Cancer Management and Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Neutrophil–lymphocyte ratio is a predictor of prognosis in patients with castration-resistant prostate cancer: a meta-analysis

This article was published in the following Dove Press journal:
Cancer Management and Research

Zhun Wang*
Shuanghe Peng*
Hui Xie
Linpei Guo
Ning Jiang
Zhiqun Shang
Yuanjie Niu

Department of Urology, Tianjin Institute of Urology, The Second Hospital of Tianjin Medical University, Tianjin 300211, China

*These authors contributed equally to this work

Background: The prognostic value of neutrophil–lymphocyte ratio (NLR) in patients with castration-resistant prostate cancer (CRPC) had been investigated in previous studies; however, the results remain inconsistent. This study was aimed to investigate the prognostic value of NLR in CRPC patients.

Materials and methods: Literature was identified from PubMed, Embase, Web of Science, and Cochrane, which investigated the relationship between pretreatment NLR and prognosis in CRPC patients. HRs for overall survival (OS) and progression-free survival (PFS) were extracted from eligible studies. Heterogeneity was assessed using the I^2 value. The fixed-effects model was used if there was no evidence of heterogeneity; otherwise, the random-effects model was used. Publication bias was evaluated using Begg's funnel plot test.

Results: A total of 5,705 patients from 16 studies were included in this analysis. The pooled results showed that an elevated NLR predict poor OS (pooled HR = 1.52, 95% CI: 1.41–1.63, $P<0.001$) and PFS (pooled HR = 1.50, 95% CI: 1.21–1.85, $P<0.001$) in patients with CRPC. Subgroup analysis revealed that an elevated NLR significantly predicted poor OS in Asian studies group (HR = 2.43, 95% CI: 1.47–4.01, $P=0.001$). The elevated NLR also significantly predicted poor PFS in Asian studies group (HR = 1.99, 95% CI: 1.30–3.06, $P=0.002$).

Conclusion: This study suggests that an elevated NLR predict poor prognosis in patients with CRPC.

Keywords: neutrophil–lymphocyte ratio, castration-resistant prostate cancer, prognosis, meta-analysis

Introduction

Prostate cancer is one of the most common malignancies in Western males, which accounts for 9% of death in males, and the second leading cause of male cancer-related death.[1] The standard treatment for advanced or metastatic prostate cancer is androgen deprivation therapy (ADT).[2] Despite the high response rate of ADT, most prostate cancer patients progressed gradually and irreversibly to castration-resistant prostate cancer (CRPC).[3] Docetaxel, the first-line use of chemotherapeutic agents to treat patients with CRPC, has been shown to confer a survival benefit in patients with CRPC.[4,5] Several other agents, including cabazitaxel (CBZ),[6] enzalutamide (ENZ),[7,8] abiraterone acetate (AA),[9,10] radium-223,[11] and sipuleucel-T,[12] also have been shown to confer a survival benefit in patients with metastatic CRPC (mCRPC). Although some prognostic factors and biomarkers have been reported, a more proper predictive and prognostic biomarker is required to predict the response of patients with CRPC-received chemotherapy accurately.

Correspondence: Yuanjie Niu, Zhiqun Shang
Department of Urology, Tianjin Institute of Urology, The Second Hospital of Tianjin Medical University, No. 23, Pingjiang Road, Hexi District, Tianjin 300211, China
Tel +86 022 8832 6725
Email yuanjieniu2014@163.com, zhiqun_shang@tmu.edu.cn

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/CMAR.S159105

Cancer-related inflammatory response plays an important role in the progression of cancer development.[13,14] Neutrophil-to-lymphocyte ratio (NLR), a marker of the systemic inflammatory response that can be easily measured from routine complete blood counts (CBCs) in the peripheral blood, has been reported to be an independent prognostic factor in cancers.[15–18] NLR has shown to predict poor survival of patient with localized prostate cancer and CRPC.[19–24] However, the results of these studies for the prognostic value of NLR are inconsistent. We conducted a comprehensive meta-analysis to drive a more precise estimate of the prognostic value of the NLR in patients with CRPC.

Materials and methods

Literature search

We comprehensively searched PubMed, Embase, Web of Science, and the Cochrane electronic databases for studies published before November 17, 2017. The search strategy combined key terms related to "castration resistant prostate cancer" or "hormone-refractory prostate cancer" or "androgen independent prostate cancer" or "metastatic prostate cancer" and "Neutrophil to Lymphocyte Ratio" or "NLR" and "prognosis" or "survival" or "outcome" in humans. Two reviewers (ZW and SP) independently screened the titles and abstracts of all initially identified studies according to the selection criteria. Full-text articles of studies that met the following selection criteria were retrieved.

Inclusion and exclusion criteria

Inclusion criteria for publication selection were as follows: 1) retrospective studies on the value of NLR in predicting prognosis in castration-resistant prostate cancer patients; 2) the HRs and their 95% CIs for overall survival (OS) or progression-free survival (PFS) analysis were reported in text or could be computed from given data; 3) the value of NLR was obtained for blood sample testing; 4) defined the cutoff value of increased NLR. When multiple reports describing the same population were published, the most recent or complete report was used.

The major exclusion criteria were as follows: abstract, review, case report or comment letter; laboratory studies; animal studies; duplicate publications; published not in English.

Data extraction and quality

Two investigators (ZW and SP) independently extracted data, and a consensus was reached in case of any inconsistency with the involvement of a third author (HX). The following data were extracted from the eligible studies: first author, year of publication, country of origin, median age (range), treatment, median follow-up time, number of elevated NLR, cutoff value, and HR for survival (OS and/or PFS). For articles that only provided survival data in a Kaplan–Meier curve, software designed by Jayne F Tierney and Matthew R Sydes was used to digitize and extract the relative risk and its 95% CI.[25]

Statistical analysis

Data were analyzed using Stata SE12.0 (StataCorp LP, College Station, TX, USA). HR with a 95% CI was selected as the effect to measure prognostic outcomes. Study heterogeneity was evaluated using the chi-squared test and I^2 statistic ($100\%\times[(Q-\mathrm{df})/Q]$),[26,27] the value of $P_{\text{heterogeneity}}<0.1$ and $I^2>50\%$ represents significant heterogeneity. The fixed-effects model was used when the value of $P_{\text{heterogeneity}}>0.1$ and $I^2<50\%$, otherwise the random-effects model was applied. Subgroup analysis was performed for OS and PFS analysis. Begg's funnel plot and Egger's linear regression test were used to evaluate the potential for publication bias. Two-tailed P-value <0.05 was considered statistically significant.

