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Original Research / Özgün Araştırma

Relationship of Systemic Immune-Inflammation Index and Neutrophil-Lymphocyte ratio with Disease Recurrence and Progression risk in Non-Muscle-Invasive Bladder Cancer

Kasa İnvaze Olmayan Mesane Kanserinde Sistemik İmmün-İnflamasyon İndeksi ve Nötrofil-Lenfosit Oranının Hastalık Nüksü ve İlerleme Riski ile İlişkisi

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Özet

Amaç: Sistemik inflamatuar yanıta dayalı biyobelirteçler, kasa invaze olmayan mesane kanseri (KİOMK) hastalarının prognozunu tahmin etmede umut vericidir ve düşük maliyetle risk sınıflandırmasına katkıda bulunabilir. Bu çalışmada, KİOMK hastalarındahastalığın nüks ve progresyon riskinin öngörülmesi için nötrofil-lenfosit oranı (NLO) ve sistemik immün-inflamasyon indeksini (Sİİ) değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışma, 2015-2019 yılları arasında üçüncü basamak bir üroloji merkezinde transüretral mesane tümörü rezeksiyonu (TUR-MT) uygulanan 211 hastanın verilerinin retrospektif bir analizini içeriyor. Eşik değeri belirlemek için receiver operating characteristic (ROC) eğrisi kullanıldı. Kaplan-Meier eğrileri ve log-rank testi, farklı inflamatuar belirteç seviyelerine göre nükssüz ve progresyonsuz sağkalım oranlarını değerlendirmek için kullanıldı. Bağımsız prognostik faktörleri tahmin etmek için çok değişkenli regresyon analizi yapıldı.

Bulgular: ROC analizinde SII'nın optimal eşik değeri 568 olarak bulundu. Çok değişkenli analize göre, SII değeri, ilk TUR-MT sırasındaki tümör sayısı ve Avrupa Kanser Araştırma ve Tedavi Örgütü (EORTC) nüks sınıflandırması, nüksü öngörmede istatistiksel olarak anlamlı parametrelerdi. Tek değişkenli analizde tümör boyutu, NLO ve SII istatistiksel olarak anlamlı

Abstract

Objective: Some systemic inflammatory response-based biomarkers are promising for predicting prognosis of non-muscle-invasive bladder cancer (NMIBC) patients and can contribute to the risk classification without any significant cost. We aimed to evaluate the neutrophil-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) for the prediction of recurrence and progression risk in patients with NMIBC.

Material and Methods: The study included a retrospective analysis of 211 patients who underwent transurethral resection of bladder (TURB) in a tertiary referral center between 2015 and 2019. The receiver operating characteristic (ROC) curve was used to determine the cut-off value. The Kaplan-Meier curves and the log-rank test were constructed to evaluate the recurrence-free and progression-free survival rates according to different levels of inflammatory markers. The multivariate regression analysis was undertaken to estimate the independent prognostic factors.

Results: The optimal cut-off value of SII was found to be 568 in the ROC analysis. According to the multivariate analysis, the SII value, number of tumors at the time of initial TURB, and European Organization for Research and Treatment of Cancer (EORTC) recurrence classification were statistically significant parameters in predicting recurrence. While

This study was reviewed and approved by the Haseki Training and Research Hospital Ethics Committee. Approval No: 04.06.2020/214.
All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

seviyelere ulaşırken, çok değişkenli analizde anlamlı değildi.

Sonuç: SII, tümör sayısı ve EORTC nüks sınıflaması, nüks değerlendirmesinde kullanılabilecek prognostik parametrelerdir. Ancak inflamatuar parametreler, progresyon hızını tahmin etmede aynı öngörü yeteneğine sahip değildir.

Anahtar Kelimeler: Mesane kanseri; progresyon; nüks; sistemik immün-inflamasyon indeksi

tumor size, NLR, and SII achieved statistically significant levels in the univariate analysis, they didn't have significance in the multivariate analysis.

Conclusion: The SII, number of tumors, and EORTC recurrence classification are prognostic parameters that can be used in the assessment of recurrence. However, inflammatory parameters do not have the same predictive ability in the prediction of the progression rate.

