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The Role of Biochemical and Hematological Parameters in Urethral Stricture Recurrence: Inflammation Indexes and De Ritis Rate

Biyokimyasal ve Hematolojik Parametrelerin Üretra Darlığı Rekürrensindeki Rolü: De Ritis Oranı ve Enflamasyon İndeksleri

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ABSTRACT

Objective: This study investigates the role of hematological inflammation markers in predicting urethral stricture recurrence. Specifically, it examines the prognostic significance of the systemic immune-inflammation index (SII) and De Ritis ratio [aspartate aminotransferase (AST)/alanine aminotransferase ALT)] in recurrence risk.

Methods: This retrospective cohort study included 51 patients who underwent direct visual internal urethrotomy between 2019 and 2023. Patients were divided into recurrence and non-recurrence groups. Clinical data, hematological, and biochemical parameters were analyzed, and the prognostic value of SII and De Ritis ratio (AST/ALT) was assessed using statistical methods.

Results: SII was identified as a significant predictor of recurrence risk (area under the curve=0.689, p=0.023). SII values exceeding 591.42 were associated with a fourfold increase in recurrence risk (odds ratio=4.0, 95% confidence interval: 1.36-11.74, p<0.05). In contrast, the De Ritis ratio (AST/ALT) was not correlated with recurrence (p=0.924). Additionally, stricture length >2 cm was significantly associated with higher recurrence risk (p=0.024).

Conclusion: SII appears to be a valuable biomarker for predicting urethral stricture recurrence. Integrating SII into clinical practice could facilitate early identification of high-risk patients and enable the development of personalized treatment strategies. For patients with high SII values, open urethroplasty may be preferable to repeated endoscopic procedures. However, prospective multicenter studies are needed to validate these findings in larger patient populations. Additionally, machine learning-based prediction models may enhance the accuracy of recurrence risk assessment.

Keywords: Urethral stricture, systemic immuno-inflammation index, De Ritis ratio

ÖZ

Amaç: Bu çalışmada, üretral darlık rekürrensinin öngörülmesinde hematolojik enflamasyon belirteçlerinin rolü incelenmiştir. Özellikle sistemik immün-inflamasyon indeksi (Sİİ) ve De Ritis oranının [aspartat aminotransferaz (AST)/alanin aminotransferaz (ALT)] rekürrens riski üzerindeki etkileri araştırılmıştır.

Yöntem: Bu retrospektif kohort çalışmasına, 2019-2024 yılları arasında doğrudan görüşlü iç üretrotomi uygulanan 51 hasta dahil edilmiştir. Hastalar rekürrens gelişenler ve gelişmeyenler olarak iki gruba ayrılmıştır. Klinik veriler, hematolojik ve biyokimyasal parametreler incelenmiş; Sİİ ve De Ritis oranının (AST/ALT) prognostik değeri istatistiksel analizlerle değerlendirilmiştir.

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Bulgular: Rekürrens riski için Sİİ'nin anlamlı bir belirteç olduğu saptanmıştır (eğri altında kalan alan=0,689, p=0,023). 591,42'nin üzerindeki Sİİ değerleri, üretral darlık rekürrens riskini 4 kat artırmıştır (olasılık oranı=4,0,, 95% güven aralığı: 1,36-11,74, p<0,05). Buna karşılık, De Ritis oranının (AST/ALT) rekürrens ile ilişkili olmadığı bulunmuştur (p=0,924). 2 cm'den uzun darlıkların rekürrens riski belirgin şekilde daha yüksektir (p=0,024).

Sonuç: Sİİ, üretral darlık rekürrensini öngörmede değerli bir biyomarker olarak öne çıkmaktadır. Klinik pratiğe entegrasyonu, yüksek riskli hastaların erken tespit edilmesine ve bireyselleştirilmiş tedavi stratejilerinin geliştirilmesine katkı sağlayabilir. Tekrarlayan endoskopik işlemler yerine açık üretroplasti, yüksek SII değerleri olan hastalar için daha uygun bir seçenek olabilir. Ancak, bu bulguların daha geniş hasta gruplarında doğrulanması için ileriye dönük çok merkezli çalışmalara ihtiyaç vardır. Ayrıca, yapay zeka tabanlı tahmin modellerinin kullanılması, rekürrens öngörüsünü daha hassas hâle getirebilir.

