Original Article
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Can the Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio Be Used to Predict the Risk of Ureteral Stricture Following Ureteroscopy?

Üreteroskopi Sonrası Üreter Darlığı Gelişme Riskini Öngörmede Nötrofil/Lenfosit Oranı ve Platelet/Lenfosit Oranı Kullanılabilir Mi?

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ÖZET

Amaç: Bu çalışmanın amacı daha önce endoskopik üst üriner sistem cerrahisi geçiren hastalarda üreter darlığı veya zor/sıkı üreter gelişim riskini öngörmede, nötrofil/lenfosit oranı (NLO) ve platelet/lenfosit oranı (PLO)'nın etkinliğini araştırmaktır.

Gereç ve Yöntem: Bu gözlemsel çalışma Nisan 2022 ile Nisan 2023 tarihleri arasında Samsun Eğitim ve Araştırma Hastanesi, Üroloji Kliniği'nde yapılmıştır. Çalışmaya daha önce endoskopik üst üriner sistem cerrahisi geçiren 130 hasta alınmıştır. Hastalar üreter darlığı olanlar (Grup 1) ve olmayanlar (Grup 2) olmak üzere iki gruba ayrılmıştır. Üreter darlığı tanısı direk endoskopik olarak veya retrograd piyelografi ile konulmuştur. Grupların sosyodemografik özellikleri, klinik verileri, NLO ve PLO değerleri karşılaştırılmıştır.

Bulgular: Çalışmaya alınan hastaların yaş ortalaması Grup 1'de 49,89 ± 14,40 ve Grup 2'de 48,92 ± 14,60 yıl olarak bulundu (p = 0,704). Vücut kitle indeksi, cinsiyet, hidronefroz, komorbidite açısından gruplar arasında istatistiksel olarak fark izlenmezken; taş düşürme öyküsü ve geçirilmiş operasyon sayısı açısından anlamlı fark izlendi (sırasıyla p = 0,001 ve p <0,001). Grupların NLO değeri sırasıyla 2,62 (0,75-9,18) ve 2,29 (0,80-6,67); PLO değeri 136,57 (55,02-475,45) ve 118,66 (37,50-244,17) olarak bulundu. Her iki değer karşılaştırıldığı zaman gruplar arasında fark izlenmedi (sırasıyla, p = 0,139 ve p = 0,076).

Sonuç: Çalışmamızda NLO ve PLO değerleri üreter darlığı olan grupta daha yüksek tespit edilmesine rağmen bu yükseklik istatistiksel olarak anlamlı bulunamamıştır. Bizim çalışmamıza göre daha önce endoskopik üst üriner sistem cerrahisi geçiren hastalarda üreter darlığı gelişmesini öngörmede NLO ve PLO değerlerinin etkisi yoktur.

Anahtar Kelimeler: üreter darlığı, zor/sıkı üreter, nötrofil/lenfosit oranı, platelet/lenfosit oranı

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ABSTRACT

Objective: The purpose of this study was to investigate whether the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) can be used to predict the development of ureteral stricture or difficult ureter in patients who had previously undergone endoscopic upper urinary tract surgery.

Materials and Methods: This observational study was performed between April 2022 and April 2023 at the Samsun Training and Research Hospital Urology Department, Türkiye. One hundred thirty patients who had undergone prior endoscopic upper urinary tract surgery were included. These were divided into two groups, with (Group 1) and without (Group 2) ureteral stricture. The diagnosis of ureteral stricture was based on direct endoscopy or retrograde pyelography. The groups' socio-demographic characteristics, clinical data, and NLR and PLR values were then compared.

Results: The patients' mean ages were 49.89±14.40 years in Group 1 and 48.92±14.60 in Group 2 (p = 0.704). No statistically significant differences were observed between the groups in terms of sex, body mass index, or comorbidity. However, significant differences were determined in terms of passage of kidney stones and numbers of surgical procedures performed (p = 0.001 and p <0.001, respectively). The groups' NLR values were 2.62 (0.75-9.18) and 2.29 (0.80-6.67), and their PLR values were 136.57 (55.02-475.45) and 118.66 (37.50-244.17), respectively. The differences between the groups were not statistically significant (p = 0.139 and p = 0.076, respectively).

