

Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Prostate Cancer

A Systematic Review and Meta-analysis

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Abstract: Inflammation is increasingly reported to be associated with the prognosis of patients with cancers. And the prognostic role of neutrophil-to-lymphocyte ratio (NLR) in patients with prostate cancer (PCa) remains inconsistent. Therefore, we conducted this systematic review and meta-analysis to obtain a more reliable assessment of prognostic significance of NLR in PCa.

A comprehensive literature research regarding the association of NLR and prognosis of PCa was performed through PubMed, Embase, Cochrane Central, and Web of Science. The hazard ratios (HRs) and its 95% confidence intervals (CIs) for overall survival (OS), progression-free survival, or recurrence-free survival were extracted and pooled using fix-effects model or random-effects model.

A total of 14 studies that met our criterion were included in this meta-analysis. Our pooled results demonstrated that elevated NLR was not significantly associated with the poor OS (HR = 1.45; 95% CI 0.77–2.71; $P = 0.248$) or recurrence-free survival (HR = 1.34; 95% CI 0.89–2.02; $P = 0.155$) of patients with localized PCa. Although elevated NLR predicted poorer OS (HR = 1.57; 95% CI 1.41–1.74; $P < 0.001$) and progression-free survival (HR = 1.97; 95% CI 1.28–3.04; $P = 0.002$) of patients with metastatic castration resistant prostate cancer (mCRPC).

Elevated NLR is a strong indicator of poorer prognosis of patients with mCRPC, whereas the NLR is not significantly associated with prognosis of patients with localized PCa. Therefore, NLR could be used in patients with mCRPC for risk stratification and decision making of individual treatment.

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Abbreviations: CI = confidence interval, CRP = C-reactive protein, HR = hazard ratio, mCRPC = metastatic castration-resistant prostate cancer, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PCa = prostate cancer, PFS = progression-free survival, PSA = prostatic-specific antigen, RFS = recurrence-free survival.

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INTRODUCTION

Prostate cancer (PCa) is the most common malignancy in men, accounting for about one-quarter of new diagnosed patients.¹ And it accounts for 9% of death in men, which is the second leading cause. With the application of prostate-specific antigen (PSA) screening and imaging modalities, most PCa are diagnosed at localized stage. For localized PCa of low and intermediate risk, radical prostatectomy or radiotherapy is the standard treatment with promising outcomes. For PCa of high risk or advanced PCa, especially metastatic castration resistant prostate cancer (mCRPC), the prognosis, however, is still poor despite the increased number of novel therapies or drugs such as abiraterone, enzalutamide, and sipuleucel-T.^{2–6} Therefore, an accurate prognostic model is important in informing patients, selecting individualized treatment, and making a proper surveillance program. Besides the tumor, nodes, metastasis staging, PSA level, and Gleason score that are conventionally used to stratify patients in terms of prognosis, relevant metabolic factors, such as platelet count, alkaline phosphatase, hemoglobin, and albumin are reported to be associated with prognosis of PCa, and are enrolled into the predictive models in some studies.^{7–9}

Inflammation is considered to be a hallmark of cancer.¹⁰ And inflammation plays an important role at different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis.¹¹ Recently, neutrophil-to-lymphocyte ratio (NLR), one of the inflammatory parameters, has been reported to be of prognostic value in some solid tumors, including PCa.^{12,13} It, however, is still inconsistent regarding the exact role of NLR in prognosis prediction of PCa. Because of the difference in study design, patient selection and other factors, some studies reported that an elevated NLR is recognized as an indication of poor prognosis, whereas several other studies did not demonstrate the significant association between NLR and survival. And no meta-analysis evaluating the prediction value of NLR in PCa is available until now.

Therefore, we conducted this systematic review and meta-analysis to obtain a more reliable assessment of prognostic significance of NLR in patients with PCa.

METHODS

Search Strategy

This meta-analysis was compiled with the guideline of Preferred Reporting Items for Systematic Reviews and Meta-analyses.¹⁴ Because the studies that included in this meta-analysis have been published, the ethical approval from ethics committees was not needed.

