

# Preoperative Inflammation Markers in Predicting Biochemical Recurrence after Robot-assisted Radical Prostatectomy

Mahmut Taha Olcucu, Kaan Karamik, Kayhan Yilmaz, Cagatay Ozsoy, Yasin Aktas and Mutlu Ates

*Department of Urology, University of Health Sciences, Antalya Training and Research Hospital, Turkey*

## ABSTRACT

**Objective:** To evaluate the importance of preoperative neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-monocyte ratio (NMR) in prostate cancer patients, who underwent robot-assisted radical prostatectomy (RARP).

**Study Design:** Observational study.

**Place and Duration of Study:** Urology Department, Antalya Training and Research Hospital, Turkey, between March 2015 and September 2019.

**Methodology:** Four hundred and fifty-four patients underwent RARP were scanned. Clinical characteristics and pathological features of patients were recorded. Patients were excluded, if they had persistent PSA; a history of any autoimmune or inflammatory disease; anti-inflammatory agents use; blood transfusion within 3 months; or a follow-up time shorter than 3 months. Systemic inflammation markers were calculated and correlated with patients' data and biochemical recurrence (BCR). Biochemical recurrence was defined as two repetitive measurements of PSA levels  $\geq 0.2$  ng/mL at 3 months after the radical prostatectomy. Mann-Whitney U-test, Fisher's exact test, and Pearson Chi-square test, ROC curve, Kaplan-Meier survival analyses, and Cox proportional hazard regression model were used as statistical methods.

**Results:** Four hundred and two patients were eligible. The median age at RP was 65.5 (61-69) years and median PSA of the patients was 8.3 (5.76-12.61) ng/mL. Median NLR, LMR, PLR, and NMR were 2 (1.55-2.61), 3.86 (3.14-5), 105.69 (85-134.29), 7.82 (6.25-9.71); and optimal cut-off values were 2.33, 3.75, 106.6, and 8.75, respectively. Low LMR was found as an important predictor of biochemical recurrence (hazard ratio, HR=1.769, 95% confidence interval, CI=1.091 - 2.868,  $p=0.021$ ). A significant association was found between lower LMR and decreased BCR-free survival ( $p < 0.001$ ).

**Conclusion:** Pretreatment low LMR might be a simple and inexpensive index, which reflects the host systemic immunity and can predict independently BCR after RARP.

**Key Words:** Biochemical recurrence, Lymphocyte-to-monocyte ratio, Neutrophil-to-lymphocyte ratio, Neutrophil-to-monocyte ratio, Platelet-to-lymphocyte ratio, Prostate cancer.

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## INTRODUCTION

Prostate cancer (PCa) is the most common solid cancer type in men.<sup>1</sup> The diagnosis of PCa has increased with screening measurement of prostate-specific antigen (PSA).<sup>2</sup> Radical prostatectomy (RP) is an effective treatment option in prostate cancer.

Compared to external beam radiotherapy, RP demonstrates equivalent oncological outcomes and also provides tumor control, accurate staging and elimination of possible PSA sources. However, biochemical recurrence (BCR) may occur in 35% of patients, after which it is usually associated with bad prognosis.<sup>3</sup>

Biochemical recurrence is known as with two repetitive measurements of PSA levels  $\geq 0.2$  ng/mL at 3 months after the RP.<sup>4</sup> Persistent PSA is described as PSA levels  $\geq 0.1$  ng/mL within 6 weeks after the RP; and it is associated with invisible metastases at the time of surgery.<sup>4</sup> Patients who experience BCR after RP, which may require secondary therapy, have poorer oncological outcomes. Several clinical and pathological factors have been proven to be independent predictors of BCR after surgery.<sup>5</sup> Nevertheless, the predictors of BCR remain unclear. Hence, effective prognostic biomarkers are needed for individualised risk assessment and clinical decision-making.

