

ORIGINAL PAPER

Prognostic value of neutrophil-to-lymphocyte ratio in mCRPC patients treated with abiraterone, enzalutamide and docetaxel: A retrospective single-center study

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Summary

Introduction: The neutrophil-to-lymphocyte ratio (NLR) has emerged as a potential prognostic biomarker in several solid tumors, including metastatic castration-resistant prostate cancer (mCRPC). However, its clinical utility remains controversial, particularly across different treatment modalities.

Aim: To evaluate the prognostic value of baseline NLR in patients with mCRPC treated with abiraterone, enzalutamide, or docetaxel, and to assess its association with survival outcomes and PSA response.

Methods: We conducted a retrospective, single-center study including patients with mCRPC treated between December 2019 and January 2022. Patients were stratified according to a pre-specified NLR cut-off of 4. The primary endpoint was overall survival (OS), and the secondary endpoint was PSA progression-free survival (PSA-PFS). PSA response at 6 months was also evaluated. Survival outcomes were estimated using the Kaplan-Meier method, and the association between NLR and OS was assessed using univariable Cox regression.

Results: A total of 186 patients were included. Median age was 77.0 years, and median baseline PSA was 31.1 ng/mL. Patients with NLR ≥ 4 (26.3%) had significantly worse OS compared to those with NLR < 4 , with median OS of 16 versus 30 months. NLR ≥ 4 was associated with an increased risk of death (HR 2.05, 95% CI 1.24-3.39, $p = 0.005$). When analyzed as a continuous variable, higher NLR was also associated with shorter OS (HR 1.12, 95% CI 1.05-1.20, $p < 0.001$). Patients with higher NLR showed shorter PSA-PFS (8.0 vs 10.5 months). However, no significant differences were observed in PSA response at 6 months, including PSA50 and PSA90 rates.

Conclusions: Elevated NLR is associated with worse overall survival and earlier disease progression in patients with mCRPC treated with contemporary systemic therapies. While NLR does not appear to predict early biochemical response, it may reflect the durability of treatment benefit. These findings support NLR as a simple and clinically useful prognostic biomarker in mCRPC.

KEY WORDS: Prostate cancer; Castration-resistant prostate cancer; Neutrophil-to-lymphocyte ratio; Overall survival; PSA progression-free survival.

INTRODUCTION

Prostate cancer remains one of the most frequently diagnosed malignancies and a leading cause of cancer-related mortality among men worldwide. Despite advances in early detection and treatment, a significant proportion of patients progress to advanced disease, ultimately developing castration-resistant prostate cancer (CRPC), which is associated with poor prognosis and limited survival outcomes (1, 2).

Over the past decade, the therapeutic landscape of CRPC has evolved substantially with the introduction of androgen receptor-targeted agents such as Abiraterone acetate and Enzalutamide, as well as cytotoxic chemotherapy including Docetaxel. These treatments have demonstrated significant improvements in overall survival (OS) and progression-free survival (PFS), becoming standard of care in both metastatic and selected non-metastatic CRPC settings (3-6). However, considerable heterogeneity in treatment response and survival outcomes persists, highlighting the need for reliable prognostic and predictive biomarkers to better stratify patients and guide therapeutic decisions.

Chronic inflammation has emerged as a key contributor to cancer progression, influencing tumor proliferation, angiogenesis, and immune evasion (7). Systemic inflammatory markers derived from peripheral blood tests have gained increasing attention due to their accessibility and cost-effectiveness. Among these, the neutrophil-to-lymphocyte ratio (NLR) has been widely investigated as a potential prognostic biomarker in several solid tumors, including colorectal, lung, and renal cancers (8-10). Elevated neutrophil counts are thought to promote tumor progression through the secretion of pro-inflammatory cytokines and growth factors, while lymphocytes play a central role in anti-tumor immune response. Therefore, a high NLR may reflect an imbalance favoring tumor-promoting inflammation over immune surveillance (11).

