GENERAL UROLOGY
Original Article

The predictive value of platelet to lymphocyte and neutrophil to lymphocyte ratio in determining urethral stricture after transurethral resection of prostate

Transüretral prostat rezeksiyonu sonrası gelişebilecek üretral darlığın belirlenmesinde platelet lenfosit ve nötrofil-lenfosit oranının öngörü değeri

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ABSTRACT

Objective: The pathology of urethral stricture disease is still unclear however progressive inflammation may contribute to the development of urethral stricture. The platelet-to- lymphocyte ratio (PLR) is a new and simple marker that indicates inflammation. In this study we aimed to investigate the predictive value of neutrophil to lymphocyte ratio (NLR) and PLR in patients with urethral stricture who underwent transurethral resection of prostate (TURP).

Material and methods: A total of 208 patients who underwent bipolar-TURP were included in this study. Patients who had previously undergone surgery due to any urethral pathology, posterior urethral strictures, previous or ongoing treatment for any cancer, hematologic disorders, presence of an active infection at the time of surgical intervention, and prior blood transfusion were excluded. PLR, NLR and red cell distribution width (RDW) levels were measured. In order to investigate the predictive values of NLR and PLR variables, binary logistic regression analysis was performed.

Results: No statistically significant differences were observed between the groups in terms of age, NLR, RDW, prostate size and operative times. Statistically significant differences were presented only in the median PLR- values. For predicting urethral stricture, the optimal cut-off value was 112.5, (sensitivity: 0.84, specificity: 0.64; AUC=0.762, 95% CI 0.684-0.84).

Conclusion: In this study we showed that PLR can be used to determine urethral stricture as a cost-effective, common, and simple biomarker in patients after TURP.

Keywords: Inflammation; neutrophil to lymphocyte ratio; platelet to lymphocyte ratio; urethral stricture.

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ÖZ

Amaç: Üretral darlığın patolojisi tam olarak açıklanamamasına rağmen progresif inflamasyonun üretral darlığın meydana gelmesinde etkisi olabilir. Trombosit Lenfosit Oranı (PLR) inflamasyonu gösteren yeni ve basit bir markerdır. Bu çalışmada PLR ve Nötrofil-Lenfosit Oranı (NLR)' (nın) prediktif değerini ve transüretral prostat rezeksiyonu (TURP) operasyonu sonrasında üretral darlığı olan hastalarda PLR'yi ölçmeyi amaçladık.

Gereç ve yöntemler: Toplam 208 hasta bu çalışmaya dahil edildi. Daha önce üretral patoloji nedeniyle herhangi bir operasyon geçiren hastalar, posterior üretral darlığı olan hastalar, herhangi bir kanser tedavisi gören hastalar, hematolojik rahatsızlıkları olan hastalar, cerrahi müdahale esnasında aktif enfeksiyonu olan hastalar ve kan transfüzyonu gereken hastalar çalışmadan çıkartıldı. PLR, NLR ve kırmızı küre dağılım genişliği (RDW) değerleri ölçüldü. NLR ve PLR'nin prediktif değerini ölçmek için ikili lojistik regresyon analizi kullanıldı.

Bulgular: Yaş, NLR, RDW, prostat büyüklüğü ve operasyon süreleri arasında anlamlı fark bulunmadı. İstatiksel olarak anlamlı fark yalnızca ortanca PLR değerlerinde gösterildi. Üretral darlık için optimal cut-off değeri 112,5 olarak değerlendirildi (sensivite 0,84, spesifite 0,64; AUC=0,762, %95 CI 0,684-0,84).

Sonuç: Bu çalışmada PLR'nin TURP sonrasında hastalarda üretral darlık gelişmesini değerlendirmede maliyeti uygun ve basit biyomarker olarak kullanılabileceğini gösterdik.

Anahtar Kelimeler: İnflamasyon; nötrofil lökosit oranı; platelet lenfosit oranı; üretral darlık.