*Correspondence to: Dr. Mahmut Taha Olcucu, Department of Urology, University of Health Sciences, Antalya Training and Research Hospital, Turkey  
E-mail: matah\_ol@hotmail.com*

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Table I: Sensitivity, specificity, PPV and NPV for NLR, LMR, PLR and NMR to predict biochemical recurrence and comparison of patients' characteristics between groups.

	Cut-off Value	AUC (95%CI)	p	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	
NLR	>2.3333	0.577(0.527-0.625)	0.035	49.35(37.8 - 61.0)	68.62(63.3 - 73.6)	27.1(20.0 - 35.3)	85.1(80.2 - 89.2)	
LMR	≤3.75	0.609(0.560-0.657)	0.003	63.64(51.9 - 74.3)	59.69(54.1 - 65.1)	27.2(20.9 - 34.3)	87.4(82.3 - 91.5)	
PLR	>106.5	0.576(0.526-0.625)	0.033	63.64(51.9 - 74.3)	54.46(48.9 - 60.0)	24.9(19.0 - 31.5)	86.3(80.9 - 90.7)	
NMR	≤8.75	0.509(0.459-0.559)	0.809	68.83(57.3 - 78.9)	37.85(32.6 - 43.4)	20.8(16.0 - 26.3)	83.7(76.7 - 89.3)	
Patients' characteristics between groups								
	NLR		PLR		LMR		NMR	
	Low (n:262)	High (n:140)	p	Low (n:205)	High (n:197)	p	Low (n:255)	High (n:147)
Age (years)	65(61-69)	66(61-70)	0.567	65(61-69)	66(61-69)	0.417	66(62-70)	65(60-69)
BMI (kg/m <sup>2</sup> )	27.36(25.28-29.4)	27.39(24.22-29.9)	0.705	27.43(24.88-29.39)	27.18(24.91-30.07)	0.936	27.33(24.44-29.9)	27.42(25.25-29.4)
PSA (ng/mL)	8.33(5.92-12)	8.19(5.13-53)	0.917	8.28(6-12)	8.53(5.63-13.06)	0.399	8.55(5.73-13.14)	8.23(5.77-12)
Biopsy ISUP grade								
1	166(63.4) <sup>a</sup>	73(52.1) <sup>b</sup>	0.004	127(62)	112(56.9)	0.183	97(53.9) <sup>a</sup>	142(64) <sup>b</sup>
2	61(23.3) <sup>a</sup>	34(24.3) <sup>a</sup>		47(22.9)	48(24.4)		45(25) <sup>a</sup>	50(22.5) <sup>a</sup>
3	20(7.6) <sup>a</sup>	10(7.1) <sup>a</sup>		18(8.8)	12(6.1)		11(6.1) <sup>a</sup>	19(8.6) <sup>a</sup>
4	12(4.6) <sup>a</sup>	22(15.7) <sup>b</sup>		11(5.4)	23(11.7)		24(13.3) <sup>a</sup>	10(4.5) <sup>b</sup>
5	3(1.1) <sup>a</sup>	1(0.7) <sup>a</sup>		2(1)	2(1)		3(1.7) <sup>a</sup>	1(0.5) <sup>a</sup>