Results

Features of included studies

The selection process for this study is shown in Figure 1. Through systematic literature searching, a total of 190 potentially relevant studies were identified. Overall, 94 duplicated articles were removed. 61 articles were excluded after screening titles and abstracts, including reviews, letters, meeting abstracts, laboratory studies, and other articles irrelevant to our study. After assessing the full text, 19 additional articles were excluded. Finally, 16 retrospective studies were included in the following meta-analysis.

Summary characteristics of these eligible studies are shown in Table 1. The 16 selected studies (17 cohorts) published between 2013 and 2017 were included in the meta-analysis.[21–24,28–39] The sample size ranged from 33 to 1,224 patients, and a total of 5,705 patients were included. All trials were conducted in adult patients with CRPC. Three studies were conducted in Asian countries (Japan[24,30] and China[35]). Thirteen studies were conducted in non-Asian countries, including Italy,[34,36,39] UK,[19,23] Australia,[29,31] Germany,[21,22] USA,[37] Turkey,[33] Canada,[38] and the Netherlands.[32] The NLR cutoff value ranged from 2.1 to 5. For the prognostic indicator of NLR in CRPC patients, six articles reported both OS

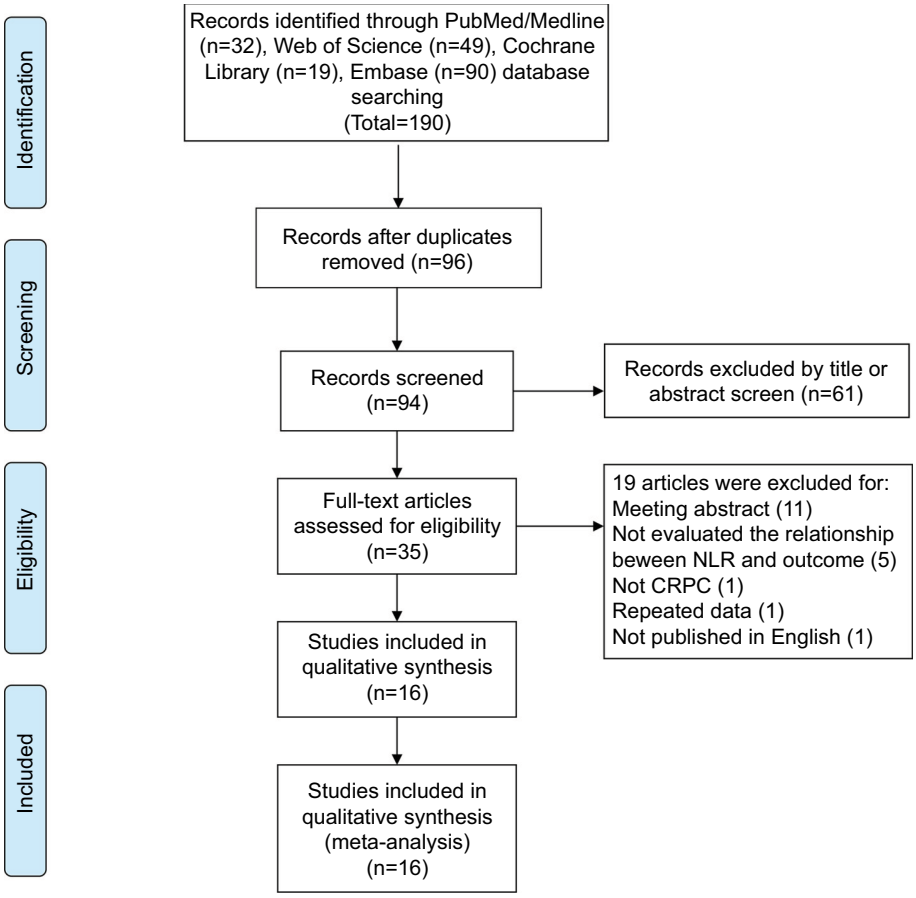

Figure 1 Flow diagram of the study selection process.
Abbreviation: CRPC, castration-resistant prostate cancer.

and PFS, nine (10 cohorts) articles reported OS, and one article reported PFS.

Survival outcome

The relationship between cancer prognosis and NLR was detected in the included studies. OS and PFS were quantitatively synthesized. OS values were available from 16 cohorts with 5,571 patients with CRPC. The elevated NLR was significantly associated with poor OS (HR=1.52, 95% CI: 1.41–1.63, $P<0.001$; $I^2=37.7\%$, $P_{\text{heterogeneity}=0.07}$; Table 2, Figure 2), which meant that patients with a higher NLR had a greater mortality risk than those with a low NLR. Seven studies with 642 patients evaluated PFS outcome. The pooled results favored the patients with low NLR (HR=1.50, 95% CI: 1.21–1.85, $P<0.001$; $I^2=0.0\%$, $P_{\text{heterogeneity}=0.507}$).

Subgroup analysis

Subgroup analysis for OS and PFS was performed according to the cutoff value of NLR, nation, and treatment (Figures 3 and 4; Table 2).

The pooled results showed that elevated NLR predicted worse OS in Asian studies (HR=2.43, 95% CI: 1.47–4.01, $P<0.001$; Table 2, Figure 3B) and second-line treatment studies (HR=1.97, 95% CI: 1.51–2.57, $P<0.001$; Table 2, Figure 3C). For PFS, elevated NLR predicted worse prognosis in cutoff value >3.3 studies (HR=1.87, 95% CI: 1.38–2.54, $P<0.001$; Table 2, Figure 4A) and Asian studies (HR=1.99, 95% CI: 1.30–3.06, $P=0.002$; Table 2, Figure 4B).

Publication bias

The publication bias in the meta-analysis was assessed by Begg's funnel plots. Funnel plots for meta-analysis of elevated NLR and OS and PFS are shown in Figure 5. The Begg's funnel plot test (OS: $P=0.096$, PFS: $P=0.230$; Figure 5) verified that there was no obvious publication bias.