Keywords: Bladder cancer; progression; recurrence; systemic immune-inflammation index

INTRODUCTION

Bladder cancer (BC) is the 11th most common cancer, with an incidence of 550 000 new cases being diagnosed every year [1]. At the time of initial diagnosis, 75% of patients present with non-muscle-invasive bladder cancer (NMIBC), and this rate is even higher in young (≤40 years old) adults [2]. Patients with NMIBC have a five-year probability of recurrence and progression, ranging from 31% to 78% and from less than 1% to 45%, respectively [3]. Since NMIBC includes very different clinical parameters, determining the risk of disease recurrence and progression in the postoperative follow-up is of quite critical importance in determining an appropriate treatment choice.

In current urology practice, the European Organization for Research and Treatment of Cancer (EORTC) and Club Urologico Espanol de Tratamiento Oncologico (CUETO) scoring systems are frequently used to evaluate the progression and recurrence rates of NMIBC [4-5]. However, the predictive accuracy of these models is suboptimal for the decision-making process [6]. In recent studies, it has been demonstrated that some inflammatory parameters determined in preoperative evaluations are methods that can be used for this purpose. In this context, the neutrophil-lymphocyte ratio (NLR) is the most frequently studied parameter, and meta-analyses have demonstrated it to be a beneficial tool to assess poor prognosis [7]. The systemic immune-inflammatory index (SII) is another inflammatory marker obtained by a formula using neutrophil, lymphocyte, and platelet counts (SII = P × N/L) and has been shown as a useful prognostic tool [8]. Two systematic meta-analyses revealed that SII might be a reliable prognostic factor for the poor outcomes of lung and hepatocellular cancers [9, 10]. In addition, studies investigating the relationship between SII and genitourinary system malignancies have recently shown that SII is a prognostic factor affecting survival analysis in MIBC and renal cell carcinomas. [11-14].

We hypothesized that these simple and easily applicable systemic inflammatory response-based biomarkers can predict the postoperative prognosis of patients with NIMBC without any significant cost and contribute to the risk classification of patients. In this context, we aimed to evaluate the prognostic significance of NLR and SII for the prediction of recurrence and progression risk in patients with NMIBC who underwent Transurethral resection of bladder (TURB) and followed up.

MATERIAL AND METHODS

Compliance with Ethical Standards

The current study was approved by the Ethic Committee of Haseki Training and Research Hospital (approval number: 04.06.2020/214) and was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices for Medical Research Involving Human Subjects. Additionally, written and verbal informed consent was obtained by all participants after an explanation of the study.

Study Design

The current study included a retrospective analysis of 211 patients under 80 years old who underwent TURB and follow-up in a tertiary referral center due to NIMBC between 2015 and 2019. The data consisted of records in the hospital's (Haseki Training and Research Hospital) digital data system. All patients had urothelial carcinoma, which was histologically verified, with only minimal (less than 10%) presence of variant components. The exclusion criteria were active infection or immune system diseases (8 patients) within the last one month, and the presence of any other neoplasm (6 patients). Fifteen patients with missing data (moving to different center in the follow-up or follow-up shorter than one year) were also excluded from the study. The remaining 182 patients were included in the final analyses (Figure 1).

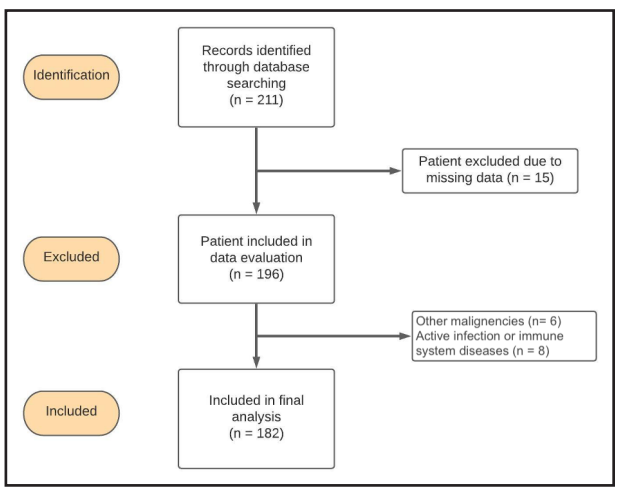

Figure 1. Flowchart of the included and excluded data

The demographic characteristics of the patients (age, sex, weight, height, and body mass index), laboratory results (hemoglobin, neutrophil, lymphocyte, monocyte and platelet counts), and pathological parameters (tumor size, number, grade, TNM stage, and concomitant carcinoma in situ were noted. The NLR, platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and SII were also calculated. Recurrence and progression risk analyses of the patients were performed using the EORTC risk tables.

