Yeni Üroloji Dergisi - *The New Journal of Urology* 2021;16(2):101-109, doi: 10.33719/yud.2021;16-2-794684

Original Research / Özgün Araştırma

An inflammatory marker for predicting prostate cancer in prostate biopsy: monocyte-to-lymphocyte ratio

Prostat biyopsisinde prostat kanserini öngörmede inflamatuar bir belirteç: monosit-lenfosit oranı

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Submitted: 2020-09-14
Accepted: 2021-01-29

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Özet

Amaç: Prostat kanseri (PCa) tanısında inflamatuvar parametrelerin, özellikle monosit-lenfosit oranının (MLR) prediktif rolünü değerlendirmek amaçlandı.

Gereç ve Yöntemler: Temmuz 2015 ile Temmuz 2019 arasında prostat biyopsisi yapılan hastaların verileri retrospektif olarak analiz edildi. Yaş, PSA, nötrofil-lenfosit oranı (NLR), platelet-lenfosit oranı (PLR), MLR ve histopatolojileri içeren veriler kaydedildi. Hastalar prostat biyopsi histopatolojisine göre benign prostat hiperplazisi (BPH), PCa ve prostatit olarak gruplandırıldı ve tüm değişkenler incelendi.

Bulgular: 338 hastanın 124 (%36.7)'ü BPH, 132 (%39.1)'si PCa ve 82 (%24.3)'sinde prostatit patolojisi mevcuttu. PCa'lı hastalar daha yaşlıydı ve PCa olmayan hastalara kıyasla daha yüksek serum PSA, PLR, NLR ve MLR değerlerine sahipti. Metastatik hastalar dışlanarak yapılan karşılaştırmada sadece serum PSA ve MLR değerleri istatistiksel olarak yüksek kaldı. Tüm kohortta her üç parametre PCa'yı tahmin etmede anlamlı AUC'ye sahipken, metastatik hastaların çıkarıldığı kohortta yalnızca MLR PCa'yı tahmin etmede anlamlı AUC'ye sahipti. Çok değişkenli lojistik regresyon analizinde, sadece serum PSA ve MLR'nin PCa'nın anlamlı bağımsız prediktörleri olduğunu görüldü.

Sonuç: PCa hastalarında tüm enflamatuar belirteçler yüksekti, ancak sadece MLR metastatik

Abstract

Objective: To evaluate the predictive role of the inflammatory parameters, especially monocyte-to-lymphocyte (MLR) ratio, on the diagnosis of prostate cancer (PCa).

Material and Methods: The data of patients undergoing prostate biopsy between July 2015 and July 2019 were retrospectively analyzed. The data including age, PSA, neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte (PLR), MLR and histopathologies were recorded. Patients were grouped as benign prostatic hyperplasia (BPH), PCa and prostatitis according to PBx histopathology and all variables were analyzed.

Results: Pathology results of 338 patients are as follows: 124 (36.7%) BPH, 132 (39.1%) PCa and 82 (24.3%) prostatitis. Patients with PCa were older and had higher serum PSA, PLR, NLR and MLR values compared to non-PCa patients. In the comparison made by excluding metastatic patients, only serum PSA and MLR values remained statistically high. All three parameters had significant AUC to predict PCa in entire-cohort, but only the MLR had significant AUC to predict PCa in the cohort which metastatic patients were excluded. Multivariate logistic regression analysis revealed that only serum PSA and MLR values were significant independent predictors of PCa.

Conclusion: In our study, it was observed that only MLR among all inflammatory markers found

The study was approved by the Ethic Committee of Kahramanmaras Sutcu Imam University Hospital (Approval number: 2020-06-133). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

PCa hastaları çıkarıldıktan sonra da yüksek kaldı. Çok değişkenli modelde PSA ve yaş ile MLR kombinasyonu, PCa'nın anlamlı bağımsız prediktörüdür.