Conclusion: Although NLR and PLR values were higher in the group with ureteral stricture in this study, that elevation was not statistically significant. The results show that the evaluation of NLR and PLR values are not useful in predicting ureteral stricture in patients who have previously undergone endoscopic upper urinary tract surgery.

Keywords: ureteral stricture, difficult ureter, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio

INTRODUCTION

Ureterorenoscopy (URS) is a method used for diagnostic and therapeutic purposes in upper urinary tract pathologies such as tumors, ureteral structure, hematuria, and renal and ureteral stones (1). URS has many complications, and one of the most feared complication is ureteral stricture (2). The reported prevalence of ureteral stricture as a severe complication of URS in the literature ranges widely, from 0.2% to 24% (3). In addition to URS, any ureteral instrumentation can also result in stricture (4). Other conditions than ureteral stricture may also make it difficult to advance the ureteroscope along the ureteral lumen (5). This is defined as difficult ureter in the literature (6).

An inflammatory process lies at the basis of the physiopathology of both ureteral stricture and difficult ureter (3,6). The neutrophil/ lymphocyte ratio (NLR), defined as the ratio between absolute neutrophil and lymphocyte counts, and the platelet/lymphocyte ratio (PLR), calculated by dividing the platelet count by the lymphocyte count, are simple and effective markers reflecting an imbalance in inflammatory cells (7,8). NLR and PLR values may therefore be useful markers in predicting this.

We conclude that insufficient information is available concerning the prediction of unsuccessful upper urinary tract surgeries. In the light of the incidence of pre-stenting, the need for a second endoscopic surgical intervention session, and complications associated with interventions directed toward stricture, a preoperative biomarker is needed in order to be able to predict the risk of ureteral stricture and a difficult ureter. The purpose of this study was to evaluate the usefulness of NLR and PLR values in predicting the risk of ureteral stricture and/or difficult ureter development in patients who had previously undergone URS and developed stricture or difficult ureter.

MATERIALS AND METHODS

Patients and Method

Following the receipt of Ondokuz Mayis University Medical Faculty local ethical committee approval (no. OMUKAEK-2022/235), this observational, prospective study was performed among patients undergoing URS for diagnostic or therapeutic purposes between April 2022 and April 2023 in Samsun Training and Research Hospital.
The inclusion criteria were as follows:

- Age over 18,
- A history of endoscopic upper urinary tract surgery (URS, retrograde intrarenal surgery (RIRS), JJ stent placement etc.) or of any ureteral instrumentation,
- In the case of the study group, the detection of ureteral stricture or difficult ureter by means of direct endoscopic visualization or retrograde pyelography (RGP),
- In the control group, the detection of a normal ureteral lumen at direct endoscopic visualization.

The exclusion criteria were:

- The presence of ureteral stricture or difficult ureter with no history of urological endoscopic upper urinary tract surgery,
- The presence of preoperative JJ stents,
- A history of iatrogenic ureteral trauma associated with urological, gynecological, colorectal, or oncological surgery,
- The presence of oncological, gynecological, or colorectal malignancy (due to suspicion that the tumor might cause stricture through direct invasion),
- Receipt of radiotherapy to the abdominopelvic region,
- The presence of anatomical abnormality in the ureter (such as bifid ureter, ectopic orifice, and ureterocele),
- The presence of active infection, liver failure, or oncological, rheumatic, or hematological disease and use of steroids or contraceptive-type drugs (since these might affect the immune system and alter the NLR and PLR values).

The sizes of the study and control groups were determined using power analysis conducted before the research using G-Power software. The analysis revealed that with an effect size of 0.05, α 0.05 and 1-β (power) 0.80, at least 64 members of each group would be required in order to determine a difference of 1.63 in the NLR in the independent groups t test to be applied for comparing mean values in patient groups with and without ureteral stricture.

One thousand thirty patients were evaluated for the study in our clinic, a regional reference center for endoscopic ureteral and kidney stone surgery, and 130 consecutive patients meeting the study criteria were enrolled. These were equally divided into a group developing ureteral stricture of difficult/tight ureter following URS (Group 1) and a control group with no such development (Group 2).

