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ORIGINAL PAPER

Lymphocyte-to-monocyte ratio is a valuable marker to predict prostate cancer in patients with prostate specific antigen between 4 and 10 ng/dl

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Summary *Objective:To evaluate the diagnostic value of serum inflammation markers derived from complete blood count in diagnosis of prostate cancer (PCa).*
Methods: We retrospectively analyzed the data of 621 patients who underwent prostate biopsy between March 2013 and April 2018. Age, prostate specific antigen (PSA), free PSA, platelet count, neutrophil count, lymphocyte count, monocyte count, prostate volume (PV) and pathology result of the patients were recorded. Patients were grouped as benign prostatic hyperplasia (BPH), prostatitis and PCa. Patients were also grouped according to PSA values, as PSA < 4 , PSA 4-10 and PSA > 10 ng/dl.
Results: The mean lymphocyte-to-monocyte ratio (LMR) value of the patients with PCa was significantly lower in the entire cohort (p = 0.047). In the PSA 4-10 ng/dl range, LMR value wassignificantly lower in patients with PCa than those with BPH or prostatitis (p = 0.012). In this PSA range, free/total PSA ratio and LMR were significant factors to predict PCa. The cut-off values of LMR, free/total PSA were 3.05 and 0.15 respectively. The sensitivities, spesificities, positive predictive values (PPV) and negative predictive values using LMR cut-off, free/total PSA cut-off and their combination were assessed. Specificity and PPV of the combination group were higher (97.2%, 83.3% respectively) compared to free/total PSA cut-off group (91.6%, 76.6%) and LMR cut-off group (67.8%, 43.7%).
Conclusions: LMR is a useful tool at detecting PCa especially in patients with PSA value between 4 and 10 ng/dl. The combination of free/total PSA ratio and LMR improves the diagnostic accuracy more than the use of free/total PSA ratio alone.

KEY WORDS: Lymphocyte-to-monocyte ratio; Prostate cancer.

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INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the fifth most common cause of cancer-associated death in men worldwide (1). Despite the recent advances in diagnostic and therapeutic approaches, it is still a major health concern especially in developed countries and especially in elderly men (2).
Serum *prostate-specific antigen* (PSA) is widely used as a biomarker for this cancer, and its widespread introduction has undoubtedly enhanced the early detection of PCa and reduced the associated mortality. However, the low specificity of PSA can lead to unnecessary biopsies, overdiagnosis and overtreatment (3).
PSA is organ but not cancer-specific, therefore it may be elevated in benign conditions such as benign prostate hyperplasia (BPH), prostatitis, urinary tract infections and trauma. After detection of elevated PSA, it is recommended to *perform prostate biopsy* (PBx) which is still the gold standard method for diagnosis of PCa.
However PBx is associated with several complications, including pain, hematospermia, haematuria, hematochezia, and potentially severe infectious complications, ranging from *urinary tract infections* (UTIs) and prostatitis to sepsis (4). Although PSA is a useful tool at detecting PCa, concern about performing unnecessary PBx considering overdiagnosis and complications is the crucial problem for urologists. Some PSA-related testing parameters (e.g., PSA density, free/total PSA ratio, PSA doubling time, and prostate health index test) have been used to improve the accuracy of PCa prediction (5). Thus, new biomarkers may be needed to improve decision-making regarding initial management, including whether to biopsy.
Over the last decade, it has become clear that systemic inflammation plays an important role in the development and progression of cancer. The markers of the systemic inflammatory response are usually based around composite ratios or cumulative scores of different circulating white blood cells representing the systemic responses of lymphoid/myeloid tissue.
The main approach is to take the ratio of different white blood cells and then apply a prognostic threshold to the ratio such that outcome is effectively stratified. The most repeatedly validated examples of this approach are the *neutrophil-lymphocyte ratio* (NLR) based on the ratio of circulating neutrophil and lymphocyte counts, the *platelet-lymphocyte ratio* (PLR) based on the ratio of circulating platelet and lymphocyte counts and the *lymphocyte-monocyte ratio* (LMR) based on the ratio of circulating lymphocyte and monocyte counts.
In this study, we aimed to investigate the role of the systemic inflammatory response markers prior to PBx at predicting histologic≠al outcomes.

No conflict of interest declared.