A literature search for published original articles was conducted in PubMed, Embase, Cochrane Central, and Web of Science. The last updated search was carried out on July 30,

2015. The following combined search items through MeSH headings, keywords, and text words were used: “NLR” (eg, “neutrophil and lymphocyte,” “NLR,” “neutrophil lymphocyte ratio,” and “NLR”) and “PCa”. In addition, references of relevant literatures were manually screened for further inclusion.

Selection Criteria and Definition

The identified studies were included if they met the following criteria: cohort studies were considered for inclusion; pre-treatment NLR values were measured by serum-based method; studies reported hazard ratios (HRs) and 95% confidence intervals (CIs) for NLR in the analysis of overall survival (OS), progression-free survival (PFS), or recurrence-free survival (RFS), and the studies that only reported HRs and P values were also included, which allowed manual calculation of 95% CI. The articles that were not written in English were excluded. Letters, case reports, or review articles were also excluded. When duplicate articles were encountered, we included the more informative and latest article. Two researchers (XY and FL) screened titles and abstracts of all searched studies, and identified the studies that met the selection criteria for next analysis. Discrepancies were resolved through discussion with YX.

Overall survival was defined as the time from the initiation of treatment to the date of death of any causes. In group of localized PCa, RFS was calculated as the time between curative treatment and the confirmation of local recurrence and distant metastasis. And in group of mCRPC, PFS was calculated as the time from the treatment to PSA value and/or radiologic progression. Prostate-specific antigen progression was defined as an increase of more than 25% or 2 ng/mL in PSA values in comparison with the pretreatment PSA value. And radiologic progression was defined as a size increase of an existing lesion, new metastatic lesions, or disease-related symptoms.

Quality Assessment

According to the guideline of meta-analysis of observational studies in epidemiology, methodological quality of all the included studies was assessed independently by 2 researchers (FL and XY).¹⁵ The checklist point comprised the following 5 aspects: clear definition of study design; clear definition of study population; sufficient study sample size ($N > 40$ in this meta-analysis); clear description of outcome assessment (OS, PFS, or RFS); sufficient follow-up time. To ensure the quality of our meta-analysis, the studies that did not mention all these 5 points were excluded. During the process discrepancies were resolved through discussion with JG.

Data Extraction

The relevant information was extracted independently by 2 researchers (SQ and ZY) using a predefined form. The information contained the following: study information: the first author's last name, year of publication, study location, research time, and sample size; patient information: age, stage of disease, treatment method, and follow-up time; cutoff value of NLR, and HR, 95% CI or *P* value of NLR for OS, PFS, or RFS. Discrepancies during data extraction were resolved by discussion.

Statistical Analysis

An $HR > 1$ implied poor prognosis of patients with an elevated NLR. A test of heterogeneity of included studies was conducted using the Mantel-Haenszel χ^2 and the Higgins I-squared statistics. I^2 values $> 50\%$ in Higgins I-squared statistics indicated the presence of significant heterogeneity among

studies, and the random-effects model was applied for the meta-analysis.¹⁶ Otherwise, the fixed-effects model was used. Pooled HR and its 95% CI of the included studies were calculated to assess the association between NLR and OS, PFS, or RFS. We also performed sensitivity analysis by sequential omission of individual study to evaluate the stability of the pooled results and investigate the potential source of the heterogeneity if the heterogeneity was significant. Publication bias was also detected by visual inspection of funnel plots, Begg and Mazumdar¹⁷ adjusted rank correlation test, and Egger¹⁸ regression asymmetry test. All the statistical analysis was carried out by the use of STATA software, version 12.0 (State Corporation, College Station, TX). For all analysis, *P* values < 0.05 was considered statistically significant.

