

Comparison of the Effectiveness of Inflammatory Parameters in Predicting Recurrence After Internal Urethrotomy: Retrospective Cross-Sectional Study

İnflamatuvar Parametrelerin İnternal Üretrotomi Sonrası Nüksü Öngörmedeki Etkinliklerinin Karşılaştırılması: Retrospektif Kesitsel Çalışma

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ABSTRACT Objective: To date, there is no consensus on which inflammatory biomarker is the best prognostic indicator and most clinically valuable in patients with recurrence after internal urethrotomy (IU). In this study our aim was to compare the ability of neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and systemic inflammatory index (SII) to predict recurrence after IU. **Material and Methods:** The data of 230 patients in the study were scanned, and age, stricture length, etiology, time of recurrence, NLR, PLR and SII values were recorded. The primary endpoint of the study was the ability of NLR, PLR and SII to predict recurrence and the secondary endpoint was to determine whether these three parameters were superior to each other in predicting early recurrence. **Results:** Our results showed that the optimal cut-off values of the NLR, the PLR and the SII for the prediction of recurrence were 1.4, 101 and 350, respectively. Using these cut-off values, SII, NLR and PLR predicted recurrence with a sensitivity of 89.2%, 75.5% and 54.9% respectively. While the positive predictive values and negative predictive values for SII were 65.3% and 89.7% respectively, these parameters were 70.4 and 80.2, 51.9 and 62.3 for NLR and PLR respectively. **Conclusion:** The SII is superior to the other hematological markers of inflammation.

Keywords: Urethral stricture; recurrence; inflammation; neutrophils; platelet count

ÖZET Amaç: Bugüne kadar internal üretrotomi (İÜ) sonrası nüks gelişen hastalarda hangi inflamatuvar biyobelirtecin en iyi prognostik gösterge olduğu ve klinik olarak en değerli olduğu konusunda bir fikir birliği yoktur. Bu çalışmada amacımız, nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR) ve sistemik inflamatuvar indeksin (Sİİ) İÜ sonrası nüksü öngörme başarısını karşılaştırmaktır. **Gereç ve Yöntemler:** Çalışmaya alınan 230 hastanın verileri taranarak yaş, striktür uzunluğu, etiyoloji, nüks zamanı, NLR, PLR ve Sİİ değerleri kaydedildi. Çalışmanın birincil sonlanım noktası NLR, PLR ve Sİİ'nin nüksü öngörebilme başarısı, ikincil sonlanım noktası ise bu üç parametrenin erken nüksü öngörmede birbirlerine üstünlüklerinin olup olmadığının belirlenmesiydi. **Bulgular:** Sonuçlarımız nüksü öngörmek için NLR, PLR ve Sİİ'nin optimal kesim değerlerinin sırasıyla 1,4, 101 ve 350 olduğunu göstermiştir. Bu kesim değerleri kullanıldığında, Sİİ, NLR ve PLR nüksü sırasıyla %89,2, %75,5 ve %54,9 duyarlılıkla öngörmüştür. Sİİ için pozitif prediktif değerler ve negatif prediktif değerler sırasıyla %65,3 ve %89,7 iken, bu parametreler NLR ve PLR için sırasıyla 70,4 ve 80,2, 51,9 ve 62,3 idi. **Sonuç:** Sİİ, inflamasyonun diğer hematolojik belirteçlerinden daha üstündür.

Anahtar Kelimeler: Üretra darlığı; yineleme; inflamasyon; nötrofiller; trombosit sayma