Methods

We retrospectively analyzed the data of 621 patients who underwent 12-core PBx between March 2013 and April 2018. PBx was performed within 4 weeks after blood tests. Age, total PSA level, free PSA level, hemoglobin level, platelet count, neutrophil count, lymphocyte count, monocyte count, prostate volume and pathology result of the patients were recorded.

Patients with symptomatic prostatitis or urinary tract infection or systemic inflammatory disease or any history of anti-inflammatory drug use within 2 weeks before PBx were excluded. Also patients with *high grade intraepithelial neoplasia* (H-PIN) and *atypical small acinar proliferation* (ASAP) were excluded due to the low number of cases. Finally the patients whose PSA was less than 100 ng/ml and those had no evidence of metastasis in imaging reports were included.

The patients were laid down in left lateral decubitus position and in the flexion of knees and hips. General Electric LOGIQ 100 PRO Series ultrasound device was used with 6.5 MHz rectal probe, the widest diameter of which was 23 mm. Biopsy samples were taken as 12 cores with the use of 30 cm 18 Gauge full automatic biopsy needle.

Data analysis

Biopsy results, Gleason scores, PSA, free/total PSA ratio, prostate volume, age, NLR results, PLR results, LMR results were assessed using the Chi-square test or Mann-Whitney U-test to determine statistically significant differences. After adjusting for confounding factors, univariate and multivariate logistic regression analyses were performed to determine the factors effecting PCa diagnosis. The predictive accuracy of the multivariate model was assessed using receiver operating characteristic (ROC)-derived area under the curve (AUC) analysis.

The IBM SPSS software package version 21.0 (*Statistical Package for Social Sciences™, Chicago, IL, USA*) weas used for statistical analysis. A two-tailed $P < 0.05$ was considered as significant for all analyses.

Results

A total of 800 patients who underwent transrectal ultrasound guided PBx were recorded. Of these, 179 did not meet inclusion criterias and were excluded (lack of data regarding CBC in 77 patients, presence of HPIN or ASAP in 30 patients, presence of metastasis in the imaging reports in 47 patients and presence of PSA higher than 100 ng/dl in 25 patients). Finally the data of 621 patients were investigated. The mean age was 64.97 ± 6.36 years. The mean prostate volume was 71.64 ± 39.9 cc.

The mean PSA and free/total PSA value were 9.86±7.43 ng/dl and 0.23 ± 0.10, respectively. The mean NLR, PLR and LMR values were 2.50 ± 1.17, 124.94 ± 51.81 and 3.84 ± 1.44, respectively. Additionally, patients were grouped with regard to histology of the biopsy. Among all

Table 1.

Comparison of the study parameters of 3 histology groups in entire cohort.

	BPH (n = 357)	Prostatitis (n = 24)	PCa (n = 240)	*p value*
Age, years (mean ± SD)	64,45 ± 6,08	64 ± 5,87	65,85 ± 6,74	**0,004**
Total PSA, ng/dl (mean ± SD)	8,82 ± 6,61	6,27 ± 2,46	11,79 ± 8,68	**0,001**
Free/total PSA (mean ± SD)	0,25 ± 0,10	0,29 ± 0,06	0,18 ± 0,10	**0.000**
Prostate volume, cc (mean ± SD)	82,82 ± 43,49	72,75 ± 51,14	54,90 ± 24,30	**0.000**
Comparison of the study parameters of 3 histology groups in PSA 4-10 range				
	BPH (n = 252)	**Prostatitis (n = 18)**	**PCa (n = 150)**	
Age, years (mean ± SD)	64.58 ± 5.89	63.17 ± 6.5	66.64 ± 6.04	**0.000**
Total PSA, ng/dl (mean ± SD)	6.6 ± 1.63	6.13 ± 1.72	6.86 ± 1.72	0.106
Free/total PSA (mean ± SD)	0.25 ± 0.09	0.30 ± 0.06	0.19 ± 0.11	**0.000**
Prostate volume, cc (mean ± SD)	80.3 ± 39.6	80.17 ± 54.75	50.78 ± 19.08	**0.000**

PCa: Prostate cancer; BPH: Benign prostate hyperplasia; SD: Standart deviation; PSA: Prostate spesific antigen.

Table 2.

Mean ± SD values of the inflammation markers and p values for comparison of the histological groups in the entire cohort.