Anahtar Kelimeler: Üretra darlığı, sistemik immün-inflamasyon indeksi, De Ritis oranı

INTRODUCTION

Urethral strictures (US) are medical conditions resulting from fibrotic changes in the urethral epithelium and corpus spongiosum. These changes can lead to lower urinary tract symptoms, posing a significant clinical concern for both patients and healthcare providers. Urethral lumen narrowing may occur due to trauma, infection, inflammation, or surgical interventions. The high recurrence rate of strictures substantially impacts patients'quality of life.[1]

Inflammation plays a crucial role in the pathogenesis of US. Chronic inflammatory processes can lead to stenosis by damaging the urethral mucosa, promoting connective tissue proliferation, and forming scar tissue. The complex interactions among various cellular components-such as neutrophils, lymphocytes, and platelets-are believed to contribute significantly to stricture recurrence.[2] However, the specific biological markers associated with this inflammatory process remain insufficiently understood.

US predominantly affect men, with a prevalence of approximately 0.6%. The associated healthcare costs exceed $200 million annually in direct expenditures.[3] Patients typically present with symptoms such as dysuria (painful urination), pollakiuria (frequent urination), and reduced urine flow. In advanced stages, US can lead to severe complications, including urinary retention and recurrent urinary tract infections.[4]

The management of US depends on various factors, including the length, location, and underlying cause of the stricture. One widely used treatment modality is endoscopic intervention, favored for its cost-effectiveness, minimally invasive nature, and reproducibility. Among these procedures, direct visual internal urethrotomy (DVIU) is particularly notable.[5] However, the high recurrence rates following DVIU highlight the need for new prognostic markers to improve patient outcomes.

Recent research has focused on hematological inflammation indices to enhance our understanding of US and improve their clinical management. Key biomarkers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and De Ritis ratio [aspartate aminotransferase (AST)/alanine aminotransferase (ALT)] have emerged as potential indicators of inflammation's role in these pathophysiological processes.[6,7]

Studies have explored the significance of inflammation indices in predicting the prognosis of various urological diseases. Specifically, NLR and SII have been investigated in relation to cardiovascular diseases, cancer, and chronic inflammatory conditions.[8] However, their impact on urethral stricture recurrence risk remains insufficiently explored.[9]

Although these biomarkers are thought to correlate with stricture severity, recurrence risk, and treatment response, they must be considered alongside other clinical and radiological findings. This study aims to assess whether the De Ritis ratio (AST/ALT) and SII can predict urethral stricture recurrence by analyzing clinical preoperative data from patients undergoing single or multiple DVIU procedures. Our findings may provide valuable insights for developing personalized treatment strategies in urethral stricture management.

METHODS

This retrospective cohort study examines the clinical outcomes of 51 patients who underwent DVIU at the Urology Clinic of İzmir Katip Çelebi University Atatürk Training and Research Hospital, between 2019 and 2024. Among them, 21 patients underwent a single DVIU, while 30 patients required multiple DVIU procedures. Data were meticulously collected from medical records within the urology service and outpatient clinic. The study was approved by the İzmir Katip Çelebi University Health Research Ethics Committee (decision number: 0063, date: 13.02.2025) and was conducted in accordance with the Declaration of Helsinki.

The study included male patients aged 18 years or older who had previously received treatment for urethral stricture. However, the following exclusion criteria were applied: patients with incomplete medical records, those diagnosed with malignancies, individuals with uncontrolled diabetes mellitus (DM), and patients with hematological, liver, or kidney dysfunction. Additionally, patients who

had received blood transfusions or had undergone open urethral surgery were excluded from the study.

The collected patient data included both demographic and clinical information. Demographic variables included age, comorbidities, and smoking status, while clinical data covered stenosis recurrence, duration of recurrence, postoperative catheterization time, and follow-up period.