RESULTS

The Search Results and Quality Assessment

A total of 97 records were identified after the primary comprehensive literature research using aforementioned strategy. Twenty-four duplicated items were excluded. After screening the titles and abstracts of identified records, 48 studies were excluded for the reasons, including animal studies, reviews, letters, case reports, and other irrelevant studies. After full text assessment, 11 studies did not evaluate the relationship between NLR and survival separately, or failed to report the key data (HR, 95% CI, or *P* value). Thus, 14 studies with 16,598 PCa patients,^{12,19–31} which met our selection criterion, were eventually included in our research. They were all of high quality for our analysis by meta-analysis of observational studies in epidemiology assessment. And the flowchart of the study selection process was shown in Figure 1.

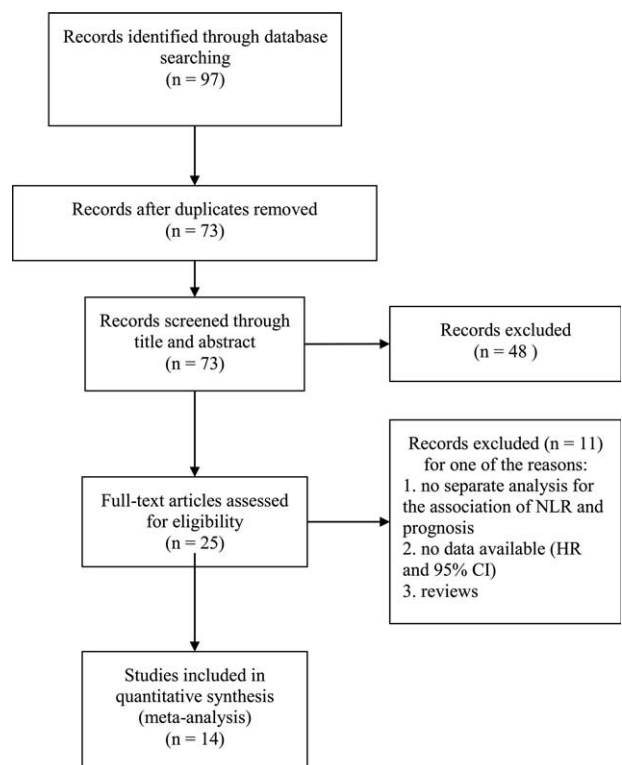


FIGURE 1. Flow chat of literature search and selection.

TABLE 1. Baseline Characteristics of the Included Studies in This Meta-analysis

Study	Year	Region	Research Time	Follow-up (Month)	Treatment	Case Number	Age (Years)	Cutoff	Survival Analysis
Localized prostate cancer									
Sharma	2015	United States	1990–2007	Median:9.7	RP	8350	NA	5	OS; RFS
Poyet	2015	Switzerland	2008–2013	Median:23	RP	399	Median: 64	NA	RFS
Langenlehner	2015	Austria	1999–2007	Median:87	RT	415	Mean:69.9	5	OS; RFS
Minardi	2015	Italy	2005–2011	Mean:51.5	RP	389	Mean:65	3	RFS
Castration-resistant prostate cancer									
Yao	2015	Japan	2008–2014	NA	Docetaxel	57	Median: 74	3.5	OS; PFS
Nakagami	2015	Japan	2003–2013	NA	Docetaxel	101	NA	2.6	OS
MacLanchlan	2015	Australia	2005–2012	Median:23.1	Docetaxel or cabazitaxel	42	Median:68.5	5	OS; PFS
Lorente	2015	United States	NA	Median:12.8	Cabazitaxel or mitoxantrone	755	Median:67	3	OS; PFS
Templeton	2014	Canada	2001–2011	NA	Docetaxel	357	Median:71	3	OS
Templeton	2014	Canada	NA	NA	Abiraterone	185	Median:69	5	OS
Sonpavde	2014	United States	2008–2010	NA	Sunitinib	848	Mean:68	NA	OS
Nuhn	2014	United States	1998–2010	Mean:15.0	Docetaxel	238	Median:68.3	3	OS
Linton	2013	Australia	2007–2009	NA	Docetaxel or AT-101	182	Median:69	5	OS
Keizman	2011	Israel	1999–2011	NA	Ketoconazole	156	Median:69	3	PFS

NA = not available, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival, RP = radical prostatectomy, RT = radiotherapy.