Transurethral Resection of Bladder Technique and follow-up

The patients were stratified into three risk groups (low-risk, intermediate-risk, and high-risk) according to the European Association of Urology (EAU) guidelines and followed up according to the recommended routine follow-up schedule [15]. After the first TURB, if the tumor was evaluated as low-risk, immediate single-dose intravesical chemotherapy installation (40 mg mitomycin-C) was added to the treatment algorithm. The patients with low-risk NMIBC were followed up by cystoscopy at the third and 12th months following TURB, and annually thereafter for up to five years. The patients with high-risk NMIBC underwent repeat TURB (re-TURB) at two to six weeks after the initial operation. Following the re-TURB, the patients were treated with six weeks of induction intravesical instillations of Bacillus Calmette-Guèrin (BCG), and then continued BCG maintenance therapy for at least one to three years according to patient compliance and the results of BCG therapy. In the high-risk group, routine cystoscopy with urine cytology was performed every three months in the first two years, followed by every six months for three years, and annually thereafter. The follow-up strategy for the intermediate-risk group was individualized according to the patient characteristics.

All patients were followed up by an experienced academician (Assoc. Prof. MFA) with a specific interest in bladder tumors. All pathological specimens were examined by a single pathologist team according to the recommendations of the TNM staging of the American Joint Committee on Cancer and the histological grading of the World Health Organization 1973 and 2004 classifications [16,17]. Disease recurrence was defined as any tumor relapse in the bladder during the follow-up after the initial TURB. Disease progression was defined as the upgrading of tumor stage to ≥ T2 or an increase in the grade from low to high during the routine follow-up [18]. The patients with recurrences in the low-risk group were treated with TURB and adjuvant intravesical treatments. Among the patients

under intravesical BCG treatment, high-grade tumor recurrence or progression to muscle-invasive disease were considered as BCG failure, and radical cystectomy was recommended to these patients.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences version 22.0. The compliance of data to normal distribution was evaluated with the Shapiro-Wilk test. Categorical variables were summarized using actual counts and percentages, and continuous variables using the mean ± standard deviation. The Pearson's chi-square or Fisher's exact test was used to compare categorical variables as appropriate. The Mann-Whitney U test or Independent t-test were used to assess the conformity of the data to a normal distribution. The receiver operating characteristic (ROC) curve was constructed to determine an appropriate cut-off value for SII. Multivariate logistic regression analysis was performed to evaluate the parameters that were predicted to be risk factors for the development of recurrence or progression. A two-tailed p value of <0.05 was considered as statistically significant.

RESULTS

Between January 2015 and December 2019, 211 patients were diagnosed with primary NMIBC. Twenty-nine patients were excluded from the study; six had concomitant malignancies, 15 were lost to follow-up, and eight had a history of active infection of any source for up to one month before the operation. Finally, a total of 182 patients were included in the sample, including 14 females (7.7%) and 168 males (92.3%), with mean age of 63.8 ± 10.9 years. At the time of the TURB, none of the patients had metastatic disease, concurrent upper tract urothelial carcinoma, or urethral cancer invasion. The mean follow-up time was 27.6 ± 12.3 months. The optimal cut-off value of SII was found to be 568 in the ROC analysis, with an area under the curve value of 0.675, p value of 0.014, sensitivity of 0.679, and specificity of 0.696 (Figure 2).

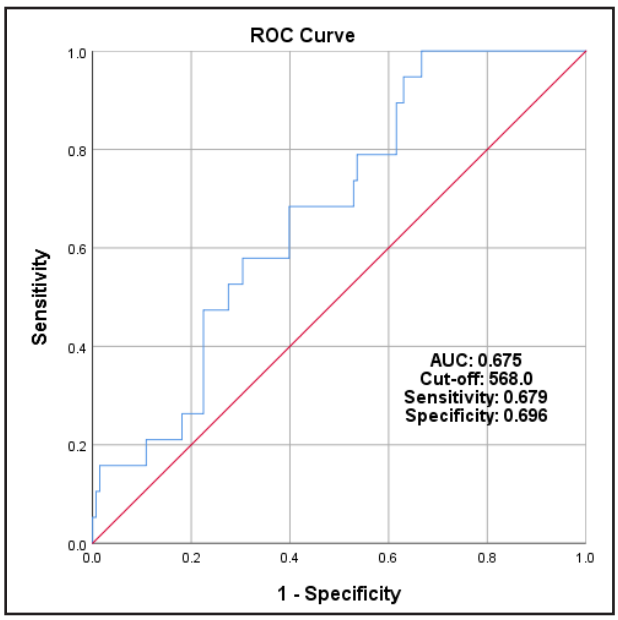

Figure 2. Receiver operating characteristic (ROC) curve of SII according to the patient outcomes. Area under the curve = 0.675, p = 0.014