		BPH (n = 357)	Prostatitis (n = 24)	PCa (n = 240)
NLR value	BPH = 2,50 ± 1,22	1	0,529	0,543
(mean ± SD)	Prostatitis = 2,34 ± 0,96	0,529	1	0,207
	PCa = 2,51 ± 1,10	0,543	0,207	1
PLR value	BPH = 124,02 ± 49,25	1	0,480	0,669
(mean ± SD)	Prostatitis = 108,93 ± 39,05	0,480	1	0,512
	PCa = 127,89 ± 56,30	0,669	0,512	1
LMR value	BPH = 3,92 ± 1,45	1	0,485	0,047
(mean ± SD)	Prostatitis = 4,11 ± 1,19	0,485	1	0,098
	PCa = 3,67 ± 1,44	0,047	0,098	1

PCa: Prostate cancer; BPH: Benign prostate hyperplasia; SD: Standart deviation; PSA: Prostate spesific antigen; NLR: Neutrophile to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio.

Table 3.

Mean ± SD values of the inflammation markers and p values for comparison of the histological groups in the cohort PSA 4-10 ng/dl range.

		BPH (n = 252)	Prostatitis (n = 18)	PCa (n = 150)
NLR value	BPH = 2.52 ± 1.31	1	0.439	0.295
(mean ± SD)	Prostatitis = 2.64 ± 0.94	0.439	1	0.982
	PCa = 2.55 ± 1.10	0.295	0.982	1
PLR value	BPH = 123.64 ± 49.58	1	0.910	0.743
(mean ± SD)	Prostatitis = 114.06 ± 28.13	0.910	1	0.782
	PCa = 124.13 ± 48.79	0.743	0.782	1
LMR value	BPH = 3.95 ± 1.54	1	0.536	0.012
(mean ± SD)	Prostatitis = 3.80 ± 1.19	0.536	1	0.533
	PCa = 3.56 ± 1.33	0.012	0.533	1

PCa: Prostate cancer; BPH: Benign prostate hyperplasia; SD: Standart deviation; PSA: Prostate spesific antigen; NLR: Neutrophile to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio.

Table 4.
Mean ± SD values of the inflammation markers and p values for comparsion of the histological groups in the patients with PSA higher than 10 ng/dl.

		BPH (n = 78)	PCa (n = 72)
NLR (mean ± SD)	BPH = 2.63 ± 1.0	1	0.839
	PCa = 2.66 ± 1.1	0.839	1
PLR (mean ± SD)	BPH = 133.3 ± 51.1	1	0.965
	PCa = 143±71	0.965	1
LMR (mean ± SD)	BPH = 3.76 ± 1.1	1	0.892
	PCa = 3.69 ± 1.3	0.892	1

PCa: Prostate cancer; BPH: Benign prostate hyperplasia; SD: Standart deviation; PSA: Prostate spesific antigen; NLR: Neutrophile to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio.

Table 5.
Mean ± SD values of the inflammation markers and p values for comparsion of the Gleason score groups in the entire cohort.

		Gleason 6 (n = 173)	Gleason > 7 (n = 67)
NLR (mean ± SD)	GS 6 = 2.5 ± 1.05	1	0.454
	GS > 7 = 2.57 ± 1.23	0,454	1
PLR (mean ± SD)	GS 6 = 122.1 ± 46.8	1	0.082
	GS > 7 = 142.8 ± 73.8	0,082	1
LMR (mean ± SD)	GS 6 = 3.7 ± 1.15	1	0.177
	GS > 7 = 3.6 ± 2.02	0,177	1

SD: Standart deviation; NLR: Neutrophile to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio; GS: Gleason score.

Table 6.
Univariate and multivariate analyses for predicting prostate cancer.

	n	Univariate analysis			Multivariate analysis		
		HR	95% CI	p	HR	%95 CI	p
Age (year)							
< 65.5	186	1	1.14-1.86	0.01	1	1.68-4.56	< 0.001
> 65.5	216	1.45			2.77		
LMR value							
> 3.05	258	1	0.99-1.37	0.04	1	1.02-2.6	0.037
< 3.05	144	1.17			1.65		
Free/total PSA value							
> 0.15		1	1.45-1.97	< 0.001	1	6.80-22.22	< 0.001
< 0.15		1.69			12.3		

PSA: Prostate spesific antigen; LMR: Lymphocyte to monocyte ratio; HR: Hazard ratio; CI: confidence interval.

the individuals, BPH was detected in 357 patients, prostatitis was detected in 24 and PCa was detected in 240. The mean age and the mean PSA value of the PCa group were significantly higher when compared to the other groups. Also the mean prostate volume and free/total PSA ratio were significantly lower (Table 1). NLR, PLR and LMR values of the histological groups were compared. Any statistically significant difference was not observed for NLR and PLR values. Mean LMR value of the patients with PCa was significantly lower than patients with BPH and prostatitis (p = 0.047) (Table 2).