The baseline characteristics of the included 14 studies were summarized in Table 1. Eleven studies were from western countries, including United States, Switzerland, Italy, Austria, Canada, and Australia. The other 3 studies were from Japan and Israel. Four studies enrolled patients with localized PCa, which were treated with radical prostatectomy or radiation therapy. And the rest 10 studies enrolled patients with metastatic castration-resistant prostate cancer (mCRPC), which were treated with chemotherapy, abiraterone, ketoconazole, or sunitinib. Of the 14 studies, 11 studies reported the survival results of OS (2 studies in localized PCa, and 9 studies in mCRPC), and 4 studies reported the survival results of RFS in localized PCa, and 4 studies reported the PFS in mCRPC. In all these studies, NLR was calculated from the white blood cell differentiated counts. And we preferred to extract the HR and its corresponding 95% CI of each studies from the multivariable analysis. If the multivariable analysis was not performed, the HR from the univariable analysis was used in our meta-analysis.

Neutrophil-to-Lymphocyte Ratio and Overall Survival in Prostate Cancer

There was significant heterogeneity between studies included for investigate the association between NLR and OS in all-stage PCa ($I^2 = 66.2\%$, $P = 0.001$). Considering the remarkable difference of prognosis between localized PCa and mCRPC, which may introduce significant heterogeneity, we performed the subgroup meta-analysis based on tumor stage.

Localized Prostate Cancer

Only 2 studies reported the HR and 95% CI from OS analysis in patients with localized PCa, with significant heterogeneity ($I^2 = 76.5\%$, $P = 0.039$). The pooled result showed that an elevated NLR was not significantly associated with the OS of localized PCa (HR = 1.45; 95% CI 0.77–2.71; $P = 0.248$; Figure 2).

Metastatic Castration-resistant Prostate Cancer

Between the 9 studies that reported the HR of OS results in patients with mCRPC, there was no significant heterogeneity ($I^2 = 5.7\%$, $P = 0.388$). And the result demonstrated that an elevated NLR was significantly associated with worse OS outcomes in mCRPC (HR = 1.57; 95% CI 1.41–1.74; $P < 0.001$; Figure 2).

Neutrophil-to-Lymphocyte Ratio and Recurrence-free Survival /Progression-free Survival in Prostate Cancer

Localized Prostate Cancer

Significant heterogeneity was detected between the 4 studies that reported the HR from RFS results in localized PCa ($I^2 = 77.1\%$, $P = 0.004$). And the pooled result indicated that an elevated NLR was not significantly associated with the poor RFS of localized PCa (HR = 1.34; 95% CI 0.89–2.02; $P = 0.155$; Figure 3).

Metastatic Castration-resistant Prostate Cancer

Four studies reported the HR from PFS results in patients with mCRPC, and significant heterogeneity was detected between the studies ($I^2 = 67.9\%$, $P = 0.025$). The pooled result merged by random-effects model demonstrated that an elevated NLR was significantly associated with a worse PFS of mCRPC (HR = 1.97; 95% CI 1.28–3.04; $P = 0.002$; Figure 3).

Sensitivity Analysis

To assess the stability of every pooled result in our meta-analysis, we performed a sensitivity analysis for every analysis by sequential omission of individual study. The pooled results regarding the association between NLR and OS or PFS/RFS were proved to be stable and credible.

