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Research Article

The Prognostic Role of Inflammatory Biomarkers in Metastatic Castration Sensitive Prostate Carcinoma

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Abstract

Objectives: Due to limited data in the literature on the prognostic value of inflammatory markers neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and derived NLR (dNLR) in metastatic castration-sensitive prostate cancer (mCSPC), we aimed to determine the role of this markers in the prognosis of mCSPC.

Methods: In this study, inflammatory marker values in mCSPC (NLR0, PLR0, dNLR0) and mCRPC (NLR1, PLR1, dNLR1) were calculated. Characteristics of the patients and the effects of inflammatory markers on overall survival (OS) and cancer-specific survival (CSS) were evaluated using appropriate statistical methods.

Results: The median age of 124 patients was 68.71 years. No significant difference was found OS in mCSPC NLR0, dNLR0 and PLR0 groups (p>0,05). While the median CSS was statistically longer in the NLR0, dNLR0 and PLR0 low groups (Median:45.9 vs 35.7 months for NLR0, 47.0 vs 34.6 months for dNLR and 46.2 vs 33.9 months, p=0.037, p=0.036, p=0.041 respectively). There was no significant difference in terms of OS and CSS in NLR1 and dNLR1 groups (p>0.05). The patients with low PLR1 showed statistical significantly better OS and CSS (p=0.027 for OS and p=0.006 for CSS).

Conclusion: Although inflammatory markers have prognostic value in many cancers, mCSPC which have heterogeneous and complex structures, are still controversial, and more studies are needed for their routine use.

Keywords: Castration, inflammation, prostate cancer, prognosis

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Prostate cancer is the most common cancer in men. It is also in the 2nd place in cancer-related deaths in men.[1] In our country, the rate of stage 4 patients at the time of diagnosis is higher than in the USA and European countries.[2] Although the majority of prostate carcinoma patients are locally or locally advanced at the time of diagnosis, recurrence or metastasis may develop despite all treatment methods. Once metastatic disease occurs, survival is much worse than with early-stage prostate cancer. The main method in the treatment of metastatic castration-sensitive PCa is testosterone suppressive therapies (androgen deprivation therapy, ADT). ADT can be applied surgically (bilateral orchiectomy) or medically (luteinizing hormone-releasing hormone [LHRH] analogues).[3] Addition of docetaxel or new generation hormonal agents (enzalutamide, abiraterone, apalutamide)

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to this treatment provides a survival advantage.[4] Despite all these efforts, almost all patients with a diagnosis of CSPC progress to the CRPC stage. Once patients progress to the CRPC stage, survival is considerably shorter.[5] However, after the new generation hormonal agents took their place in the treatment, these periods started to get longer.[6] Except for markers such as CHAARTED and LATITUDE criteria, Gleason score, PSA level, PSA response to treatment, and tumor volume in predicting survival and treatment benefit, there are no biomarkers that can help us determine survival in mCSPC. Although not yet reflected in clinical practice, new biomarkers continue to be studied.[7-9] Recent studies have shown that the prognosis of various cancer types is also affected by patient-related factors such as inflammation, immunocompetence, and nutrition, and the correlation between some inflammatory parameters and cancer prognosis is remarkable.[10] Studies on the prognostic value of inflammatory parameters in cancer patients are still ongoing. Among these parameters, the most commonly used ones include lymphocyte, neutrophil, platelet and C-reactive protein levels and their combined use with certain formulas.[9] Neutrophil/lymphocyte (NLR), platelet/lymphocyte (PLR), which can be easily calculated by leukocyte, neutrophil, lymphocyte and platelet counts in the blood, and derived NLR (dNLR), which can be calculated by the formula of neutrophil count/ (leukocyte-neutrophil), are biomarkers that have been shown to have prognostic importance in many cancer types.[10] Many studies have shown that NLR, one of these parameters, has prognostic importance in mCRPC patients.[11] Although a different cut-off point was used in each study, it has become widespread that patients with NLR values above the reference values have a worse survival.[11] Similarly, some studies have shown that other inflammatory markers such as dNLR and PLR may be important in determining the prognosis in mCRPC patients.[12] However, the vast majority of studies with these inflammatory biomarkers have been performed on patients in the castration resistant stage.[13] There is little data in the literature regarding the role of these biomarkers in castration-sensitive disease. From this point of view, we aimed to test the prognostic power of NLR, dNLR and PLR in both castration-sensitive and resistant stages.