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Introduction

Urethral stricture is one of the oldest and bothersome urologic disease. It is widespread and has a substantial impact on quality of life and health-care costs.[1] Inflammatory, ischemic, or traumatic processes may result in a scar that can cause an urethral stricture. While urethritis was the most common reason of urethral strictures in 1960s, and 1980s, today urethritis was replaced by urethral strictures caused by transurethral resection of prostate (TURP) and radical prostatectomy especially in patients older than age 45.[2]

The pathology of urethral stricture disease is still obscure but it would seem that a scar develops as a consequence of inflammatory changes in the urethral epithelium and the subepithelial spongy tissue causing a fibrotic narrowing of the urethra.[3] Several risk factors such as age, resection time, prostate volume, presence of urinary infection and experience of surgeon were attributed to the development of urethral stricture after TURP.[4] However, which patient will develop urethral stricture after TURP is unknown and no predictive marker is available today.

The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) can be easily calculated by a complete blood count analysis and are recommended as a potential predictive marker to determine inflammation.[5] When the role of inflammation in the pathogenesis of urethral stricture is considered, we hypothesize that, preoperative NLR and PLR values can be used to predict development of urethral stricture after TURP. In this paper, we aimed to investigate the relationship between the preoperative NLR and PLR values and postoperative urethral stricture in patients undergoing TURP.

Material and methods

Data obtained from 302 patients who underwent bipolar-TURP [GyrusPlasmaKineticTM (Gyrus ACMI, USA)] between March 2012 and May 2015, were evaluated retrospectively after obtaining the permission from the local ethics committee and informed consent from patients. All patients were operated by the same experienced surgeon. Transurethral resection was performed by using a standard continuous irrigating resectoscope with a 27 French outer sheath. Thick loop was used during the operation. At the end of the surgery, a tri-way 20 F Foley catheter was left for 2-4 days. The catheters were removed when the urine became clear without continuous saline irrigation.

Patients' demographics, pre-intervention routine hematologic analysis, postoperative uroflowmetry patterns and previous perioperative details such as prostate size, resection and catheter removal time were collected and two groups were formed based on the presence of urethral stricture. Diagnosis of urethral stricture was suspected by uroflowmetry (maximum flow rate of less than 10 mL per second) and confirmed by both urethrogram and flexible cystoscopy under local anesthesia in each stricture patient.[6]

Patients who had a history of surgery due to any urethral pathology, posterior urethral strictures, previous or ongoing treatment for any cancer, hematologic disorders, presence of an active infection at the time of surgical intervention, stricture at the previous resection site and prior blood transfusion were excluded. Only anterior urethral strictures were included in the study. All of the previous TURP operations performed by the same experienced surgeon.

The neutrophil to lymphocyte ratio (NLR) was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. Similarly, PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. Red cell distribution width (RDW) is a measurement obtained from the red blood cell distribution curves generated on automated hematology analyzers. Serum values for the NLR, PLR and RDW were measured on the day before the operation to ascertain the baseline values for neutrophil and lymphocyte counts.

Statistical analysis

In order to investigate the predictive values of NLR and PLR variables, binary logistic regression analysis was performed. Accordingly, the created model was explained as 18.1% of the variation. Details regarding the model are presented in Table 1. All statistical analysis was performed using Statistical Package for the Social Sciences 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp., USA). A p value of less than 0.05 was considered statistically significant.

Results

Out of 302 patients, 208 patients meeting the necessary inclusion criteria were included in the present retrospective study.

Table 1. The clinical and laboratory results of the patient and control group

	Patients (n=35)	Controls (n=173)	p*
Age (year)	38.48±10.31	37.37±10.75	0.593
Prostat size (cm)	53.23±7.64	55.42±8.22	0.301
Operation time (min)	45.4±12.1	43.8±12.8	0.794
NLR	2.22±1.26	2.1±1.72	0.684
RDW	12.21±0.84	12.84±0.69	0.524
PLR	177.9±70.43	124.05±58.85	0.001
Catheter removal time	3.20±0.4	3.1±0.8	0.783

NLR: neutrophil lymphocyte ratio; RDW: Red cell distribution width; PLR: platelet to lymphocyte ratio

Results were given as mean±SD

*p value <0.05 considered significant.

