	2013	2008–2011	Retrospective	Advanced non-small cell lung cancer	USA	112	62	Bevacizumab	VEGF	> 4	Pretreatment	15	RR, PFS, OS	7
Cetin et al.	2013	2008–2011	Retrospective	Metastatic renal cell carcinoma	Turkey	100	58 (24–80)	VEGF-TKIs	VEGF	>3.04	Pretreatment	15 (1–53)	PFS, OS	8
Dirican et al.	2013	2006–2011	Retrospective	Metastatic renal cell carcinoma	Turkey	23	59 (43–76)	Sunitinib	VEGFR, PDGFR	> 3	Pretreatment	13 (2–41)	RR, PFS, OS	8
Zheng et al.	2013	2011–2012	Retrospective	Hepatocellular carcinoma	China	65	55	Sorafenib	VEGFR, PDGFR	> 4	Pretreatment	9 (2–26)	RR, PFS, OS	8
Kobayashi et al.	2013	2008–2012	Retrospective	Metastatic renal cell carcinoma	Japan	58	64 (53–81)	Sorafenib, sunitinib	VEGFR, PDGFR	> 3.32	Pretreatment	12 (1–49)	PFS, OS	8
Fonseca et al.	2014	2009–2013	Retrospective	Hepatocellular carcinoma	Brazil	120	60 (19–80)	Sorafenib	VEGFR, PDGFR	> 3.5	Pretreatment	11 (0.5–27)	OS	8
Gunduz et al.	2014	2009–2013	Retrospective	Metastatic renal cell carcinoma	Turkey	45	63 (41–90)	Sunitinib, sorafenib and pazopanib	VEGFR, PDGFR	> 2	Pretreatment	24	PFS, OS	7
Keizman et al.	2014	2004–2013	Retrospective	Metastatic renal cell carcinoma	Israel	278	63 (22–87)	Sunitinib	VEGFR, PDGFR	> 3	Pretreatment	55 (12–109)	RR, PFS, OS	8
Dana et al.	2014	2006–2013	Retrospective	Metastatic renal cell carcinoma	Israel	145	65	Sunitinib	VEGFR, PDGFR	> 3	Pretreatment	NR	PFS, OS	6

Table 1 (continued)

Authors	Year	Inclusion period	Study design	Tumor type and stage	Country of origin	Number of cases	Age (years)	Treatment	Main targets	NLR cutoff	Time of assessment	Follow-up period (months)	Study endpoints	Quality score
Park et al.	2014	2005–2011	Retrospective	Metastatic celaer cell renal cell carcinoma	Korea	109	61 (49–67)	Sunitinib	VEGFR, PDGFR	> 2.5	Pretreatment	24 (10–35)	OS	8
Wang et al.	2014	2006–2011	Retrospective	Metastatic renal cell carcinoma	China	41	53 (24–81)	Sorafenib	VEGFR, PDGFR	> 4	Pretreatment	NR	PFS	6
Ferrucci et al.	2015	2010–2013	Retrospective	Metastatic melanoma	Italy	187	62 (33–87)	Ipilimumab	CTLA-4	> 5	Pretreatment	NR	RR, PFS, OS	6
Namikawa et al.	2015	2007–2012	Retrospective	Gastric cancer	Japan	190	68 (56–80)	Protein-bound polysaccha- ride K	Unknown	> 2.5	Pretreatment	NR	OS	6
Santoni et al.	2015	2005–2014	Retrospective	Metastatic renal cell carcinoma	Italy	151	64 (29–88)	Sunitinib, sorafenib and pazopanib	VEGFR, PDGFR	> 3	Pretreatment	52	PFS, OS	7
Gardini et al.	2016	2012–2015	Retrospective	Hepatocellular carcinoma	Italy	56	NR	Sorafenib	VEGFR, PDGFR	> 3	Pretreatment	NR	RR, PFS, OS	6
Chrom et al.	2016	2010–2014	Retrospective	Metastatic renal cell carcinoma	Poland	266	61 (22–85)	Sunitinib, sorafenib and pazopanib	VEGFR, PDGFR	> 4	Pretreatment	NR	OS	6
Ferrucci et al.	2016	2010–2012	Prospective	Metastatic melanoma	Italy	720	NR	Ipilimumab	CTLA-4	> 3	Pretreatment	17	PFS, OS	7
Keizman et al.	2016	2004–2014	Retrospective	Metastatic Chromophobe Renal Cell Carcinoma	Israel and USA	72	64 (26–87)	Sunitinib	VEGFR, PDGFR	> 3	Pretreatment	NR	RR, PFS, OS	6
Passardi et al.	2016	2007–2012	Retrospective	Metastatic colorectal cancer	Italy	289	65 (33–83)	Bevacizumab	VEGF	> 3	Pretreatment	36 (1–65)	PFS, OS	8