Recurrence was observed in 20 patients (10.9%) and progression in 11 (6%). The recurrence and progression data are presented in separate tables (Table 1 and Table 2, respectively). According to the univariate analysis, the number of tumors at the time of initial TURB, EORTC recurrence classification, and SII value were statistically significant parameters in predicting the recurrence rate (p = 0.010, 0.018, and 0.010, respectively). However, well-known prognostic parameters, including pathological T stage, tumor grade, tumor size, and other inflammatory parameters (NLR, PLR, and LMR) were not statistically significant in the prediction of the recurrence rates (Table 1).

When prognostic parameters concerning progression were investigated, tumor size at the time of initial TURB, NLR, and SII were the parameters that achieved statistically significant levels (p = 0.010, 0.049, and 0.047, respectively). On the other hand, tumor grade, number of tumors, EORTC progression classification, and other inflammatory parameters (LMR and PLR) were not associated with the risk of progression (Table 2).

All the parameters found statistically significant in the univariate analysis (EORTC recurrence classification, SII, and number of tumors) for the recurrence rate also reached significant levels in the multivariate analysis (p = 0.049, 0.002, and 0.008, respectively) (Table 3a). However, although NLR, SII, and tumor size were found to be statistically significant in the univariate analysis regarding the progression rate, they did not demonstrate the same significance in the multivariate analysis (Table 3b).

Table 1. Comparison of the recurrence status according to the patients' demographic characteristics and pathological findings

	Overall (n = 182)	Recurrence Present (n = 20)	Recurrence Absent (n = 162)	P value
Age (years)*	63.8 ± 10.9	59.4 ±1 0.9	64.4 ± 10.9	0.056ᵀ
Gender, n (%)				0.371†
Male	168 (92.3%)	20 (100.0%)	148 (91.3%)	
Female	14 (7.7%)	0 (0%)	14 (8.7%)	
BMI (kg/m²)*	27.1 ± 5.7	27.5 ± 3.8	26.9 ± 5.6	0.657ᵀ
TURB pathology, n (%)				0.488†
Ta	105 (57.7%)	13 (65.0%)	92 (56.8%)	
T1	77 (42.3%)	7 (35.0%)	70 (43.2%)	
CIS, concomitant	13 (7.1%)	2 (10.0%)	11 (6.8%)	0.639†
Tumor grade, n (%)				0.542†
Low-grade	85 (46.7%)	8 (40.0%)	77 (47.5%)	
High-grade	97 (53.3%)	12 (60.0%)	85 (52.5%)	
Number of tumors, n (%)				***0.010***†
1	100 (54.9%)	6 (30.0%)	100 (61.7%)	
≥ 2	82 (45.1%)	14 (70.0%)	62 (38.3%)	
Tumor size (mm), n (%)				0.266†
< 30	85 (46.7%)	7 (35.0%)	78 (48.1%)	
≥ 30	97 (53.3%)	13 (65.0%)	84 (51.9%)	
EORTC recurrence class, n (%)				***0.018***†
1-4	91 (50.0%)	5 (20.0%)	86 (53.1%)	
5-9	90 (49.5%)	15 (80.0%)	75 (46.3%)	
≥ 10	1 (0.5%)	0 (0%)	1 (0.6%)	
Neutrophil count (10^3/mm³)*	5.3 ± 2.7	5.7 ± 3.0	5.2 ± 2.7	0.386ᵀ
Lymphocyte count (10^3/mm³)*	2.3 ± 1.2	2.6 ± 0.8	2.2 ± 1.3	0.246ᵀ
Platelet count (10^3/mm³)*	241.4 ± 64.1	258.8 ± 69.9	241.0 ± 65.3	0.229ᵀ
NLR*	2.7 ± 1.9	2.4 ± 1.6	2.9 ± 2.7	0.431ᵀ
PLR*	128.4 ± 85.3	109.9 ± 40.5	131.4 ± 93.3	0.313ᵀ
LMR*	3.4 ± 1.2	3.5 ± 1.0	3.4 ± 1.4	0.713ᵀ
SII*	511.8 ± 259.7	563.3 ± 192.5	466.7 ± 179.5	***0.010***ᵀ

