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REVIEW ARTICLE

Revealing the prognostic landscape of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in metastatic castration-resistant prostate cancer patients treated with abiraterone or enzalutamide: a meta-analysis

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Abstract

Background The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), as markers of systematic inflammation response, have been reported to be indicators in metastatic castration-resistant prostate cancer (mCRPC), whereas their prognostic values remain conflict. This study was to assess the prognostic value of NLR and PLR in mCRPC patients and to assess the response of abiraterone or enzalutamide through using NLR and PLR.

Methods Databases searching was conducted in the PubMed, EMBASE, Google Scholar, and the Cochrane Library for relevant published literature up to October 2019. Data extraction and quality evaluation were performed on the eligible studies. STATA 14.0 software was used to pooled hazard ratios (HRs) and their 95% confidence intervals (CIs) for overall survival (OS) and progression-free survival (PFS).

Results A total of 3144 mCRPC patients were enrolled from 15 cohort studies in this meta-analysis. The pooled results demonstrated that elevated NLR had a significant association with inferior OS in mCRPC patients treated with abiraterone (HR = 1.63, 95% CI: 1.43–1.85, $P < 0.001$) and enzalutamide (HR = 1.48, 95% CI: 1.27–1.72, $P < 0.001$), whereas elevated NLR had no significant association with unfavorable PFS treated with abiraterone and enzalutamide, respectively. Elevated PLR had a significant association with an inferior OS (HR = 1.52, 95% CI: 1.16–1.98, $P < 0.001$) in mCRPC patients treated with abiraterone.

Conclusions NLR and PLR were effective biomarkers for predicting prognosis in mCRPC patients and served as indicators of the efficacy of personalized treatment of mCRPC using abiraterone or enzalutamide. Future, more randomized control trials (RCTs) are needed to investigate the promising value of hematologic parameters.

Introduction

Prostate cancer (PCa) is the most common cancerous malignancy and the leading cause of cancer-related mortality among men worldwide [1]. As diagnostic methods and surgical procedures have progressed, localized PCa, an early stage of the tumor, can have a favorable outcome [2]. For tumor heterogeneity, however, a large proportion of cases are prone to metastatic castration-resistant prostate cancer (mCRPC), and their prognosis is not satisfactory, in spite of previous treatment, such as androgen deprivation therapy or chemotherapy [3]. Lately, several novel agents, including docetaxel, cabazitaxel, sipuleucel-T [4], abiraterone [5], enzalutamide [6, 7], and radium-223 [8] have proved beneficial to the survival of mCRPC patients.

Abiraterone is a CYP17A1 enzyme inhibitor that restrains testosterone synthesis. Enzalutamide is an androgen receptor (AR) inhibitor that blocks nuclear translocation and AR biding [9]. Both are recommended to use either before or after chemotherapy to improve the survival of mCRPC patients. Nevertheless, the indicator of these two new hormonal agents remains unclear.

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Hence, effective prognostic biomarkers are needed for therapy management and to guide individual-based treatment.

Increasing evidence indicates that systemic inflammatory response plays an essential role in many solid tumors, including PCa [10]. Currently, two circulating hematologic parameters, the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), are recognized as hallmarks of malignancy progression and, as a research hotspot, have been reported to have prognostic value for mCRPC. The conclusions of various studies, however, are inconsistent [11]. What is more, therapy selection and medication sequences are still challenging issues for both clinicians and patients, putting better prognostic biomarkers in high demand. Nevertheless, no meta-analysis has yet evaluated the prognostic value of pretreatment NLR and PLR for mCRPC, and no specific indicator exists to evaluate the responses to abiraterone and enzalutamide. To fill this gap, we synthesized the relevant studies published in recent years and conducted this meta-analysis.

Methods

The present study was conducted following the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [12].

Search strategy

Database searching was conducted in the PubMed, EMBASE, Google Scholar, and the Cochrane Library for relevant published literature up to October 2019. The language was restricted to English. The following keywords and medical subject headings were used as search terms: ("metastatic castration-resistant prostate cancer," OR "mCRPC,") AND ("neutrophil-to-lymphocyte ratio," OR "NLR," OR "platelet-to-lymphocyte ratio," OR "PLR,") AND ("abiraterone acetate," OR "enzalutamide"). The literature searching process was performed iteratively until no additional article could be identified. The references cited in the literature were manually retrieved.

Selection criteria

Studies were eligible if they met the following defined criteria: (1) mCRPC patients were treated with abiraterone or enzalutamide prior to or post chemotherapy; (2) they were cohort studies of the evaluated prognostic value of pretreatment NLR or PLR and reported survival outcomes including overall survival (OS) and progression-free survival (PFS). OS was defined as the time from the start of abiraterone or enzalutamide until death from any cause; PFS was defined as the time from the start of abiraterone or enzalutamide until disease progression or death from any cause or last tumor evaluation; (3) the original hazard ratio (HR) with a 95% confidence interval (CI) could be extracted from sufficient information. Duplicate studies, reviews, case reports, comments, letters, unpublished studies, abstracts of conferences, animal experiments, and incomplete or erroneous data were excluded. Radiographic-PFS and prostate-specific antigen (PSA)-PFS were also excluded.

Data extraction

Two investigators (YPG and TYT) independently extracted and cross-checked the following data: first author, publication year, nation, region, duration time, data source, study design, sample size, mean age, hormonal agents, sequence, median follow-up, analysis mode, NLR cutoff value, PLR cutoff value, survival outcome, and quality scores. Engauge Digitizer software was used to digitize and extract the relevant survival data of the Kaplan–Meier curves. In case of a disagreement, discrepancies were resolved through discussion or third-party ruling.