Table 1 (continued)

Authors	Year	Inclusion period	Study design	Tumor type and stage	Country of origin	Number of cases	Age (years)	Treatment	Main targets	NLR cutoff	Time of assessment	Follow-up period (months)	Study endpoints	Quality score
Taipale et al.	2016	2007–2012	Retrospective	Solid tumors	Finland	290	NR	Adenoviral oncolytic immunotherapy	Oncolytic viruses	NR	Pretreatment	NR	PFS, OS	6
Zhang et al.	2016	2006–2014	Retrospective	Metastatic renal cell carcinoma	China	373	58 (17–90)	Sunitinib, sorafenib	VEGFR, PDGFR	> 2.2	Pretreatment	NR	PFS, OS	6
Bagley et al.	2017	2015–2016	Retrospective	Advanced non-small cell lung cancer	USA	175	68 (33–88)	Nivolumab	PD-1	> 5	Pretreatment	NR	RR, PFS, OS	6
Cassidy et al.	2017	2006–2011	Retrospective	Metastatic melanoma	USA	197	NR	Ipilimumab	CTLA-4	> 5	Pretreatment	54 (5-109)	PFS, OS	8
Jung et al.	2017	2014–2015	Retrospective	Metastatic melanoma	Korea	104	58 (50–66)	Ipilimumab	CTLA-4	> 5	Pretreatment	NR	RR, PFS, OS	6
Kuzman et al.	2017	2003–2012	Retrospective	Metastatic renal cell carcinoma	USA	71	55 (49–59)	High dose interleukin-2	Interleukin-2 receptor	> 4	Pretreatment	NR	RR, PFS, OS	6
Tanaka, et al.	2017	NR	Retrospective	Metastatic renal cell carcinoma	Japan	277	66 (59–73)	Sunitinib, sorafenib, axitinib, and pazopanib	VEGFR, PDGFR	> 3.6	Pretreatment	18 (8–30)	OS	8

NR not reported, *VEGF* vascular endothelial growth factor, *PDGF* platelet derived growth factor, *CTLA-4* cytotoxic T-lymphocyte associated protein 4, *PD-1* programmed death 1, *RR* response rate, *PFS* progression-free survival, *OS* overall survival