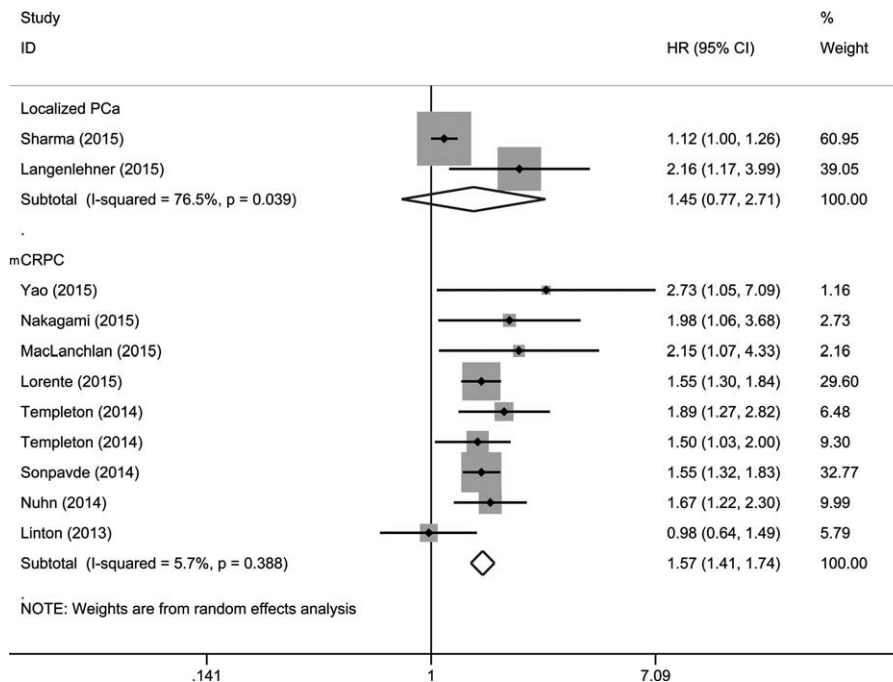


FIGURE 2. Forest plot of studies evaluating the association between neutrophil-to-lymphocyte ratio and overall survival in prostate cancer.

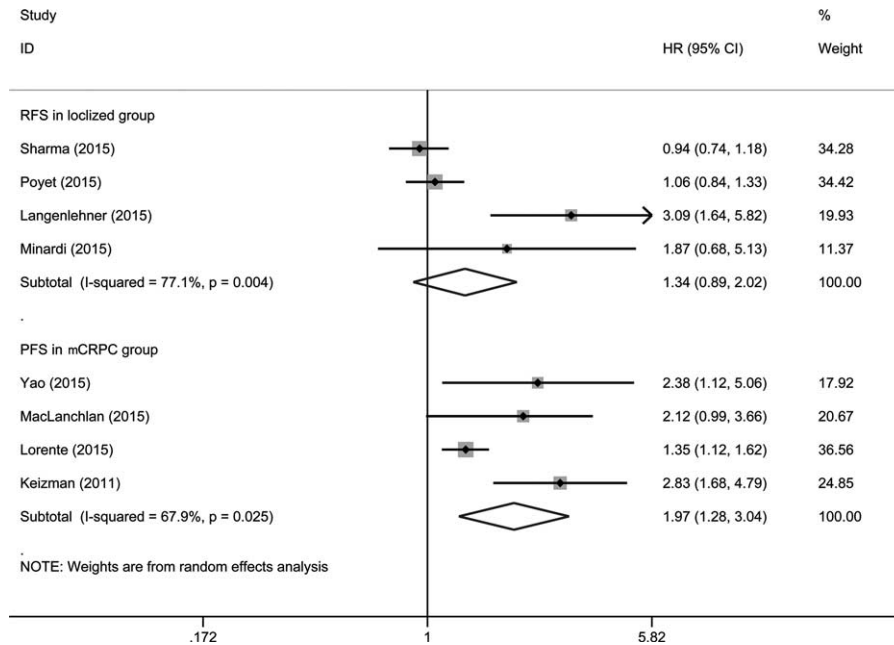


FIGURE 3. Forest plot of studies evaluating the association between neutrophil-to-lymphocyte ratio and recurrence-free survival in localized prostate cancer, and progression-free survival in metastatic castration resistant prostate cancer.