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Internal urethrotomy (IU) is recommended in the European Association of Urology guidelines for urethral stricture (US) in primary, non-obliterative bulbar strictures of less than 2 cm in length.¹ Although IU is a useful and minimally invasive procedure with a high short-term success rate of 80-100%, the recurrence rate is 30-60% 2 years after the first IU and increases to 50-100% after the second IU.² Recurrence after treatment for US is a problem in daily urology practice, because it reduces quality of life and is an additional financial burden.³ It is thought that IU causes additional scarring in recurrent USs, which may adversely affect the length and severity of the stricture. The reported long-term success rate is 55% to 60% after the first IU, decreasing with repeated urethrotomies to 0-40% at 48 months after the second urethrotomy and 0 at 24 months after the third urethrotomy.⁴ Therefore, open urethroplasty has a higher success rate and lower chance of recurrence than IU in patients with recurrent USs, long USs or dense periurethral fibrous tissue.⁵ Success rates of up to 90% have been reported with anastomotic repair or free graft urethroplasty.^{2,6} It is well known that the success rate of a subsequent urethroplasty is reduced as a result of repeated urethrotomies.^{7,8} For this reason, it is important that urethroplasty is carried out without delay. It is not known which patients will develop a relapse after IU. There is currently no predictive marker. Therefore, there is a growing body of research into predicting recurrence.

The pathology of US disease is still unclear, but it is thought that inflammatory changes in the urethral epithelium and subepithelial spongy tissue lead to scarring and fibrotic narrowing of the urethra.⁹ In this context, inflammatory markers such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and systemic inflammatory index (SII) have been investigated to predict recurrence after IU.¹⁰⁻¹² To date, there is no consensus on which inflammatory biomarker is the best prognostic indicator and most clinically valuable in patients with recurrence.

In light of this information, our aim was to compare the ability of NLR, PLR and SII to predict recurrence after IU.

MATERIAL AND METHODS

The study was designed as a single-centre retrospective study. Patients who underwent primary IU for US less than 2 cm, bulbar localization were included in the study. The data of 230 patients in the study were scanned, and age, stricture length, etiology, time of recurrence, NLR, PLR and SII values were recorded. Stricture lengths were measured according to pre-operative retrograde urethrograms. Blood samples were taken from all patients three days before urethrotomy. The SII was calculated using the formula $\text{platelets} \times (\text{neutrophils}/\text{lymphocytes})$.

Patients with penile or posterior US, stricture length greater than 2 cm, history of IU or urethroplasty, history of surgery or radiotherapy for prostate cancer, patients who had received radiotherapy to the pelvic region for causes other than urinary tract disease, history of pelvic fracture, hypothalamic or pituitary endocrine disorders, recent blood transfusions, active autoimmune disease, chronic inflammatory or haematological disease, failure to attend regular check-ups and growth in preoperative urine culture were excluded. IU was applied to all patients using standard technique. The foley catheter was removed from all patients on the fifth day.

All patients were evaluated every 3 months for the first postoperative year and every 6 months thereafter. Uroflowmetry was performed to assess strictures. Urethroscopy was performed if patients complained of voiding difficulties and the maximum flow rate (Qmax) was <10 mL/s. Urethrography was planned if urethroscopy showed luminal stricture. If USs were present, they were considered recurrent strictures and IU was performed a second time. The procedure was considered successful if the patient did not complain of voiding difficulties and Qmax was >12 mL/s.

Patients were divided into three groups to study the effect of parameters on recurrence time. Patients with recurrence in the first three months were defined as Group 1, patients with recurrence between 3-12 months were defined as Group 2 and patients with recurrence after 12 months were defined as Group 3.

The primary endpoint of the study was the ability of NLR, PLR and SII to predict recurrence and

the secondary endpoint was to determine whether these three parameters were superior to each other in predicting early recurrence.

STATISTICAL ANALYSES

The analyzes were made via IBM SPSS statistics 27.0 (IBM Corp., Armonk, NY). To examine numeric variables' normality, we used the Shapiro-Wilk test. The numerical variables with a normal distribution were expressed as mean±standard deviation. Data without a normal distribution were presented as median (min-max). Categorical variables were presented as number and percent. T-test, Mann-Whitney U test were used for statistical analysis. Chi-squared was used to determine negative and positive predictive values (PPV) and the effect of differences in etiology on recurrence. ROC analysis was used to determine the predictive values of NLR, PLR and SII cut-off values for recurrence. Overall survival curves for recurrence and non-recurrence were calculated using Kaplan-Meier analysis and compared using the log-rank test. Cox regression analysis was used to determine which values were associated with recurrence after IU. One-way ANOVA and Kruskal-Wallis tests were used to compare the mean differences of SII,

NLR and PLR between three groups according to recurrence time. Subgroups were compared using the Tukey post hoc test and Mann-Whitney U test. p values <0.05 were considered statistically significant.