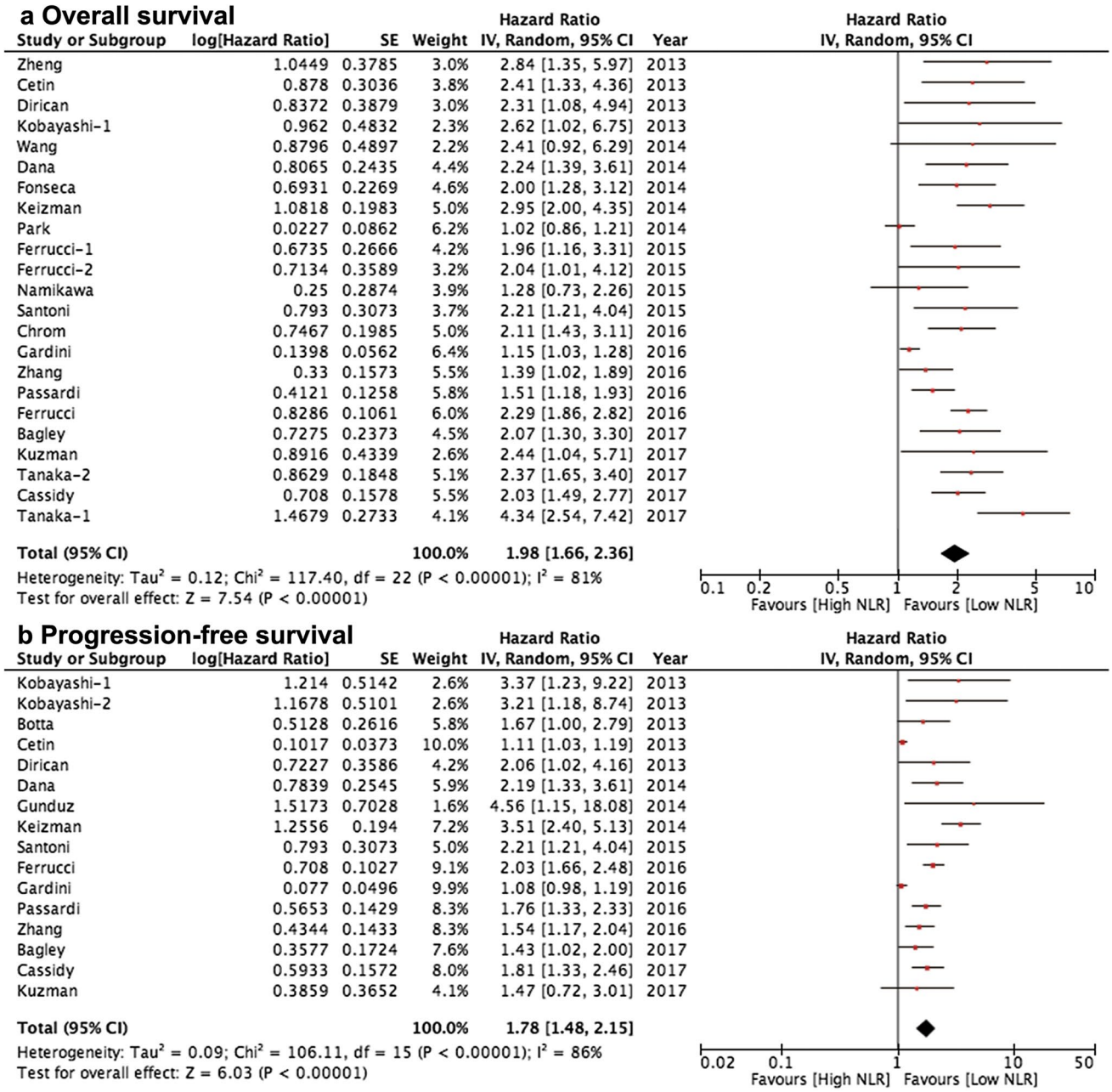

Fig. 2 Meta-analysis of the associations between pretreatment blood neutrophil-to-lymphocyte ratio and **a** overall survival, **b** progression-free survival

Association between pretreatment NLR and progression-free survival

Fifteen studies with 2793 cases were included in the final analysis of pretreatment NLR and PFS. The pooled result suggested that low pretreatment NLR was correlated with significantly longer PFS (HR = 1.78, 95% CI 1.48–2.15, $P < 0.001$; Fig. 2b), among which metastatic renal cell carcinoma ($n = 9$, HR = 2.11, 95% CI 1.47–3.02, $P < 0.001$; $I^2 = 85\%$, $P < 0.001$) was the most common types of cancer involved. Table 2 lists the results of the subgroup analyses by the potential sources of heterogeneity among several related clinical parameters of the included studies for PFS. The pooled results for most subgroups were not markedly changed by the study characteristics. However, there was no statistical significance in patients with hepatocellular carcinoma (HR = 1.08, 95% CI 0.98–1.20, $P = 0.129$). Most stratified factors cannot reduce the level of statistical heterogeneity. However, stratified analysis by pretreatment NLR cutoff value could significantly reduce the level