Quality evaluation

Two investigators (YPG and HYX) independently evaluated eligible studies using the Newcastle–Ottawa Scale (NOS) quality assessment tool. Each cohort study included was assessed by three categories: selection, comparability, and outcome. A study was awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars could be given for the comparability category. Up to nine stars could be awarded. Each star represented one score. Studies with scores above 6 were regarded as high-quality. In case of a disagreement, discrepancies were resolved through discussion or third-party ruling.

Statistical analysis

STATA 14.0 software was used to conduct the present meta-analysis. HRs with 95% CIs were pooled to evaluate survival values. The I^2 statistic and Cochrane Q test were used to evaluate the heterogeneity of the selected studies. An α value equal to 0.1 and a P value smaller than 0.05 were considered statistically significant. An I^2 greater than 50% was considered a significant level of heterogeneity. The fixed-effect model was used to calculate the pooled effect when a $P_{\text{heterogeneity}}$ value greater than 0.1 or

an I^2 statistic was equal to or smaller than 50%; otherwise, the random effect model was used. Sensitivity analysis was performed to assess the stability of the pooled results by omitting any single study in sequence. Egger's tests were used to test publication bias, a P value greater than 0.05 indicating negligible potential publication bias.

Results

Search results

The flow chart (Fig. 1) illustrates the literature selection process. The initial searching retrieved a total of 94 studies including 89 studies form database searching and five studies were identified through other sources. Forty studies remained after duplicated studies were removed, and 17 studies were excluded after scanning their titles and abstracts. Full-text article assessments for eligibility were conducted in 23 studies, eight of which studies were excluded due to five being reviews, case reports, and comments, two lacking available data, and one having an overlapping subject. Eventually, 15 studies were eligible and included in the qualitative synthesis [11, 13–26]. All included studies were retrospective cohorts written in English.

Characteristics of eligible studies

Table 1 summarizes the general characteristics of the fifteen eligible cohort studies [11, 13–26]. A total of 3144 mCRPC patients were included in the present meta-analysis, the mean age of whom ranged from 42.8 to 92 years old. The sample size ranged from 101 to 872 patients. The publication year ranged from 2014 to 2019, the duration time ranged from 2014 to 2018, and the median follow-up time ranged from 0.3 to 55 months. The overall quality of the eligible studies was good, and the range of NOS scores being 6–9, with an average score of 7.5 (Table 2). Five articles came from Asia (Japan [13, 16], Korea [17], China [25], and Turkey [21]) and ten from non-Asian regions (Italy [15, 18, 23], France [14], Spain [19], Germany [20, 22], America [24, 26], and Canada [11]). Ten studies investigated the agent response of abiraterone [11, 13, 14, 18–22, 24, 25], and five studies [15–17, 23, 26] investigated the agent response of enzalutamide. Fifteen studies evaluated NLR [11, 13–26], of which the cutoff values ranged from 2.14 to 5. Three studies evaluated PLR [18, 19, 21] of which the cutoff values ranged from 150 to 210. Fifteen studies reported on OS and four studies reported on PFS. Four studies provided univariate analysis [14, 18, 19, 22], five studies provided multivariate analysis [13, 15, 16, 25, 26], and six provided both univariate and multivariate analysis modes [11, 17, 20, 21, 24].

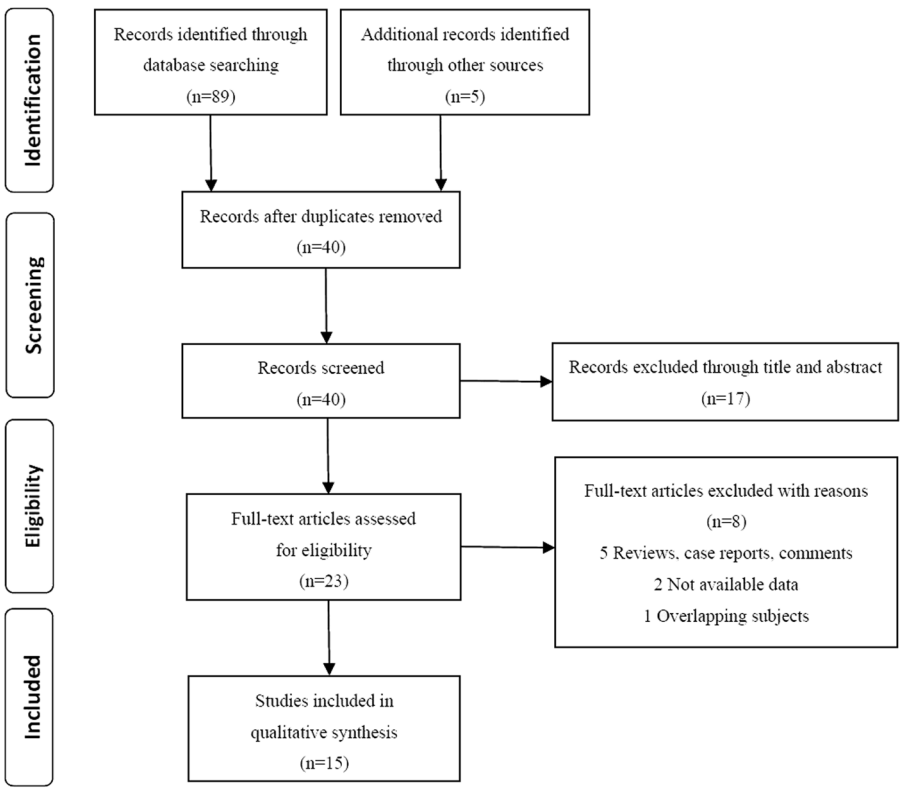

Fig. 1 The flow chart of the literature selection process.

