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Baseline neutrophil-lymphocyte ratio is associated with outcomes in patients with castration-resistant prostate cancer treated with Docetaxel in South China

Zhi-guo Jiang, MD, PhD[a], Shao-Guang Liao, MD, PhD[b,*]

Abstract

The aim of this study is to investigate the association between baseline neutrophil-to-lymphocyte ratio (NLR) and progression-free survival (PFS), overall survival (OS) and radiological response in castration-resistant prostate cancer patients treated with docetaxel.

Forty-one prostate cancer patients who were treated with docetaxel were selected. Univariable and multivariable Cox regression models were used to predict the association of baseline NLR as a dichotomous variable with PFS and OS after chemotherapy initiation.

In Kaplan–Meier analysis, the median PFS (9.8 vs 7.5 months, $P = .039$, Fig. 1) and OS (17.6 vs 14.2 months, $P = .021$, Fig. 2) was higher in patients who did not have an elevated NLR than in those with an elevated NLR. In univariate analysis, the pretreatment NLR was significantly associated with PFS ($P = .049$) and OS ($P = .023$). In multivariable analysis, patients with a NLR of >3 were at significantly higher risk of tumor progress (hazard ratio 2.458; 95% confidence interval 1.186–5.093; $P = .016$) and death (hazard ratio 3.435; 95% CI 1.522–7.750; $P = .003$)than patients with a NLR of ⩽3.

NLR may be an independent predictor of PFS and OS in castration-resistant prostate cancer patients treated with docetaxel. The findings require validation in further prospective, big sample-sized studies.

Abbreviations: CRPC = castration-resistant prostate cancer, ECOG = Eastern Cooperative Group, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PFS = progression free survival, RECIST = Response Evaluation Criteria in Solid Tumors.

Keywords: neutrophil-to-lymphocyte ratio, Castration-resistant prostate cancer, outcomes

1. Introduction

Prostate cancer is one of the most common cancers in man. According to the statistics in 2015, the incidence of male prostate cancer accounts for the top in the United States. Meanwhile, the prostate cancer is the second most common cause of cancer-related death, accounting for 9% of all malignant tumors.[1] After androgen suppression therapy, most of the prostate patients can be endocrine resistant and progress to castration-resistant prostate cancer (CRPC) after endocrine therapy. Chemotherapy with docetaxel is the standard initial systemic therapy for men with CRPC.[2,3] In recent years, many chemotherapeutic agents have been approved as therapeutic options to CRPC.[4] Prognostic and predictive biomarkers to assist in the selection of treatment are needed.

Cancer-related inflammatory response and associated inflammatory markers plays an important role in the progression of several solid tumors.[5–7] As a marker of systemic inflammatory response, the neutrophil-to-lymphocyte ratio (NLR) has been reported an easily accessible and reliable marker to predict cancer Patients' survival.[8–11] Recent studies have evaluated the prognostic significance of NLR in CRPC treated with docetaxel, but the result remains conflicted.[12,13]

To further explore the predictive and prognostic value of NLR in CRPC, we performed a retrospective analysis to investigate the association between baseline NLR and progression-free survival (PFS), overall survival (OS), and radiological response in CRPC patients treated with docetaxel.

2. Materials and methods

The study was approved by the hospital ethics committee, and all patients signed informed consent form.

2.1. Patients

Histologically confirmed prostate cancer patients who were treated with docetaxel chemotherapy were selected from 2016 to 2019. All patients showed evidence of CRPC (by the following

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

[a] Department of General Surgery, [b] Department of Oncology, Huangyan Hospital of Wenzhou Medical University, Taizhou First People's Hospital, Taizhou, China.

[*] Correspondence: Shao-Guang Liao, Huangyan Hospital of Wenzhou Medical University, Taizhou First People's Hospital, Taizhou 318020, China (e-mail: liaosg1982@126.com).