Postoperative ISUP grade								
1	114(43.5) <sup>a</sup>	46(32.9) <sup>b</sup>	0.021	82(40) <sup>a</sup>	78(39.6) <sup>a</sup>	0.011	69(38.3)	91(41)
2	88(33.6) <sup>a</sup>	42(30) <sup>a</sup>		80(39) <sup>a</sup>	50(25.4) <sup>b</sup>		50(27.8)	80(36)
3	35(13.4) <sup>a</sup>	27(19.3) <sup>a</sup>		23(11.2) <sup>a</sup>	39(19.8) <sup>b</sup>		32(17.8)	30(13.5)
4	10(3.8) <sup>a</sup>	14(10) <sup>b</sup>		9(4.4) <sup>a</sup>	15(7.6) <sup>a</sup>		13(7.2)	11(5)
5	15(5.7) <sup>a</sup>	11(7.9) <sup>a</sup>		11(5.4) <sup>a</sup>	15(7.6) <sup>a</sup>		16(8.9)	10(4.5)
Clinical stage								
T1	184(70.2)	86(61.4)	0.160	143(69.8)	127(64.5)	0.525	113(62.8)	157(70.7)
T2	75(28.6)	53(37.9)		60(29.3)	68(34.5)		65(36.1)	63(28.4)
T3	3(1.1)	1(0.7)		2(1)	2(1)		2(1.1)	2(0.9)
D'Amico risk								
Low risk	120(45.8) <sup>a</sup>	48(34.3) <sup>b</sup>	0.027	96(46.8) <sup>a</sup>	72(36.5) <sup>b</sup>	0.013	61(33.9) <sup>a</sup>	107(48.2) <sup>b</sup>
Intermediate risk	101(38.5) <sup>a</sup>	57(40.7) <sup>a</sup>		81(39.5) <sup>a</sup>	77(39.1) <sup>a</sup>		72(40) <sup>a</sup>	86(38.7) <sup>a</sup>
High risk	41(15.6) <sup>a</sup>	35(25) <sup>b</sup>		28(13.7) <sup>a</sup>	48(24.4) <sup>b</sup>		47(26.1) <sup>a</sup>	29(13.1) <sup>b</sup>
Pathological stage								
T2	177(67.6)	84(60)	0.130	135(65.9)	126(64)	0.691	109(60.6)	152(68.5)
T3	85(32.4)	56(40)		70(34.1)	71(36)		71(39.4)	70(31.5)
Extraprostatic extension	74(28.2)	53(37.9)	0.051	62(30.2)	65(33)	0.575	68(37.8)	59(26.6)
Lymphovascular invasion	47(17.9)	33(23.6)	0.184	38(18.5)	42(21.3)	0.500	42(23.3)	38(17.1)
Perineural invasion	199(76)	113(80.7)	0.305	159(77.6)	153(77.7)	0.947	144(80)	168(75.7)
Seminal vesicle invasion	40(15.3)	18(12.9)	0.503	31(15.1)	27(13.7)	0.671	26(14.4)	32(14.4)
Positive surgical margin	56(21.4)	45(32.1)	0.019	53(25.9)	48(24.4)	0.710	57(31.7)	44(19.8)
Lymph node invasion	9(3.4)	7(5)	0.444	6(2.9)	10(5.1)	0.270	8(4.4)	8(3.6)