Table 1 Characteristics of included studies.

Reference	Publication year	Nation	Region	Duration time	Data source	Study design	Sample size	Mean age (IQR)/years	Hormonal agents	Sequence	Median follow-up (IQR)/months	Analysis mode	NLR cutoff	PLR cutoff	Survival outcome	NOS score
Boegemann et al. [20]	2019	Germany	Europe	Dec 2009–Jul 2015	Single-center (Muenster University Medical Center)	Cohort	117	70 (64–76)	Abiraterone	Pre-CT: 69 Post-CT: 48	15.5 (8–25)	UV + MV	3.7	NR	OS	8
Schiff et al. [24]	2019	America	North America	2012–2018	Single-center (Tulane Cancer Center)	Cohort	110	74.5 (53–94)	Abiraterone	Post-CT: 43 CT-naive: 67	NR	UV + MV	5	NR	OS	6
Onal et al. [21]	2019	Turkey	Asia	Nov 2012–Oct 2017	Multicenter (three institutions)	Cohort	102	71 (47–92)	Abiraterone	Pre-CT: 52 Post-CT: 50	24 (0.3–54.9)	UV + MV	3.1	163	OS, PFS	9
Loubersac et al. [14]	2019	France	Europe	2015–2017	Multicenter	Cohort	542	70	Abiraterone	CT-naive: 542	NR	UV	2.5	NR	OS^{KM}	9
Fan et al. [25]	2017	China	Asia	2012–2016	Single-center (Renji hospital)	Cohort	112	72 (66–77)	Abiraterone	Post-CT: 42 CT-naive: 70	20.2	MV	3	NR	OS	8
Lozano Martinez et al. [19]	2017	Spain	Europe	Jan 2012–Nov 2015	Multicenter (two hospitals)	Cohort	101	73 (50–92)	Abiraterone	Post-CT: 40 CT-naive: 61	NR	UV	5	150	OS^{KM}	7
Yasui et al. [13]	2018	Japan	Asia	2011–2016	Multicenter (three centers)	Cohort	90	73.2	Abiraterone	CT-naive: 90	NR	MV	3.8	NR	OS	7
Boegemann et al. [22]	2017	Germany	Europe	2009–2015	Single-center	Cohort	96	70 (62–76.3)	Abiraterone	Pre-CT: 52 Post-CT: 44	20 (11–28)	UV + MV	5	NR	OS, PFS	8
Lolli et al. [18]	2016	Italy	Europe	Apr 2004–May 2015	Multicenter (seven institutions)	Cohort	230	74 (45–90)	Abiraterone	Post-CT: 230	29 (1–55)	UV	3	210	OS	8
Templeton et al. [11]	2014	Canada	North America	Apr 2004–Nov 2012	Single-center (Princess Margaret Cancer Center)	Cohort	126	67 (46–85)	Abiraterone	Pre-CT: 35 Post-CT: 91	NR	UV + MV	3	NR	OS	6
Kumano et al. [16]	2019	Japan	Asia	2011–2016	Multicenter (three centers)	Cohort	106	73.5	Enzalutamide	Post-CT: 38 CT-naive: 68	NR	MV	2.1	NR	OS^{KM}	6
Conteduca et al. [23]	2018	Italy	Europe	Mar 2011–Oct 2016	Multicenter (seven institutions)	Cohort	234	75 (42–91)	Enzalutamide	NR	18.4 (1–46)	UV	3	NR	OS, PFS	7
Choi et al. [17]	2018	Korea	Asia	Apr 2014–Apr 2017	Single-center	Cohort	113	72.2 (67–78)	Enzalutamide	CT-naive: 113	14.1 (8.2–21.9)	UV + MV	3	NR	OS	7
Armstrong et al. [26]	2018	America	North America	2010–2016	Multicenter	Cohort	872	NR	Enzalutamide	CT-naive: 872	22	MV	2.5	NR	OS	8
Conteduca et al. [15]	2016	Italy	Europe	Aug 2012–Nov 2014	Multicenter (nine centers)	Cohort	193	73.1 (42.8–72.4)	Enzalutamide	Post-CT: 193	11.7 (0.5–27.4)	MV	3	NR	OS, PFS	9

NLR neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *CT* chemotherapy, *OS* overall survival, *PFS* progression-free survival, *IQR* interquartile range, *NOS* Newcastle–Ottawa scale, *NR* not reported, *UV* univariate, *MV* multivariate.

^{KM}Represented for data extracted from Kaplan–Meier curve.

Table 2 Newcastle–Ottawa scale (NOS) for cohort studies quality assessment.

Reference	Selection				Comparability		Outcome			Quality score
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	outcome of interest was not present at start of study	Comparability of cohorts on the basis		Assessment of outcome	follow-up long enough for outcomes	Adequacy of follow-up	
					Design	Analysis				
Boegemann et al. [20]	★	★	★	–	★	★	★	★	★	8
Schiff et al. [24]	★	★	★	★	–	★	★	–	–	6
Onal et al. [21]	★	★	★	★	★	★	★	★	★	9
Loubersac et al. [14]	★	★	★	★	★	★	★	★	★	9
Fan et al. [25]	★	★	★	★	★	–	★	★	★	8
Lozano Martinez et al. [19]	★	★	★	★	★	★	★	–	–	7
Yasui et al. [13]	★	★	★	★	★	★	★	–	–	7
Boegemann et al. [22]	★	★	★	–	★	★	★	★	★	8
Lolli et al. [18]	★	★	★	–	★	★	★	★	★	8
Templeton et al. [11]	★	★	★	–	★	–	★	–	★	6
Kumano et al. [16]	★	★	★	–	★	–	★	–	★	6
Conteduca et al. [23]	★	★	★	★	★	–	★	–	★	7
Choi et al. [17]	★	★	★	★	★	–	★	–	★	7
Armstrong et al. [26]	★	★	★	★	–	★	★	★	★	8
Conteduca et al. [15]	★	★	★	★	★	★	★	★	★	9

A maximum of one star ★ for each item within the selection and outcome categories.