Table 2 Subgroup analyses of the associations between NLR and survival

Variables	No of studies	Test of association			Test of heterogeneity	
		HR	95% CI	*P* value	I^2	*P* value
Overall survival						
Total	21	1.98	1.66–2.36	< 0.001	81%	< 0.001
Publication year						
Before year 2015	9	2.15	1.46–3.16	< 0.001	82%	< 0.001
After year 2015	12	1.92	1.55–2.37	< 0.001	82%	< 0.001
Initial inclusion period						
Before year 2010	14	1.86	1.49–2.32	< 0.001	73%	< 0.001
After year 2010	6	1.94	1.37–2.74	< 0.001	87%	< 0.001
Study design						
Retrospective	20	1.96	1.63–2.34	< 0.001	79%	< 0.001
Prospective	1	2.29	1.86–2.82	< 0.001	–	–
Tumor types						
Metastatic renal cell carcinoma	11	2.18	1.63–2.92	< 0.001	82%	< 0.001
Advanced non-small cell lung cancer	1	2.07	1.30–3.30	< 0.001	–	–
Hepatocellular carcinoma	3	1.72	1.00-2.96	0.050	82%	0.004
Gastric cancer	1	1.28	0.73–2.25	0.368	–	–
Metastatic colorectal cancer	1	1.76	1.33–2.32	0.001	–	–
Metastatic melanoma	3	2.17	1.85–2.55	< 0.001	0%	0.890
Research region						
Asia	7	1.96	1.32–2.91	< 0.001	84%	< 0.001
Europe and America	11	1.92	1.53–2.41	< 0.001	80%	< 0.001
Others	3	2.06	1.49–2.85	< 0.001	66%	0.030
Sample size						
> 100	14	1.96	1.10–2.40	< 0.001	80%	< 0.001
≤ 100	7	2.09	1.36–3.20	0.001	71%	0.002
Median age (years)						
> 60	11	2.03	1.56–2.63	< 0.001	81%	< 0.001
≤ 60	7	1.85	1.51–2.26	< 0.001	7%	0.370
Main targets						
VEGF/VEGFR	14	2.04	1.61–2.60	< 0.001	84%	< 0.001
Immune checkpoints	4	2.16	1.86–2.51	< 0.001	0%	0.960
Others	2	1.63	0.89–2.99	0.120	34%	0.220
NLR cutoff						
> 3	18	2.17	1.78–2.63	< 0.001	79%	< 0.001
> 4	7	2.11	1.77–2.53	< 0.001	0%	1.000
> 5	3	2.03	1.63–2.53	< 0.001	0%	1.000
Follow-up period (months)						
> 24	4	2.05	1.51–2.78	< 0.001	65%	0.030
≤ 24	7	2.20	1.49–3.24	< 0.001	88%	< 0.001
NR	10	1.73	1.37–2.18	< 0.001	67%	0.001
Study quality						
> 7	10	2.17	1.61–2.92	< 0.001	84%	< 0.001
≤ 7	11	1.84	1.45–2.33	< 0.001	79%	< 0.001
Progression-free survival						
Total	15	1.78	1.48–2.15	< 0.001	86%	< 0.001
Publication year						
Before year 2015	7	2.28	1.41–3.69	< 0.001	88%	< 0.001
After year 2015	8	1.60	1.26–2.05	< 0.001	85%	< 0.001

Table 2 (continued)

Variables	No of studies	Test of association			Test of heterogeneity	
		HR	95% CI	*P* value	I^2	*P* value
Initial inclusion period						
Before year 2010	12	1.97	1.51–2.57	< 0.001	84%	< 0.001
After year 2010	3	1.46	0.93–2.28	0.010	94%	< 0.001
Study design						
Retrospective	14	1.74	1.44–2.10	< 0.001	83%	< 0.001
Prospective	1	2.03	1.66–2.47	< 0.001	–	–
Tumor types						
Metastatic renal cell carcinoma	9	2.11	1.47–3.02	< 0.001	85%	< 0.001
Advanced non-small cell lung cancer	2	1.50	1.13–1.99	0.005	0%	0.620
Hepatocellular carcinoma	1	1.08	0.98–1.20	0.129	–	–
Metastatic colorectal cancer	1	1.51	1.18–1.95	0.001	–	–
Metastatic melanoma	2	1.96	1.66–2.32	< 0.001	0%	0.540
Research region						
Asia	2	2.14	1.21–3.80	0.009	47%	0.150
Europe and America	11	1.57	1.30–1.89	< 0.001	84%	< 0.001
Others	2	2.36	1.52–3.68	< 0.001	76%	0.020
Sample size						
> 100	9	1.91	1.62–2.25	0.020	51%	0.040
≤ 100	5	1.21	1.03–1.42	0.020	61%	0.020
Median age (years)						
> 60	8	2.17	1.68–2.80	< 0.001	53%	0.030
≤ 60	4	1.37	1.03–1.81	0.030	64%	0.040
Main targets						
VEGF/VEGFR	10	1.80	1.43–2.25	< 0.001	85%	< 0.001
Immune checkpoints	3	1.80	1.48–2.19	< 0.001	35%	0.220
NLR cutoff						
> 3	13	1.92	1.51–2.44	< 0.001	84%	< 0.001
> 4	3	1.61	1.30-2.00	< 0.001	0%	0.580
> 5	2	1.63	1.30–2.04	< 0.001	2%	0.310
Follow-up period (months)						
> 24	4	2.19	1.58–3.04	< 0.001	68%	0.020
≤ 24	6	1.54	1.22–1.93	< 0.001	87%	< 0.001
NR	5	1.43	1.10–1.86	0.008	72%	0.007
Study quality						
> 7	6	2.06	1.38–3.10	< 0.001	90%	< 0.001
≤ 7	9	1.67	1.28–2.18	< 0.001	83%	< 0.001