Ureteral stricture or difficult ureter were diagnosed either by means of direct visualization by experienced endourologists using a ureteroscope (Figures 1a and 1b) or by intraoperative RGP (Figures 1c and 1d). Preoperative hydronephrosis as graded using the classification system recommended by the Society for Fetal Urology (9). Under that classification, grade 0 describes a non-dilated pelvis with no change in renal parenchyma thickness. A mildly dilated pelvis is present in Grade 1, although the calyces are normal. In Grade 2, the pelvis is dilated together with a few calyceal dilatations. In Grade 3, the pelvis and all calyces are equally dilated, and the renal parenchyma is normal. Parenchymal loss is present in Grade 4. The Clavien-Dindo grading system was employed in the evaluation of postoperative complications (10). Complete blood count values one day before surgery were used in the calculation of NLR and PLR values. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, and PLR by dividing the absolute platelet count by the absolute lymphocyte count.

Socio-demographic and clinical data, stone passage history, NLR and PLR values, and complication rates were compared between the two groups.

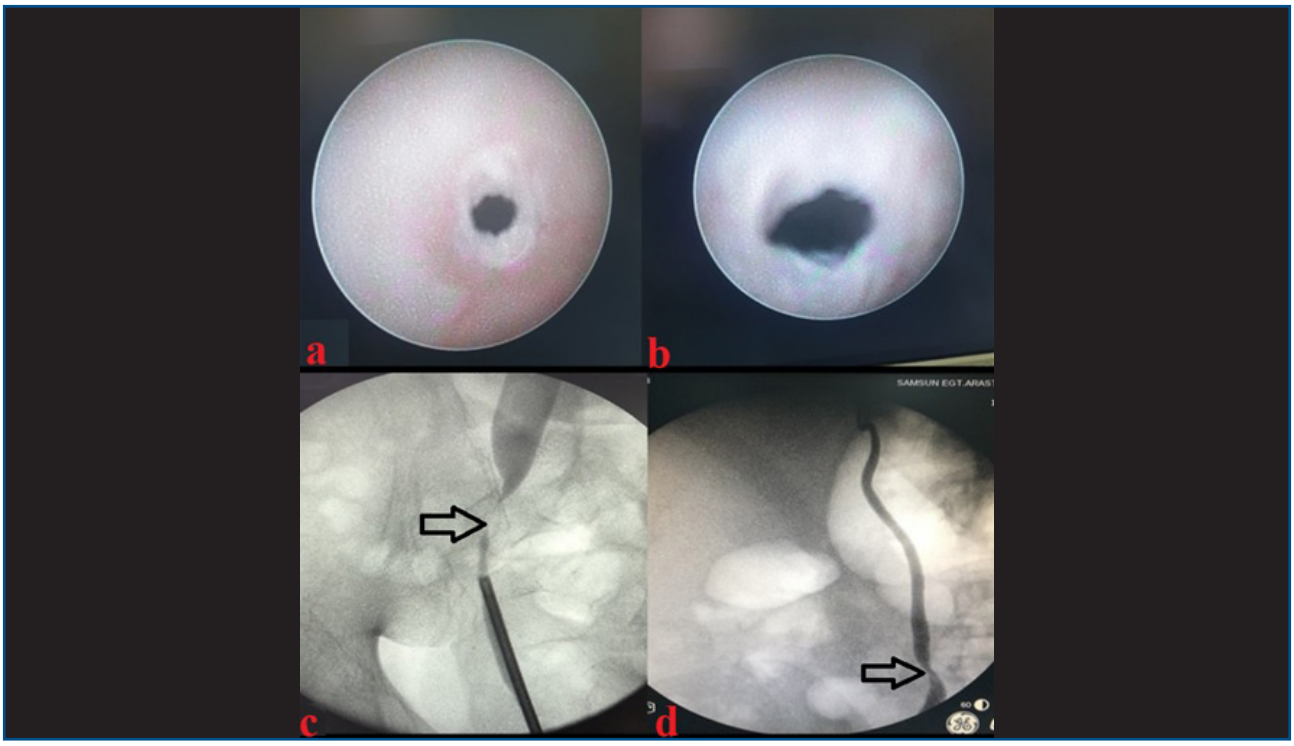

Figure 1. Diagnostic methods for ureteral stricture (a, b: Direct endoscopic visualization; c, d: Retrograde pyelography. Arrow: Stricture line)