Publication Bias

We used the funnel plot, Egger test and Begg test to evaluate the potential publication bias of the included studies in each analysis (Figure 4). The funnel plot results did not demonstrated obvious evidence of asymmetry in all these pooled analysis. Furthermore, the Egger and Begg test did not indicated any significant publish bias in the analysis of OS in mCRPC (*P*_{Begg} = 0.118, *P*_{Egger} = 0.376), RFS in localized PCa (*P*_{Begg} = 0.734, *P*_{Egger} = 0.179), and PFS in mCRPC (*P*_{Begg} = 0.734, *P*_{Egger} = 0.093). Thus, low potential publication bias existed in our meta-analysis. Because only 2 studies were included in the analysis of OS in localized PCa, publication bias was not assessed in this analysis.

DISCUSSION

Currently, the estimate of prognosis in patients with PCa is mainly based on the D’amico risk classification system, which focuses on tumor, nodes, metastasis staging, PSA level, and Gleason scores.³² This system, however, is rough and limited, many patients in the same risk group turned out to be significantly different in prognosis. And with the increasing number of available novel therapies for PCa, such as abiraterone, enzalutamide, and sipuleucel-T, it becomes more important to estimate the prognosis of patients precisely and individually, so that patients can receive the most optimal treatment. Therefore, considerable efforts went into the development of new methods for prognosis prediction of PCa. Eastern Cooperative Oncology Group performance status, presence of visceral metastases, presence of pain, PSA levels, hemoglobin, albumin, lactate dehydrogenase, and alkaline phosphatase levels have been reported to be associated with OS.

Recently, the systemic inflammation status is found to be associated with the prognosis of solid tumors in several studies. NLR could be recognized as a marker for general immune response to various stress stimuli. And an elevated NLR has

been found to be an indicator of poor prognosis in patients with renal cell carcinoma,³³ colorectal cancer,³⁴ and nonsmall-cell lung cancer.³⁵ In terms of PCa, some studies confirmed the prognostic role of NLR,¹² whereas several other studies did not find the significant association between NLR and prognosis.^{24,27} And until now, to our knowledge, there is not a meta-analysis assessing the prognostic role of NLR in PCa.

In this study, we performed a meta-analysis, including 14 studies to evaluate the prognostic role of NLR in PCa. The outcome of PCa in different stage is significantly different. The patients with localized PCa could receive definite therapies, including radical prostatectomy and radiotherapy, and their 15-year cancer-specific survival rate could be more than 85%. For patients with mCRPC, the prognosis, however, is significantly worse and the median OS is only approximately 40 months. Considering the significant difference of prognosis between different stages, we performed the analysis in localized PCa and mCRPC, respectively, which obviously decreased the heterogeneity in each analysis. Our results demonstrated that elevated NLR could not predict the poor OS or RFS in patients with localized PCa. The localized PCa can be eradicated by radical prostatectomy or radiotherapy, and its prognosis is excellent. After radical treatment, most patients may not suffer from the PCa and die from other diseases in the end. We think that is why the prognostic role of NLR in localized PCa is negative. And for patients with mCRPC, an elevated pretreatment NLR was significantly associated with poor OS and PFS, respectively. Besides, our result was proved to be robust by sensitivity analysis, and no significant publication bias was found through funnel plot visualization, Begg test, and Egger test. Compared with other biologic factors that predict the prognosis of PCa such as cancer stem cell markers and gene polymorphism, the NLR is easily obtained from the widely available blood routine test. It does not need a specific assay equipment or kit, and also does not increase the medical expenditure. The great cost-effect and accessibility make NLR more applicable in hospitals,