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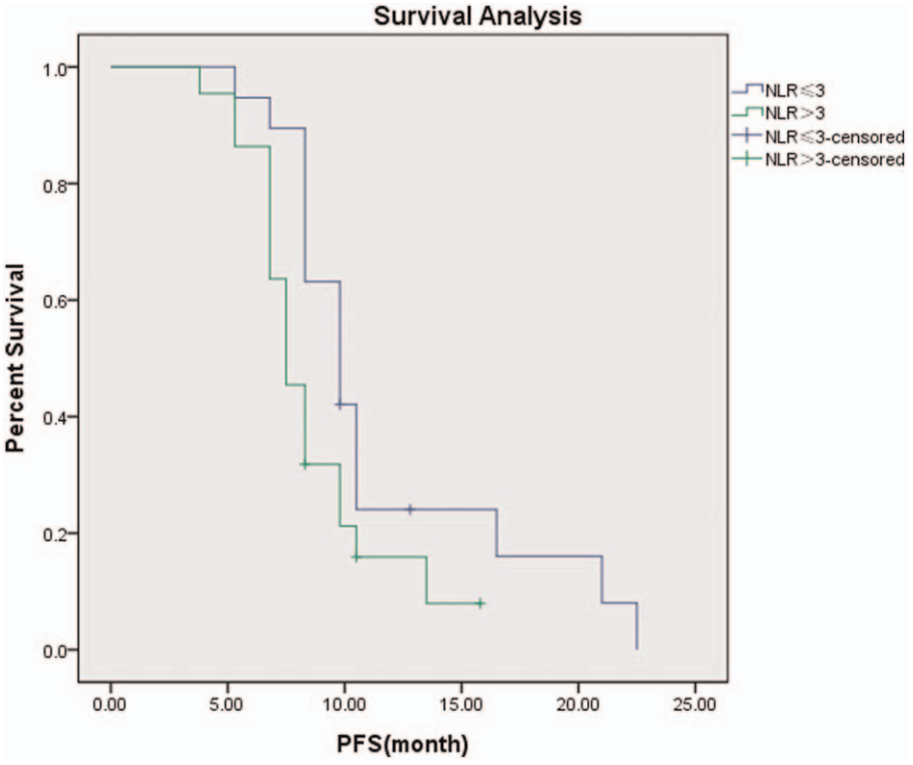

Figure 1. Kaplan–Meier curves for progression-free survival of prostate cancer patients categorized by the neutrophil-to-lymphocyte ratio.

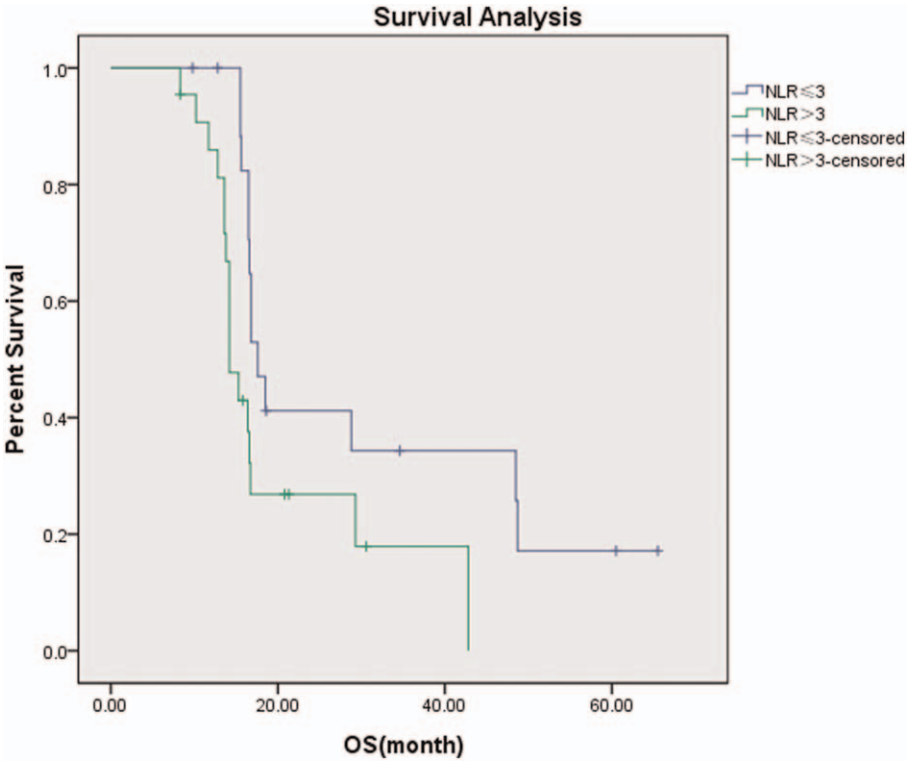

Figure 2. Kaplan–Meier curves for overall survival of prostate cancer patients categorized by the neutrophil-to-lymphocyte ratio.