Anahtar Kelimeler: inflamatuar belirteçler, monosit-lenfosit oranı, prostat biyopsisi, prostat kanseri

to be high in PCa patients continued to be high in nonmetastatic PCa patients. In the multivariate regression model created from age, PSA and MLR, MLR was found to be a significant independent predictor of PCa like PSA. MLR can be used as an inexpensive, easily accessible and applicable new marker to predict PCa.

Keywords: inflammatory markers, monocyte-to-lymphocyte ratio, prostate biopsy, prostate cancer

INTRODUCTION

Prostate cancer (PCa) is a common malignancy and disease burden is increasing worldwide. According to Global Cancer Statistics about PCa, there will be nearly 1.3 million new cases and 359,000 related deaths worldwide in 2018. Also, it will be the second most frequent cancer and the fifth leading cause of cancer death in men (1). Despite recent advances, early PCa screening and treatment is still one of the most challenging and controversial topics (2). Serum prostate-specific antigen (PSA) is commonly used to screen for PCa. If an increase in the serum PSA level is detected, prostate biopsy (PBx), an invasive and currently available method to confirm the diagnosis of PCa, is recommended. However, serum PSA does not have enough sensitivity and specificity for PCa, which leads to unnecessary biopsies, overdiagnosis and overtreatment (3, 4). Therefore, there is a need for easily available and inexpensive new biomarkers that can detect clinically important PCas and prevent unnecessary biopsies.

Inflammation is considered to contribute significantly to the development and progression of malignancies and, there is a complex interaction between local immune reaction and systemic inflammation (5). Inflammatory parameters have been investigated as a possible marker for the diagnosis of PCa (6, 7). Of these markers, it was widely reported that the serum neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) predict prostate cancer in men undergoing needle biopsy (8-11). However, there are not enough studies in which monocyte-to-lymphocyte ratio (MLR) is reported as a diagnostic marker in prostate cancer. Hayashi et al. showed that MLR and serum monocyte count were higher in patients with high gleason score (≥7) PCa (12). In one study, it has been reported that LMR may be a useful marker for the detection of PCa, especially in patients with PSA value of 4 to 10 ng/dl (13).

In this study, we aimed to evaluate the predictive role of the inflammatory parameter, especially MLR, on the diagnosis of PCa.

MATERIAL AND METHODS

By the approval of the Institutional Review Board at the Kahramanmaras Sutcu Imam University Hospital (Approval number: 2020-06-133), the data of 338 patients who underwent prostate biopsy due to suspicion of PCa between July 2015 and July 2019 were retrospectively analyzed. In case of clinical suspicion based on high PSA and abnormal DRE, ıt was ruled out urinary tract infections and prostatitis in all patients and then 12 core transrectal ultrasound-guided prostate biopsy (TRUS-PBx) was performed. If serum PSA > 15 ng/dl, samples from the seminal vesicles were also taken. Those who had blood tests within 1 month before TRUS-PBx were included. Patients with history of any oncologic, hematologic and systemic inflammatory diseases, prostatic surgery, anti-inflammatory drug usage within 2 weeks before TRUS-PBx and irrelevant or incomplete data were excluded. In addition, high-grade intraepithelial neoplasia (HGPIN) (n = 4) and atypical small acinar proliferation (ASAP) (n = 10) were excluded because inadequate number of. NLR, PLR and MLR were determined by dividing each neutrophil count, platelet count and monocyte count by the lymphocyte count. The data including age, PSA, platelet count, neutrophil count, lymphocyte count, monocyte count, NLR, PLR, MLR and histopathology of patients were recorded. International Society of Urologic Pathologists (ISUP) grade score and metastasis status were also recorded in those diagnosed with PCa. Patients were grouped based on PBx histopa-

thology (benign prostate hyperplasia (BPH), PCa and prostatitis) and ISUP grade score (ISUP grade <3 and ISUP grade ≥3) and metastasis status, and all variables were analyzed. Clinically significant PCa is considered to be ISUP grade ≥ 3.