A maximum of two stars could be given for the comparability category.

Up to nine stars could be awarded.

Each star ★ represented one score.

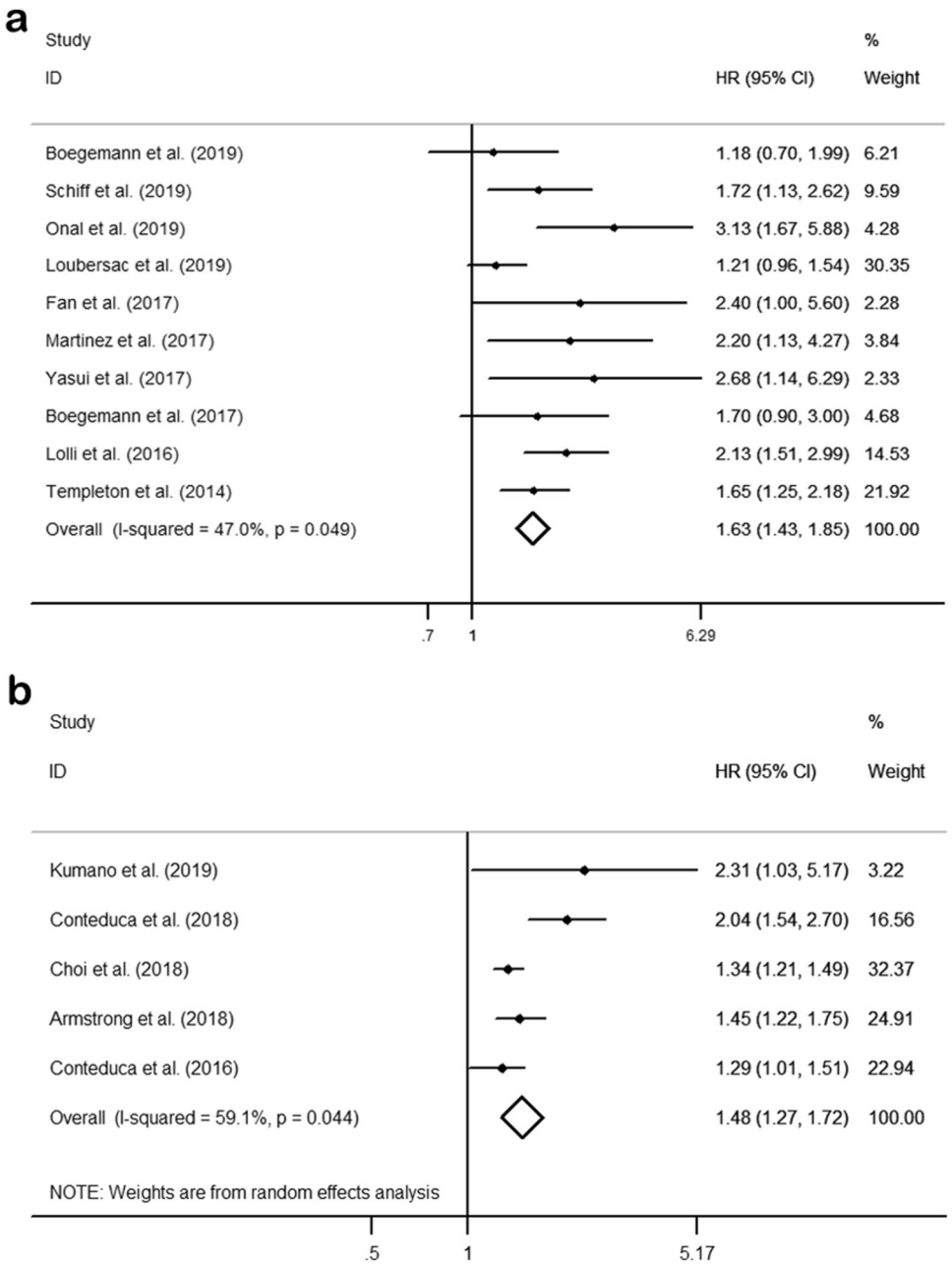

Fig. 2 Forest plots of pooled NLR on OS in mCRPC patients. a Abiraterone. **b** Enzalutamide.

The prognostic value of the neutrophil-to-lymphocyte ratio (NLR) on overall survival (OS) in mCRPC

Forest plots (Fig. 2a, b) shows the pooled results. Ten studies demonstrated that elevated NLR had a significant association with inferior OS in mCRPC patients treated with abiraterone (HR = 1.63, 95% CI: 1.43–1.85, P <0.001) with slight heterogeneity ($I^2 = 47\%$, $P_{\text{heterogeneity}} = 0.049$) [11, 13, 14, 18–22, 24, 25]. Similarly, five studies demonstrated that elevated NLR had a significant association with inferior OS in mCRPC patients treated with enzalutamide (HR = 1.48, 95% CI: 1.27–1.72, $P < 0.001$) with significant heterogeneity ($I^2 = 59.1\%$, $P_{\text{heterogeneity}} = 0.044$) [15–17, 23, 26].