Additionally, a complete blood count and biochemical analyses were conducted as part of the preoperative anesthesia evaluation. These included neutrophil and lymphocyte counts, hematocrit (HTC) levels, albumin levels, NLR, De Ritis ratio (AST/ALT), and SII. The SII was calculated using the formula: SII = (neutrophil count × platelet count)/lymphocyte count. All laboratory tests were performed using standardized methods in the hospital's laboratory.

Preoperative evaluation of US was performed using retrograde urethrography. The frequency and duration of stricture recurrence were recorded based on follow-up uroflowmetry and cystoscopy results. Recurrence duration was defined as the time until either the first clinical signs appeared (including symptoms and uroflowmetry findings) after DVIU, or when a repeat DVIU became necessary. Patients were monitored through clinical evaluations and uroflowmetry every three months during the first year post-DVIU, and every six months in the subsequent two years.

Statistical Analysis

All analyses were carried out using IBM SPSS Statistics 27 (Statistical Package for the Social Sciences) software. Before conducting the statistical analyses, the distribution of the data was assessed, and non-parametric tests were selected for use when the data did not conform to a normal distribution. The Mann-Whitney U test was employed for group comparisons. For the analysis of categorical variables, the chi-square (χ^2) test and Fisher's exact test were utilized. Furthermore, the receiver operating characteristic analysis was conducted to evaluate the discriminatory power of continuous variables, with the area under the curve (AUC) calculated accordingly. Descriptive statistics are presented as mean ± standard deviation or mean±standard error, depending on the specific type of variable. A significance level of $p<0.05$ was established for all statistical tests.

RESULTS

A total of 51 patients were included in the study. The mean age was 63.7±2.5 years in the non-recurrence group and 64.6±2.7 years in the recurrence group. No significant difference in age was observed between the two groups (p>0.05).Smoking prevalence was 66.7% in the non-recurrence group and 76.7% in the recurrence group; however, this difference was not statistically significant. The mean time to recurrence was 24.6±8.4 months. The follow-up period was 15.3±1.9 months (range: 3-32 months) for non-recurrent cases, while it was 25±4.6 months (range: 1-120 months) in recurrent cases (Table 1).

The prevalence of hypertension (HT), DM, and coronary artery disease (CAD) did not differ significantly between the recurrence and non-recurrence groups. HT prevalence was 47.6% in the non-recurrence group and 53.3% in the recurrence group. DM incidence was 28.6% in the non-recurrence group and 20% in the recurrence group. CAD was observed in 4.8% of non-recurrent cases, while it affected 26.7% of recurrent cases (Table 1). The mean postoperative catheterization duration was 6.76±0.3 days in the non-recurrence group and 7.37±0.2 days in the recurrence group. Notably, patients with a stricture length >2 cm had a significantly higher risk of recurrence (p=0.024).

Of the non-recurrence group, 59.1% of patients had a stricture length <2 cm, whereas of the recurrence group,

Table 1. Demographic data (non-recurrence and recurrence groups)

	No recurrence (N) (Mean±SD)	**Recurrence (N) (Mean±SD)**	**p value**
Age (years)	63.7±2.5	64.6±2.7	p>0.05
Smoking (%)	66.7%	76.7%	
Stenosis recurrence time (months)	-	24.6±8.4	
Follow-up period (months)	15.3±1.9 (3-32)	25±4.6 (1-120)	
Hypertension (%)	10 (47.6%)	16 (53.3%)	
Diabetes (%)	6 (28.6%)	6 (20.0%)	
Coronary artery disease (%)	1 (4.8%)	8 (26.7%)	
Post-operative catheter duratiom (days)	6.76±0.3	7.37±0.2	
Stricture length <2 cm (%)	13 (59.1%)	9 (40.9%)	**p=0.024**
Stricture length >2 cm (%)	8 (27.6%)	21 (72.4%)	

SD: Standard deviation

72.4% had a stricture length >2 cm (Table 1). HTC levels were 40.8±0.69 in both groups and showed no significant association with recurrence (p>0.05). Additionally, AST and ALT levels were comparable between groups (p>0.05). No significant differences were found in neutrophil, platelet, lymphocyte, or monocyte levels (Table 2).