Statistical Analysis

A post hoc Gpower analysis showed that total sample of 338 patient had 100% statistical power with large effects (d=0.59) and alpha at 0.05 to detect a difference in MLR between groups. Continuous variables shown as median (interquartile range (IQR)) were compared using Kruskal-Wallis test and Mann-Whitney U test in three and two groups, respectively. In order to determine the optimal cut-off point and predictive power of NLR, PLR and MLR in PCa diagnosis, the receiver operating characteristic (ROC) curve analysis was used in entire cohort and in cohort which metastatic patients were removed. The cut-off points were determined by Youden's Index criterion in Medcalc software (version 19, MedCalc Software Ltd, Belgium). Univariate logistic regression analysis was performed to predict PCa using age, PSA, NLR, PLR and MLR variables. Then, the effect of these variables in the diagnosis of PCa was determined by the model created by multivariate logistic regression analysis. By using the SPSS software (version 22.0, IBM, USA), all statistical analyses were performed. The statistical significant value was determined as $p < 0.05$.

RESULTS

The median (IQR) age and serum PSA of patients were 67.00 (11.25) and 9.60 (12.00). Pathology results of 338 patients are as follows: 124 (36.7%) BPH, 132 (39.1%) PCa and 82 (24.3%) prostatitis. Of 132 PCa biopsy results, 32 (24.2%) were ISUP grade 1, 28 (21.2%) were ISUP grade 2, 20 (15.2%) were ISUP grade 3, 22 (16.7%) were ISUP grade 4 and 30 (22.7%) were ISUP grade 5. Among the PCA patients, 72 (54.5%) were high-grade PCa (ISUP grade ≥3) and 42 (31.8%) were metastatic. The median (IQR) age, serum PSA, PLR, NLR and MLR values of BPH, PCa and prostatitis groups are presented in Table 1 in all cohorts and in the cohort which metastatic patients were removed.

Patients with PCa were older and had higher serum PSA, PLR, NLR and MLR values compared to non-PCa patients who having BPH and prostatitis histologies. In the comparison made by excluding metastatic patients, only serum PSA and MLR values remained statistically higher in PCa patients than non-PCa patients (Table 2).

Based on the ROC analysis, we determined cut-off points of PLR, NLR and MLR which were 109.04 with area under the curve (AUC) =0.623 ($p<0.001$, 95% CI, 0.569–0.675), 3.25 with AUC=0.600 (p:0.001, 95% CI, 0.546–0.653) and 0.28 with AUC=0.654 ($p<0.001$, 95% CI, 0.600–0.704), respectively, to predict PCa (Figure 1). Then, we performed ROC analysis for cut-off points of PLR, NLR and MLR values again to predict PCa in cohort which metastatic patients were removed. Of these 3 parameters, only MLR had significant AUC to predict PCa in this cohort, and the cut-off points for PLR, NLR and MLR were as follows; 95.6 with AUC =0.549 (p:0.172, 95% CI, 0.490–0.607), 1.82 with AUC=0.561 (p:0.086, 95% CI, 0.502–0.618) and 0.28 with AUC=0.624 ($p<0.001$, 95% CI, 0.566–0.680), respectively (Figure 2).

Univariate logistic regression analysis showed that all age, serum PSA, PLR, NLR and MLR variables were predictors of PCa. While creating the multivariate logistic regression model, only one of the PLR, NLR and MLR variables were added to the age and PSA which were independent variables, because all three variables are derived from lymphocytes. Therefore, three multivariate logistic regression models were performed using PLR, NLR and MLR separately. Multivariate logistic regression analysis revealed that only serum PSA and MLR values were significant independent predictors of PCa (Table 3). Furthermore, after the removal of metastatic PCa patients from the entire cohort, the aforementioned univariate and multivariate logistic regression analyses were performed again. Likewise, while all variables were independent predictors of PCa in univariate logistic regression analysis, only PSA and MLR were independent predictors in multivariate logistic regression analysis (Table 3).