Methods

This retrospective cross-sectional study included 169 patients who were admitted to the Health Sciences University Tepecik Training and Research Hospital Medical Oncology Clinic between April 2009 and December 2020 with the diagnosis of CRPC. Of these patients, 124 participant who met the study criteria were included in this study. 69 of these 124 patients, who were able to obtain hemogram values when transitioning to the castration resistant stage, were also evaluated at the castration resistant stage. The dependent variable of the study was NLR, dNLR and PLR calculated by neutrophil, lymphocyte and platelet values at the time of diagnosis; the independent variables were determined as PSA level, systemic treatments applied, age, presence and number of comorbidities, and tumor burden. PCa patients were divided into two groups as low and high volume according to the CHAARTED trial criteria,[8] and low and high risk according to the LATITUDE trial criteria.[9] Sociodemographic and clinicopathological data and laboratory parameters of the patients were obtained retrospectively from the hospital database.

Assessment of the NLR

The pretreatment NLR, dNLR, PRL [dNLR calculation: neutrophil / (leukocyte - neutrophil); NLR calculation: neutrophil / lymphocyte; PLR calculation: platelet / lymphocyte] was calculated using the complete blood cell count (CBC). NLR0, PLR0 and dNLR0 were defined as NLR measured at the castration sensitive stage, while NLR1, PLR1 and dNLR1 were defined as NLR measured at the castration resistant stage. The candidate cut-off of the NLR were attempted to be determined by the area under the receiver operator characteristic curve (ROC).

Statistical Analysis

In the evaluation of the data, descriptive statistics, means, median values and standard deviations of the patients were calculated. The Mann-Whitney U test, chi-square tests and Fisher exact test were used to examine the patient's characteristics and preoperative variables. AUROC curve analysis was applied to select the most appropriate cut-off point for NLR, dNLR, pRL to discriminate patients at high risk of cancer-related death. According to the ROC curves, the cutoff point was determined as 2,43 for NLR0 ($p=0.006$), 1,67 for dNLR0 ($p=0.005$), and 129,27 for PLR0 ($p=0.012$). The patients were divided into two groups as those with a value below this cut-off points and those above the cut-off points. Kaplan-Meier method was used to estimate cancer specific survival, overall survival, and PFS time in terms of NLR, dNLR and PRL. The log-rank test was performed to investigate the difference in survival. SPSS (version 24.0) package program was used in the analysis of all data. Statistical significance was determined as $p<0.05$.

Results

A total of 124 patients were included in this study. Descriptive and clinicopathological features of the research