ETHICS APPROVAL

The study was compatible with The Helsinki Declaration for laws and regulations, good clinical practice, and ethical principles and was approved by Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee (no: E-48670771-514.10/02.07.2021).

RESULTS

This study involving 230 participants, 102 patients experienced a recurrence while the remaining 128 did not. The stricture recurrence rate was recorded as 44.3% at the 5-year follow-up. Causes of stricture include idiopathic, transurethral resection and having been catheterised in the past for any reason. While the mean age in the group with a recurrence was 63.9±3.06 years, the mean age in the group without a recurrence was 63.2±2.8 years. The difference between groups were not statistically significant (p=0.196). There was a statistically significant difference between stricture length, SII, NLR and PLR

TABLE 1: Characteristic features of patients.

Parameters	Recurrence		p value
	Yes	No	
Age (year)	63.9±3.06	63.2±2.8	0.196 ^a
Platelet (10 ³ /uL)	242 (133-475)	250 (133-350)	0.474 ^b
Neutrophil(10 ³ /uL)	4 (1.4-9.9)	3.45 (1.7-5.2)	0.001 ^{b*}
Leukocyte (10 ³ /uL)	2.5 (0.9-6.9)	2.9 (1.3-4)	0.028 ^{b*}
SII	400.5±44.2	315.8±43	0.001 ^{a*}
NLR	1.6 (0.9-3.3)	1.2 (1-2.4)	0.001 ^{b*}
PLR	102.7 (46.1-280)	94.6 (56.9-192.3)	0.028 ^{b*}
Length (mm)	15 (10-20)	10 (10-20)	0.001 ^{b*}
Transurethral intervention n (%)	44 (42.3)	60 (57.7)	
Catheter application n (%)	47 (43.1)	62 (56.9)	0.213 ^c
Idiopathic	11 (64.7)	6 (35.3)	
SII≥350 n (%)	91 (83.5)	18 (16.5)	
SII<350 n (%)	11 (9.1)	110 (90.9)	0.001 ^{c*}
NLR≥1.4	77 (74)	27 (26)	
NLR<1.4	25 (19.8)	101 (80.2)	0.001 ^{c*}
PLR≥101	56 (51.9)	52 (48.1)	
PLR<101	46 (37.7)	76 (62.3)	0.021 ^{c*}

^aT-test; ^bMann-Whitney U test; ^cChi-square test; *Significant (p<0.05); SII: Systemic inflammatory index; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio.

in the recurrence and non-recurrence groups (p=0.001, 0.001, 0.001 and 0.028 respectively), but no difference was found between etiologies (p=0.213) (Table 1).

The ROC curves were used to select the optimal cut-off values for NLR, PLR and SII for the prediction of recurrence. Our results showed that the optimal cut-off values of the NLR, the PLR and the SII for the prediction of recurrence were 1.4, 101 and 350, respectively. Using these cut-off values, SII, NLR and PLR predicted recurrence with a sensitivity of 89.2%, 75.5% and 54.9% respectively (Figure 1). This result taught us that SII is superior to the other parameters.

While the PPV and negative predictive values (NPV) for SII were 65.3% and 89.7% respectively, these parameters were 70.4 and 80.2, 51.9 and 62.3 for NLR and PLR respectively (Table 1). For these values, too, the SII was found to be superior to the other parameters.

SII, NLR, PLR and stricture length, which were thought to affect recurrence and showed significant differences among groups, were assessed for their predictive power of recurrence using multivariate Cox regression analysis. As a result of this analysis, SII was found to be more effective in predicting recurrence (Table 2).