Table 2. Predictive value of NLR and PLR based on binary logistic regression analysis

			95% Confidence Interval		
	p	Wald	Odds Ratio	Lower	Upper
PLR	0.000*	15.192	1.01	1.006	1.017
NLR	0.511	2.54	1.00	0.992	1.012
Nagelkerke R^2=0.171					

NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio
*p<0.05 is considered significant for statistical analyses.

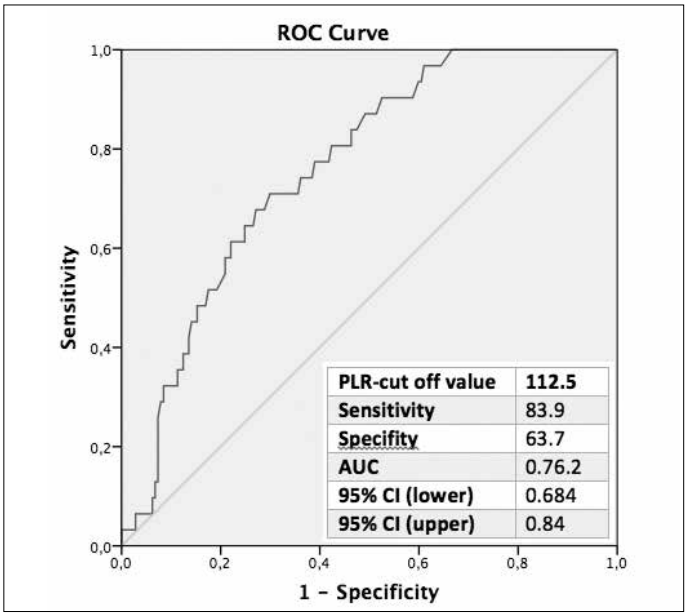


Figure 1. Receiver-operating characteristic (ROC) analysis of PLR in patients with urethral stricture

Hundred and seventy-three patients without urethral stricture were in the control group and 35 with urethral stricture in the study group. The mean age, previous operation time, NLR, RDW and PLR values are presented in Table 1. No statistically significant differences were observed between the groups in terms of age, NLR, RDW, prostate size and previous-operation time. The median follow up after TURP and the median time interval between TURP and recurrence was 12 (range 9-49) and 5.2 months, respectively. Statistically significant differences were presented only in the study group related to mean PLR-values (61.23.±70.43 vs. 124.05±177.9; p=0.001).

Receiver Operating Characteristic (ROC) analysis was performed to determine the cut-off value of PLR to predict urethral stricture, and a ROC/area under curve (AUC) was drawn by plotting the sensitivity versus the specificity for different cut-off levels (Figure 1). For predicting urethral stricture, the optimal cut-off value for 112.5 had a sensitivity of 0.84, and a specificity of 0.64 [AUC=0.762, 95% CI 0.684-0.84] (Figure 1).

Further, we conducted the binary logistic regression analysis to assess the predictive value of NLR and PLR levels for urethral stricture. The results are shown in Table 2. It was found that PLR was independently associated with the urethral stricture after adjustment for NLR.

Discussion

In the present study NLR and PLR analysis of the two groups revealed that NLR and PLR levels increased in urethral stricture patients but only PLR levels displayed statistically significant difference (p=0.043). Besides, PLR is an independent risk factor for developing urethral stricture and could predict the development of urethral stricture after TURP with a cut- off value of 125.5.

According to the literature, the incidence of urethral stricture after TURP varies between 2.2% and 9.8%.[7] Fibroblasts are probably the main cells responsible for the development of urethral stricture, however whatever the reason, the mechanism of urethral stricture is related to urine extravasation into the subepithelial space causing increased inflammation and subsequent scar formation.[8] On that basis; Sciarra et al.[9] used anti-inflammatory drugs to reduce urethral strictures after TURP and suggested that COX-2 inhibitors can prevent development of post TURP urethral stricture. Yet, based on the same logic, several adjuvant therapies including colchicine[10], mitomycin-c[11], triamcinolone[12], and corticosteroids[13], which all have anti–inflammatory effects, have been used to treat urethral strictures either systematically or locally.