group are presented in Table 1. The median age was 68.71 (62.42-74.85) years, and the median PSA at the time of diagnosis was 100.00 (31.95-156.85) µg/L. 87.1% (n=108) of the patients have no history of primary surgery (de novo metastatic disease). While no comorbidity was observed in 47.6% (n=59) of the study group, one and two or more comorbidities were detected in 33.1% (n=41) and 19.4% (n=24) of them, respectively. The median of NLR1 was 2.85 (1.95-4.06), PLR1 median was 140.00 (36.20-190.99), and dNLR1 median was 1.83 (1.36-2.57) at the castration-resistant stage. Other descriptive and clinicopathological features of the patients were examined and presented in Table 1. The relationship between PSA levels and age groups (<70 and ≥70) was evaluated. It was determined that the serum PSA levels of individuals under 70 years of age (median:79.30) were significantly lower than those of 70 years and older (median: 127.79) (p=0.035). The relationship between NLR0, dNLR0 and PLR0 groups and metastasis regions was investigated. There was no significant difference between the groups (p>0.05). When the relationship between age groups and NLR0, dNLR0 and PLR0 groups was examined, no significant difference was observed between the groups (p>0.05) (Table 2). In addition, the NLR0, dNLR0, and PLR0 groups were evaluated according to the LATITUDE study risk levels (low risk-high risk). According to the analysis results, there is no significant difference between low-risk patients and high-risk patients in terms of NLR0, dNLR0 and PLR0 (p>0.05). When the NLR0, dNLR0 and PLR0 groups were analyzed according to the volume levels of the CHAARTED study (low volume-high volume), a significant difference was found in terms of PLR0 (p=0.040). Disease volume and risk discordance were evaluated according to the CHAARTED and LATITUDE studies and presented in Table 2. According to the CHAARTED criteria, 27.8% of our patients in the high-volume disease group were in the low-risk group according to the LATITUDE criteria. On the other hand, 2.9% of our patients in the high-risk group according to the LATITUDE criteria were in the low volume disease group according to the CHAARTED criteria (p<0.001). Overall OS and CSS were analyzed by Kaplan-Meier method. In the analyzes performed, no significant difference was found in terms of OS (month) in the castration-sensitive stage NLR0 (0-2.43 and >2.43)(Fig. 1a), dNLR0 (0-1.67 and >1.67) (Fig. 1b) and PLR0 (0-129.27 and >129.27) (Fig. 1c) groups (p>0.05). When CSS was evaluated in dNLR0 (0-1.67 and>1.67) groups, CSS was found to be significantly higher in the group with dNLR0 ratio 0-1.67 (Median:47.1, %95 CI :35.2-58.9) compared to the other group (Median: 34.60, %95 CI:27.1-42.1) (p=0.036) (Fig. 2a). Similarly, when PLR0 (0-129.27 and>129.27) groups were examined in terms of CSS, CSS was found to be significantly higher in the 0-129.27group (Median: 46.2, %95 CI: 35.1-57.3) than in the >129.27group (Median: 33.9, %95 CI: 27.3-40.5) (p=0.041) (Fig. 2b). Also, there is a significant difference between NLR0 (0-2.43 and >2.43) groups in terms of CSS (45.9 vs 34.7 months, p=0.037) (Fig. 2c). OS and CSS were evaluated in NLR1 (0-2.85 and >2.85), dNLR1 (0-1.82 and >1.82) and PLR1 (0-139.37 and >139.37) groups. According to Kaplan-

Table 1. Distribution of the study group by descriptive and clinicopathological characteristics

Parameters	Total (n=124)
Age (median, interquartile range) years	68.71 (62.42-74.85)
Age grup, n (%)	
<70	69 (55.6)
≥70	55 (44.4)
PSA (median, interquartile range) µg/L	100.00 (31.95-156.85)
Castration resistant stage	
NLR1 (median, interquartile range)	2.85 (1.95-4.06)
PLR1 (median, interquartile range)	140.00 (36.20-190.99)
dNLR1 (median, interquartile range)	1.83 (1.36-2.57)
Status, n (%)	
Alive	50 (40.3)
Dead	74 (59.7)
Primary surgery, n (%)	
No	108 (87.1)
Radical	16 (12.9)
Comorbidity, n (%)	
None	59 (47.6)
One	41 (33.1)
Two	24 (19.4)
CHAARTED volume, n (%)	
Low volume	34 (27.4)
High volume	90 (72.6)
LATITUDE risk, n (%)	
Low risk	58 (46.8)
High risk	66 (53.2)
Metastatis, n (%)	
M0	1 (0.8)
M1a	15 (12.1)
M1b	86 (69.4)
M1c	22 (17.7)
CRPC development, n (%)	
Yes	84 (67.7)
No	40 (32.3)
ISUP grade group, n (%)	
Grade 2	15 (12.1)
Grade 3	18 (14.5)
Grade 4	27 (21.8)
Grade 5	57 (46.0)

OS: overall survival; CSS: cancer spesific survival; CRPC: castration-resistant prostate cancer.