of statistical heterogeneity (NLR > 3, $I^2 = 84\%$; NLR > 4, $I^2 = 0\%$; NLR > 5, $I^2 = 2\%$;) while the pooled HRs did not significantly alter.

Correlation between distinct NLR cutoff values and clinical outcome

As we previously mentioned, stratified analysis by pretreatment NLR cutoff value could significantly reduce the level of statistical heterogeneity for both OS and PFS. We further investigated the correlation between distinct NLR cutoff values and clinical outcome of advanced cancer patients treated with immunotherapy. As shown in Fig. 3a, the results indicated that there was no correlation between distinct NLR cutoff values and OS benefit ($r^{\text{Pearson}} = 0.218$, $P = 0.329$). Although higher NLR cutoff value seemed to be associated with the decreased HRs of PFS, there was no statistical significance ($r^{\text{Pearson}} = -0.386$, $P = 0.140$; Fig. 3b). Interestingly, HRs of PFS showed significant correlation with HRs of OS ($r^{\text{Pearson}} = 0.656$, $P = 0.015$), indicating PFS was a potential surrogate for OS in these trials' designs (Supplemental Figure S1).

Publication bias

As shown in Supplemental Figure S2, the funnel plots were almost symmetrical and the test results indicated that no publication bias existed regarding the HRs of OS (Begg's test, $P = 0.673$; Egger's test, $P = 0.100$) or PFS (Begg's test, $P = 0.760$; Egger's test, $P = 0.356$).

Discussion

To our best knowledge, this is the first time to report that pretreatment blood NLR is associated with outcome of advanced-stage cancer patients treated with immunotherapy. The present study summarized the available evidence from twenty-seven studies with a total of 4647 cases. The pooled results indicated that elevated pretreatment blood NLR was significantly associated with inferior OS (HR = 1.98, $P < 0.001$) and PFS (HR = 1.78, $P < 0.001$) in all groups. Subgroup analyses stratified by publication year, initial inclusion period, study design, research region, sample size, median age, follow-up period, main targets, NLR cutoff and quality scores showed that the results remained constant. It is worth mentioning that there was no correlation between distinct NLR cutoff values and OS benefit. Although higher NLR cutoff value seemed to be correlated with the decreased HRs of PFS, there was no statistical significance. Notably, HRs of PFS showed significant correlation with HRs of OS, suggesting PFS was a potential surrogate for OS in these trials' designs.