All these aspects represent the basis and rationale for the present study. According to all of these reports, urethral stricture is a result of inflammatory changes in the epithelium of urethra and can be treated by interfering with the inflammatory process. In our study, we tested the role of NLR and PLR to predict the development of post-TURP urethral strictures. It has been shown that in systemic inflammation white blood cells go some changes such as neutrophilia and lymphopenia.[14] PLR was also introduced as a novel inflammation marker in several studies.[15-17] However, although NLR levels were higher in urethral stricture group, we found no significant correlation between NLR levels and urethral stricture in our study. On the other hand, PLR values showed significant changes in urethral stricture patients. To the best of our knowledge, a study of the relationship between PLR and urethral stricture has not been reported yet and this is the first study showing a relationship between PLR and urethral stricture. We can base our findings on the following hypothesis.

A typical blood specimen comprises 93% red blood cells, 6% platelets, and 1% white blood cells.[7] Platelets are small discoid cells with a life span of about 7 to 10 days and responsible for hemostasis, construction of new connective tissue

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and revascularization. Most of the research over the past century has been focused on this primary function.[18] Only in the past two decades we have learned that platelet activation in the body releases healing proteins called growth factors. Following injury that causes bleeding, platelets are activated and aggregate together to release their granules containing growth factors that stimulate the inflammatory cascade and healing process.[19] Examples of growth factors that are secreted from α-particles by the activation of platelets include platelet-derived growth factor (PDGF), vascular-endothelial growth factor (VEGF), insulin-like growth factor (IGF), epidermal growth factor (EGF) and transforming growth factor-β (TGF-β).[20] A profibrotic factor -TGF-β1- has been shown to play a crucial role in the pathophysiology of fibrotic diseases such as pulmonary fibrosis, oral submucosal fibrosis, systemic sclerosis, renal fibrosis and Peyronie's disease.[21-24] Besides, TGF-β1 was proven to create fibrosis of the urethra in several animal studies.[25,26] These data may indicate a correlation between platelet counts and TGF-β1 levels.

The main reason of urethral stricture after TURP is still unknown. However, there are some possible mechanisms such as mucosal injury and monopolar current leakage which may play role in developing urethral stricture.[7] Besides, some reports discussed other factors that may be related to urethral stricture including resectoscope size, the type of urethral instrumentation, patient's age and operation time.[8] Although several factors may lead to urethral stricture, in our study, we found no relationship between the development of urethral stricture after TURP and patient's age, prostate volume and operation time. PLR was the only factor that effected the development of urethral stricture after TURP.

The present study has some limitations. Firstly, the study was designed as a retrospective study. Secondly, the sample size is not large enough. Thirdly, we didn't investigate the TGF-β1 levels hence the positive correlation between PLR and TGF-β1 levels may not be established. Despite all these limitations we found significant correlation between PLR and urethral stricture and we assumed that the higher the PLR values the higher the TGF-β1 levels lead to urethral fibrosis. Although, according to binary logistic regression analysis, the decrease in PLR levels is a protective factor in terms of stricture, the model considers PLR as a liminal variable (p=0.000), and therefore this result makes us think that there is a need for more studies to be conducted with more patients in order to understand the significance of NLR in urethra stricture patients.

In conclusion, the platelet to lymphocyte ratio (PLR) can be used to determine urethral stricture as a cost-effective, common, and simple biomarker in patients after TURP. Early dilatation or clean intermittent self-catheterization may be used in these patients to prevent urethral stricture. Further studies are needed in order to evince PLR as a preoperative predictor for urethral stricture that may facilitate institution of appropriate therapy and reduce morbidity and cost.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Selcuk University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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