Table 2. Relationship between NLR, dNLR, PLR or PSA and clinicopathological parameters in prostate cancer

	Age group		p**
	<70	≥70	.035
PSA (median, IQR) µg/L	79.30 (20.44 - 150.00)	127.79 (38.22 – 317.00)	

	CHAARTED volume						
	Low volume		High volume		Total		
	n	%	n	%	n	%	p*
NLR0 group							
0-2.43	16	28.1	41	71.9	57	100.0	.881
>2.43	18	26.9	49	73.1	67	100.0	
dNLR0 group							
0-1.67	20	33.9	39	66.1	59	100.0	.123
>1.67	14	21.5	51	78.5	65	100.0	
PLR0 group							
0-129.27	21	36.2	37	63.8	58	100.0	.040
>129.27	13	19.7	53	80.3	66	100.0	

	LATITUDE risk						
	Low risk		High risk		Total		
	n	%	n	%	n	%	p*
CHAARTED volume							
Low volume	33	97.1	1	2.9	34	100.0	<.001
High volume	25	27.8	65	72.2	90	100.0	

*Chi-square test; **Mann Whitney u test; IQR: interquartile range.

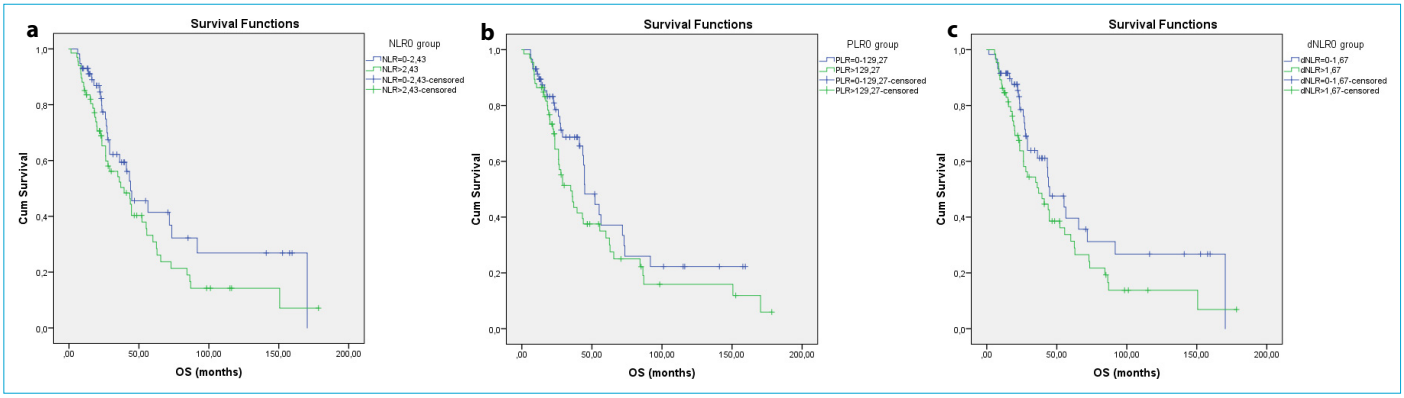

Figure 1. Relationship between NLR **(a)**, PLR **(b)**, dNLR **(c)** and OS in mCSPC.

Meier analysis results, there was no significant difference in terms of OS and CSS in NLR1 and dNLR1 groups (p>0.05). When the PLR1 groups were evaluated, the groups with low PLR1 showed significantly better OS (73.8 vs 42.5 months, p=0.027) and CSS (48.5 vs 28.1 months, p=0.006) (Figs. 3, 4).