The patients were divided into 3 groups as; with PSA lower than 4 ng/dl, with PSA between 4 and 10 ng/dl and with PSA higher than 10 ng/dl. In the patients with PSA between 4 and 10 ng/dl, LMR value was significantly lower in patients with PCa than those with BPH or prostatitis (p = 0.012) (Table 3). Any statistically significant difference between the groups was not observed in NLR and PLR in the PSA 4-10 ng/dl range. In the group of the patients with PSA higher than 10 ng/dl, there was not any statistically significant variation for NLR, PLR and LMR (Table 4). In this group, the presence of prostatitis could not be compared due to the low number of patients.

The patients with PCa were seperated into 2 groups as patients with Gleason score 6 and patients with Gleason score 7 and above. There was no statistically significant difference between the groups in NLR, PLR and LMR value (Table 5).

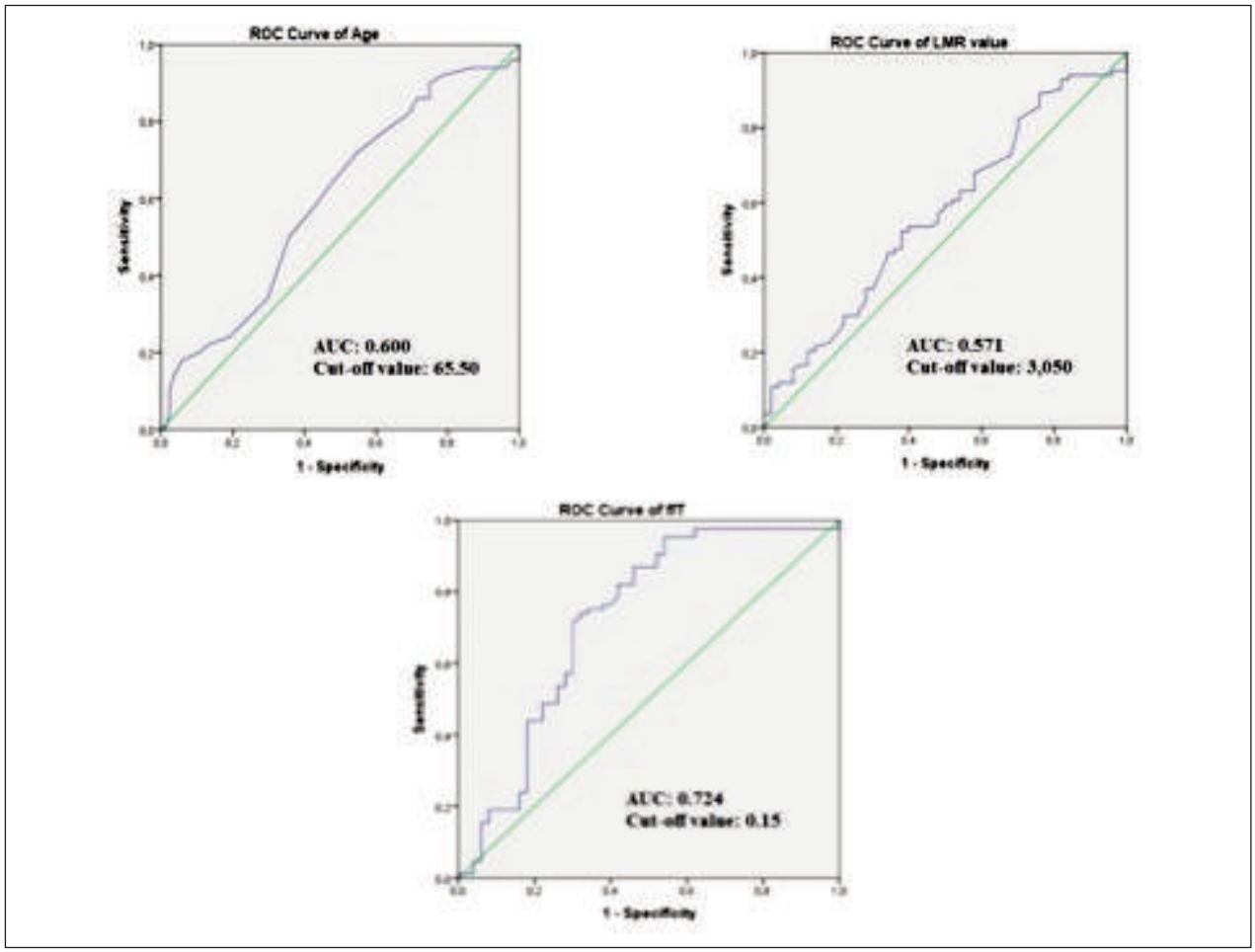
In the patients with PSA between 4 and 10 ng/dl, age, free/total PSA ratio and LMR were significant factors to predict PCa. Based on the AUROC curve, the cut-off points of LMR, free/total PSA and age were 3.05, 0.15 and 65.5 respectively (Figure 1). Multivariate analysis showed that LMR (HR = 1.65), age (HR = 2.77) and free/total PSA ratio (HR = 12.3) were independent risk factors to predict PCa (Table 6). The sensitivities, spesificities, positive predictive values and negative predictive values using LMR cut-off, free/total PSA cut-off and their combination were showed in Table 7. Specificity and positive predictive value of the combination group were higher (97.2%, 83.3% respectively) compared to the free/total PSA cut-off group (91.6%, 76.6% respectively) and LMR cut-off group (67.8%, 43.7% respectively) (Table 7).