There have been two high-quality published meta-analyses to investigate the prognostic value of pretreatment blood NLR in advanced cancer patients. The first study included 100 studies incorporating a total of 40,559 patients and the pooled analyses suggested that a high NLR was associated with an adverse OS in all groups (HR = 1.81, 95% CI 1.67–1.97; $P < 0.001$) [58]. Furthermore, NLR greater than cutoff was also significantly associated poor PFS and DFS and these effects were observed in all disease subgroups, sites and stages. In another study, the authors included 66 studies involving a total of 24,536 patients for the meta-analysis [32]. Pooled results indicated high pretreatment NLR was correlated with inferior OS (HR = 1.70, 95% CI 1.57–1.84; $P < 0.001$) and PFS (HR = 1.70, 95% CI 1.57–1.84; $P < 0.001$) in advanced cancers. Similarly, the results remain constant in the subgroup analyses. However, both studies just investigated the prognostic role of NLR in advanced cancers, whether pretreatment NLR had the predictive value in patients with advanced tumor treated with immunotherapy remains unknown. In our study, we comprehensively demonstrated both the predictive and prognostic value of pretreatment blood NLR in advanced cancer patients treated with immunotherapy. The integrated results elucidated that elevated pretreatment blood NLR was significantly associated with poor OS and PFS in all groups, suggesting pretreatment blood NLR was a promising predictive and prognostic biomarker in advanced cancer patients treated with immunotherapy. Taken together with previous meta-analyses, well-designed, prospective clinical trials are needed to confirm the prominent role of pretreatment blood NLR in advanced cancer patients treated with immunotherapy. In addition, we performed the correlation analysis between NLR cutoff value and OS/PFS benefit. The result showed that different NLR cutoffs were not correlated with OS but higher cutoff seemed to be associated with less PFS benefit. Similarly, Mei et al. reported that higher cutoff value was associated with worse PFS (HR = 2.23, 95% CI 1.54–3.23; $P = 0.019$). However, the optimal NLR cutoff value remains undetermined and further large-scale prospective studies are warranted.

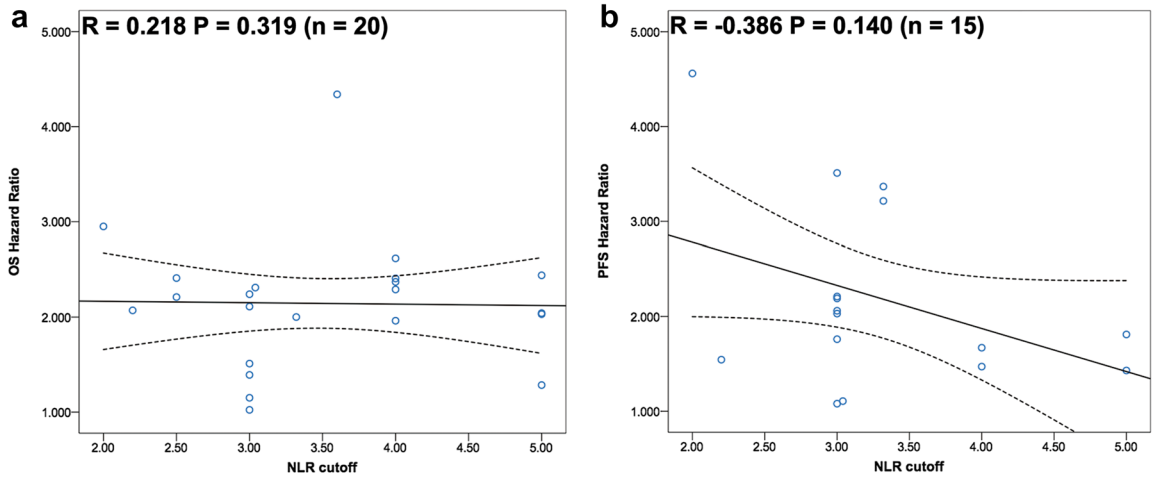

Fig. 3 Correlation analysis between pretreatment blood neutrophil-to-lymphocyte ratio and **a** overall survival, **b** progression-free survival