Sensitivity analysis

To evaluate the stability of the pooled results, a sensitivity analysis was performed. The result of the sensitivity analysis showed that for OS and PFS, the pooled result did not tend

Table 1 Main characteristics of the included studies

Authors	Year	Duration	Country	No. of patients	Median age (range) (years)	Treatment	Median follow-up (months)	NLR(+) No. (%)	NLR cutoff value	Survival analysis
Linton et al[29]	2013		Australia	182	NA	Docetaxel	NA	104 (56.5%)	≥5	OS
Nuhn et al[21]	2014	1998–2010	Germany	238	68.3 (44.6–84.5)	Docetaxel	15.0 (1.5–90.2)	168 (70%)	>3	OS
Sonpavde et al[37]	2014	2008–2010	USA	848	68 (NA)	Docetaxel	NA	NA	>3.4	OS
Sümbül et al[33]	2014	2009–2013	Turkey	33	71.24* (NA)	Docetaxel	NA	18 (54.6%)	>3	PFS
Templeton et al[38]	2014	2001–2011	Canada	357	71 (44–90)	Docetaxel	NA	260 (73%)	>3	OS
Lorente et al[19]	2015	NA	UK	755	67 (62–73)	Docetaxel or mitoxantrone	NA	NA	>3	OS
McLachlan et al[31]	2015	2005–2012	Australia	42	(50–84)	Docetaxel or Cabazitaxel	NA	14 (33.3%)	≥5	OS, PFS
van Soest et al[32]	2015	NA	The Netherlands	1,224	68 (40–88)	VENICE (Docetaxel)	NA	NA	≥2	OS
				1,006	68 (36–92)	TAX327 (D3+ Docetaxel)	NA	NA	≥2.1	OS
Yao et al[30]	2015	2009–2014	Japan	57	74.0 (55–91)	Docetaxel	19.0 (1–61)	27 (47.4%)	≥3.5	OS, PFS
Conteduca et al[34]	2016	2012–2014	Italy	193	73.1 (42.8–90.7)	Enzalutamide	10.4 (NA)	105 (54.4%)	>3	OS, PFS
Lolli et al[39]	2016	2011–2015	Italy	230	74 (45–90)	Abiraterone	29 (1–55)	104 (45.2%)	≥3	OS
Boegemann et al[22]	2017	NA	Germany	96	70 (NA)	Abiraterone	22 (NA)	17 (17.7%)	>5	OS, PFS
Buttigliero et al[36]	2017	2004–2016	Italy	110	68 (48–85)	Docetaxel	31.7 (NA)	64 (58%)	>3	OS, PFS
Mehra et al[23]	2017	NA	UK	75	NA	Prednisolone or dexamethasone	NA	NA	≥2.6	OS
Pei et al[35]	2017	2009–2016	China	111	71 (43–86)	Docetaxel	16 (1–50)	42 (37.8%)	>3.3	OS, PFS
Uemura et al[24]	2017	2014–2016	Japan	47	NA	Cabazitaxel	NA	20 (42.6%)	≥3.83	OS

Note: *mean age.
Abbreviations: NA, not available; NLR, neutrophil–lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

to exhibit alterations when an individual study was excluded (Figure 6).

Discussion

The incidence of prostate cancer has been increasing in the past few years.[40] Most of the prostate cancer patients progressed to CRPC eventually.[3] Several chemotherapeutic agents, including docetaxel, CBZ, ENZ, and AA, have been shown to confer a survival benefit in patients with mCRPC. A more proper predictive and prognostic biomarker is required to predict the response of patients with CRPC-received chemotherapy accurately. It is reported that inflammatory status is associated with the progression of cancer development.[13,14] The marker of the systemic inflammatory response, NLR, suggests an independent prognostic factor in cancers.[15–18] NLR has shown to predict poor survival in patients with CRPC. In this meta-analysis, we included 5,705 patients from 16 selected studies (17 cohorts) to evaluate the prognostic role of the NLR in CRPC patients. The pooled results indicated that an elevated NLR is an independent predictor of poor prognosis in CRPC patients.

According to the subgroup analysis, an NLR cutoff value >3.3 had a more significant prognostic value than a cutoff value <3.3 (Table 2), which indicated that a higher NLR cutoff is more specific to predict a poor prognosis in patients with CRPC. An elevated NLR in Asian group had a more significant prognostic value than that in non-Asian group, indicating that a higher NLR is more specific to predict a poor prognosis in Asian patients with CRPC. Given the limited number of the eligible studies in the meta-analysis, although the pooled results showed that an elevated NLR is associated with a poor prognosis, it will need further investigation to identify that NLR can serve as a clinical marker of prognosis in CRPC patients.

The heterogeneity was relatively small in the included studies. It may be partially explained by nation, sample size, cutoff value, and treatment. And the subgroup analysis showed that the prognostic value of NLR was not affected by the factors included in the analysis. The sensitivity analysis also indicated that the pooled results were relatively conclusive.

Both increased neutrophil-dependent systemic inflammatory response and a lower lymphocyte-mediated antitumor immune response will lead to an elevated NLR.[41,42] As a predominant leukocyte subset in human peripheral blood,