Table 7.
Mean ± SD values of the inflammation markers and p values for comparison of the histological groups in the cohort PSA 4-10 ng/dl range.

	Sensitivity	Specificity	PPV	NPV
Free/total PSA < 0.15	46% (69 of 150)	%91.6 (231of 252)	%76.6 (69 of 90)	%71.7 (231 of 322)
LMR < 3.050	%42 (63 of 150)	%67.8 (171 of 252)	%43.7 (63 of 144)	%73 (171 of 234)
Free/total PSA < 0.15 & LMR < 3.050	%16.6 (25 of 150)	%97.2 (247 of 252)	%83.3 (25 of 30)	%66.4 (247 of 372)

PPV: Positive predictive value; NPV: Negative predictive value; PSA: Prostate spesific antigen; LMR: Lymphocyte to monocyte ratio.

Figure 1.
AUROC for variables to predict prostate cancer.



Discussion

The immune system plays an important role in cancer pathogenesis. Serum biomarkers which can be easily derived from *complete blood count* (CBC) are useful tools to estimate the prognosis and survival in many solid cancers. The presence of low LMR, high PLR and high NLR values were associated with poor *overall survival* (OS) in the published systemic reviews (6-8). In the study performed by *Gu et al.*, elevated NLR was closely associated with poor OS in PCa (9). Also a similar study in Japan, revealed that elevated NLR was correlated with both poor cancer-spesific survival (p = 0.018) and OS (p = 0.008) in patients with metastatic PCa.10 Besides, nonsteroidal anti-inflammatory drug medications have been suggested to reduce the development risk of PCa (11, 12).

Additionally to the prognostic value of serum inflammation markers, there are also many studies assessing the diagnostic value of those prior to the PBx with controversial results in the literature.

In the study performed by *Kamali et al.*, 500 patients who underwent PBx were evaluated but statistically significant difference was obtained between the NLR of the patients with positive biopsy and those with negative biopsy p = 0.112): NLR was not described as a predictive factor for positive PCa biopsy (13).

In another study, 3913 men who underwent PBx were analyzed retrospectively. The NLR value was higher in the biopsy-positive group than in the biopsy-negative group (p < 0.001). Also the NLR value was significantly higher in high-grade Gleason PCa group than the biopsy-negative group and low-grade PCa group (p < 0.001). On multivariate analyses, a higher NLR was associated with PCa detection (OR = 1.37, 95% CI: 1.017-1.850, p = 0.038) (14).