Subgroup analyses were performed for OS. For mCRPC patients using abiraterone (Fig. 3a–c: (a) region, (b) analysis mode, (c) cutoff), the results showed that elevated NLR predicted inferior OS in Asian patients (HR = 2.54, 95% CI: 1.38–4.65, $P = 0.003$), multivariate analysis (HR = 1.76, 95% CI: 1.46–2.11, $P < 0.001$), and NLR cutoff >3 (HR = 1.84, 95% CI: 1.46–2.33, $P < 0.001$). Similarly, for mCRPC patients using enzalutamide (Fig. 3d, e: (d) region, (e) analysis mode), the pooled results showed that elevated NLR predicted inferior OS in non-Asian patients (HR = 1.53, 95% CI:

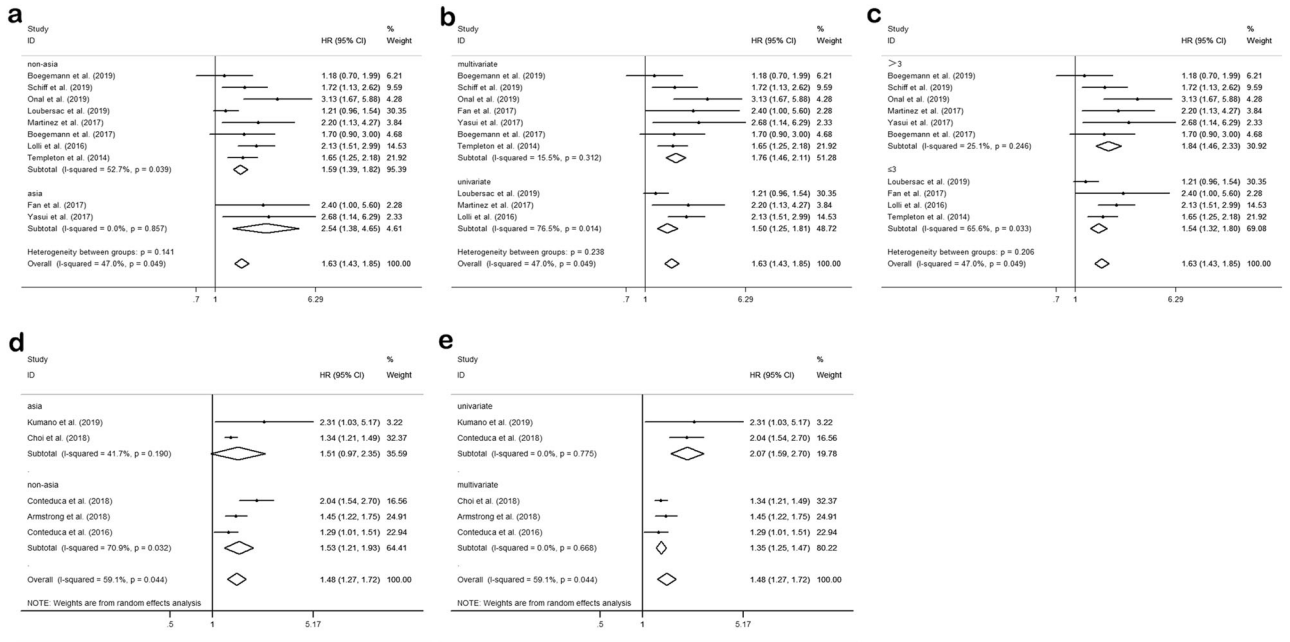

Fig. 3 Forest plots of subgroup analysis of pooled NLR on OS in mCRPC patients treated with abiraterone or enzalutamide.

Table 3 Summary of subgroup analysis results of NLR in overall survival (OS).

Subgroup	Abiraterone					Enzalutamide				
	Studies, no	HR (95% CI)	*P* value	I^2 (%)	$P_{heterogeneity}$	Studies, no	HR (95% CI)	*P* value	I^2 (%)	$P_{heterogeneity}$
Overall	10	1.63 (1.43–1.85)	<0.001	47	0.049	5	1.48 (1.27–1.72)	<0.001	59.1	0.044
Region										
Asia	2	2.54 (1.38–4.65)	0.003	0	0.857	2	1.35 (1.22–1.50)	0.067	41.7	0.19
Non-Asia	8	1.59 (1.39-1.82)	<0.001	52.7	0.039	3	1.48 (1.31–1.67)	<0.001	70.9	0.032
Analysis mode										
Univariate	3	1.50 (1.25–1.81)	<0.001	76.5	0.014	2	2.07 (1.59–2.70)	<0.001	0	0.775
Multivariate	7	1.76 (1.46–2.11)	<0.001	15.5	0.312	3	1.35 (1.25–1.47)	<0.001	0	0.668
Cutoff										
≤3	4	1.54 (1.32–1.80)	<0.001	65.6	0.033	NR				
>3	6	1.84 (1.46–2.33)	<0.001	25.1	0.246	NR				

NLR neutrophil-to-lymphocyte ratio, *HR* hazard ratio, *NR* not reported.

1.21–1.93, $P < 0.001$) and univariate analysis (HR = 2.07, 95% CI: 1.59–2.70, $P < 0.001$). The pooled results were shown in Table 3.