Surgical Technique

Endoscopic upper urinary tract surgery was performed with the patient in the lithotomy position under general or spinal anesthesia using an 8 Fr rigid ureteroscope (4 Fr-8 Fr Single Channel Ureteroscope, Karl Storz, Germany). A hydrophilic guidewire was advanced to the renal collecting system under endoscopic control through the ureteral orifice. The ureteroscope was passed through the orifice using the hydrophilic guidewire with endoscopic assistance. RGP was performed in cases in which the lower and middle parts of the ureter could not be passed due to stricture. Ureteral stricture was diagnosed in patients with no or only partial passage of contrast material to the proximal part at RGP. An 8 Fr nephrostomy catheter was installed in patients with complete ureteral stricture, while a 4.8 or 6 Fr JJ stent was inserted in cases with partial contrast material passage and which were suitable for JJ stent placement. Patients with partial passage of contrast material observed at RGP but who were not suitable for JJ stent placement first underwent laser endoureterectomy (single flex holmium laser fiber, Dornier MedTech, Germany) or ureteral balloon dilatation using a 270 µm holmium YAG laser, after which a 4.8 Fr JJ stent was installed.

A difficult ureter was suspected if the rigid URS did not permit upward passage in the ureteral lumen or was unable to progress to the proximal part of the relatively narrow ureteral segment. The procedure continued in these cases with the application of active dilatation using a second guidewire or with balloon dilatation with an appropriate dilatator. If the URS could not be advanced proximally despite all these manipulations, passive dilatation was performed with the insertion of a 4.8 Fr JJ stent.

Statistical Analysis

The study data were analyzed on SPSS version 23.0 software (Statistical Package for Social Sciences - IBM Corp., Armonk, NY, USA). Categorical variables were presented as number and percentage, distributions were compared using the chi square test. The normality of distribution of numerical variables was examined using the Kolmogorov-Smirnov or Shapiro–Wilk tests. Normally distributed data were compared using Student's t test and were expressed as mean ± standard deviation. Non-normally distributed data were compared using the Mann-Whitney U test and were

expressed as median values (interquartile range, 25% - 75%). P values <0.05 were regarded as significant in statistical comparisons.

RESULTS

One hundred thirty patients, 86 (66.15%) of whom were men, were enrolled in the study. Men constituted 40 of the patients in Group 1 (61.5%) and 46 (70.8%) of those in Group 2 (p = 0.266). Mean ages were 49.89 ± 14.40 years in Group 1 and 48.92 ± 14.60 in Group 2 (p = 0.704). Diabetes mellitus was present in seven (10.8%) patients in Group 1 and 12 (18.5%) of those in Group 2 (p = 0.214). The patients' body mass indices were 24.71 ± 2.85 kg/m^2 in Group 1 and 24.07 ± 2.86 kg/m^2 in Group 2 (p = 0.204). Growth in preoperative urine culture was present in one (1.5%) in Group 1 and five (7.7%) in Group 2 (p = 0.095).

Histories of surgery with URS were present in 87.6% of the patients in Group 1, of RIRS in 6.2%, and of URS/RIRS + percutaneous nephrolithotomy in 6.2%. The equivalent figures in Group 2 were 72.3%, 21.5% and 6.2% (p = 0.038). In addition, 90.8% of the patients in Group 1 and 66.8% of those in Group 2 had undergone one endoscopic surgical procedure (p = 0.001). Histories of passage of kidney stones were present in 34 (52.3%) patients in Group 1 and 13 (20%) patients in Group 2 (p <0.001). Hydronephrosis was present in 67.7% of the patients in Group 1 and 50.8% of those in Group 2 (p = 0.05). No differences were observed between the groups in terms of the time elapsed since the latest operation, histories of shockwave lithotripsy, or serum creatinine values.

NLR values were 2.62 (0.75 - 9.18) in Group 1 and 2.29 (0.80 - 6.67) in Group 2 (p = 0,139). PLR values were 136.57 (55.02 - 475.45) in Group 1 and 118.66 (37.50 - 244.17) in Group 2 (p = 0.076). Although both NLR and PLR were higher in Group 1, that elevation was not statistically significant. The groups' socio-demographic, clinical, and laboratory data are summarized in Table 1.