<sup>(a,b)</sup> Different lowercases in a row indicate statistically significant difference between groups. Cut-off values were calculated with Youden index. Mann-Whitney U-test and Pearson Chi-square test were used for statistical analysis. Data are presented with frequency (%), and median (IQR). AUC, Area under the curve; BMI, Body mass index; CI, Confidence interval; ISUP, International Society of Urological Pathology; LMR, Lymphocyte-to-monocyte ratio; NLR, Neutrophil-to-lymphocyte ratio; NPV, Negative Predictive Value; PLR, Positive Predictive Value; PSA, Prostate-specific antigen; p, p-value; p, p

<sup>(a,b)</sup> Different lowercases in a row indicate statistically significant difference between groups. Cut-off values were calculated with Youden index. Mann-Whitney U-test and Pearson Chi-square test were used for statistical analysis. Data are presented with frequency (%) and median (IQR). AUC: Area under the curve; BMI: Body mass index; CI: Confidence interval; ISUP: International Society of Urological Pathology; LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; NPV: Negative predictive value; PLR: Platelet-to-lymphocyte ratio; PPV: Positive predictive value; PSA: Prostate specific antigen.

Tumor-associated inflammation is considered as a key factor for cancer development and progression.<sup>6</sup> The ratio of neutrophil-to-lymphocyte (NLR), neutrophil-to-monocyte (NMR), lymphocyte-to-monocyte (LMR), platelet-to-lymphocyte (PLR) can be calculated from complete blood counts (CBC); and these have been suggested as an emerging marker of systemic inflammation. The body's response to inflammation has a critical role in patients with malignancies.<sup>7,8</sup> Consequently, the NLR has been evaluated for predicting BCR in PCa; however, results of respective studies are controversial.<sup>9-11</sup>

In cancer patients, the inflammation markers are increasingly important in terms of prognosis. Moreover, the inflammation markers are an accessible and inexpensive clinical parameters in daily practice.

The aim of the present study was to evaluate the inflammation markers in predicting biochemical recurrence in prostate cancer patients who underwent robot-assisted RP (RARP).

## METHODOLOGY

This observational study was conducted at the Urology Department, Antalya Training and Research Hospital. After Local Ethics Committee approval, the data of 454 patients who had underwent robot-assisted radical prostatectomy without neo-adjuvant treatment between March 2015 and September 2019 at the Urology Department of Antalya Training and Research Hospital were retrospectively identified. Patients were excluded, if they had PSA levels  $\geq 0.1$  ng/mL within 6 weeks after RP (persistent PSA); a history of any autoimmune or inflammatory disease; anti-inflammatory drug use; blood transfusion within 3 months; or a follow-up time shorter than 3 months.

Da Vinci Xi Robotic System® (Intuitive Surgical System Technologies, Sunnyvale, CA, USA) was used to perform surgeries. Patients with a lymph node metastasis risk of above 5% according to the Briganti nomogram had extended lymph node dissection. Clinical characteristics and pathological features of patients including age, preoperative PSA, biopsy of International Society of Urological Pathology (ISUP) grade, clinical T stage, postoperative ISUP grade, pathological T stage, surgical margin (SM), lympho-vascular invasion (LVI), extraprostatic extension (EPE), presence of perineural invasion (PNI), seminal vesicle invasion (SVI) and presence of lymph node metastasis were noted. The CBCs was obtained 3-10 days before surgery. The NLR, PLR, LMR and NMR were computed and noted. After the RARP, the patients were followed up postoperatively with PSA. BCR presence was defined as two repetitive measurements of PSA levels  $\geq 0.2$  ng/mL at 3 months after the RP. BCR-free survival (BCRFS) was calculated from the time of RP to BCR.

SPSS (version 23.0, IBM Corp., Armonk, NY) and MedCalc Statistical Software (Unlicensed copy-free trial, version 19.3.1, MedCalc Software Ltd, Ostend, Belgium) were used for statistical analysis. Qualitative data were given as frequency (%), while quantitative as median (IQR). The normality of patients' data was controlled by the Shapiro-Wilk test. Mann-Whitney U-test was used to determine the differences between the groups. The Fisher's exact test and Pearson Chi-square test were used for categorical variables. The receiver operating characteristic (ROC) curve analysis was applied to evaluate the predictive performance of CBC parameters for BCR. The area under the curve (AUC), sensitivity, specificity, negative and positive predictive values (NPV-PPV) were computed and found with 95% confidence intervals. Youden's index was used to find the optimal cut-off points. The Kaplan-Meier analysis was used to demonstrate survival curves; and the log-rank test was used to evaluate the differences. Univariate and multivariate analyses of independent predictors of BCR was performed with a Cox proportional hazard regression model. The variables which showed significant association with BCR in the univariate analyses were further tested in a backward stepwise multivariate model. Hazard ratio (HR), with corresponding 95% confidence intervals (95% CIs), was reported.  $P < 0.05$  was accepted as significant.

## RESULTS

Four hundred and two patients were found eligible for the study. The entire cohort aged 65.5 (61-69) years on median (IQR) and median PSA of the patients were 8.3 (5.76-12.61) ng/mL. Median NLR, LMR, PLR, and NMR were 2 (1.55-2.61), 3.86 (3.14-5), 105.69 (85-134.29), and 7.82 (6.25-9.71), respectively. After RARP, patients were followed-up with a median of 19 months.