The ability of these parameters to predict recurrence time was assessed using one-way ANOVA and

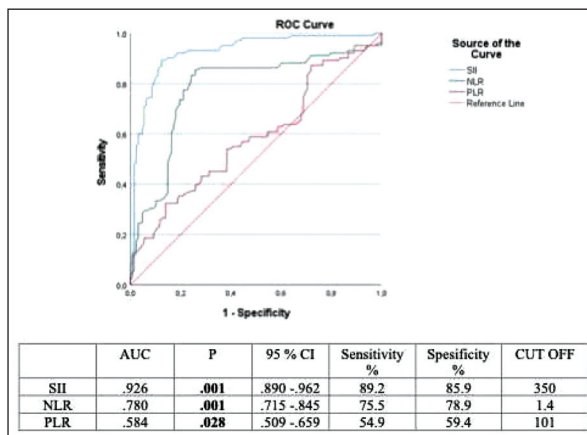


FIGURE 1: Determination of the optimal cut off values. SII: Systemic inflammatory index; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio.

TABLE 2: Results of multivariate Cox regression analyses.

Recurrence	B	P	Exp (B)	95% CI
SII	2.599	0.001	13.452	6.888-26.272
NLR	0.572	0.023	1.772	1.081-2.905
PLR	0.423	0.039	1.527	1.021-2.283
Length	0.080	0.003	1.083	1.028-1.141

SII: Systemic inflammatory index; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio.

TABLE 3: Comparison of parameters between within the three groups.

	Groups of recurrence		
	Group 1	Group 2	Group 3
SII	430.42±32.5 ^{a,*}	423.85±19.3	391.97±44.6
NLR	1.5 (0.9-2.3)**	1.5 (0.9-2.4)**	1.6 (1-3.3)**
PLR	102.5 (78.6-192.3)**	117.6 (85.5-280)**	102.5 (46.1-280)**

^aSignificantly different from Group 3, (p<0.05); *One way ANOVA, post hoc Tukey test; **Kruskal-Wallis test, Mann-Whitney U test; SII: Systemic inflammatory index; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio.

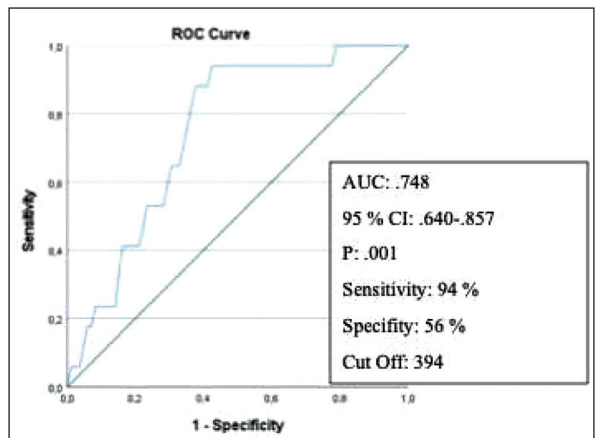


FIGURE 2: Determination of the optimal cut off value for recurrence within first three month.

Kruskal-Wallis tests. While there are differences between the groups for SII, no differences were found for other parameters. This result was thought high SII can determine recurrence on the first three months (Table 3). The cut-off value of 394 for recurrence in the first three months was found using ROC analysis. Using this score, we found that the SII predicted recurrence in the first three months with 94% sensitivity (Figure 2).

DISCUSSION

The natural history of US is unclear, but it is well known to be recurrent. In recurrent USs, IU is thought to cause additional scarring, which may negatively affect the length and severity of the stricture. Therefore, open urethroplasty has a higher success rate and lower risk of recurrence than IU in patients with recurrent USs, long USs or dense periurethral fibrous tissue.⁵ Therefore, in order not to delay urethroplasty, it is very important to identify patients who may have a recurrence. Studies show that inflammatory cells have important effects on recurrence, and systemic inflammatory markers may be useful in predicting recurrence after IU. Therefore, more convenient and dynamic biomarkers should be identified to predict recurrence rates in patients treated with IU.