criteria: testosterone<50 ng/mL; 3 consecutive rises of Prostate Specific Antigen (PSA), 1 week apart, resulting in 50% increases over the nadir). The patients with active infection, history of inflammatory disease, or medication that might affect hematological parameters were excluded. Docetaxel chemotherapy cycles were defined as 21-day treatment periods with docetaxel 75 mg/m^2 administered on day 1 of each treatment cycle, and prednisone 5 mg twice daily. All patients continued to receive the LHRH analogue during systemic chemotherapy. Biphosphonate was given to patients with bone metastases if there was no contraindication.

Age, sites of metastases, Eastern Cooperative Group (ECOG) performance status, combined Gleason score, basal PSA level, full blood count (including absolute neutrophil and lymphocyte counts), and biochemistry of the patients were obtained. Full blood counts were performed every week (day 1, 8, 15 of each cycle). Biochemistry and serum PSA text was performed every 3 weeks (day 1 of each cycle). Imaging studies (computed tomography and bone scintigraphy) were performed every 12 weeks.

2.2. Response evaluation

All data were analyzed retrospectively. An increase ⩾25% or 2 ng/mL in PSA values in comparison with the pretreatment PSA value, confirmed with a second reading at least 3 weeks later, was considered as PSA progression.[14] Patients with measurable soft tissue lesions were evaluated by the Response Evaluation Criteria in Solid Tumors standards.[15] PFS was defined as the time from the first chemotherapy treatment with docetaxel to the date of progression by radiological or PSA criteria. OS was defined as the time from the first chemotherapy treatment with docetaxel to the date of death from any cause or patients were censored at the date of last follow-up.

2.3. Statistical analyses

The baseline NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count measured in day 1 of the first cycle. According to previously published studies, an NLR >3 was selected as cutoff value for external validation.[13,16] The comparison of patient characteristics between subgroups based on NLR was carried out using χ^2 test and t test. The association of baseline NLR as a dichotomous variable with survival was evaluated in univariable and multivariable Cox regression models. Covariates with significant P values (<.05) in univariate analysis were included in the multivariable analysis. Multivariable regression model was constructed using stepwise forward-selection method with entry criteria set to 0.15. Survival analysis was performed by Kaplan–Meier method with the log-rank test. All statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL) analysis software. A 2-sided $P < .05$ was considered to indicate statistical significance.

3. Result

A total of 41 CRPC patients were included in this study. Baseline clinicopathological characteristics of the entire cohort of 41 patients are summarized in Table 1. Nineteen patients had a pretreatment NLR ⩽3and 22 patients had a pretreatment NLR >3. The mean age at time of diagnosis was 73.4 ± 3.1 years. The mean Gleason score was 7.51 ± 0.93. Bone metastases, lymph node metastases, and visceral metastases were found in 20 patients (48.8%), 8 patients (19.5%), and 7 patients (36.6%), respectively. Eighteen patients had measurable soft-tissue disease. According to Response Evaluation Criteria in Solid Tumors standards,[15] tumor response rates to docetaxel chemotherapy were 38.9% among patients with measurable disease. None of the clinicopathological features were associated with the NLR as shown in Table 1. In Kaplan–Meier analyses, the median PFS (9.8 vs 7.5 months, P=.039, Fig. 1) and OS (17.6 vs 14.2 months, P=.021, Fig. 2) was higher in patients who did not have an elevated NLR than in those with an elevated NLR.

Table 1

Baseline characteristics.

	NLR ⩽3	NLR >3	P
Age	73.1 ± 3.1	73.6 ± 3.3	.63
Base line PSA	217.6 ± 145.0	251.1 ± 192.5	.54
Glison score			
⩽6	2	3	
7	8	9	1.00
⩾8	9	10	
Primary treatment			
Surgery	12	16	.75
Radiation	7	6	
ECOG			
0	3	2	
1	12	13	.73
2	4	7	
T stage			
T1/2	12	14	1.00
T3/4	7	8	
Presence of bone metastases			
Yes	7	13	.27
No	12	9	
Presence of lymph node metastases			
Yes	3	5	.70
No	16	17	
Presence of organ metastases			
Yes	6	9	.77
No	13	13	

ECOG = Eastern Cooperative Group, NLR = neutrophil-to-lymphocyte ratio.