In univariate analyses, high NLR0, PLR0, dNLR0, PLR1, high volume disease according to CHAARTED, and higher risk disease according to LATITUDE were associated with worse CSS (p =0.040, p=0.043, p=0.038, p=0.007, p<0.001, p<0.001, respectively) (Table 3). In multivariate analyses, ISUP grade group and NLR0, PLR0, dNLR0 were evaluated in pairs and summarized in Table 4. In the analyzes, it was concluded that ISUP grade 4-5 and high NLR0 (HR: 2.303, 95% CI: 1.351-3.925, p=0.002), PLR0 (HR: 1.754, 95% CI: 1.056-2.914, p=0.030), dNLR0 (HR: 2.349, 95% CI: 1.385-3.984, p=0.002) and PLR1 (HR: 1.907, 95% CI: 1.030-3.530, p=0.040) were associated with poor CSS.

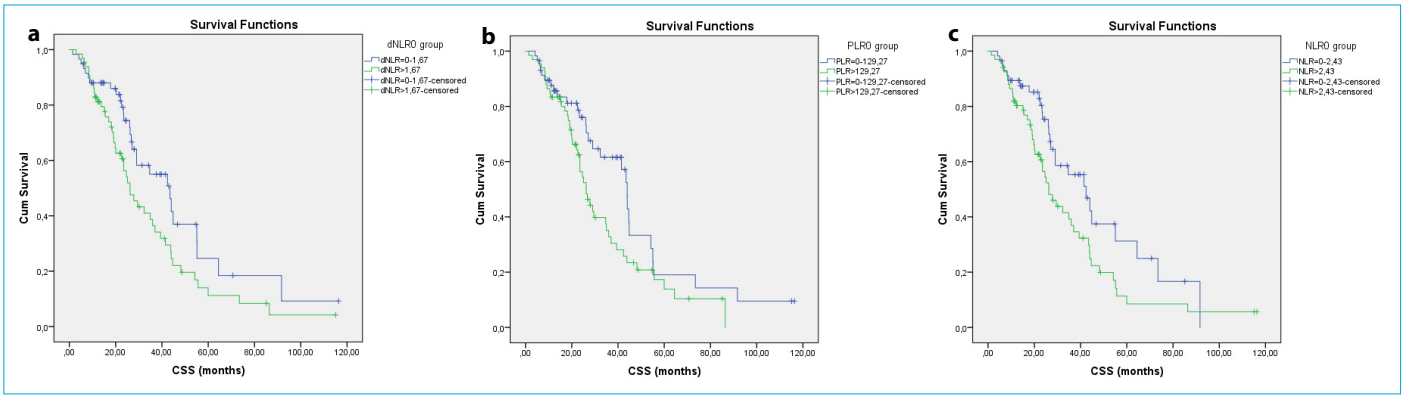

Figure 2. Relationship between dNLR **(a)**, PLR **(b)**, NLR **(c)** and CSS in mCSPC.

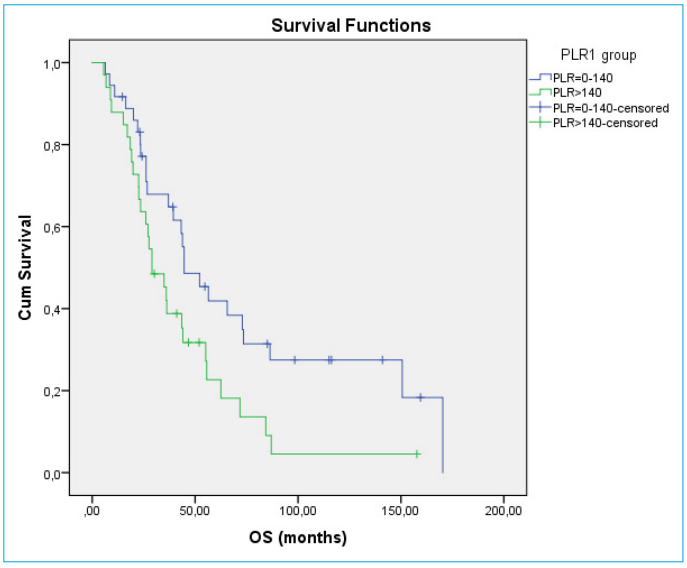

Figure 3. OS stratified by PLR in mCRPC.