In prostate cancer, the prognostic significance of NLR remains controversial. Some studies have demonstrated an association between elevated NLR and worse survival outcomes in patients with metastatic CRPC, particularly in those treated with chemotherapy or androgen receptor-targeted therapies (12-14). Conversely, other reports have failed to confirm its independent prognostic value,

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possibly due to differences in study design, patient populations, and NLR cut-off values (15). Furthermore, limited data are available comparing the prognostic role of NLR across different treatment modalities within the same cohort.

Given these inconsistencies, further investigation is warranted to clarify the clinical utility of NLR in CRPC. The aim of this study was to evaluate the prognostic value of baseline NLR in patients with CRPC treated with abiraterone acetate, enzalutamide, or docetaxel in a tertiary care center, and to assess its association with survival outcomes and *prostate-specific antigen* (PSA) response.

MATERIALS AND METHODS

Study design and patient population

This was a retrospective, single-center study including patients diagnosed with *metastatic castration-resistant prostate cancer* (mCRPC) treated at our institution between December 2019 and January 2022.

Castration-resistant prostate cancer (CRPC) was defined as disease progression despite ongoing androgen deprivation therapy and castrate levels of testosterone (< 50 ng/dL), according to contemporary clinical guidelines. *Metastatic CRPC* (mCRPC) was defined by the presence of radiologically confirmed metastatic disease.

Eligible patients were those who received systemic treatment with abiraterone, enzalutamide, or docetaxel during the castration-resistant disease setting. Patients were included if baseline clinical data and neutrophil-to-lymphocyte ratio (NLR) values were available prior to treatment initiation.

Data collection

Collected variables included age at treatment initiation, baseline *prostate-specific antigen* (PSA), *International Society of Urological Pathology* (ISUP) grade, prior local treatments (radical prostatectomy and radiotherapy), prior exposure to docetaxel, and type of systemic therapy administered. Prior exposure to docetaxel referred to chemotherapy administered before the development of the mCRPC setting, mainly in patients with metastatic hormone-sensitive prostate cancer according to CHAARTED/STAMPEDE criteria.

Laboratory values used to calculate NLR were obtained from routine blood tests performed prior to treatment initiation. NLR was defined as the ratio between absolute neutrophil and lymphocyte counts.

NLR assessment

Patients were stratified according to a pre-specified NLR cut-off value of 4 into two groups: low NLR (< 4) and high NLR (≥ 4). Additionally, NLR was analyzed as a continuous variable to assess its prognostic impact.

Outcomes

The primary endpoint of the study was *overall survival* (OS), defined as the time from initiation of systemic therapy in the castration-resistant setting to death from any cause or last follow-up.

The secondary endpoint was PSA progression-free sur-

vival (PSA-PFS), defined as the time from treatment initiation to biochemical progression or last follow-up. PSA progression was assessed based on rising PSA values according to clinical practice.

PSA response at 6 months was also evaluated. The percentage change in PSA was calculated as the relative difference between baseline PSA and PSA at 6 months. PSA50 and PSA90 responses were defined as $\geq 50\%$ and $\geq 90\%$ reductions from baseline PSA, respectively.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics. Continuous variables were reported as median and *interquartile range* (IQR), while categorical variables were expressed as frequencies and percentages. Overall survival and PSA-PFS were estimated using the Kaplan-Meier method and compared descriptively between groups.

The association between NLR and overall survival was assessed using univariable Cox proportional hazards regression analysis, with results reported as *hazard ratios* (HR) and 95% *confidence intervals* (CI). NLR was analyzed both as a categorical variable (cut-off = 4) and as a continuous variable.

Multivariable analysis was not performed due to missing data and model instability.