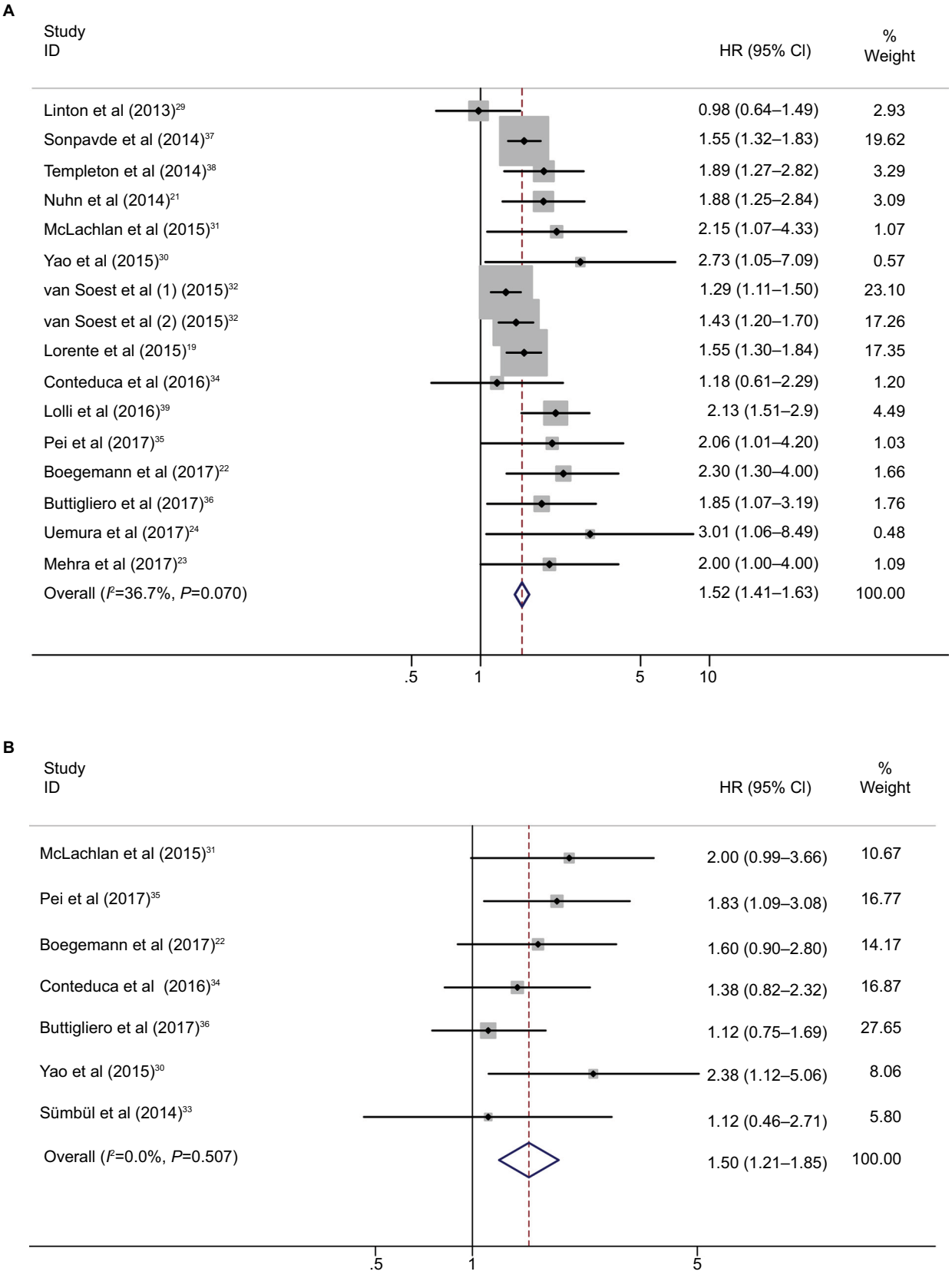

Figure 2 Forest plot HR for the correlation between neutrophil–lymphocyte ratio and overall survival (**A**) and progression-free survival (**B**) in castration-resistant prostate cancer patients.

Table 2 NLR pooled HRs and 95% CIs in meta-analysis for OS and PFS

Stratified analysis	OS								Begg's test *P*-value	PFS								Begg's test *P*-value
	No. of studies	Chi-squared	$P_{heterogeneity}$	I^2 (%)	Pooled HR (95% CI)					No. of studies	Chi-squared	$P_{heterogeneity}$	I^2 (%)	HR (95% CI)				
					Fixed effect	*P*-value	Random effect	*P*-value						Fixed effect	*P*-value	Random effect	*P*-value	
Overall																		
	16	23.7	0.07	37.7	1.52 (1.41–1.63)	<0.001	1.59 (1.42–1.77)	<0.001	0.096	7	5.29	0.507	0	1.50 (1.21–1.85)	<0.001	1.50 (1.21–1.85)	<0.001	0.23
Nation																		
Asian	3	0.43	0.807	0	2.43 (1.47–4.01)	0.001	2.43 (1.47–4.01)	0.001		2	0.31	0.577	0	1.99 (1.30–3.06)	0.002	1.99 (1.30–3.06)	0.002	
Non-Asian	13	19.82	0.071	39.5	1.50 (1.40–1.62)	<0.001	1.56 (1.39–1.74)	<0.001		5	2.72	0.606	0	1.36 (1.07–1.74)	0.014	1.36 (1.07–1.74)	0.014	
Treatment																		
First selected	13	16.97	0.151	29.3	1.49 (1.38–1.60)	<0.001	1.53 (1.38–1.70)	<0.001		5	5.14	0.273	22.2	1.51 (1.17–1.95)	0.002	1.55 (1.14–2.10)	0.005	
Second selected	3	2.8	0.247	28.5	1.97 (1.51–2.57)	<0.001	1.92 (1.37–2.69)	<0.001		2	0.14	0.706	0	1.48 (1.01–2.17)	0.046	1.48 (1.01–2.17)	0.046	
No. of patients																		
<182	7	1.04	0.984	0	2.16 (1.66–2.80)	<0.001	2.16 (1.66–2.80)	<0.001		6	5.18	0.394	3.4	1.52 (1.20–1.93)	<0.001	1.53 (1.20–1.94)	0.001	
≥182	9	15.15	0.056	47.2	1.47 (1/37–1.59)	<0.001	1.50 (1.34–1.69)	<0.001		1	–	–	–	1.38 (0.82–2.32)	0.225	1.38 (0.82–2.32)	0.225	
Cutoff																		
>3.3	7	10.68	0.099	43.8	1.58 (1.38–1.82)	<0.001	1.72 (1.32–2.25)	<0.001		4	0.73	0.867	0	1.87 (1.38–2.54)	<0.001	1.87 (1.38–2.54)	<0.001	
≤3.3	9	12.52	0.13	36.1	1.49 (1.37–1.63)	<0.001	1.56 (1.38–1.76)	<0.001		3	0.41	0.814	0	1.20 (0.89–1.62)	0.233	1.20 (0.89–1.62)	0.233	

Abbreviations: NLR, neutrophil–lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