In univariate analysis, patient age, baseline PSA level, primary treatment, Gleason score, ECOG performance status, presence of metastases to bone or lymph node were not associated with PFS. And patient age, primary treatment, Gleason score, ECOG performance status, presence of metastases to bone, lymph node or visceral organs were not associated with OS. In contrast, PFS was associated with tumor stage and presence of metastases to visceral organs. And OS was associated with tumor stage and baseline PSA level. The pretreatment NLR was significantly associated with PFS (P=.049) and OS (P=.023) (Table 2).

In multivariable analysis, tumor stage was significantly associated with PFS. Tumor stage and baseline PSA level were all significantly associated with OS. Patients with a NLR of >3 were at significantly higher risk of tumor progress (hazard ratio [HR] 2.458; 95% confidence interval [CI] 1.186–5.093; P=.016) and death (HR 3.435; 95% CI 1.522–7.750; P=.003) than patients with a NLR of ⩽3. The result showed that NLR was an independent predictor of PFS and OS in the multivariable model as a dichotomous variable (Table 3).

Table 2

Univariate Cox proportional hazards analysis of the association between clinical parameters and progression-free survival and overall survival.

Variable	Categories	PFS		OS	
		HR (95% CI of HR)	*P*	HR (95% CI of HR)	*P*
Age	Continuous	0.972 (0.880–1.073)	.572	1.056 (0.945–1.180)	.340
Basal PSA	Continuous	1.002 (1.001–1.030)	.092	1.002 (1.000–1.004)	**.025**
Tumor stage	T1/2 vs T3/4	2.657 (1.282–5.506)	**.009**	3.221 (1.424–7.286)	**.005**
Gleason score	Continuous	1.195 (0.844–1.693)	.316	1.029 (0.724–1.463)	.873
ECOG	Continuous	1.195 (0.694–2.056)	.520	1.269 (0.759–2.120)	.364
Primary treatment	Surgery vs radiation	1.714 (0.792–3.712)	.172	1.969 (0.878–4.417)	.100
Presence of bone metastases	Yes vs no	1.523 (0.764–3.035)	.232	1.350 (0.636–2.867)	.435
Presence of lymph node metastases	Yes vs no	1.019 (0.438–2.370)	.965	1.253 (0.473–3.320)	.650
Presence of organ metastases	Yes vs no	2.081 (1.012–4.279)	**.046**	1.991 (0.918–4.319)	.081
NLR	≤3 vs >3	2.021 (1.003–4.073)	**.049**	2.379 (1.103–5.134)	**.027**

CI = confidence interval, HR = hazard ratio, ECOG = Eastern Cooperative Group, HR = hazard ratio, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PFS = progression-free survival.

4. Discussion

The incidence of prostate cancer is on the rise in recent years and grows more quickly.[17] Prognosis of prostate cancer largely depends on its clinicopathological and treatment-related characteristics. Several variables, such as Gleason score, tumor stage, grade, and PSA level have been showed to be prognostic factors in prostate cancer patients. Among these variables, PSA level is one of the most important and wildly used prognostic factor in men with CRPC.[18,19] However, more studies are still needed to provide more predictive markers of prognosis for patients with CRPC. Nearly all patients develop into CRPC. Docetaxel plus prednisone is the present standard of care in first-line chemotherapy for advanced CRPC. Therefore, a marker is needed to predict the response of docetaxel for those people with CRPC. In recent years, several studies have previously shown that the inflammatory status were associated with clinical outcome of patients with different cancers.[20,21] Neutrophilia and lymphopenia were common in people with advanced cancer, but absolute counts can be affected by different factors such as physiological, pathological, and physical factors. The NLR seems to be more stable and more suitable to be used.[22] As an inflammation marker, NLR has been shown to be a prognostic marker for CRPC patients treated with docetaxel. Nuhn et al reviewed 238 consecutive patients with CRPC who were treated with first-line docetaxel-containing chemotherapy. The result showed that men who were treated with first-line docetaxel for mCRPC who had a low pretreatment NLR (≤3.0) had significantly longer OS. The median OS was higher (18.3 vs 14.4 months) in patients that did not have an elevated NLR than in those with an elevated NLR (log-rank; $P < .001$).[13] In another study, NLR was found to be correlated with post-treatment PSA levels in patients with CRPC. However, no relationship was found between NLR and the response to docetaxel + prednisone therapy in those patients.[12]