Based on the ROC curve and Youden's index, the potential NLR cut-off point was 2.33 for BCR (AUC=0.577). The value of 3.75 for LMR (AUC=0.609) and 106.5 for PLR (AUC=0.576) were found to be a cut-off point. Finally, a cut-off point of 8.75 was calculated for NMR (AUC=0.509). Table I reports the sensitivity, specificity, PPV, and NPV for study parameters to predict BCR. According to cut-off points, low and high groups were created (Table I). High-NLR group had a higher biopsy and postoperative ISUP grade and D'Amico risk classification than those in the low-NLR group ( $p=0.004$ ,  $p=0.021$ , and  $p=0.027$ , respectively). Furthermore, patients with NLR  $> 2.33$  were more likely to harbour positive SMs ( $p=0.019$ ). The high-PLR group was correlated with higher postoperative ISUP grade and D'Amico risk classification

( $p=0.011$  and  $p=0.013$ ). The high-LMR group was slightly younger than the low-LMR group ( $p=0.002$ ). D'Amico risk classification and biopsy ISUP grade of the low-LMR group were significantly higher than the high-LMR group. Additionally, the low-LMR group had more EPE and positive SM than the high-LMR group ( $p=0.018$  and  $p=0.007$ ).

**Table II: Comparison of patients' characteristics between BCR groups and demonstration of univariate and backward stepwise multivariate Cox regression analysis for determining the risk factors associated with biochemical recurrence.**

BCR				
Variables	No (n:325)	Yes (n:77)	p	
Age (years)	65(61-69)	66(61-70)	0.700	
BMI (kg/m²)	27.22(24.84-29.41)	27.68(25.1-29.63)	0.422	
PSA (ng/mL)	7.95(5.63-11.92)	11.7(7-22)	<0.001	
WBC, 10³/mm³	7400(6400-8700)	7900(6500-8700)	0.384	
Neutrophil, 10³/mm³	4400(3500-5400)	4500(3900-5500)	0.250	
Lymphocyte, 10³/mm³	2200(1800-2700)	2100(1600-2600)	0.167	
Monocyte, 10³/mm³	500(500-700)	600(500-800)	0.077	
Platelet, 10³/mm³	235000(193000-270000)	239000(198000-286000)	0.242	
NLR	1.95(1.5169-2.4815)	2.3043(1.7083-2.8)	0.036	
LMR	4(3.2-5)	3.33(2.75-4.57)	0.003	
PLR	102.5(83.89-133.68)	116.33(90-137.5)	0.038	
NMR	7.8(6.25-9.75)	8(6.38-9.5)	0.811	
Biopsy ISUP grade				
1	216(66.5) <sup>a</sup>	23(29.9) <sup>b</sup>	<0.001	
2	69(21.2) <sup>a</sup>	26(33.8) <sup>b</sup>		
3	25(7.7) <sup>a</sup>	5(6.5) <sup>a</sup>		
4	13(4) <sup>a</sup>	21(27.3) <sup>b</sup>		
5	2(0.6) <sup>a</sup>	2(2.6) <sup>a</sup>		
Postoperative ISUP grade				
1	150(46.2) <sup>a</sup>	10(13) <sup>b</sup>	<0.001	
2	109(33.5) <sup>a</sup>	21(27.3) <sup>a</sup>		
3	43(13.2) <sup>a</sup>	19(24.7) <sup>b</sup>		
4	13(4) <sup>a</sup>	11(14.3) <sup>b</sup>		
5	10(3.1) <sup>a</sup>	16(20.8) <sup>b</sup>		
Clinical stage				
T1	232(71.4) <sup>a</sup>	38(49.4) <sup>b</sup>	0.001	
T2	90(27.7) <sup>a</sup>	38(49.4) <sup>b</sup>		
T3	3(0.9) <sup>a</sup>	1(1.3) <sup>a</sup>		
D'Amico risk				
Low risk	156(48) <sup>a</sup>	12(15.6) <sup>b</sup>	<0.001	
Intermediate risk	128(39.4) <sup>a</sup>	30(39) <sup>a</sup>		
High risk	41(12.6) <sup>a</sup>	35(45.5) <sup>b</sup>		
Pathological stage				
T2	234(72)	27(35.1)	<0.001	
T3	91(28)	50(64.9)		
Extraprostatic extension	83(25.5)	44(57.1)	<0.001	
Lymphovascular invasion	48(14.8)	32(41.6)	<0.001	
Perineural invasion	243(74.8)	69(89.6)	0.006	
Seminal vesicle invasion	31(9.5)	27(35.1)	<0.001	
Positive surgical margin	64(19.7)	37(48.1)	<0.001	
Lymph node invasion	3(0.9)	13(16.9)	<0.001	
Cox regression analysis				
	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	p	HR (95% CI)	p
Age (years)	1.007(0.969-1.045)	0.734	-	-
BMI (kg/m²)	1.023(0.961-1.09)	0.472	-	-
PSA (ng/mL)	1.034(1.024-1.043)	<0.001	1.014(1.001-1.026)	0.032
Log <sub>10</sub> WBC	2.082(0.29-14.962)	0.466	-	-
NLR>2.3333	2.066(1.319-3.236)	0.002	-	-
LMR≤3.75	2.573(1.614-4.101)	<0.001	1.769(1.091-2.868)	0.021
PLR>106.5	2.103(1.319-3.354)	0.002	-	-
NMR≤8.75	1.269(0.783-2.057)	0.334	-	-
Postoperative ISUP grade				
1	Reference	-	Reference	-
2	2.782(1.309-5.911)	0.008	1.803(0.824-3.944)	0.140
3	6.067(2.818-13.061)	<0.001	2.45(1.058-5.673)	0.037
4	10.665(4.503-25.262)	<0.001	6.392(2.544-16.064)	<0.001
5	12.064(5.441-26.747)	<0.001	3.855(1.568-9.477)	0.003
Continued..				
Clinical stage				
T1	Reference	-	-	-
T2-T3	2.375(1.516-3.721)	<0.001	-	-
D'Amico risk				
Low risk	Reference	-	Reference	-