Kawahara et al. investigated the data of 810 men with PSA value between 4 and 10 ng/ml who underwent PBx. NLR value was significantly higher in men with positive biopsy than in those with negative biopsy (p < 0.001). Using NLR cut-off point of 2.40 determined by the AUROC curve, positive/negative predictive values of NLR alone and NLR combined with free/total PSA ratio (cut-off: 0.15) were 56.6%/60.8% and 80.7%/60.1%, respectively (15).

Huang et al. analyzed a total of 662 patients who underwent transperineal template guided PBx. In the entire cohort, any significant difference was not found in NLR when patients were grouped with regard to histology of the biopsy (cancer and no cancer) (p = 0.424). However, they observed additional significant difference in NLR

value (p = 0.002) when analyses were restricted to patients with PSA ranged from 4 to 10 ng/ml (cut-off value was set at 2.44). Accordingly the patients were classified into high-NLR and low-NLR group. The high-NLR showed significantly high PCa detection rate in the entire cohort and in the cohort with PSA ranged from 4 to 10 ng/ml (175/338, 142/324, p = 0.041 and 36/77, 14/87, p < 0.001 respectively) (16).

Gokce et al. investigated the data of 1836 patients. Patients were divided as follows: the group with BPH, the group with prostatitis and the group with PCa. Pre-biopsy mean NLR value of the prostatitis group was significantly higher compared to the PCa and BPH groups (p = 0.0001). The mean NLR of PCa group was significantly higher compared to the BPH group (p = 0.002). Also, the PCa patients with high Gleason score (GS) (GS 8 and above) had a significantly higher mean NLR compared to the PCa patients with GS 5-6 and GS 7 (p = 0.0001) (17).

In the present study; when evaluating the NLR, any statistically significant difference was not observed based on the biopsy results. Also, cohort were seperated into 3 groups as men with PSA value of < 4, PSA between 4 and 10 and PSA of > 10 ng/dl. No statistically significant NLR difference was observed based on the biopsy results in any PSA range. We divided the PCa patients into 2 groups as the group with GS 6 and GS 7 and above. There was not a statistically significant difference between the GS groups.

Additionally, controversial to the study performed by Gokce et al., we did not observe a significant highness in the prostatitis group compared to the PCa and BPH group. Our data showed that chronic prostatitis does not effect the inflammation markers derived from CBC considerably.

Kaynar et al. retrospectively reviewed the data of 201 patients. Pathological sample results were categorized as chronic prostatitis, BPH and PCa. PSA levels were also categorized as 0-4 ng/ml, 4-10 ng/ml, and 10 ng/ml and above.Any statistically significant difference was not observed between benign or malign groups in terms of age, NLR and mean prostate volume. Statistically significant differences were present only in the PSA 10 ng/ml and above group related to mean PLR values (p: 0.044) (18). In another study, PLR value was statistically higher in PCa group than in BPH group while NLR value was not (19). In our study, pre-biopsy PLR value was not associated with higher PCa detection rate in any PSA range or in any Gleason score range.

To our knowledge, there is not any study assessing the predictive value of LMR for PCa risk. In the present study, LMR was the only inflammation marker associated with PCa diagnosis (p = 0.047). Interestingly, in the 4-10 ng/dl PSA range LMR value was extremely lower in patients with positive biopsy than those with negative biopsy (p = 0,012). In this group free/total PSA ratio lower 0.15 and age higher than 65.5 were also risk factors to predict PCa. Additionally our data showed that, when LMR and free/total PSA cut-off values were combined, the specificity and positive predictive value were higher compared to the use of LMR or free/total PSA ratio alone.

There are many limitations in our study. Firstly, our data derived from retrospective cohort. The next, we could not evaluate the factors, such as body mass index, smoking, metabolic syndrome which may be associated with the inflammatory response. Also the number of patients was relatively low. Especially, the low number of the patients with prostatitis inhibited some analysis. However we think that, regarding our limited data, asymptomatic prostatitis does not effect CBC parameters. Furthermore, the initial PBx may miss cancer in some men and 20% of men may be diagnosed as PCa in repeated biopsy (20).

Conclusions

Regarding our data LMR value is a useful tool at detecting PCa especially in patients with PSA value between 4 and 10 ng/dl. The combination of free/total PSA ratio and LMR improves the diagnostic accuracy more than the use of free/total PSA ratio alone. This model can assist urologists in deciding whether prostate biopsy is advisable.

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