The relationship between NLR and outcome of patients with other cancers receiving chemotherapy has been reported in different studies. In a recent study included 109 metastatic RCC patients treated with sunitinib, low NLR ≤3 was associated with PFS (HR = 0.285, $P < .001$) and OS (HR = 0.3, $P = .043$).[10] In another study, NLR >5 was associated with increased risk of progression and worse OS in patients with advanced colorectal cancer treated with chemotherapy.[11] In patients with breast cancer, NLR >3.3 before initiation of chemotherapy was an independent significant predictor of higher mortality.[22]

The association between NLR and outcome of patients with cancer undergoing surgery was also shown in several studies. In a study including 177 patients with non-small cell lung cancer receiving complete resection, increasing neutrophil/lymphocyte ratios was found to be associated with higher stage. On multivariable analysis, increasing neutrophil/lymphocyte ratios remained an independent prognostic indicator.[9] NLR was also found to be associated with OS and cancer-specific survival in patients undergoing radical cystectomy for muscle-invasive bladder cancer.[23] In another study, patients who underwent full resection of localized (T1-3 N0/+ M0) nonclear cell renal cell carcinoma by radical or partial nephrectomy were included in analysis. The NLR was found to be significantly associated with disease-free survival.[24]

In the present study, we sought to investigate the relationship between the pretreatment NLR and PFS and OS in men with CRPC treated with docetaxel containing chemotherapy. The result showed that NLR >3 was associated with significantly higher risk PFS and OS in patients with CRPC treated with docetaxel. Our findings were consisitent with Nuhn et al.[13]

Table 3

Multivariate Cox proportional hazards analysis of clinical parameters for the prediction of progression-free survival and overall survival.

Variable	Categories	PFS		OS	
		HR (95% CI of HR)	*P*	HR (95% CI of HR)	*P*
Tumor stage	T1/2 vs T3/4	2.657 (1.282–5.506)	**.003**	5.226 (2.108–12.959)	**.000**
Basal PSA	Continuous	—	—	1.003 (1.001–1.005)	**.004**
NLR	≤3 vs >3	2.458 (1.186–5.093)	**.016**	3.435 (1.522–7.750)	**.003**

CI = confidence interval, HR = hazard ratio, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PFS = progression-free survival.

These findings confirmed the important role of NLR in predicting survival and provides an early marker both to predict outcome in CRPC patients treated with docetaxel containing chemotherapy and to assist clinical decision making.

However, there are some limitations in our study. Some clinicopathologic parameters in our patient cohort that may have biased the observed results were unable to exclude because of its retrospective design. Some other factors like concurrent infection and drugs that may influence neutrophil and lymphocyte counts were also unable to account for in this analysis. In addition, the small and under-powered sample size may have some impact to our study. A prospectively designed, big sample-sized multicenter study is needed to confirm the result. Moreover, Our study did not assess NLR changes during treatment since Lorente et al[16] showed that conversion from high (≥3) to low (<3) NLR was associated with improved survival (HR 0.66; 95% CI 0.51–0.85; $P=.001$) and higher PSA response rates (66.4% vs 33.6%; $P=.000$).

In conclusion, based on our study, baseline NLR may have the potential to become as an important biomarker in in CRPC patients due to its association with PFS and OS after treated with docetaxel. Considering its inexpensive and easy to assess character, NLR may serve as an effective biomarker in daily clinical practice. These findings require validation in further prospective, big sample-sized studies.

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Author contributions

Conceptualization: shao-guang liao.
Data curation: Zhi-guo Jiang, shao-guang liao.
Formal analysis: Zhi-guo Jiang.
Methodology: Zhi-guo Jiang.
Supervision: shao-guang liao.
Writing – original draft: Zhi-guo Jiang.
Writing – review & editing: shao-guang liao.

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