BMI: Body mass index, TURB: Transurethral resection of bladder, CIS: carcinoma in situ, EORTC: European Organization for Research and Treatment of Cancer, LMR: lymphocyte-monocyte ratio NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, SII: systemic immune-inflammation index

* : mean ± standard deviation, ᵀ: Student's t test, †: Pearson's Chi-Square test

Table 2. Comparison of the progression status according to the patients' demographic characteristics and pathological findings

	Overall (n = 182)	Progression Present (n = 11)	Progression Absent (n = 171)	P value
Age (years)*	63.8 ± 10.9	59.4 ±1 0.9	64.4 ± 10.9	0.483ᵀ
Gender, n (%)				0.569†
Male	168 (92.3%)	10 (90.9%)	158 (92.4%)	
Female	14 (7.7%)	1 (9.1%)	13 (7.6%)	
BMI (kg/m²)*	27.1 ± 5.7	28.2 ± 4.1	26.9 ± 5.5	0.440ᵀ
TURB pathology, n (%)				0.360†
Ta	104 (57.1%)	8 (72.7%)	96 (56.2%)	
T1	76 (42.9%)	3 (27.3%)	73 (42.7%)	
CIS, concomitant	2 (1.1%)	0 (0%)	2 (1.1%)	NA
Tumor grade, n (%)				0.189†
Low-grade	84 (46.1%)	3 (27.3%)	81 (47.4%)	
High-grade	97 (53.9%)	8 (72.7%)	89 (52.6%)	
Number of tumors, n (%)				0.206†
1	102 (56.0%)	4 (36.4%)	98 (57.3%)	
≥ 2	73 (44.0%)	7 (63.6%)	67 (42.7%)	
Tumor size (mm), n (%)				***0.010***†
< 30	85 (46.7%)	1 (9.1%)	84 (49.1%)	
≥ 30	97 (53.3%)	10 (90.9%)	87 (50.9%)	
EORTC recurrence class, n (%)				0.536†
1-4	79 (43.4%)	3 (27.3%)	76 (44.4%)	
5-9	76 (41.8%)	6 (54.5%)	70 (40.9%)	
≥ 10	27 (14.8%)	2 (18.2%)	25 (14.6%)	
Neutrophil count ($10^3/mm^3$)*	5.3 ± 2.7	5.7 ± 3.0	5.2 ± 2.7	0.222ᵀ
Lymphocyte count ($10^3/mm^3$)*	2.3 ± 1.2	2.2 ± 0.7	2.2 ± 1.2	0.917ᵀ
Platelet count ($10^3/mm^3$)*	241.4 ± 64.1	241.0 ± 39.2	243.3 ± 67.6	0.914ᵀ
NLR*	2.7 ± 1.9	2.3 ± 2.2	2.8 ± 2.4	0.464ᵀ
PLR*	128.4 ± 85.3	114.5 ± 20.6	129.9 ± 89.9	0.573ᵀ
LMR*	3.4 ± 1.2	4.2 ± 1.2	3.4 ± 1.3	***0.049***ᵀ
SII*	511.8 ± 259.7	683.6 ± 729.9	505.5 ± 204.9	***0.047***ᵀ

BMI: Body mass index, CIS: carcinoma in situ, EORTC: European Organization for Research and Treatment of Cancer, LMR: lymphocyte-monocyte ratio NLR: neutrophil-lymphocyte ratio, PLR: platelet-lymphocyte ratio, SII: systemic immune-inflammation index, NA: Not Applicable

* : mean ± standard deviation, ᵀ: Student's t test, †: Pearson's Chi-Square test

Table 3a. Multivariate analysis of recurrence

	Odds Ratio	95% confidence interval		P value
		Lower	Upper	
EORTC	2.991	0.9	9.7	***0.049***
SII	1.005	1.0	1.1	***0.002***
Number of tumors	4.876	1.5	15.7	***0.008***

EORTC: European Organization for Research and Treatment of Cancer, SII: systemic immune-inflammation index

Table 3b. Multivariate analysis of progression

	Odds Ratio	95% confidence interval		P value
		Lower	Upper	
NLR	1.569	0.7	3.2	0.212
SII	1.002	1.0	1.3	0.075
Tumor size	8.256	0.9	21.7	0.052

NLR: neutrophil-lymphocyte ratio, SII: systemic immune-inflammation index

DISCUSSION

Today there are several prognostic tools to evaluate the recurrence and progression possibilities of NMIBC. In our study multivariate analysis revealed that SII, number of tumors, and EORTC recurrence classification were independent prognostic parameters to assess the recurrence rate. Although the univariate analysis showed statistically significant results for SII, NLR, and tumor size, the multivariate analysis did not produce the same results concerning the progression rate.