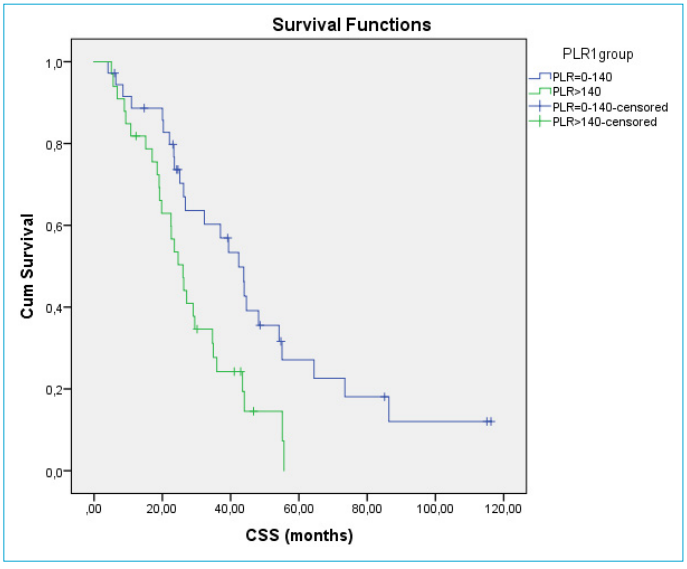

Figure 4. CSS stratified by PLR in mCRPC.

Table 3. Univariate analysis of various clinical parameters in prostate cancer patients

Parameter	Cancer Specific Survival (CSS)	
	HR (95% CI)	p
Age (years)	1.019 (0.989-1.049)	.220
PSA (µg/L)	1.001 (1.000-1.001)	.895
ISUP grade group		
1-3	1	.062
4-5	1.673 (0.975-2.870)	
NLR0		
0-2.43	1	.040
>2.43	1.647 (1.024-2.648)	
PLR0		
0-129.27	1	.043
>129.27	1.637 (1.015-2.640)	
dNLR0		
0-1.67	1	.038
>1.67	1.645 (1.027-2.636)	
NLR1		
0-2.85	1	.298
>2.85	1.335 (0.775-2.298)	
PLR1		
0-140	1	.007
>140	2.187 (1.233-3.878)	
dNLR1		
0-1.83	1	.326
>1.83	1.316 (0.761-2.276)	
LATITUDE		
Low risk	1	<.001
High risk	2.791 (1.716-4.537)	
CHAARTED		
Low volume	1	<.001
High volume	3.670 (1.821-7.396)	

Table 4. Multivariate analysis of various clinical parameters in prostate cancer patients

Parameter	Cancer Specific Survival (CSS)		Parameter	Cancer Specific Survival (CSS)	
	HR (%95 CI)	p		HR (%95 CI)	p
ISUP grade group			NLR0	1	.002
1-3	1	.003	0-2.43		
4-5	2.399 (1.337-4.306)		>2.43	2.303 (1.351-3.925)	
ISUP grade group			PLR0		
1-3	1	.038	0-129.27	1	.030
4-5	1.776 (1.031-3.058)		>129.27	1.754 (1.056-2.914)	
ISUP grade group			dNLR0		
1-3	1	.004	0-1.67	1	.002
4-5	2.307 (1.306-4.077)		>1.67	2.349 (1.385-3.984)	
ISUP grade group			NLR1		
1-3	1	.004	0-1.67	1	.494
4-5	2.565 (1.348-4.882)		>1.67	1.223 (0.687-2.177)	
ISUP grade group			PLR1		
1-3	1	.025	0-1.67	1	.040
4-5	2.135 (1.099-4.147)		>1.67	1.907 (1.030-3.530)	
ISUP grade group			dNLR1		
1-3	1	.004	0-1.67	1	.503
4-5	2.567 (1.348-4.885)		>1.67	1.217 (0.685-2.161)	