A two-sided p -value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics (version 27.0; IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

A total of 186 patients were included in the analysis. The median age was 77.0 years (*interquartile range* [IQR] 71.0-83.0). The median baseline prostate-specific antigen (PSA) level was 31.1 ng/mL (IQR 9.9-120.2), and the median neutrophil-to-lymphocyte ratio (NLR) was 2.7 (IQR 2.0-4.1).

Most patients presented with intermediate- to high-grade disease. ISUP grade 3 was the most frequent (46.2%), followed by ISUP grades 2 and 5 (both 17.7%). ISUP grade 4 accounted for 12.4% of cases, while ISUP grade 1 was less common (5.9%).

Regarding prior treatments, 24.8% of patients had undergone radical prostatectomy and 17.8% had received prior radiotherapy. Prior exposure to docetaxel was observed in 19.0% of patients. However, data regarding prior treatments were missing in approximately 46-47% of cases.

In terms of systemic treatment for castration-resistant disease, abiraterone was the most frequently administered therapy (44.6%), followed by enzalutamide (27.4%) and docetaxel (24.7%). A small proportion of patients (3.2%) received other treatments.

At the time of data cut-off, 66 patients (35.5%) had died, whereas 120 patients (64.5%) were alive.

Baseline characteristics of the study population are summarized in Table 1.

Baseline characteristics according to NLR (cut-off = 4)

Patients were stratified according to a pre-specified NLR

Table 1.

Baseline characteristics of the study population.

Variable	Overall (n = 186)
Age (years), median (IQR)	77.0 (71.0-83.0)
Baseline PSA (ng/mL), median (IQR)	31.1 (9.9-120.2)
NLR, median (IQR)	2.7 (2.0-4.1)
ISUP ≥ 3 , n (%)	142 (76.3%)
Prior prostatectomy, n (%)	25 (24.8%)
Prior radiotherapy, n (%)	18 (17.8%)
Prior docetaxel, n (%)	19 (19.0%)
Systemic Treatment: Abiraterone	83 (44.6%)
Systemic Treatment: Enzalutamide	51 (27.4%)
Systemic Treatment: Docetaxel	46 (24.7%)
Deaths, n (%)	66 (35.5%)

cut-off of 4. A total of 137 patients (73.7%) had $NLR < 4$, while 49 patients (26.3%) had $NLR \geq 4$.

Baseline characteristics according to NLR group are summarized in Table 2.

Patients with $NLR \geq 4$ tended to present with higher baseline PSA values compared to those with $NLR < 4$. Median PSA was numerically higher in the high NLR group, suggesting a greater tumor burden in these patients.

No major differences were observed between groups in terms of age distribution. Due to the presence of missing data and limited sample size for some variables, formal statistical comparisons were not performed for all baseline characteristics.

Overall survival according to NLR

Kaplan-Meier analysis demonstrated a clear separation between survival curves according to NLR group (Figure 1).

Table 2.

Baseline characteristics according to NLR (cut-off = 4).

Variable	NLR < 4 (n = 137)	NLR ≥ 4 (n = 49)
Age (years), median (IQR)	76.0 (70.0-82.0)	79.0 (73.0-84.0)
Baseline PSA (ng/mL), median (IQR)	22.3 (7.8-100.0)	47.6 (34.6-241.2)
ISUP ≥ 3 , n (%)	100 (73.0%)	42 (85.7%)
Prior prostatectomy, n (%)	24 (17.5%)	6 (12.2%)
Prior radiotherapy, n (%)	16 (11.7%)	2 (4.1%)
Prior docetaxel, n (%)	16 (11.7%)	3 (6.1%)
Deaths, n (%)	42 (30.7%)	24 (49.0%)

Patients with $NLR \geq 4$ had consistently worse survival probabilities over time compared to those with $NLR < 4$. The separation of the survival curves was evident early during follow-up and remained consistent over time.

Median overall survival was markedly shorter in the $NLR \geq 4$ group compared to the $NLR < 4$ group (16 vs 30 months), indicating a clinically relevant difference.