In our study group, we found the recurrence rate as 10.9%. According to the EORTC trials, the recurrence rate ranged between 15 and 61% [4]. Our results were lower than the lower limit given in the literature, which we think may be due to our small sample size. We combined the EORTC risk classification with patient characteristics, pathological results, and follow-up data. We showed that the EORTC classification was a prognostic factor. The number of tumors, which is a part of the EORTC risk assessment, was also determined to be a prognostic factor when evaluated alone. The above-mentioned parameters have been previously investigated and showed high power in the assessment of the recurrence rate in NMIBC. However, there is lack of information concerning the biochemical or inflammatory parameters of this model, which are also known as prognosticators.

Most oncological prognostic biomarkers are determined as a result of expensive and time-consuming analyses, such as polymerase chain reaction and immunohistochemistry methods [19]. Routine blood tests provide adequate clinical information about a patient's inflammatory status by formulating the values of blood contents. Mediators and cytokines released during an inflammatory reaction are considered to cause cell damage and assist in the development of gene mutations, which are essential in cancer cell development and create a microenvironment that promotes cancer cell proliferation. Neutrophil, lymphocyte, and thrombocyte formulations are the most commonly used inflammatory parameters. SII is a parameter obtained as a result of the combination of all these blood elements, and it is one of the most actively studied parameters for predicting disease characteristics in a variety of cancer types [9,10]. Firstly, SII has been shown as a better predictor of prognosis than NLR and PLR MIBC patients by Zhang et al. [12]. Subsequently, a multicenter European cohort showed that SII also has predictive relevance in the patient population with NMIB, underlining the crucial role of SII in current medical care [20]. We also, determined SII as another prognostic factor to determine the recurrence rate, which is consistent with the literature currently available.

In our study, the progression rate was found to be 6.1%, and this result was in the range of one-year risk of progression in the EORTC trial [4]. In the univariate analysis, tumor size, which is part of the EORTC risk classification, reached a statistically significant level. However, the same results were not obtained from the multivariate analysis, and therefore we cannot state that tumor size is a prognostic parameter for evaluating the rate of progression. Furthermore, we were not able to demonstrate a relationship between NLR and the progression rate in our study. A recent study showed that a high NLR value and a high progression rate were associated in patients with NMIBC [21]. However,

similar to our study, some studies did not demonstrate the same relationship NLR and progression rate [22,23]. We consider that this situation lowers the reliability of NLR in relation to the prognosis rate. In another meta-analysis showing the significance of a high NLR value in predicting the recurrence, progression, and survival of bladder tumors, mainly muscle-invasive bladder tumor studies were included in the analysis (14 MIBC and four NMIBC studies) [24]; therefore, that meta-analysis can be considered limited in effectively assessing the ability of NLR to determine progression in the non-muscle invasive group.

We found that the best cut-off value of SII was 568 in the ROC analysis. In a large multicenter European cohord which investigates the prognostic value of SII in NMIBC, optimal cut-off value of SII was determined as 580 [20]. In an article investigating whether SII predicts BCG failure, the threshold value was found to be 672.75 [25]. In an additional study, the researchers reported that SII is an independent predictor of RFS in NMIBC patients and that individuals with high SII (525.26) have a significantly increased chance of tumor progression or recurrence [26]. In another study investigating inflammatory markers to predict postoperative recurrence among NMIBC patients treated with intravesical chemotherapy and intravesical chemo-hyperthermia, the SII threshold was 575.3 [27]. In light of our findings and current literature search, we think that SII values of above 500 should alert the clinician to suspect an NIMBC prognosis.

This study has several limitations. First, it had a retrospective nature with a single-center experience. Second, it had a short follow-up period. Third, we did not analyze the results using the CUETO classification. Despite these limitations, we consider that our results are promising and should be supported by further studies with large sample sizes and longer follow-up periods.

CONCLUSIONS

Our study suggests that SII, number of tumors, and EORTC recurrence classification are prognostic parameters for the assessment of the recurrence rate. However, neither inflammatory parameters nor pathological findings had similar value in relation to the progression rate.

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