Table 1. Comparison of study parameters in all three groups (BPH, PCa and prostatitis)

	BPH[1] (N=124) Median (IQR)	PCa[2] (N=132) Median (IQR)	Prostatitis[3] (N=82) Median (IQR)	[a] p	[b] Post-hoc
Entire cohort (N=338)					
Age	66.50(61.00-71.00)	68.00(63.00-76.00)	67.00(57.75-71.00)	***0.006***	1&2: 0.003 2&3: 0.003
PSA(ng/dl)	7.88(5.24-11.15)	20.52(8.90-59.00)	8.29(5.29-10.94)	***<0.001***	1&2: <0.001 2&3: <0.001
PLR	118.55(98.70-147.79)	140.91(106.32-198.56)	113.69(88.67-162.54)	***0.001***	1&2: <0.001
NLR	2.44(1.66-3.14)	2.71(1.86-4.18)	2.38(1.62-3.44)	***0.007***	1&2: 0.002
MLR	0.27(0.22-0.39)	0.34(0.27- 0.44)	0.28(0.19-0.41)	***<0.001***	1&2: <0.001 2&3: 0.017
Cohort which metastatic PCa was removed (N=296)					
Age	66.50(61.00-71.00)	67.00(63.00-74.25)	67.00(57.75-71.00)	0.222	-
PSA(ng/dl)	7.88(5.24-11.15)	12.49(8.19-31.30)	8.29(5.29-10.94)	***<0.001***	1&2: <0.001 2&3: <0.001
PLR	118.55(98.70-147.79)	122.67(101.51-168.73)	113.69(88.67-162.54)	0.329	-
NLR	2.44(1.66-3.14)	2.61(1.85-3.46)	2.38(1.62-3.44)	0.243	-
MLR	0.27(0.22-0.39)	0.32(0.27-0.41)	0.28(0.19-0.41)	0.004	-

[a]. Kruskal Wallis Test was used for comparison and statistical significance was p <0.05. Significant important values were shown in italics and bold.

[b].Tamhane's T2 test for post-hoc comparison.

IQR: inter quartile range, PSA: prostate spesific antigen, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio.

Table 2. Comparison of study parameters in PCa and non-PCa groups

	No prostate cancer (N=206) Median (IQR)	Prostate cancer (N=132) Median (IQR)	P value*
Entire cohort (N=338)			
Age	67.00(59.00-71.00)	68.00(63.00-76.00)	***0.001***
PSA(ng/dl)	8.10(5.24-11.15)	20.52(8.90-59.00)	***<0.001***
PLR	117.14(94.80-153.67)	140.91(106.32-198.56)	***<0.001***
NLR	2.43(1.64-3.15)	2.71(1.86-4.18)	***0.002***
MLR	0.27(0.21-0.39)	0.34(0.27-0.44)	***<0.001***
Cohort which metastatic PCa was removed (N=296)			
Age	67.00(59.00-71.00)	67.00(63.00-74.25)	0.084
PSA(ng/dl)	8.10(5.24-11.15)	12.49(8.19-31.30)	***<0.001***
PLR	117.14(94.80-153.67)	122.67(101.51-168.73)	0.179
NLR	2.43(1.64-3.15)	2.61(1.85-3.46)	0.096
MLR	0.27(0.21-0.39)	0.32(0.27-0.41)	***0.001***

**.Mann-Whitney U Test was used for comparison and statistical significance was p <0.05. Significant important values were shown in italics and bold.*

IQR: inter quartile range, PSA: prostate spesific antigen, PLR: platelet-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, MLR: monocyte-to-lymphocyte ratio.