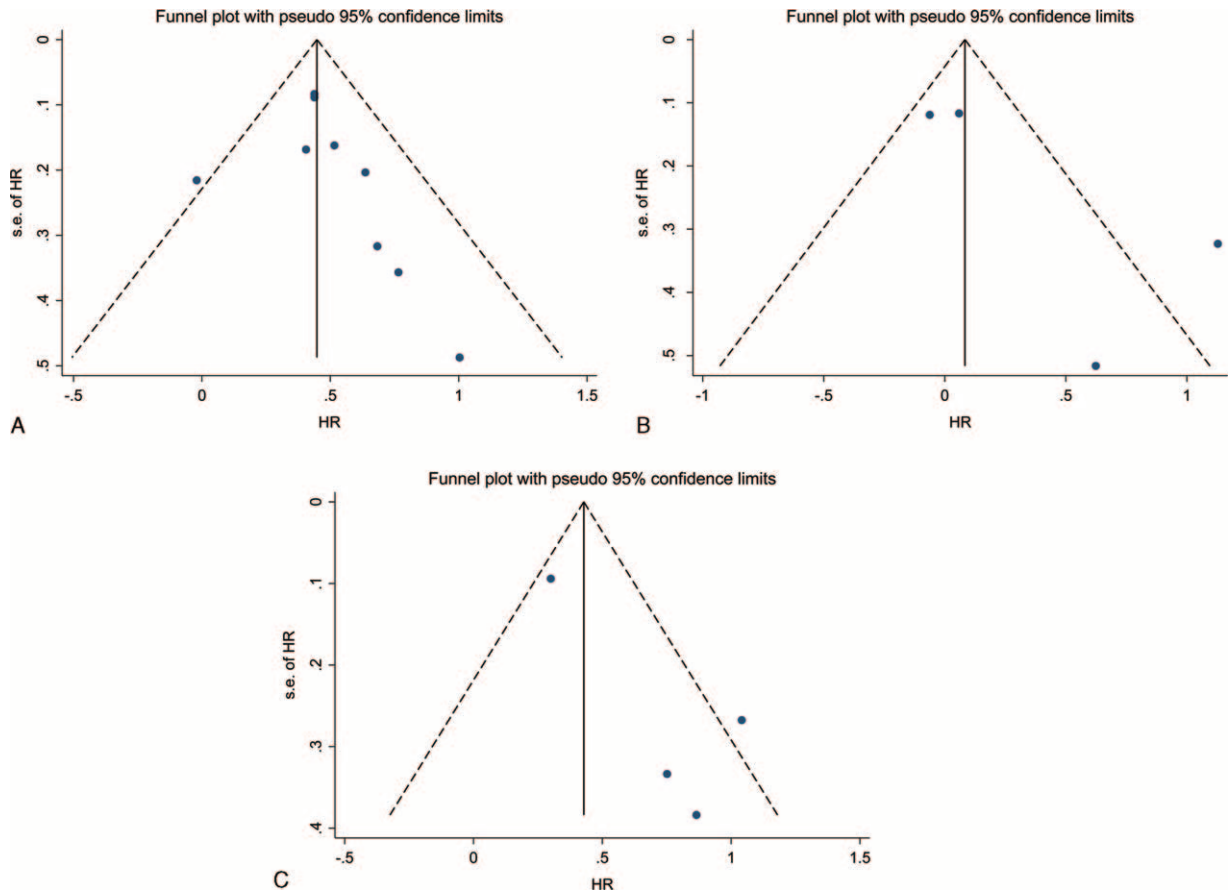


FIGURE 4. Funnel plots for the evaluation of publication bias. Plots are ranged as follow: A, overall survival in metastatic castration resistant prostate cancer; B, recurrence-free survival in localized prostate cancer; C, progression-free survival in metastatic castration resistant prostate cancer.

especially those in areas with limited medical resources. Taken all these into consideration, NLR could be a promising prognostic indicator, which benefits the clinical decision-making process regarding PCa treatment and outcomes.