In recent years, there are studies in the literature showing that hematological parameters can be used as the predictive markers in predicting recurrence in US. In a retrospective study, Urkmez et al. evaluated the preoperative NLR and postoperative recurrence rates in 512 patients who underwent IU.¹⁰ According to the results of this study, NLR was found to be a useful predictor for possible recurrences before the operation, and choosing open urethroplasty operation instead of IU in patients with high NLR increased the success rate.¹¹ Another study investigated the predictive value of the SII for the recurrence of US in patients undergoing IU and showed that a high SII level correlated with recurrence.¹²

SII is a new and promising inflammatory biomarker associated with poor outcomes in patients with genitourinary cancers.¹³⁻¹⁵ SII shows inflammation is more balanced, and its predictive value is higher than PLR and NLR.¹⁵ The results of the present study support this. In this study showed that a high SII was more effective marker in predicting recurrence. When the cut off value of 350 was used, the sensitivity was 89.2 and the specificity was 85.9. It was also found that, compared with the other parameters, a high SII (>350) was associated with a 13-fold increased risk of recurrence. As shown in Figure 3, patients with an SII above 350 have a shorter recurrence-free survival than those with an SII below 350. Similar as a result of the log rank test, the average

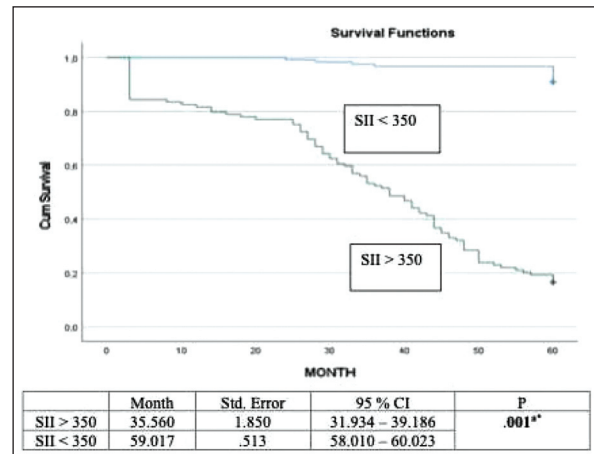


FIGURE 3: Kaplan-Meier survival analyses according to SII optimal cut off values.

*Log-Rank Test; *Significant; SII: Systemic inflammatory index; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio.

time to recurrence in the $SII \geq 350$ group was 35.5 months, while the average time to recurrence in the $SII < 350$ group was 59 months.

Time to recurrence is an important parameter in US.¹⁶ Most reports show that if recurrence occurs it is most likely to do so within 3-12 months.¹⁷⁻¹⁹ A previous study by Heyns et al. showed that if there was no stricture recurrence at 3 months after the first IU, 60% of patients would remain stricture-free at 48 months. If a recurrence occurred at 3 months and a second IU was performed, there was virtually no chance of the patient being stricture-free at 48 months, but if a recurrence occurred ≥ 6 months after the first IU, there was a 40% chance of long-term cure with a second IU.⁴ In our study, 24 patients (23.5%) had a recurrence in the first year. Of these, 17 (16.6%) patients had a recurrence in the first three months. As shown in Table 3, the results of a one way ANOVA test showed that there were significant differences between Group 1 and Group 3 in terms of SII. But no similar relationship found for NLR and PLR. It is important to see that the SII is effective in detecting early recurrence. This is perhaps the most important finding of the study.

This study has limitations due to it being conducted at one centre and retrospective in nature. As the study is retrospective, there may be selection bias resulting in the need for careful evaluation of the conclusions. However, we believe that this study, which will be the first in the literature, is important because there has been no similar comparative study to date

and its predictive value has not been investigated, especially in early recurrences.

CONCLUSION

Recurrence after IU can be predicted by SII, NLR and PLR but especially in terms of predicting early recurrence, the SII is superior to the other hematological markers of inflammation. If SII values are high, especially more than 394, then it may be reasonable to option for urethroplasty instead of a second IU in the event of recurrent stricture. Larger prospective studies will need to be performed to confirm these preliminary results.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct con-

nection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Ahmet Boylu, Kahraman Aksoy; **Design:** Levent Özcan; **Control/Supervision:** Emre Can Polat; **Data Collection and/or Processing:** Mustafa Erkoç; **Analysis and/or Interpretation:** Eyyüp Daniş; **Literature Review:** Muammer Bozkurt; **Writing the Article:** Mehmet Gökhan Çulha; **Critical Review:** Alper Ötünçtemur.

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