Discussion

Prostate cancer incidence increases with advancing age, and it remains a deadly disease despite all the successes achieved in recent years, especially for the metastatic stage. Once the patients pass to the castration resistant stage, despite all these developments, the disease changes in character and the expected life expectancy of the patients decreases dramatically.[5] A standard biomarker for predicting survival has not been found yet, except for markers such as disease volume according to the CHAARTED study, disease risk according to the LATITUDE study, PSA doubling time, and PSA response to the treatments, which we reviewed while planning treatment for a patient diagnosed with metastatic prostate carcinoma. Inflammatory biomarkers, which have been more emphasized in recent years, may play an important role in determining prognosis in the near future. In a study conducted by Salah et al. on 189 mCSPC patients to elucidate the prognostic importance of NLR, one of the inflammatory biomarkers, it was found to be closely associated with OS.[14] In this study, it was concluded that pretreatment NLR was associated with survival but not with time to PSA progression in mCSPC patients. Similarly, in a study by Kawahara et al. in which 1464 patients with mCSPC were included, the NLR cut-off value was accepted as 3.37. In this study, it was concluded that the overall survival in patients with NLR values above the cut-off point was significantly worse than in patients with NLR values below the cut-off point.[15] In contrast to these studies we found that, when the NLR cutoff value was taken as 2.43, there was no significant difference between the patients who were above this value and those below this value in terms of overall survival but there was a significant differences in terms of cancer-specific survival. Similar to our study, Shimodaira et al. concluded that NLR was not associated with overall survival in their study of 167 PCa patients, approximately 71% of whom were in the metastatic stage.[16] In a meta-analysis by Peng and Luo, it was emphasized that NLR may be more associated with survival in mCRPC.[17] Most studies of the prognostic significance of NLR in PCa have been conducted in mCRPC patients. However, in our study, it was found that NLR significantly predict CSS but not OS in patients with mCPSC. And aslo NLR did not significantly predict OS or CSS in patients with mCRPC. This may be due to the small number of patients in our study. As can be seen, the relationship between NLR and survival in patients with mCSPC has not yet been clarified in the literature.

In our study, it was concluded that NLR, dNLR and PLR could predict CSS but not OS in mCSPC patients. As in our study, the relationship between PLR and OS was not found in the multivariate analysis of a study conducted by Önal

et al. in patients with a diagnosis of mCRPC.[18] In contrast to our data, in a study by Shi et al. in patients with mCSPC, NLR and PLR were found to be associated with OS.[19] In another study by Yamada et al., contrary to our study, it was concluded that dNLR has a direct relationship with OS.[20] The small number of the patient population selected for the study, the effect of other prognostic features, or the heterogeneity of the treatments applied could change the results. Therefore, these data should be interpreted with caution until supported by larger studies. The limitations of our study include its retrospective design, small number of patients, heterogeneity between the prognostic characteristics of the patient group and treatment choices.

Conclusion

When many studies on systemic inflammatory biomarkers are evaluated together, conflicting results are encountered. Almost all of these studies are of a retrospective nature. Moreover, the fact that different patient groups were included in each study and a different cut-off was determined in each study also increases the heterogeneity considerably. Although inflammatory biomarkers such as NLR, PLR and dNLR have been found to be associated with survival in many studies, it does not seem possible for these biomarkers to be used routinely to determine the prognosis of patients with mCSPC or mCRPC due to a highly heterogeneous and complex data.

Disclosures

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Ethics Committee Approval: This study was approved by Health Science University, Tepecik Education and Research Hospital ethics committee (Approval Date: 15.04.2022, Approval No: 2022/ 04-16). Due to the retrospective observational nature of the study, written informed permission was not required, and all techniques followed the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Conflict of Interest: I certify that all of my affiliations with or without financial involvement, within the past 5 years and foreseeable future and, any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, and royalties).

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