Inflammation has been considered to be associated with different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis. But the mechanism underlying the association between elevated NLR and poor prognosis of PCa is still not clear. In general, neutrophils represents the activity of systemic inflammation, and could be triggered by granulocyte colony stimulating factor secreted by tumor cells.³⁶ Meantime, neutrophils play a promotion role in tumor growth and metastasis. It is found that neutrophils could enhance the producing of many inflammation mediators such as tumor necrosis factor, interleukin 1, interleukin 6, and therefore promote the survival and proliferation of tumor cells.³⁷ In addition, the secretion of the vascular endothelial growth factor, which a potent angiogenesis cytokine, is also enhanced by increased neutrophils, therefore the tumor development is further accelerated.^{38,39} Nevertheless, lymphocytes play an important role in tumor-specific immune response, which mediates the most antitumor activity in vivo. Cytotoxic lymphocyte, which is a subtype of lymphocyte, is just responsible for killing the tumor cells directly.⁴⁰ In several studies, the increased infiltration of lymphocytes in tumor tissue is found to be associated with better prognosis

in cancer patients, which reflects the importance of lymphocytes.⁴¹ In addition, the lymphopenia is also an indicator of immune escape of tumor cells from immune system, which results in a poor outcome of cancer patients.⁴² Moreover, cytolytic ability of lymphocytes can be suppressed by the neutrophils when they are cocultured in vitro, and the extent of suppression is positively correlated with the number of neutrophils.⁴³ Taken together, the elevated NLR is mainly caused by the increase of neutrophils along with the decrease of lymphocytes, which reflects the enhancement of tumor promotion and the impaired tumor immunity. Therefore, an elevated NLR predicted the poor prognosis of patients with mCRPC in this meta-analysis.

The association between inflammation and outcome of patients with PCa is also proved by other inflammation related markers. C-reactive protein (CRP) and modified Glasgow prognosis score, which is calculated using CRP and albumin level, are also predictors of prognosis in patients with PCa.^{27,44} C-reactive protein, however, is not routinely examined in the pretreatment assessment of patients. And the measure of NLR is more accessible and costs less, which makes NLR be of wider availability, especially in primary hospitals.

There are several limitations in our meta-analysis. First, the included studies in our meta-analysis were all retrospective observational studies. And no prospective cohort study was identified until now. The qualities of evidence of the included

studies were still poor. Second, reporting bias is another inevitable problem. Studies with significant results are easier to be published than those with null or insignificant results. Thus the pooled HR may be potentially overestimated. Third, marked heterogeneity was detected in some analysis (OS, PFS, or RFS). Considering the tumor stage as a significant source of heterogeneity, we attempted to categorize the included 14 studies into 2 independent groups, localized PCa and mCRPC, respectively, to decrease the potential heterogeneity. But the heterogeneity remained in some analysis, which might be derived from several other factors, such as the study design, patient's baseline characteristics, patients' treatments, the cutoff value of NLR, and the length of follow-up. NLR was defined as continuous variable in 2 studies, and was defined as categorical variable in the other 12 studies. And in studies which defined NLR as categorical variable, most cutoff values were higher than 3. Because of limited studies, we did not performed subgroup analysis based on categorical NLR or cutoff value lower than 3, which was indeed another limitation of our meta-analysis. We pooled these studies together and still demonstrated that elevated NLR was a strong indicator of poorer prognosis of patients with mCRPC. But the specific risk value should be regarded with consideration. In addition, the HR and corresponding 95% CI in different studies was not adjusted for identical confounders in multivariate models, which might pose a potential heterogeneity. So the current analysis by current available data did not find the significant contributor to the heterogeneity in some analysis. Finally, 4 of the included 14 studies were from conference abstracts, which were of relatively low quality. There, more well-designed and prospective cohort studies are needed to further confirm the association of NLR and prognosis in PCa.

CONCLUSIONS

In summary, our meta-analysis demonstrates that an elevated NLR is a strong indicator of poorer prognosis of patients with mCRPC, whereas the NLR is not significantly associated with prognosis of patients with localized PCa. Besides, the excellent accessibility and cost-effect of NLR further promote its wider application in patients with mCRPC for risk stratification and decision making of individual treatment. Well-designed and prospective cohort studies are expected to confirm our results.

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