The relationship between inflammation and cancer has been extensively explored for a long period. In the nineteenth century, Rudolf Virchow had observed the presence of leukocytes within tumors giving the first indication of potential relationship between inflammation and cancer [23]. Subsequently, a series of studies demonstrated that inflammation could promote the tumor initiation by secreting growth factors, cytokines or inducing gene mutations [59–61]. Epidemiological study indicated that about 25% of all cancer cases could ascribe to infection and chronic inflammation [62]. Although the accurate molecular mechanism remains largely unknown, the role of inflammation in cancer initiation, promotion, invasion and distant metastasis has been gradually acknowledged. Hence, several studies attempted to use the inflammatory mediators and measurable parameters of systemic inflammatory response to predict the therapeutic effect or prognosis in patients with advanced cancers. Neutrophils could substantially contribute to cancer progression in multiple ways including direct effect on the tumor cells and indirect effect on the TME [63]. Neutrophils and other immune cells such as MDSC and macrophages could also secrete tumor growth promoting factors including TGF-beta, VEGF, IL-6, IL-8 and matrix metalloproteinases [58]. Furthermore, a recent study revealed a strong negative correlation between neutrophil and CD8+ cellular content in NSCLC [64], suggesting neutrophilia as an inflammatory response to inhibit anti-tumor immune response via suppressing the cytotoxic activity of immune cells especially activated T cells [65]. Lymphocytes play an important role in the anti-tumor immune response. The increased infiltration of lymphocytes in the tumor region has been correlated with better responsiveness to therapy and prognosis in patients with solid tumors [66]. Theoretically, lymphopenia reflects the impaired cell-mediated immunity, whereas neutrophilia represents the response to systematic inflammation. Therefore, elevated NLR would be associated with poor response to immunotherapy in patients with advanced cancers.

The TME is being increasingly recognized as a significant element in cancer progression, immune-escaping and metastatic dissemination [67]. TME-targeting therapies have achieved huge success in the treatment of advanced solid tumors. The most successful cases were immune checkpoints blockade and anti-VEGF/VEGFR-mediated angiogenesis. Nevertheless, these two approaches faced the same dilemma: lack of effective predictive biomarkers. In the current study, our results suggested that elevated NLR was significantly correlated with inferior OS and PFS in patients treated with immune checkpoints inhibitors or anti-VEGF/VEGFR therapy. Whereas high NLR was not associated with OS and PFS in patients treated with other immunotherapies including high-dose IL-2 and adenoviral oncolytic immunotherapy. The exact mechanism that explains these relationships has not been clearly clarified. Emerging evidence suggested that elevated NLR represented the relative reduction of circulating lymphocytes and elevated circulating inflammatory cytokines or mediators. The reduction of circulating lymphocytes would weaken the efficacy of immune checkpoint inhibitors, which mainly unleash the inhibitory signal of T cell function (main subtypes of lymphocytes). The elevated inflammatory cytokines or mediators such as VEGF, TGF-beta and IL-8 would promote angiogenesis [23]. However, these explanations were the potential hypotheses and further research should be performed to uncover the underlying mechanisms.

The present meta-analysis has several limitations that should be acknowledged. First, the number of the eligible studies was relatively small and some of these studies had small sample sizes. Although all of the included studies were well-performed studies, our conclusions should be interpreted with caution due to the overestimation of the treatment effect in smaller studies. Second, NLR cutoff values and main study targets were different among the included studies that make therapy comparisons difficult. For instance, the cutoff value of NLR was 3 in most of eligible studies while other studies used 4 or 5 as the cutoff value. Most of studies reported the data of anti-VEGF/VEGFR and immune checkpoints inhibitors, while two of them studied other targets of TME. Thirdly, it is possible that there may be some degree of publication bias in this area of research. We identified several abstracts describing articles without further detailed publications; hence, we excluded these articles in this meta-analysis. Last but not least, it is not an individual patient data analysis. There was the considerable heterogeneity in the meta-analyses. The pooled results based on published data tend to overestimate treatment effects compared with individual patient data analyses. Herein, clinicians should interpret our findings with caution when applying them in daily clinical practice.

In conclusion, the current study indicated that elevated pretreatment blood NLR was a promising prognostic and predictive biomarker for advanced-stage cancer patients treated with immunotherapy. The optimal NLR cutoff value remains undetermined and further large-scale prospective studies are warranted to confirm this relationship in specific tumor types. In the future, clinical trials in advanced cancer patients are advocated to determine whether pretreatment NLR could be evolved in cancer prognostic risk assessment to help stratify patients who could benefit from immunotherapy.

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Zhao and Guanghui Gao performed the quality assessment; Tao Jiang, Meng Qiao and Shengxiang Ren performed statistical analyses; Caicun Zhou gave critical comments and suggestions; Tao Jiang and Shengxaing Ren drafted the manuscript; all authors approved the final version of the manuscript.

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Compliance with ethical standards

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Animal source None.

Cell line authentication None.

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