In univariable Cox regression analysis, $NLR \geq 4$ was significantly associated with an increased risk of death (hazard ratio [HR] 2.05, 95% confidence interval [CI] 1.24-3.39, $p = 0.005$).

When analyzed as a continuous variable, higher NLR was also significantly associated with shorter overall survival (HR 1.12, 95% CI 1.05-1.20, $p < 0.001$).

Multivariable analysis was not performed due to missing data and model instability.

PSA progression-free survival according to NLR

PSA progression-free survival (PSA-PFS) was evaluated as a secondary endpoint. Patients with $NLR \geq 4$ showed shorter PSA-PFS compared to those with $NLR < 4$ (median 8.0 vs 10.5 months).

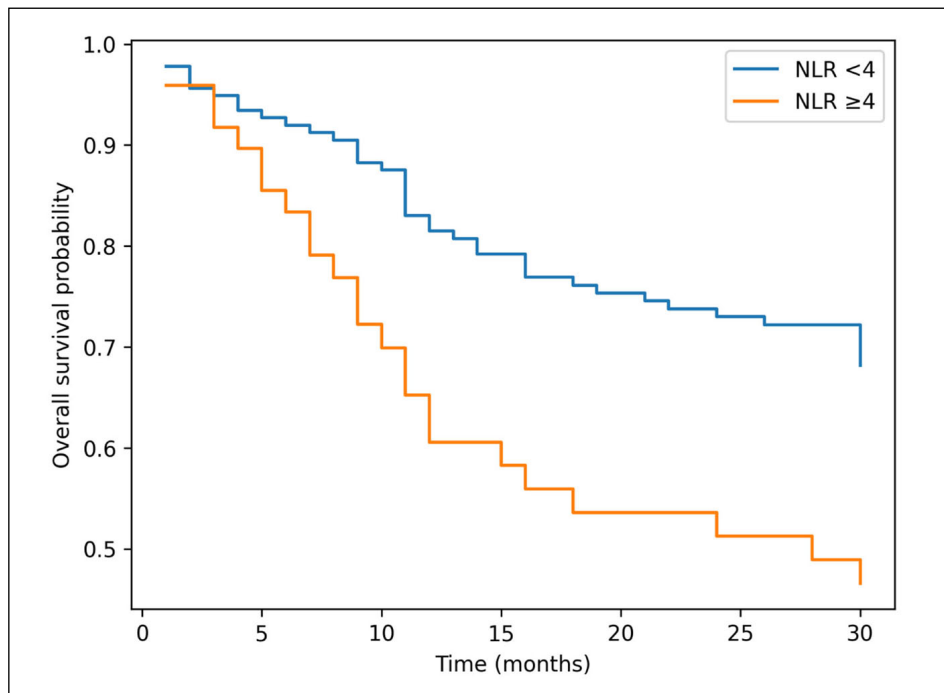


Figure 1.
Overall Survival according
to NLR (cut-off = 4).