Note. non-PCa group was composed of BPH and prostatitis pathologies

Table 3. Univariate and multivariate analysis for predicting PCa

	Univariate analysis			Multivariate analysis		
	P	**OR**	**95% CI**	**P***	**OR**	**95% CI**
Entire cohort (N=338)						
Age	***<0.001***	1.056	1.027-1.086	0.316	1.017	0.984-1.051
PSA(ng/dl)	***<0.001***	1.086	1.056-1.116	***<0.001***	1.083	1.052-1.115
PLR (≥109.04 vs <109.04)	***<0.001***	2.419	1.502-3.897	0.53	1.719	0.993-2.974
NLR (≥3.25 vs <3.25)	***0.002***	2.140	1.330-3.443	0.243	1.407	0.793-2.495
MLR (≥0.28 vs <0.28)	***<0.001***	3.176	1.973-5.115	***0.001***	2.512	1.437-4.394
Cohort which metastatic PCa was removed (N=296)						
Age	***0.016***	1.040	1.007-1.073	0.348	1.017	0.982-1.053
PSA(ng/dl)	***<0.001***	1.073	1.043-1.104	***<0.001***	1.072	1.041-1.104
PLR (≥83.87 vs <83.87)	***0.012***	3.954	1.355-11.540	0.63	2.822	0.946-8.422
NLR (≥1.82 vs <1.82)	***0.009***	2.133	1.205-3.776	0.52	1.725	0.995-3.655
MLR (≥0.28 vs <0.28)	***<0.001***	2.713	1.549-4.616	***0.002***	2.509	1.394-4.519

**. Multivariate analysis model included age, PSA and PLR (≥109.04 vs <109.04) or NLR (≥3.25 vs <3.25) or MLR (≥0.28 vs <0.28) in entire cohort. Multivariate analysis model included age, PSA and PLR (≥83.87 vs <83.87) or NLR (≥1.82 vs <1.82) or MLR (≥0.28 vs <0.28) in cohort which metastatic PCa was removed.*

***PSA:** prostate spesific antigen, **PLR:** platelet-to-lymphocyte ratio, **NLR:** neutrophil-to-lymphocyte ratio, **MLR:** monocyte-to-lymphocyte ratio, **OR**: odds ratios, **CI**:confidence interval.*

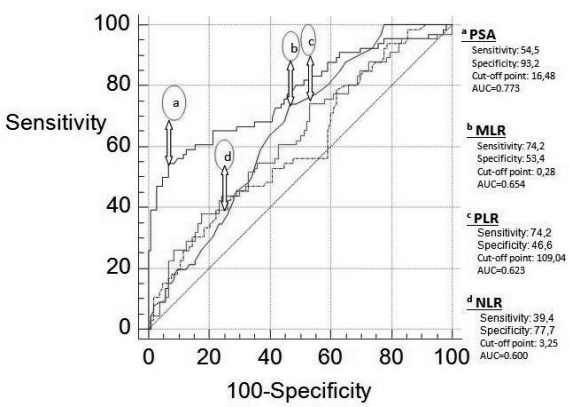

Figure 1. ROC curves for PSA, PLR, NLR and MLR to predict PCa

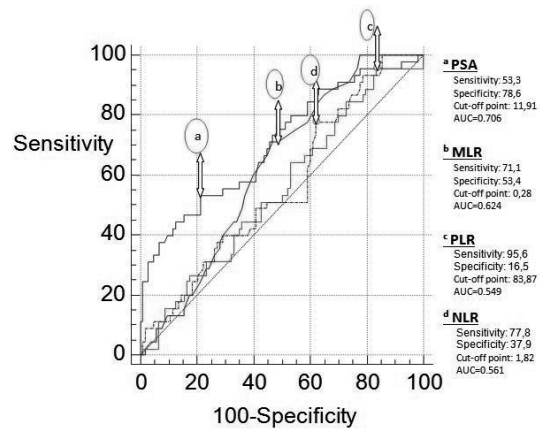

Figure 2. ROC curves for PSA, PLR, NLR and MLR to predict PCa (after excluding metastatic PCa patients)