Intermediate risk	3.244(1.657-6.348)	<b>0.001</b>	2.389(1.168-4.886)	<b>0.017</b>
High risk	9.46(4.885-18.321)	<b>&lt;0.001</b>	2.731(1.248-5.978)	<b>0.012</b>
<b>Pathological stage</b>				
T2	Reference	-	-	-
T3	3.898(2.438-6.233)	<b>&lt;0.001</b>	-	-
Extraprostatic extension	3.307(2.104-5.198)	<b>&lt;0.001</b>	-	-
Lymphovascular invasion	3.26(2.07-5.132)	<b>&lt;0.001</b>	-	-
Perineural invasion	2.389(1.147-4.976)	<b>0.020</b>	-	-
Seminal vesicle invasion	3.932(2.458-6.288)	<b>&lt;0.001</b>	-	-
Positive surgical margin	3.079(1.968-4.817)	<b>&lt;0.001</b>	2.302(1.431-3.705)	<b>0.001</b>
Lymph node invasion	11.912(6.402-22.165)	<b>&lt;0.001</b>	3.672(1.737-7.761)	<b>0.001</b>

(a, b) Different lowercases in a row indicate statistically significant difference between groups. Mann-Whitney U-test, Pearson Chi-square test and Fisher's Exact test were used for statistical analysis. Data are presented with frequency (%) and median (IQR). BMI: Body mass index; CI: Confidence interval; HR: Hazard ratio; ISUP: International Society of Urological Pathology; LMR: Lymphocyte-to-monocyte ratio, NLR: Neutrophil-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio; PSA: Prostate specific antigen; WBC: White blood cell.