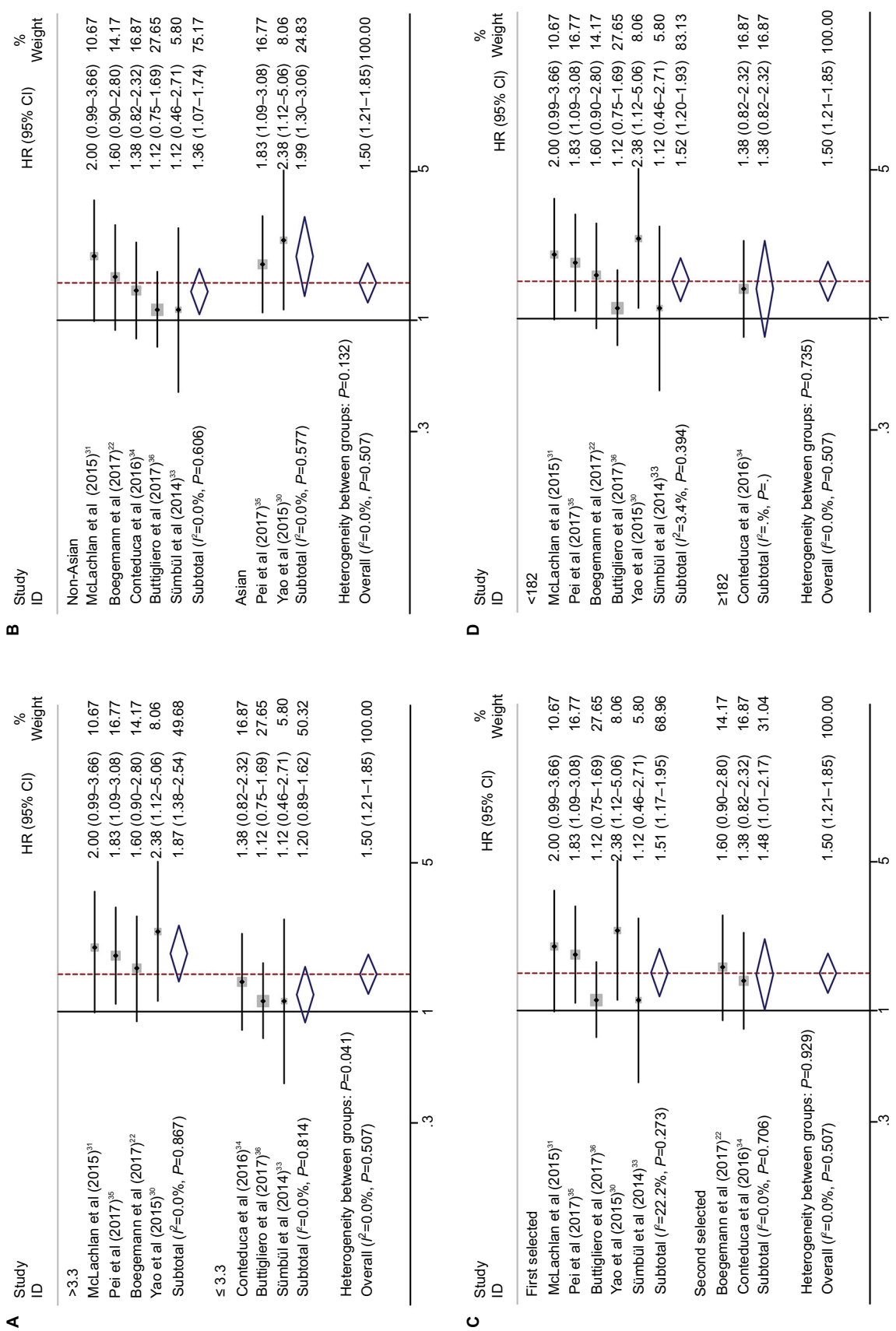

Figure 3 Subgroup analysis of pooled overall survival based on a neutrophil–lymphocyte ratio cutoff value (A), nation (B), treatment (C), and number of patients (D).

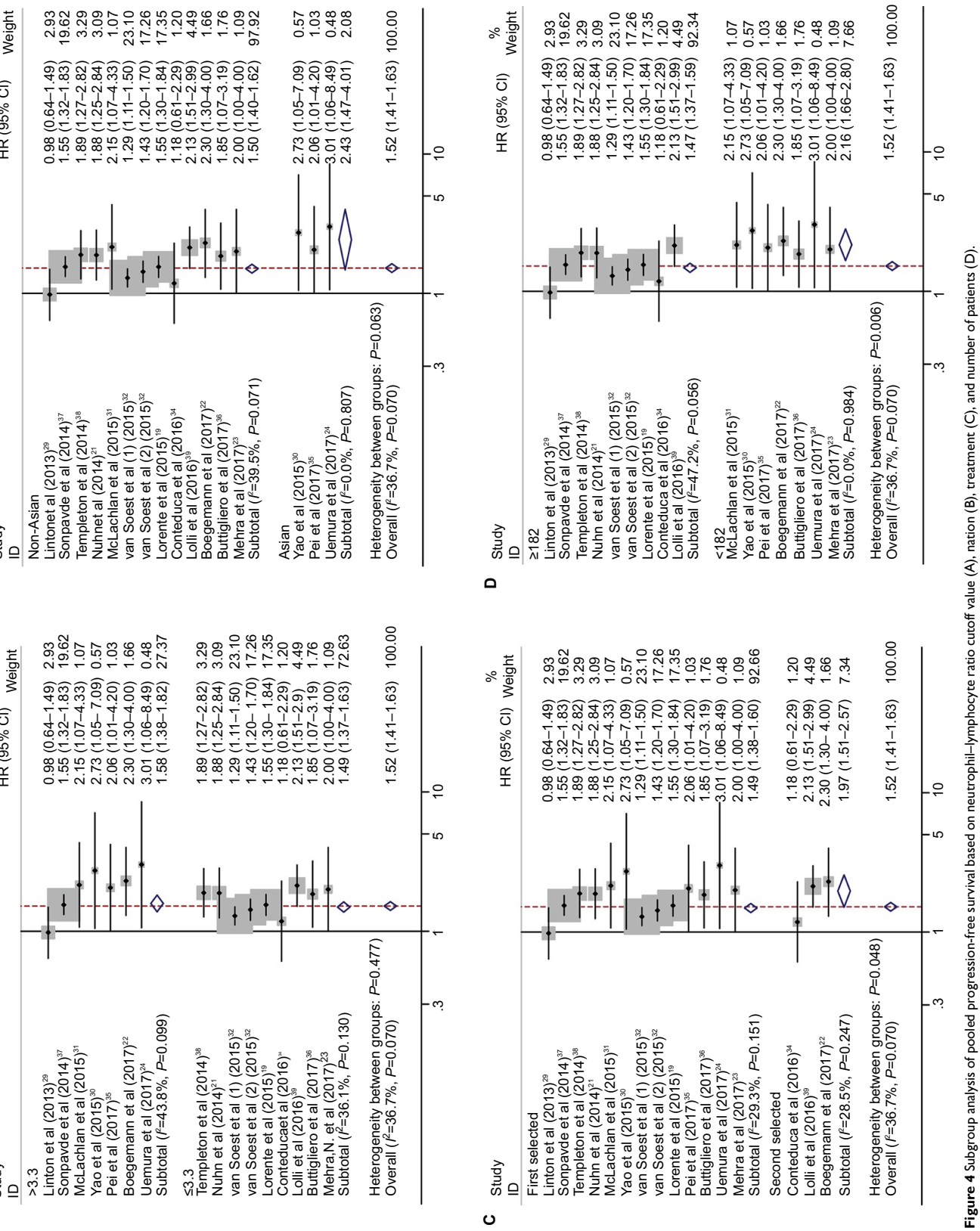

Figure 4 Subgroup analysis of pooled progression-free survival based on neutrophil–lymphocyte ratio cutoff value (A), nation (B), treatment (C), and number of patients (D).