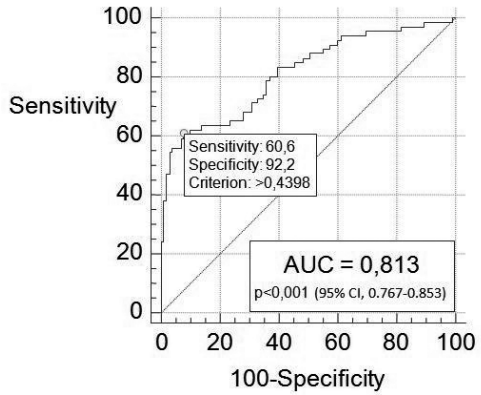

Figure 3. ROC curve for the multivariate logistic regression model with age, PSA and MLR ≥0.28

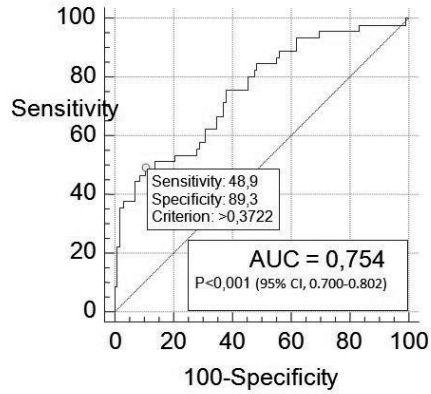

Figure 4. ROC curve for the multivariate logistic regression model with age, PSA and MLR ≥0.28 (excluded metastatic patients)

We performed ROC analysis of the multivariate model(including age, PSA and MLR >0.28). The sensitivity and specificity of model were 60.2% and 92.2% with AUC=0.813 (p<0.001, 95% CI, 0.767-0.853) (Figure 3). Finally, after the removal of metastatic patients, in the ROC analysis the predictive accuracy of the model with the same variables was decreased, but remained statistically significant. The sensitivity and specificity of model were 48.9% and 89.3% with AUC=0.754 (p<0.001, 95% CI, 0.700-0.802) (Figure 4).

DISCUSSION

The use of serum PSA is a breaking point in the diagnosis of PCa(14). However, PSA does not only increase in PCa because it is organ specific rather than cancer. It may also increase in benign conditions such as BPH and prostatitis. Therefore, the specificity of PSA is low, but its sensitivity is sufficient, which may result in unnecessary biopsy and this condition has been demonstrated in studies (15-18). There are new biomarkers and imaging studies, including the Prostate Health Index (PHI) test, four kallikrein (4K) testing, and multiparametric magnetic resonance imaging (mpMRI) to improve specificity of PSA in PCa detection, but they are neither cheap nor easily accessible and applicable. In this direction, the role of inflammatory markers in PCa diagnosis is investigated recently.

Many studies have supported that intraprostatic inflammation plays a role in the formation of PCa (19-21). Regarding PCa and inflammatory marker relationship, Keizman et al. first investigated the prognostic role of neutrophil count in PCa, a castration-resistant metastatic PCa under ketoconazole therapy (22). Currently, systemic reviews and meta-analyzes on the prognostic role of inflammatory markers such as NLR and PLR in PCa have been published and high NLR and PLR are associated with poor oncological results (23-25). In addition, studies with controversial results about the predictive value of NLR and PLR in the diagnosis of PCa have been published (6, 7, 10, 11, 26-29). However, there are not enough studies in which MLR is reported as a predictive marker in PCa diagnosis. Hayashi et al. showed that MLR and serum monocyte count were higher in patients with high gleason score (≥7) PCa (12). In one study, it has been reported that LMR may be a useful marker for PCa diagnosis, especially in patients with PSA value of 4 to 10 ng/dl (13).