The prognostic value of the neutrophil-to-lymphocyte ratio (NLR) on progression-free survival (PFS) in mCRPC

Forest plots (Fig. 4a, b) shows the pooled results. Two studies demonstrated that elevated NLR had no significant association with PFS in mCRPC patients treated with abiraterone (HR = 1.62, 95% CI: 0.81–3.26, $P = 0.176$) with significant heterogeneity ($I^2 = 71.5\%$, $P_{heterogeneity} = 0.061$) [20, 21]. Similarly, two studies demonstrated that elevated NLR had no significant association with inferior OS in mCRPC patients treated with enzalutamide (HR = 1.55, 95% CI: 0.98–2.45, $P < 0.001$) with significant heterogeneity ($I^2 = 89.9\%$, $P_{heterogeneity} = 0.002$) [15, 23].

The prognostic value of the platelet-to-lymphocyte ratio (PLR) in mCRPC

Forest plots (Fig. 5) shows the pooled results. Three studies demonstrated that elevated PLR had a significant association with inferior OS in mCRPC patients treated with abiraterone (HR = 1.52, 95% CI: 1.16–1.98, $P < 0.001$) with slight heterogeneity ($I^2 = 4.1\%$, $P_{heterogeneity} = 0.352$) [18, 19, 21].

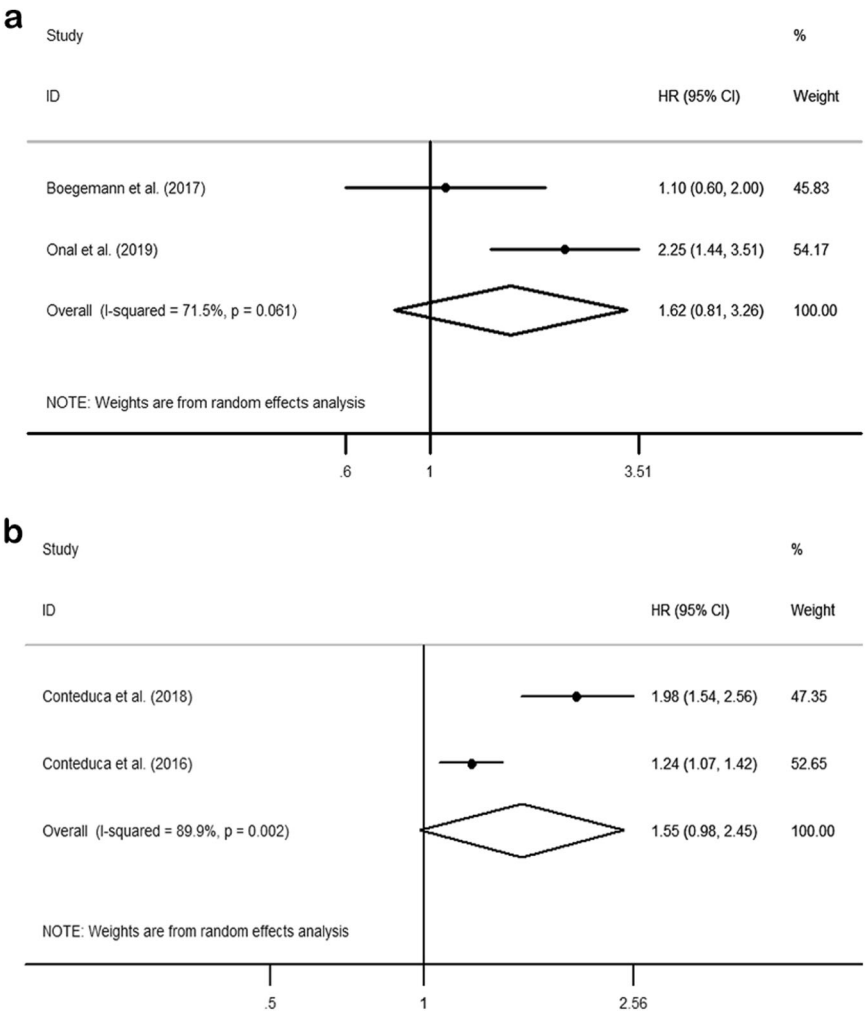

Fig. 4 Forest plots of pooled NLR on PFS in mCRPC patients. a Abiraterone. **b** Enzalutamide.

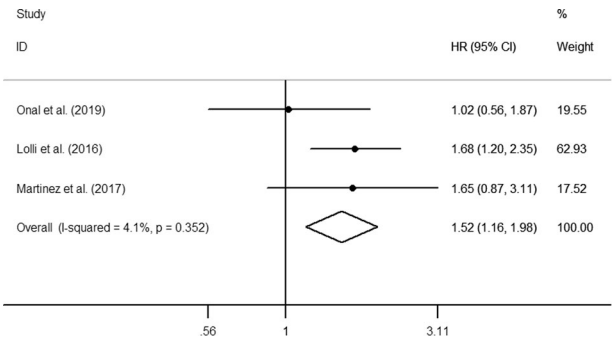

Fig. 5 Forest plots of pooled PLR on OS in mCRPC patients treated with abiraterone.

Sensitivity analysis and publication bias

A sensitivity analysis was performed to assess the stability of the pooled results by omitting any single study in sequence. The sensitivity analysis results demonstrated that the pooled HRs for OS and PFS did not significantly change, suggesting the robustness of the results (Fig. 6a, b). Publication bias was assessed by Egger's test. A study was considered to have significant publication bias when $P < 0.05$. OS of mCRPC patients treated with abiraterone ($P = 0.111$) and enzalutamide ($P = 0.391$) for NLR, respectively, and the OS ($P = 0.441$) for PLR. The results of Egger's test did not indicate and publication bias in the present meta-analysis (Fig. 6c, d).