Table 1. The groups' sociodemographic characteristics and clinical and laboratory data

Variables	Group 1 (n = 65)	Group 2 (n = 65)	p
Age (year, mean ± SD)	49.89 ± 14.40	48.92 ± 14.60	0.704
Female sex (n, %)	25 (%38.5)	19 (%29.2)	0.266
Comorbidity (n, %)			
Diabetes mellitus	7 (10.8%)	12 (18.5%)	0.214
Hypertension	25 (38.5%)	19 (29.2%)	0.266
Body mass index (kg/m^2, mean ± SD)	24.71 ± 2.85	24.07 ± 2.86	0.204
Type of surgery undergone (n,%)			
Ureterorenoscopy	57 (87.6%)	47 (72.3%)	0.038
Retrograde intrarenal surgery	4 (6.2%)	14 (21.5%)	
Others	4 (6.2%)	4 (6.2%)	
Number of operations performed (n, %)			
1	59 (90.8%)	43 (66,2%)	0.001
≥2	6 (9.2%)	22 (33.8%)	
Time elapsed since the latest operation (month)	48.43 (21-60)	43.83 (24-60)	0.907*
History of shock wave lithotripsy (n, %)	14 (21.5%)	16 (24.6%)	0.677
History of passing stones (n, %)	34 (52.3%)	13 (20%)	<0.001

Degree of hydronephrosis (n, %) **Grade 0** **Grade 1** **Grade 2** **Grade 3** **Grade 4**	21 (32.3%) 11 (%16.9) 25 (%38.5) 6 (%9.2) 2 (%3.1)	32 (49.2%) 18 (27.7%) 12 (18.5%) 3 (4.6%) 0 (0%)	0.05
Neutrophil/lymphocyte ratio	2.62 (1.72 -3.29)	2.29 (1.57 -2.72)	0.139*
Platelet/lymphocyte ratio	136.57 (99.41-154.39)	118.66 (91.50 -136.34)	0.076*
Creatinine (mg/dL)	0.98 (0.70-1.10)	0.97 (0.70-1.15)	0.515*

*Data presentation of median and interquartile range (IQR, 25th-75th percentile)

Abbreviation: SD, Standard deviation.

A 7 Fr ureterorenoscope was used in 44 (67.7%) in Group 1 and in 21 (32.3%) of those in Group 2. Only an 8 Fr ureterorenoscope was employed in the control group (Group 2). The ureterorenoscope could not be extended to the proximal ureter, despite having passed the narrow/difficult ureter segment in 23 (35.3%) patients in Group 1. The ureterorenoscope was unable to enter the proximal section from the narrow segment in the ureteral lumen in 42 (64.7%) patients. Complete ureteral stricture was present in three (4.7%) of these 42 patients. The characteristics of the stenotic region and operations of the patients in Group 1 are shown in Table 2.

Table 2. Specific characteristics in Group 1 patients

Variables	Number (n)	Percentage (%)
Stricture place		
Distal	37	56.9
Medial	12	18.5
Proximal	16	24.6
Stricture diagnosis method		
Retrograde pyelography	21	32.3
Endoscopic visualization	44	67.7
Operation		
JJ stent	32	49.2
Dilation with URS + JJ stent	23	35.4
Nephrostomy	4	6.2
Endoureterotomy	5	7.7
Balloon dilation	1	1.5
Continuation with URS		
No continuation from narrow segment to proximal	39	60.1
No proximal passage allowed	23	35.3
Complete ureteral stricture	3	4.6

Complications based on the Clavien-Dindo classification developed in 28 (43.1%) patients in Group 1 and 9 (13.8%) of those in Group 2. No significant difference was determined between the two groups in terms of general complication rates (p = 0.068). No complications greater than grade 3 occurred in any case. Detailed information concerning complications is shown in Table 3.

Table 3. Complications seen in the first 30 days according to the Clavien-Dindo classification

Complications (n, %)	Group 1 (n = 65)	Group 2 (n = 65)	p
Total (n, %)	28 (43.1%)	18 (27.7%)	0.068
Grade 1	18 (27.6%)	12 (18.5%)	
Mucosal damage	8	8	
Renal colic	2	2	
Hematuria	8	2	
Grade 2	9	5	
Fever	4	3	
Urinary tract infection	5	2	
Grade 3a	1	1	
JJ stent revision	1	1	