The relationship of BCR with study parameters after RP is shown in Table II. PSA, NLR, LMR, PLR, biopsy and postoperative ISUP grade, clinical stage, D'Amico risk, pathological stage, positive SM, EPE, LVI, PNI, SVI, and lymph node invasion were found to be statistically significant. The independent predictors of BCR were shown in Table II. BCR was independently associated with PSA (hazard ratio, HR=1.014,  $p=0.032$ ), positive SM (HR=2.302,  $p=0.001$ ), and lymph node invasion (HR=3.672,  $p=0.001$ ). Only LMR (HR=1.769,  $p=0.021$ ) remained to be a significant predictor of BCR among inflammation markers.

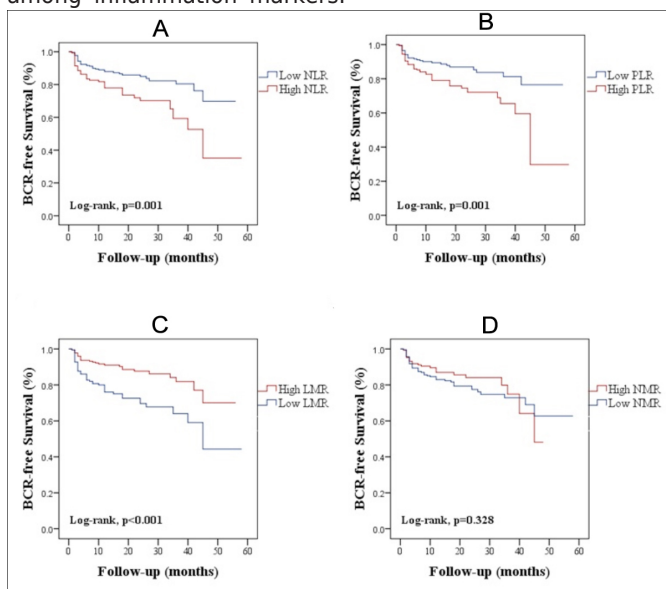
group ( $p<0.001$ ) (Figure 1C). In terms of BCRFS, low and high NMR groups were not significantly different ( $p=0.328$ ) (Figure 1D).

## DISCUSSION

The present study demonstrated that preoperative low LMR might be an independent factor in prediction of BCR after RARP. After scanning literature, no study was found to demonstrate an association between LMR and BCR. This study is the first to demonstrate lower LMR was associated with higher BCR rates. It is also found here that increased NLR and PLR, decreased LMR were associated with poor BCRFS.

Previous studies reported the association between the inflammation markers and the clinical outcome of the malignancies.<sup>7,12</sup> However, the exact mechanisms underlying the prognostic capacity of systemic inflammation markers remain to be clarified. The effects of neutrophils on the proliferation of tumor cells are well known.<sup>13</sup> Lymphocytes have a major role in inhibiting cancer cell proliferation and migration.<sup>14</sup> They have an antitumor effect. The decreased lymphocyte counts are correlated with an immunosuppressive status. Monocytes might differentiate into tumor-associated macrophages (TAM) when necessary, and TAM might support tumor growth, invasion, metastasis and angiogenesis.<sup>15</sup> Therefore, the number of monocytes could be representative of TAMs reflecting the tumor burden. The body's inflammatory response to malignancy is lymphocyte dependent, and there is an association between the high level of TAM and tumor invasiveness and clinical outcomes. Thus, LMR could reflect the inflammation states in the tumor microenvironment. Because of a reduction in lymphocytes or an increase in monocytes, low LMR would be associated with unfavourable oncological outcomes in cancer patients. CBC tests are frequently used in routine practice and LMR is an accessible and inexpensive clinical parameter. LMR is a cost-effective parameter that can be used in clinical practice to estimate the outcomes of cancer patients.