Discussion

Currently, mCRPC is a global cause of one of the highest mortality rates across the world, threatening male populations everywhere but especially in Western countries [1]. As a novel generation of hormonal agents, abiraterone and enzalutamide have been reported to prolong the survival of mCRPC patients [27]. However, despite the emergence of these new drugs, the prognosis of mCRPC remains inadequate, as the responses of patients to these new agents is still

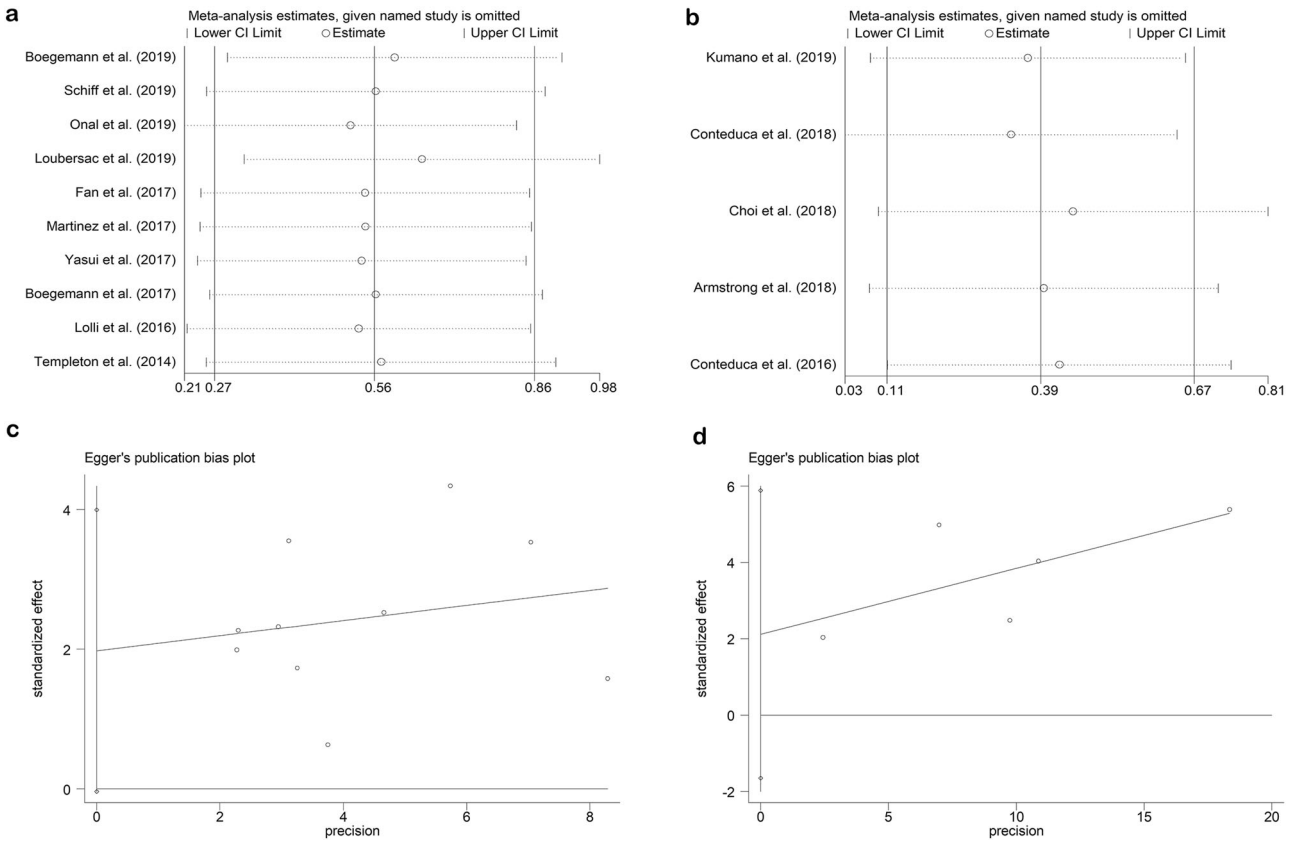

Fig. 6 Sensitivity analysis and Egger's test of pooled NLR on OS in mCRPC patients. a, **c** Abiraterone. **b**, **d** Enzalutamide.

unclear. Previous meta-analyses have focused on the correlations between CRPC and hematologic parameters, but their conclusions have been inconsistent. Therefore, the present study conducted a comprehensive systematic review and meta-analysis to assess the precise values of NLR and PLR in mCRPC patients treated with abiraterone or enzalutamide and thus provide valuable information and optimized choices to clinicians and patients.

The main finding of this meta-analysis demonstrated that elevated NLR was significantly associated with inferior OS in mCRPC patients treated with abiraterone or enzalutamide, whereas elevated NLR had no significant correlation with unfavorable PFS. Similarly, increasing PLR was associated with poor OS in mCRPC patients treated with abiraterone. In addition, according to subgroup analyses, an elevated NLR was more specific to predict an inferior prognosis in Asian patients of mCRPC treated with abiraterone than non-Asian patients, whereas, an elevated NLR appeared to be a stronger predictor of risk in non-Asian patients treated with enzalutamide. An NLR cutoff value >3 had a more significant prognostic value than a cutoff value ≤3, which indicated that a higher NLR cutoff was more specific to predict a poor prognosis in patients of mCRPC treated with abiraterone. Due to insufficient study data, the relationship between PLR and PFS could not be estimated. It is worth notice that the PREVAIL study prognostic model demonstrated that NLR acted as an independent prognostic factor for OS in mCRPC during enzalutamide treatment but not predictive factor [26], the incorporation of NLR may prove useful for risk stratification in mCRPC patients. Intriguingly, Loubersac et al. suggested that baseline NLR may predict response to abiraterone in mCRPC, however, the changes in NLR could not hold significant value during treatment to predict subsequent response to continued therapy [14].