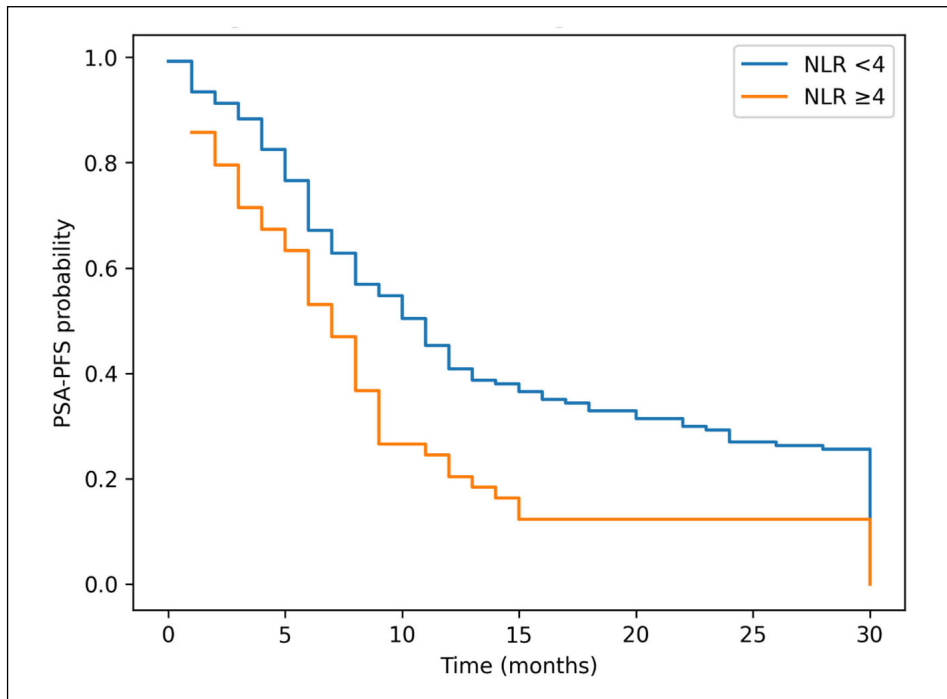


Figure 2.
PSA-PFS according to NLR
(cut-off = 4).

Kaplan-Meier curves (Figure 2) demonstrated a trend toward earlier biochemical progression in patients with higher NLR values, consistent with the hypothesis that systemic inflammation may contribute to disease progression. These findings should be interpreted with caution, as PSA-PFS was defined based on biochemical progression and lacked formal event adjudication.

PSA response at 6 months

PSA response at 6 months was analyzed in patients with available baseline and follow-up PSA values, as defined in the Methods section (Table 3).

Patients with $\text{NLR} \geq 4$ had numerically higher PSA levels at 6 months compared to those with $\text{NLR} < 4$, suggesting a less favorable biochemical response. However, this difference did not reach statistical significance.

The median percentage reduction in PSA from baseline to 6 months was similar between groups, indicating that the magnitude of PSA decline was comparable regardless of NLR status.

Similarly, the proportion of patients achieving a $\geq 50\%$ PSA reduction (PSA50 response) and $\geq 90\%$ reduction (PSA90 response) was comparable between groups.

Table 3.
PSA response at 6 months according to NLR.

Variable	NLR < 4	NLR ≥ 4
Patients with available PSA data, n	79	18
Baseline PSA (ng/mL), median (IQR)	22.9 (8.4–100.0)	47.6 (34.6–241.2)
PSA at 6 months (ng/mL), median (IQR)	6.0 (0.4–21.3)	18.2 (1.9–74.4)
PSA reduction (%), median (IQR)	76.9 (41.4–97.1)	72.8 (19.8–94.7)
PSA50 response, n (%)	56 (70.9%)	12 (66.7%)
PSA90 response, n (%)	35 (44.3%)	8 (44.4%)

These findings suggest that, while NLR is associated with survival outcomes and time to progression, it may not significantly influence the initial biochemical response to treatment, but rather the durability of that response.

Exploratory treatment subgroup analysis

An exploratory analysis was performed to assess outcomes according to treatment modality.

Although limited by sample size, the association between higher NLR and worse overall survival appeared consistent across treatment subgroups, including abiraterone, enzalutamide, and docetaxel.

These findings suggest that the prognostic impact of NLR may be independent of the type of systemic therapy administered.

DISCUSSION

In this retrospective study, we evaluated the prognostic value of NLR in patients with mCRPC treated with abiraterone, enzalutamide, or docetaxel. Our results demonstrate that an elevated NLR (≥ 4) is significantly associated with worse overall survival, with patients presenting a two-fold increased risk of death compared to those with lower NLR values. This association was consistent when NLR was analyzed both as a categorical and continuous variable.