There is increasing evidence correlating the lower LMR with poorer oncological results in patients with several malignan-



**Figure 1: Biochemical recurrence-free survival curves according to predictive factors. The high-NLR (A), high-PLR (B), low-LMR (C) were significantly associated with decreased BCR-free survival. No association was found between NMR and BCR-free survival (D). BCR: Biochemical recurrence; LMR: Lymphocyte-to-monocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio; PLR: Platelet-to-lymphocyte ratio.**

BCR developed in 77 patients; and the mean time between RP and BCR was  $18.09 \pm 12.49$ . Kaplan-Meier survival analyses of patients are presented in Figure 1. The BCRFS was significantly shorter in the high-NLR group ( $p=0.001$ ) (Figure 1A). The high PLR was significantly associated with decreased BCRFS ( $p=0.001$ ) (Figure 1B). A significantly higher risk of experiencing BCR was found in the low-LMR

cies.<sup>16-18</sup> This study demonstrated that LMR is an independent factor to estimate BCR after RARP. Nishijima *et al.* performed a systematic review and meta-analysis including the patients with non-hematologic solid tumors. A low LMR represented an unfavorable factor for clinical outcomes.<sup>19</sup> Li *et al.* also published a meta-analysis to demonstrate the importance of LMR in the urologic malignancies.<sup>20</sup> However, there was no PCa patient in the studies including this meta-analysis. In a study including 214 castration-resistant PCa patients, absolute monocyte count (AMC) and LMR had associated with bad prognosis according to univariate analysis.<sup>21</sup> However, AMC remained an independent prognostic factor for prognosis.

Several meta-analyses have been performed to further validate the prognostic importance of NLR in PCa.<sup>22,23</sup> Tang *et al.* reported that NLR could be a marker in predicting the outcomes of locally advanced and/or castration-resistant PCa patients.<sup>22</sup> A recent systematic review also demonstrated that high NLR was associated with bad prognosis in all of the stratified categories except localised PCa.<sup>23</sup> The importance of NLR in PCa is not yet clear. High NLR had a significant association with BCR in univariate analysis, which was found in the present study.

BCR may occur in 35% after RP.<sup>3</sup> Detecting BCR after RP is important in identifying treatment failure and considering salvage therapy. Several clinical and pathological findings, such as PSA, stage of the disease, high Gleason score (GS), and positive surgical margin (PSM) are well-known predictors of BCR.<sup>5,24</sup> In this study, PSA, high GS, PSM, and lymph node invasion were independently predicted BCR. The authors had previously described the importance of the De Ritis ratio in predicting BCR after RP,<sup>25</sup> and found that it was an independent prognostic factor for prediction of BCR.

The mean time between radical prostatectomy and BCR was 18.09 months in the present study, which is relatively short when compared with the literature. RARP technique has a learning curve to gain experience. Initial RARP cases were included in this study, which were in the learning curve. This may cause shorter BCR mean time after RARP.

Most of the studies on this subject are retrospective. Therefore, there might be a bias to select patients. Large-scale prospective studies are needed to assess the presence of biomarkers to predict BCR after RP.

The present study also has some limitations. It has a retrospective design and the data are obtained from a single institution. Second, the population was also small with a short follow-up duration. Third, the role of other various medical conditions such as smoking, metabolic syndrome, cardiovascular diseases and some other unknown factors that could affect the results, was not evaluated in multivariate analyses.

## CONCLUSION

Preoperative low LMR might be an independent predictor for BCR in the patients who underwent RARP, which is a simple and inexpensive method. Low LMR was also more likely to have poor BCRFS. The prognostic utility of LMR should be evaluated in further large prospective cohorts.

## ETHICAL APPROVAL:

Ethics Committee approval was received for this study from the Ethics Committee of Antalya Training and Research Hospital (Approval No. 4/10 – 03.2020).

## PATIENTS' CONSENT:

Data of this retrospective study was collected from clinical archive.

## CONFLICT OF INTEREST:

Authors declared no conflict of interest.

## AUTHORS' CONTRIBUTION:

MTO: Conception, materials, data collection, analysis, writing and critical review.

KK: Conception, materials and writing.

KY: Materials and critical review.

CO: Data collection.

YA: Data collection.

MA: Material and critical review.

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