Some past meta-analyses have also investigated hematologic parameters [28–31]. Gu et al. [32], for instance, demonstrated that elevated NLR predicted poor OS and PFS in 16,266 patients with prostate cancer. Interestingly, Li et al. [33] investigated the prognostic significance of PLR in urological cancers and found that elevated PLR was negatively related to OS in urological cancers, except for bladder cancer. These studies reported that elevated NLR or PLR levels were significantly associated with the inferior survival outcomes (OS, PFS, RFS, and cancer-specific survival (CSS)) of prostate cancer patients (localized PCa or CRPC), whereas the correlation between mCRPC and survival outcomes has not been investigated synthetically. In

addition, the prognostic values of NLR and PLR in gauging responses to specific agents, including abiraterone or enzalutamide, have also not been evaluated. In contrast to those meta-analyses, the present study mainly focused on NLR and PLR values by connecting the survival outcomes of mCRPC patients and their responses to abiraterone or enzalutamide. The present study also included more updated, eligible studies that could provide the multivariate HRs, as data are more reliable through multivariate analysis adjusting.

The systemic inflammatory response has been considered as a hallmark of cancer [10, 34, 35]. Neutrophils, lymphocytes, platelets, and monocytes from peripheral blood all play roles in the systemic inflammatory response. Lately, the most evaluated indices are NLR, PLR, and the lymphocyte-to-monocyte ratio [36, 37]. Accumulating evidence shows these ratios to reliable prognostic factors of the survival of many solid tumors, including non-small-cell lung cancer [38], breast cancer [39], melanoma [40], colorectal cancer [41], hepatocellular carcinoma [42], prostate cancer [22], bladder cancer [43], and others. Unlike abiraterone, enzalutamide is not taken with prednisone, which might alter NLR values by redistributing lymphocytes in the bone marrow, lymph nodes, and spleen by reducing and accelerating the release of neutrophils from the bone marrow to the peripheral blood [7]. Nonetheless, the mechanisms underlying the mutual effects of elevated NLR and PLR on the inferior oncologic outcomes of mCRPC patients have remained indistinct.

Inflammation exerts a crucial role in oncogenesis, progression, and metastasis by facilitating angiogenesis, proliferation, and antiapoptosis [44]. Tumor cells attract proinflammatory cells into the tumor microenvironment by secreting a variety of chemokines [10]. Neutrophils act as a significant factor not only in promoting an array of cytokines such as IL-1β, IL-6, tumor necrosis factor, or granulocyte colony-stimulating factor secreting but also in facilitating angiogenesis and vascular endothelial growth production and subsequently stimulating tumor cells growth [34]. On the contrary, lymphocytes play a crucial role in regulating the immunologic antitumor activity, meaning that a decreased lymphocyte count may indicate tumor cells escaping from the normal immune system, thus worsening the survival outcomes of cancer patients. In Brief, the inflammatory response is characterized by increasing neutrophil-dependent levels accompanied by decreasing lymphocyte-mediated levels. For one thing, platelets accelerate tumor aggressiveness by deriving cytokines, such as platelet-derived growth factor and vascular endothelial growth factor, and promoting cancer cell adhering to the vascular endothelium; for another thing, platelets might interact with tumor cells through their ligands and help guard tumor cells from the elimination of immune system, which are regarded as correlations with inferior cancer prognosis [35]. NLR and PLR, therefore, seem to reflect a systemic inflammatory response to cancer progression leading to pronounced ratios in advanced cancer. NLR and PLR can thus provide Supplementary Information in therapeutic surveillance and decision-making regarding treatment changes regarding mCRPC. The present study supports the use of pretreatment NLR and PLR in mCRPC, along with other hematologic parameters and physical functional status, providing effective estimates of host response in determining long-term survival.

Several limitations of this study should be acknowledged. First, relevant studies were scarce, so we could not acquire robust conclusions in some endpoint analyses. Second, CSS, biochemical recurrence-free survival, and disease-free survival, essential outcomes for cancer survival analysis, were not pooled due to a lack of sufficient survival data. In addition, we lacked research from Southern America and Oceania, shrinking the number of included studies. Third, searching only relevant studies published in English may have excluded studies with negative results published in other languages. Fourth, the cutoff values of NLR and PLR varied among the eligible studies, ranging from 2.14 to 5 and 150 to 210, respectively. This heterogeneity might impede the clinical application of these ratios. Accordingly, more credible evidence is needed to identify the optimal cutoff values of these hematologic parameters. Fifth, the NLR and PLR values were derived from peripheral blood and were thus easily affected by patients' elementary conditions such as age, tumor burden, histological features, stage of disease, infection, inflammatory disease, chronic disease, specific medications, and so on. Sixth, only retrospective cohort studies were included in this study. We, therefore, interpreted the results of the present meta-analysis with caution.

In the future, more randomized control trials (RCTs) and wider-ranging researches are pressing needed to study the prognostic role of hematologic parameters in predicting the survival of mCRPC patients and the therapeutic evaluation of abiraterone and enzalutamide.

Conclusions

In summary, hematologic parameters, including NLR and PLR, can be promising biomarkers for the prognosis of mCRPC, and pretreatment NLR and PLR can provide useful information for individual-based treatment by reflecting patient responses to abiraterone and enzalutamide. In the future, more RCTs and large sample sizes are called for to confirm the potentially profound values of hematologic parameters.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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