The De Ritis ratio (AST/ALT) was not a significant predictor of urethral stricture recurrence (AUC=0.508, p=0.924). In contrast, SII was a significant predictor of recurrence [AUC=0.689, 95% confidence interval (CI): 0.541-0.837, p=0.023]. The optimal SII cut-off was 591.42. Patients with SII >591.42 had a fourfold increased risk of recurrence (odds ratio=4.0, 95% CI: 1.36-11.74, p<0.05) (Figure 1).

No significant association was found between smoking, DM, HT, CAD, and stricture recurrence risk (p>0.05). However, stricture length >2 cm was significantly associated with recurrence (p=0.024).

DISCUSSION

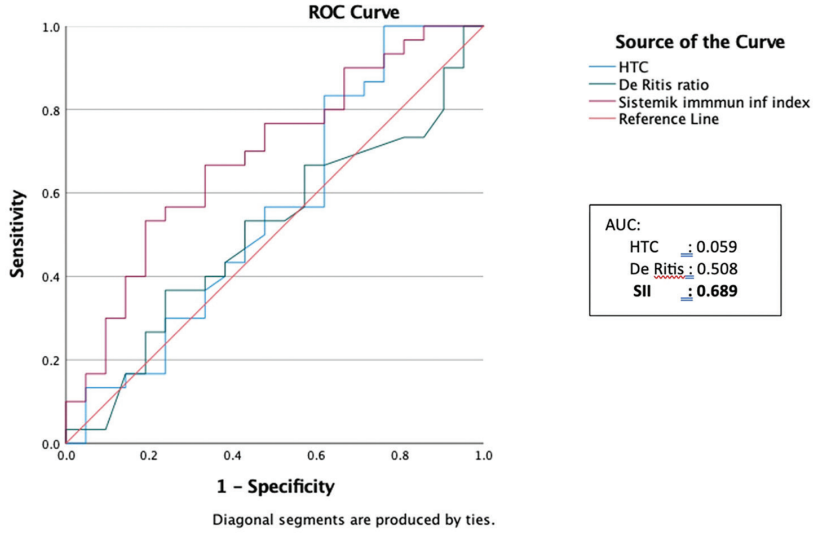
US is a chronic condition characterized by inflammation and spongiofibrosis, posing a significant clinical challenge in urology due to its high recurrence rates.[1] In recent years, interest in hematological inflammation indices has increased, particularly for predicting recurrence risk and optimizing treatment strategies.[7]

This study aimed to evaluate whether specific inflammatory markers could predict urethral stricture recurrence. Our findings indicate that SII is a strong predictor of recurrence risk (AUC=0.689, p=0.023). Notably, patients with SII >591 had a markedly higher recurrence

Table 2. Laboratory data (non-recurrence and recurrence groups)

	No recurrence (Mean±SD)	Recurrence (Mean±SD)	p value
HTC (%)	40.8±0.69	40.8±0.69	p>0.05
ALT (U/L)	17.4±1.0	17.4±1.0	
AST (U/L)	19.2±5.81	19.2±5.81	
Neutrophil (x10^9/L)	5.67±2.68	5.67±2.68	
Platelet (x10^9/L)	270±82.1	270±82.1	
Lymphocyte (x10^9/L)	1.99±0.73	1.99±0.73	
Monocyte (x10^9/L)	0.707±0.467	0.707±0.467	

SD: Standard deviation; HTC: Hematocrit, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase



	Cut-Off	Sensitivity	Specificity	Area	OR	95% Confidence Interval	p
SII	591.42	%67	%66	0.689	4.0	1.36 – 11.74	0.023

Figure 1. Sensitivity, specificity and ROC curve analysis of SII, De Ritis and HTC

ROC: Receiver operating characteristic; AUC: Area under the curve; HTC: Hematocrit; OR: Odds ratio; SII: Systemic immune-inflammation index

risk. This result aligns with previous studies exploring the link between inflammation and fibrosis development.[7]

A large-scale study by Özsoy et al.[7] (703 patients) identified a clear association between SII and urethral stricture recurrence. Their findings suggest that SII may serve as a reliable biomarker for predicting recurrence.

Similarly, a study by Urkmez et al.[8] found a strong correlation between NLR and urethral stricture recurrence. Our results further reinforce the potential role of inflammatory biomarkers in predicting recurrence risk.