Additionally, patients with higher NLR values exhibited shorter PSA-PFS, suggesting an association between systemic inflammation and earlier disease progression. However, no significant differences were observed in PSA response rates at 6 months, indicating that NLR may not predict initial biochemical response to treatment but rather the durability of disease control.

The prognostic role of NLR has been widely described across several solid tumors, reflecting the impact of sys-

temic inflammation on cancer progression and survival outcomes (8-10). In prostate cancer, previous studies have also demonstrated that elevated NLR is associated with worse outcomes in advanced disease settings (12, 13, 15). *Van Soest et al.* (12) showed that higher baseline NLR was associated with poorer survival in patients with mCRPC receiving first-line chemotherapy, while *Lorente et al.* (13) reported similar findings in the context of second-line chemotherapy. Our results are consistent with these observations, reinforcing the role of NLR as a prognostic biomarker in mCRPC. Importantly, our study extends these findings to a real-world population treated with a heterogeneous range of therapies, including androgen receptor-targeted agents and chemotherapy, reflecting contemporary clinical practice.

The association between elevated NLR and worse outcomes can be explained by the interplay between systemic inflammation and tumor biology. Chronic inflammation is recognized as a hallmark of cancer and plays a key role in tumor progression, angiogenesis, and immune evasion (7, 11). Neutrophils are known to promote tumor growth through the secretion of pro-inflammatory cytokines and growth factors, while lymphocytes are essential for antitumor immune responses.

DECLARATIONS

Ethical approval and consent for participate: According to institutional policies for retrospective anonymized studies, formal ethical committee approval and informed consent were not required.

Consent for publication: Not applicable.

Availability of data and material: The datasets generated and/or analyzed during the current study are not publicly available due to ethical and legal restrictions imposed by the hospital's data protection policies, but de-identified data may be available from the corresponding author upon reasonable request and with appropriate institutional approvals.

Competing interests: The authors declare that they have no competing interests.

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Therefore, a high NLR reflects a relative increase in pro-tumor inflammatory activity and a decrease in immune surveillance, resulting in more aggressive disease behavior (8, 11).

An interesting finding of our study is the lack of association between NLR and early PSA response at 6 months. Although patients with higher NLR values tended to have numerically worse PSA levels at follow-up, the magnitude of PSA decline and response rates (PSA50 and PSA90) were similar between groups. This suggests that NLR may not significantly influence initial sensitivity to treatment but rather the duration of response. In other words, patients with elevated NLR may initially respond to therapy but experience earlier progression, which is consistent with the observed differences in PSA-PFS and overall survival.

The identification of simple and accessible prognostic biomarkers is of particular importance in mCRPC, where treatment decisions are increasingly complex. NLR is an inexpensive and widely available marker that can be easily incorporated into routine clinical practice. Our findings suggest that NLR may help identify patients at higher risk of poor outcomes, potentially aiding in risk stratification and treatment selection. However, given the lack of association with early PSA response, NLR should not be used in isolation to predict treatment efficacy.

This study has several limitations that should be acknowledged. First, its retrospective design introduces inherent biases, including selection bias and missing data. In particular, information regarding prior treatments was incomplete in a substantial proportion of patients. Second, the heterogeneity of systemic treatments may have influenced outcomes, although exploratory analyses suggested consistent effects of NLR across treatment groups. Third, PSA-PFS was based on biochemical progression without formal event adjudication, which may limit the robustness of this endpoint. Finally, multivariable analysis could not be reliably performed due to missing data and model instability, which limits the ability to adjust for potential confounders.

In conclusion, our study demonstrates that elevated NLR is associated with worse overall survival and earlier disease progression in patients with mCRPC treated with contemporary systemic therapies. While NLR does not appear to predict early biochemical response, it may reflect the durability of treatment benefit. These findings support the role of NLR as a simple and clinically useful prognostic biomarker in mCRPC. Prospective studies are warranted to further validate its utility and explore its integration into clinical decision-making.

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