DISCUSSION

Ureteral stricture is a rare but highly morbid and increasingly common complication, the prevalence of which following URS, RIRS, or ureteral instrumentation is rising (11,12). The risk factors for the development of ureteral stricture include perforation due to direct trauma, transient ischemia associated with lengthy ureteroscope use, large-caliber instruments, stone impacted in the lumen, a lengthy operative time, and thermal trauma such as laser (13). Intraoperative ureteral stricture is a problematic and troubling phenomenon for the surgeon. Various simple markers are needed to determine the presence of ureteral stricture in patients who have previously undergone surgical interventions to the ureter. Since the inflammatory process represents the underlying pathophysiology of ureteral stricture, this study was based on the hypothesis that NLR and PLR values can constitute hematological markers in the prediction of such stricture. Since the inflammatory process underlies the physiopathology of ureteral stricture, the present study was conducted around the hypothesis that PLR and NLR values may represent useful hematological markers in predicting stricture. However, the results showed that these values were not appropriate markers for predicting this.

Irrespective of the underlying predisposing factor, inflammatory cells such as lymphocytes, neutrophils, and eosinophils initiate the inflammatory process by migrating to the region following ureteral mucosa injury. The inflammatory process is essential for tissue renewal but can also result in fibrosis instead of healing. Inflammatory cells activate the oval-shaped fibroblasts present in organs' interstitial spaces. The most basic function of fibroblasts is to produce a collagen-and elastin-rich extracellular matrix. Large quantities of collagen are produced due to excessive communication between inflammatory cells and fibroblasts. However, this collagen produced cannot be sufficiently vascularized, and this results in fibrosis, rather than normal healing. In addition, when excessive communication between lymphocytes and fibroblasts commences, lymphocytes increase the levels of type 2 collagen, while reducing those of type 1 and type 3 collagen. This alteration in collagen content results in fibrosis rather than normal healing (14). Since inflammatory cells play an important role in the development of ureteral stricture, it might be expected that elevation will occur in various inflammatory markers such as PLR and NLR in patients developing such stricture.

Previous studies have used NLR and PLR values in various different ureteral pathologies (15-18). One retrospective study investigated the efficacy of NLR in the spontaneous passage of ureteral stones smaller than 10 mm and reported a high probability of such passage in cases with NLR values smaller than 2.3. In addition, that study recommended early surgical intervention in cases with NLR values greater than 2.3 (15). Another similar study described both NLR and PLR values as effective biomarkers in the prediction of spontaneous passage (16). Another study with the same design as those two papers, but this time prospective and multi-center in nature, described NLR values as a successful marker for spontaneous passage (17). A retrospective, 557-patient study investigating the relationship between NLR values and early JJ stent decompression for the treatment of renal colic developing in association with ureteral stone

observed a close correlation between high NLR values and prolonged hospitalization and high mortality. Those authors recommended emergency JJ stent insertion in patients with NLR values exceeding 2.1 (18). A study examining the relationship between unsuccessful ureteral sheath placement and inflammation reported an association between high PLR values and sheath insertion failure (19). In contrast to all these studies describing NLR and PLR as successful biomarkers in ureteral diseases, NLR and PLR values did not emerge as predictive markers of ureteral stricture in the present study. This may be attributable to NLR or PLR not representing adequate markers for determining the risk of ureteral stricture and/or difficult ureter or to a larger number of patients being needed in our study.

There are a number of limitations to this research, the most important of which is that it was not conducted as a randomized, controlled study. Its single-center nature represents another significant limitation. In addition, due to a fear of difficulty in reaching the target patient number, patients with difficult/tight ureter were enrolled in addition to those with ureteral stricture. Although both conditions emerge due to similar predisposing factors, they are clinically distinct entities, and NLR or PLR values may therefore differ between them. In addition, factors such as undiagnosed diabetes mellitus, hypertension, a sedentary lifestyle, smoking, and alcohol consumption can affect NLR and PLR values. Unfortunately, these patients were not excluded from this study. For all these reasons, our findings therefore need to be supported by further multi-center, randomized, controlled studies involving larger patient numbers. The particular strengths of this study include its prospective character, its representing one of the first studies involving the prediction of ureteral stricture, and the strict patient selection criteria.

CONCLUSION

NLR and PLR do not represent effective biomarkers in predicting the risk of ureteral stricture or difficult ureter developing following endoscopic upper urinary tract surgery.

Conflict of Interest: There is no conflict of interest in this study.

Ethics Committee: This study was approved by Ondokuz Mayıs University Clinical Research Ethics Committee. Date: 28.04.2022 Number: 2022/235.

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