A study (208 patients) by Tokuc et al.[10] aimed to develop a preoperative method for predicting primary urethroplasty success. Their innovative approach integrates machine learning algorithms with inflammation indices such as NLR, PLR, SII, and pan-immune-inflammation values. These findings represent a notable advancement in clinical practice and provide promising opportunities for the development of personalized treatment strategies.

In a study conducted by Gul et al.[11] involving 303 patients, various risk factors for recurrent urethral stricture following internal urethrotomy were investigated, and a significant association was found between stricture recurrence and inflammation parameters. The study particularly highlighted that hematological inflammation indices might play a crucial role in predicting recurrent US. Our findings are consistent with this study and further support the impact of inflammation on urethral scar formation.

Our study did not establish a meaningful relationship between the De Ritis ratio (AST/ALT) and recurrence (p=0.924), suggesting that its role in urethral stricture pathophysiology may be limited. Conversely, our results highlight a clear association between SII and recurrence, reinforcing the idea that systemic inflammation plays a key role in urethral scar formation mechanisms. In the literature, the effects of inflammation on epithelial damage and fibrotic tissue development have been widely studied, and cytokines such as TGF-β and IL-6 are known to play a significant role in this process.[2,12]

When evaluating patient comorbidities, no statistically significant differences were detected between recurrence and non-recurrence groups regarding smoking, HT, diabetes, or CAD (p>0.05). However, patients with a stricture length >2 cm exhibited a substantially higher recurrence risk (p=0.024).

A systematic meta-analysis by Endo et al.[9] examined recurrence risk factors after internal urethrotomy. Their study emphasized the impact of stricture length, surgical technique, inflammation, and patient characteristics on recurrence rates. Our findings are in line with previous studies, further underscoring the importance of inflammatory and anatomical factors in recurrence prediction.

Another meta-analysis by Ma et al.[13] identified smoking as an independent risk factor for stricture recurrence after urethroplasty. Smoking has been shown to contribute to chronic inflammation and impair vascular endothelial function, thereby increasing the risk of stricture recurrence. In our study, smoking rates were higher in the recurrence group, but this difference did not reach statistical significance. Future research involving larger patient cohorts may provide more conclusive evidence regarding the influence of smoking on urethral stricture recurrence.[14]

This study has certain limitations. Its retrospective design hinders the assessment of dynamic changes in inflammatory markers over time, while the relatively small, single-center sample may limit the generalizability of the findings. To validate these results and enhance their clinical applicability, future prospective, multicenter studies with larger patient populations are needed.

CONCLUSION

This study demonstrates that SII is a significant biomarker for predicting urethral stricture recurrence after DVIU. When SII levels exceed a specific threshold, the risk of recurrence increases substantially. In contrast, the De Ritis ratio (AST/ALT) was not found to be associated with urethral stricture recurrence, indicating that its prognostic value in this context is limited.

Our findings also suggest that patients with a stricture length greater than 2 cm face a significantly higher recurrence risk. This emphasizes that both inflammatory processes and anatomical factors contribute to stricture recurrence. Therefore, for patients with longer strictures, it may be beneficial to consider surgical treatment options at an earlier stage.

Integrating SII into clinical practice could help identify high-risk patients at an earlier stage, allowing for the development of personalized treatment strategies. In cases where SII values are particularly high, open urethroplasty techniques may be preferable over repeated endoscopic procedures.

Additionally, incorporating machine learning algorithms into recurrence prediction models may further enhance their accuracy and clinical utility. By leveraging advanced predictive tools, clinicians may be able to make more informed decisions and optimize patient management in urethral stricture treatment.

Ethics

Ethics Committee Approval: The study was approved by the İzmir Katip Çelebi University Health Research Ethics Committee (decision number: 0063, date: 13.02.2025)

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.Ö., Y.A., Concept: S.Ö., S.N.G., Design: S.Ö., K.D., Data Collection or Processing: K.D., S.N.G., Analysis or Interpretation: E.M.Y., O.K., Y.A., Literature Search: E.M.Y., O.K., Writing: S.Ö., K.D.

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