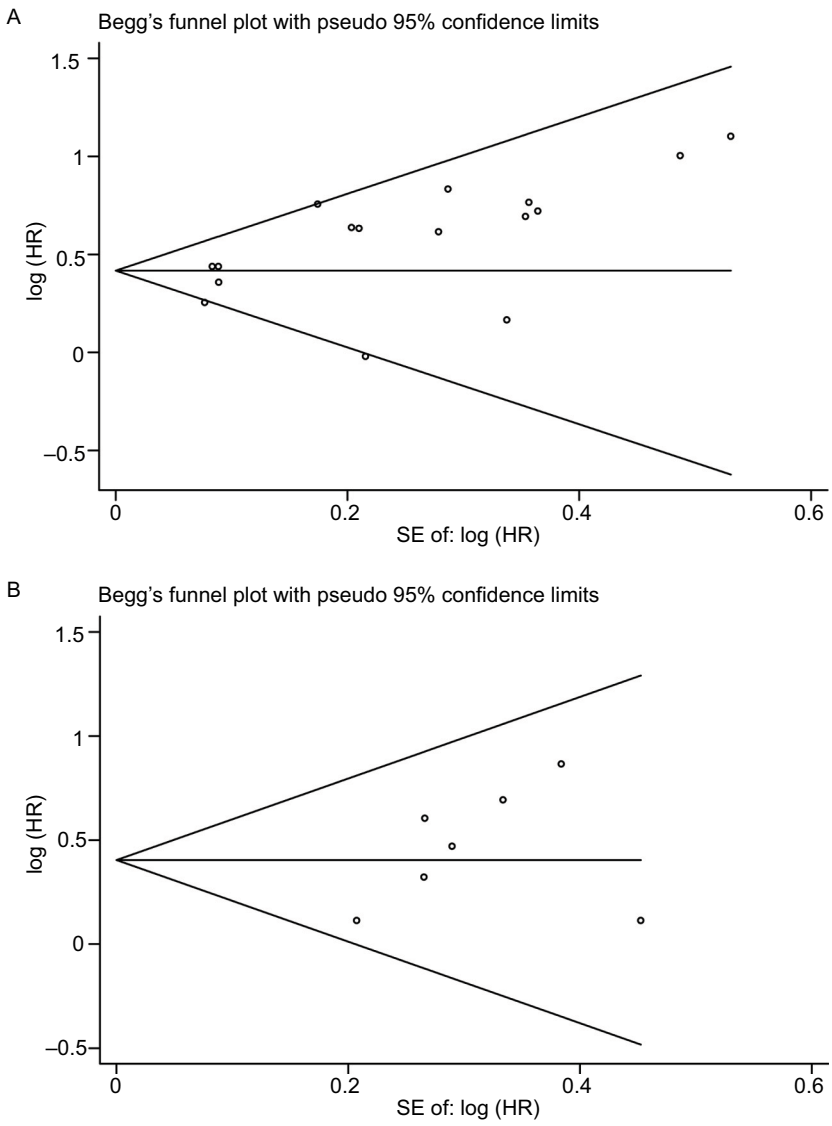

Figure 5 Funnel plots based on overall survival (A) and progression-free survival (B) (Begg's test).
Abbreviation: SE, standard error.

neutrophils play an important role in tumor progression.[43] In comparison, lymphocytes are critical components of antitumor immunity.[44,45] NLR is an indicator of systemic inflammatory and immune response of the host; it is also associated with the progression of cancers.[15–18] NLR can be easily measured from routine CBCs in the peripheral blood, which is low cost, convenient, and reproducible. Moreover, NLR is closely related to the prognosis of CRPC. These reasons indicate that NLR could serve as a prognostic marker for patients with CRPC.

Several meta-analyses have been conducted on the prognosis of NLR for localized prostate cancer and mCRPC; however, the studies included in their meta-analysis were relatively small and the heterogeneity were high.[46–48] We conducted a comprehensive meta-analysis for the prognostic value of NLR for CRPC, which included 5,705 patients from 16 selected studies (17 cohorts); the pooled results indicated that an elevated NLR is an independent predictor of poor prognosis in patients with CRPC.

Limitations

Several limitations should be acknowledged in the meta-analysis. First, the NLR cutoff value differed among the included studies, potential heterogeneity may exist. Therefore, more studies are required to identify the most suitable NLR cutoff value. Second, NLR could be affected by other diseases, such as inflammatory diseases, infection, renal diseases, and liver diseases.[49,50] Third, the number of eligible