In a study from Japan, where prostate biopsy was performed on 810 patients with serum PSA level of 4-10 ng/ml, ıt was found that patients with PCa had significantly higher NLR than in those without PCa (p<0.001). Also, ıt was revealed that NLR, along with the F/T PSA ratio, is an independent risk factor for PCa in multivariate analysis. (6). Unlike, Yuksel et al. analyzed a total of 873 patients who underwent prostate biopsy and saw that there was no significant difference

between the mean NLR values of patients with and without PCa, 3.03±3.88 (2.27) and 3.04±3.28 (2.21), (p=0.944), respectively (10). In the present study, the NLR value of PCa patients was higher than those without PCa, 2.71(1.86-4.18) and 2.43(1.64-3.15), (p<0.001), respectively. But, no significant difference was observed for NLR between two groups after the removal of metastatic patients, 2.61(1.85-3.46) and 2.43(1.64-3.15) (p=0.096), respectively.

In a retrospective study analyzing 298 patients by Adhyatma et al., ıt was seen that the PLR value of PCa patients was significantly higher than BPH patients (169.55 ± 78.07 vs 160.27 ± 98.96, p=0.02, respectively). Based on the ROC analysis, the cut-off point of PLR was 143 with AUC of 57.9%, sensitivity of 56.4% and specificity of 55.6% (p=0.02) (11). However, Eren et al. were not found the relationship between PCa and PLR in their study. There was no significant PLR difference between BPH and PCa patients, even lower in PCa (p=0.932) (29). In our study, the PLR value of PCa patients was higher than those without PCa, 140.91(106.32-198.56) vs 117.14(94.80-153.67), p<0.001, respectively. However, no significant difference was observed for PLR between two groups after the removal of metastatic patients, 122.67(101.51-168.73) vs 117.14(94.80-153.67), p=0.179, respectively.

Hayashi et al. investigated the association between the monocyte fraction of WBCs and high Gleason score PCa. The serum monocyte fraction was significantly higher in patients with high Gleason score PCa than in non-high Gleason score PCa, both in all men and in men with PSA <10 ng/ml. While MLR was a significant predictor of high Gleason score cancer in univariate analysis but was not in stepwise multiple logistic regression analysis (12). Additionally, Caglayan et al. assessed the predictive value of LMR in PCa diagnosis in their study. Only MLR value from NLR, PLR and MLR had a significant difference between BPH, prostatitis and PCA groups (p=0.047), and the difference was increased especially in patients with PSA 4-10 ng/dl (p=0.012). LMR with age and free/total PSA ratio was an independent risk factor in both univariate analysis and multivariate analysis in those with PSA 4-10 ng/dl (13). In our study, only PSA and MLR values were higher in PCa patients than non-PCa patients both in all cohort and in cohort which metastatic PCa patients were removed (for both, p<0.001). Based on the ROC analysis, we determined 0.28 cut-off point of MLR with AUC=0.654 (p<0.001, 95% CI, 0.600–0.704). Multivariate logistic regression analysis revealed that only serum PSA and MLR values were significant independent predictors of PCa.

The most obvious limitations of our study are retrospective nature and relatively low number of patients. Some independent risk factors related to inflammation such as smoking, body mass index and metabolic syndrome are absent due to the study is retrospective. Therefore, we think that we could not fully evaluate to what extent MLR contributed to the predictive value of PCa diagnosis. In our study, it was important to include cases with prostatitis, which are highly abundant in PBx pathologies and to evaluate MLR separately in BPH, prostatitis and PCa groups. In addition, analyzing the value of MLR in the entire cohort and in the cohort from which metastatic patients were excluded allowed for multi-stage evaluation.

CONCLUSION

All inflammatory markers evaluated in our study like NLR, PLR and MLR were high in PCa patients. But, only MLR value remained high after metastatic PCa patients were removed from the entire cohort. In the multivariate model, MLR combination with PSA and age is a significant independent predictor of PCa. With new studies supporting the relationship between MLR and Pca, MLR can be considered to use as a cheap, easily accessible and applicable new marker in PCa prediction.

Conflict of interest

All authors declare no conflict of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethical Approval

The study was approved by the Ethic Committee of Institutional Review Board at the Kahramanmaras Sutcu Imam University Hospital (Approval number: 2020-06-133). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

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