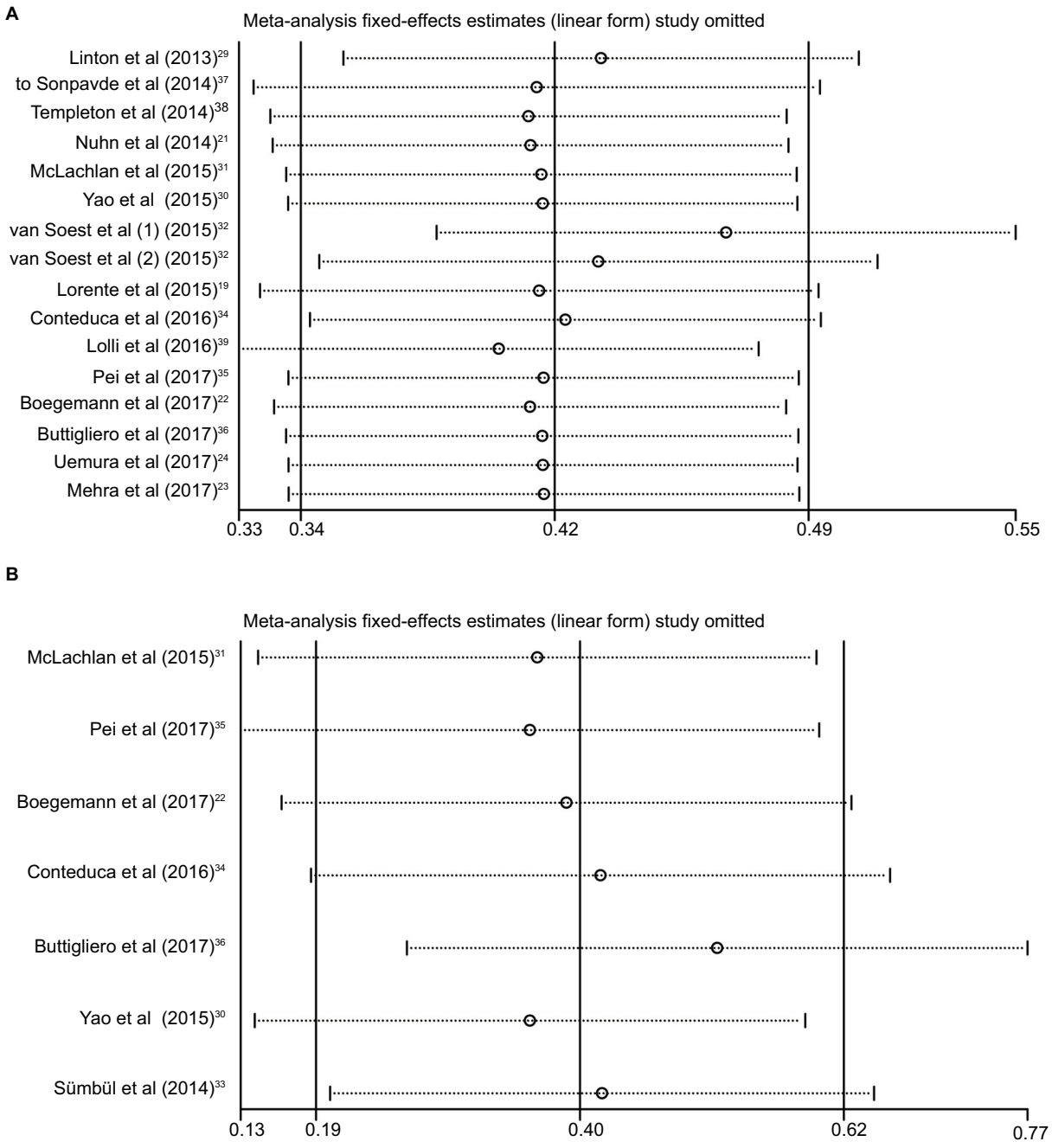

Figure 6 Sensitivity analysis for overall survival (A) and progression-free survival (B) in this meta-analysis.

studies in the meta-analysis is relatively small. Finally, studies with positive results are potentially more likely published than work with negative results, which could cause publication bias.[51]

Conclusion

Our analysis on the currently available clinical evidence suggests that elevated NLR predicted a poor OS and PFS in patients with CRPC. The NLR could serve as an indicator of the efficacy of the treatment of CRPC.

Acknowledgment

This work was supported by National Natural Science Foundation of China (grants 81472682 and 81772756), and Natural Science Foundation of Tianjin (17JCZDJC35300, 15JCZDJC35400 and 15JCYBJC27200).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014.. *CA Cancer J Clin*. 2014;64(1):9–29.
2. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. *Eur Urol*. 2014;65(2):467–479.
3. Friedlander TW, Ryan CJ. Targeting the androgen receptor. *Urol Clin North Am*. 2012;39(4):453–464.
4. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J Clin Oncol*. 2008;26(2):242–245.
5. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502–1512.
6. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376(9747):1147–1154.
7. Froehner M, Wirth MP. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(18):1755–1755.
8. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187–1197.
9. Berruti A, Pia A, Terzolo M. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;365(8):766–766.
10. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138–148.
11. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213–223.
12. Pezaro C, Attard G. Prostate cancer in 2011: redefining the therapeutic landscape for CRPC. *Nat Rev Urol*. 2012;9(2):63–64.
13. Kowalewska M, Nowak R, Chechlinska M. Implications of cancer-associated systemic inflammation for biomarker studies. *Biochim Biophys Acta*. 2010;1806(2):163–171.
14. Saito K, Kihara K. C-reactive protein as a biomarker for urological cancers. *Nat Rev Urol*. 2011;8(12):659–666.
15. Akinci Ozyurek B, Sahin Ozdemirel T, Buyukyaylaci Ozden S, Erdogan Y, Kaplan B, Kaplan T. Prognostic value of the neutrophil to lymphocyte ratio (NLR) in lung cancer cases. *Asian Pac J Cancer Prev*. 2017;18(5):1417–1421.
16. Orditura M, Galizia G, Diana A, et al. Neutrophil to lymphocyte ratio (NLR) for prediction of distant metastasis-free survival (DMFS) in early breast cancer: a propensity score-matched analysis. *ESMO Open*. 2016;1(2):e000038.
17. Ha H, Nam AR, Bang JH, et al. Soluble programmed death-ligand 1 (sPDL1) and neutrophil-to-lymphocyte ratio (NLR) predicts survival in advanced biliary tract cancer patients treated with palliative chemotherapy. *Oncotarget*. 2016;7(47):76604–76612.
18. Li S, Xu X, Liang D, Tian G, Song S, He Y. Prognostic value of blood neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with gastric cancer. *Zhonghua Zhong Liu Za Zhi*. 2014;36(12):910–915.
19. Lorente D, Mateo J, Templeton AJ, et al. Baseline neutrophil–lymphocyte ratio (NLR) is associated with survival and response to treatment with second-line chemotherapy for advanced prostate cancer independent of baseline steroid use. *Ann Oncol*. 2015;26(4):750–755.
20. Correa RG, Krajewska M, Ware CF, Gerlic M, Reed JC. The NLR-related protein NWD1 is associated with prostate cancer and modulates androgen receptor signaling. *Oncotarget*. 2014;5(6):1666–1682.
21. Nuhn P, Vaghasia AM, Goyal J, et al. Association of pretreatment neutrophil-to-lymphocyte ratio (NLR) and overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with first-line docetaxel. *BJU Int*. 2014;114(6b):E11–E17.
22. Boegemann M, Schlack K, Thomes S, et al. The role of the neutrophil to lymphocyte ratio for survival outcomes in patients with metastatic castration-resistant prostate cancer treated with abiraterone. *Int J Mol Sci*. 2017;18(2):380.
23. Mehra N, Sharp A, Lorente D, et al. Neutrophil to lymphocyte ratio in castration-resistant prostate cancer patients treated with daily oral corticosteroids. *Clin Genitourin Cancer*. 2017;15(6):678–684.
24. Uemura K, Kawahara T, Yamashita D, et al. Neutrophil-to-lymphocyte ratio predicts prognosis in castration-resistant prostate cancer patients who received cabazitaxel chemotherapy. *Biomed Res Int*. 2017;2017:7538647–7538655.
25. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*. 2007;8:16.
26. Handoll HH. Systematic reviews on rehabilitation interventions. *Arch Phys Med Rehabil*. 2006;87(6):875.
27. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
28. Lorente D, Mateo J, Templeton AJ, et al. Baseline neutrophil-lymphocyte ratio (NLR) is associated with survival and response to treatment with second-line chemotherapy for advanced prostate cancer independent of baseline steroid use. *Ann Oncol*. 2015;26(4):750–755.
29. Linton A, Pond G, Clarke S, Vardy J, Galsky M, Sonpavde G. Glasgow prognostic score as a prognostic factor in metastatic castration-resistant prostate cancer treated with docetaxel-based chemotherapy. *Clin Genitourin Cancer*. 2013;11(4):423–430.
30. Yao A, Sejima T, Iwamoto H, et al. High neutrophil-to-lymphocyte ratio predicts poor clinical outcome in patients with castration-resistant prostate cancer treated with docetaxel chemotherapy. *Int J Urol*. 2015;22(9):827–833.
31. McLachlan JM, Chan DL, Crumbaker MA, Marx GM. Neutrophil–lymphocyte ratio prior to steroids as a prognostic marker in men with metastatic castration-resistant prostate cancer. *Cancer Treat Commun*. 2015;4:81–85.
32. van Soest RJ, Templeton AJ, vera-Badillo FE, et al. Neutrophil-to-lymphocyte ratio as a prognostic biomarker for men with metastatic castration-resistant prostate cancer receiving first-line chemotherapy: data from two randomized phase III trials. *Ann Oncol*. 2015;26(4):743–749.
33. Sümbül AT, Sezer A, Abalı H, et al. Neutrophil-to-lymphocyte ratio predicts PSA response, but not outcomes in patients with castration-resistant prostate cancer treated with docetaxel. *Int Urol Nephrol*. 2014;46(8):1531–1535.
34. Conteduca V, Crabb SJ, Jones RJ, et al. Persistent neutrophil to lymphocyte ratio >3 during treatment with enzalutamide and clinical outcome in patients with castration-resistant prostate cancer. *PLoS One*. 2016;11(7):e0158952.
35. Pei XQ, He DL, Tian G, et al. Prognostic factors of first-line docetaxel treatment in castration-resistant prostate cancer: roles of neutrophil-to-lymphocyte ratio in patients from Northwestern China. *Int Urol Nephrol*. 2017;49(4):629–635.
36. Buttigliero C, Pisano C, Tucci M, et al. Prognostic impact of pretreatment neutrophil-to-lymphocyte ratio in castration-resistant prostate cancer patients treated with first-line docetaxel. *Acta Oncol*. 2017;56(4):555–562.
37. Sonpavde G, Pond GR, Armstrong AJ, et al. Prognostic impact of the neutrophil-to-lymphocyte ratio in men with metastatic castration-resistant prostate cancer. *Clin Genitourin Cancer*. 2014;12(5):317–324.
38. Templeton AJ, Pezaro C, Omlin A, et al. Simple prognostic score for metastatic castration-resistant prostate cancer with incorporation of neutrophil-to-lymphocyte ratio. *Cancer*. 2014;120(21):3346–3352.
39. Lolli C, Caffo O, Scarpi E, et al. Systemic immune-inflammation index predicts the clinical outcome in patients with mCRPC treated with abiraterone. *Front Pharmacol*. 2016;7:376.

40. Ishioka J, Saito K, Sakura M, et al. Development of a nomogram incorporating serum C-reactive protein level to predict overall survival of patients with advanced urothelial carcinoma and its evaluation by decision curve analysis. *Br J Cancer*. 2012;107(7):1031–1036.
41. Coffelt SB, Kersten K, Doornebal CW, et al. IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis. *Nature*. 2015;522(7556):345–348.
42. Tazzyman S, Niaz H, Murdoch C. Neutrophil-mediated tumour angiogenesis: subversion of immune responses to promote tumour growth. *Semin Cancer Biol*. 2013;23(3):149–158.
43. Grivennikov SI, Greten FR, Karin M, Immunity KM. Immunity, inflammation, and cancer. *Cell*. 2010;140(6):883–899.
44. Ramanathan S, Gagnon J, Ilangumaran S. Antigen-nonspecific activation of CD8+ T lymphocytes by cytokines: relevance to immunity, autoimmunity, and cancer. *Arch Immunol Ther Exp*. 2008;56(5):311–323.
45. Muranski P, Restifo NP. Adoptive immunotherapy of cancer using CD4(+) T cells. *Curr Opin Immunol*. 2009;21(2):200–208.
46. Cao J, Zhu X, Zhao X, Li XF, Xu R. Neutrophil-to-lymphocyte ratio predicts PSA response and prognosis in prostate cancer: a systematic review and meta-analysis. *PLoS One*. 2016;11(7):e0158770.
47. Gu X, Gao X, Li X, et al. Prognostic significance of neutrophil-to-lymphocyte ratio in prostate cancer: evidence from 16,266 patients. *Sci Rep*. 2016;6:22089.
48. Tang L, Li X, Wang B, et al. Prognostic value of neutrophil-to-lymphocyte ratio in localized and advanced prostate cancer: a systematic review and meta-analysis. *PLoS One*. 2016;11(4):e0153981.
49. Alkhouri N, Morris-Stiff G, Campbell C, et al. Neutrophil to lymphocyte ratio: a new marker for predicting steatohepatitis and fibrosis in patients with nonalcoholic fatty liver disease. *Liver Int*. 2012;32(2):297–302.
50. Balta S, Cakar M, Demirkol S, Arslan Z, Akhan M. Higher neutrophil to lymphocyte ratio in patients with metabolic syndrome. *Clin Appl Thromb Hemost*. 2013;19(5):579.
51. Sutton AJ, Song F, Gilbody SM, Abrams KR. Modelling publication bias in meta-analysis: a review. *Stat Methods Med Res*. 2000;9(5):421–445.