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The systemic immune-inflammation index (SII) in predicting postoperative systemic inflammatory response syndrome (SIRS) after ureteroscopy

Sedat Yahşi, Kazım Ceviz

Department of Urology, Ankara City Hospital, Ankara, Turkey

ABSTRACT

Objectives: The predictive value of some preoperative inflammatory markers for postoperative infective complications in urinary system stone disease has been demonstrated. We investigated how valuable the systemic immune-inflammation index (SII) is as a marker for the development of postoperative systemic inflammatory response syndrome (SIRS) in patients undergoing ureteroscopy.

Methods: The data of 495 patients who met the study criteria were evaluated retrospectively. The patients were divided into groups according to whether they developed SIRS postoperatively or not. The clinical and demographic data of the patient groups as well as blood parameters were evaluated.

Results: Postoperative systemic inflammatory response syndrome was detected in 105 (21.2%) of the patients. Age, diabetes, cardiovascular disease, preoperative urinary culture positivity, SII, neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR) and platelet-lymphocyte ratio (PLR) were found to be significant for the development of SIRS. When the areas under the curve were measured in the ROC analysis, it was seen that the SII, NLR, LMR and PLR had high predictive values for the development of SIRS (area under the curve values of 0.73, 0.76, 0.72, 0.67, respectively). In the multivariate logistic regression analysis, among the risk factors, age, cardiovascular disease, preoperative urinary culture positivity and NLR were determined as independent risk factors.

Conclusions: Study revealed that only NLR among inflammatory markers is an independent risk factor for the development of SIRS. Although there is a relationship between the preoperative SII and the development of SIRS, it is not an independent risk factor. Along with many other variables, it may contribute to the development of SIRS.

Keywords: Biomarkers, systemic inflammatory response syndrome, ureterolithiasis, ureteroscopy

The incidence of urinary tract stones depends on geographical, ethnic, dietary and genetic factors. The risk of recurrence in stone disease is associated with the underlying disorder. The prevalence of urinary system stone disease is up to 20% with regional differences. The prevalence is higher in North American and European countries with high living standards. Management of ureteral stones is determined by the location and size of the stone and the clinical characteristics of the patient. In the current urology guideline, treatment options for ureteral stones are medical expulsive therapy, shock wave lithotripsy

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Address for correspondence: *Sedat Yahşi, MD., Ankara City Hospital, Department of Urology, Üniversiteler Mah., 1604. Cad., NO:9, 06800 Çankaya, Ankara, Turkey. E-mail: sedatyahsi@yahoo.com, Phone: +90 312 552 360 00*

(SWL), and ureteroscopy (URS) [1]. Infectious complications are observed at a rate of 9-25% after URS. These infections can progress to serious conditions such as urosepsis and septic shock [2]. Therefore, it is of great importance to be able to predict infectious complications before surgery. Systemic inflammatory response syndrome (SIRS) can occur for many reasons such as infection, trauma and surgery. It refers to the clinical condition, which can lead to organ damage, caused by an excessive inflammatory response. In the literature, the relationship between biomarkers such as neutrophil- lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR) and platelet-lymphocyte ratio (PLR) and inflammatory response has been reported [4]. In some studies, these markers have been shown to have predictive value for postoperative SIRS after urinary stone surgery [4,5]. The systemic immune-inflammation index (SII) (platelet x neutrophil/lymphocyte) is another marker showing high inflammatory processes. The role of SII in many malignant diseases has been evaluated [6-8]. In this study, the predictive value of preoperative SII in the development of SIRS after URS was investigated.

METHODS

Patients who underwent URS in our clinic between January 2021 and September 2022 were evaluated retrospectively (Ethics committee approval number: E2-22-2677). Oncology patients, immunosuppressive patients, patients with hematological disease, patients with previous ureteral stent, patients with active infection and patients with preoperative SIRS criteria were not eligible for the study. Of 655 patients who underwent URS in our clinic, 495 were counted in the study. Detailed medical histories of all patients were obtained. The comorbidities of the patients were questioned. Those with diabetes mellitus, hypertension, and cardiovascular disease were noted. Patients with atherosclerotic heart disease such as previous myocardial infarction or coronary bypass surgery were included in the cardiovascular disease group. The size and localization of the stones were evaluated with direct urinary system radiography (DUSG) and non-contrast computed tomography (CT). Patients were given 1 g of cefazolin as routine perioperative antibiotic prophylaxis.

Patients who met two or more of the following criteria were diagnosed with SIRS: body temperature < 36 °C or > 38 °C, heart rate > 90 bpm, respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg and white blood cell count > 12×109 cells/ L or < 4×109 cells/L.

The patients were divided into groups according to whether they developed SIRS postoperatively or not. The groups were statistically compared in terms of demographic data and preoperative inflammatory markers, and it was evaluated whether there was a significant relationship.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS 25.0 software package. Normality of distribution for continuous variables was evaluated with the One-Sample Kolmogorov-Smirnov Test. Mann-Whitney U test was used to analyze the quantitative variables of the groups that did not show normal distribution, and the Chi-Square test was used to analyze the categorical variables. $P < 0.05$ was considered to be significant. The optimal threshold value was calculated by performing ROC analysis for the variables that were found to be significant. The diagnostic values of the biomarkers were determined by calculating the areas under the curve. Variables found to be significant were evaluated using a multivariate logistic regression model to identify independent risk factors for the development of SIRS after URS.

RESULTS

All clinical characteristics and laboratory values are shown in Table 1. One hundred and sixty-eight (33.9%) of the patients were female and 327 (66.1%) were male. SIRS were detected in 105 (21.2%) of the patients. The incidence of SIRS was found to be 19% (32/168) in women and 22% (73/327) in men. There was no difference between the groups with and without SIRS in terms of gender, stone size, stone localization, hydronephrosis grade, and serum platelet count. The age of the group with SIRS was significantly higher ($p < 0.001$). Further, SIRS was found to be significantly higher in those treated for urinary tract infection in the preoperative period ($p < 0.001$). In patients who were evaluated in the emergency outpatient clinic, SIRS was significantly higher than those oper-

Table 1. Comparison of clinical characteristics and laboratory values between SIRS group and non-SIRS group

	No SIRS n = 390 (78.8%)	SIRS, n = 105 (21.2%)	*p* value
Age (years), median (min-max)	50 (20 - 88)	56 (20 - 88)	**< 0.001****
Gender, n (%)			0.419*
Male	254 (65.1)	73 (69.5)	
Female	136 (34.9)	32 (30.5)	
Hypertension, n (%)	60 (15.4)	24 (22.9)	0.07*
Diabetes mellitus, n (%)	67 (17.2)	32 (30.5)	**0.002***
Cardiovascular disease, n (%)	31 (7.9)	25 (23.8)	**< 0.001***
Outpatient, n (%)			**0.001***
Elective	364 (93.3)	87 (82.9)	
Emergency	26 (6.7)	18 (17.1)	
Stone size (mm), median (min-max)	8 (5-20)	8 (5-20)	0.34**
Stone Localization, n (%)			0.41*
Proximal ureter	129 (33.1)	28 (26.7)	
Mid ureter	106 (27.2)	29 (27.6)	
Distal ureter	155 (39.7)	48 (45.7)	
Hydronephrosis grade, n (%)			0.78*
1	159 (40.8)	41 (39)	
2	155 (39.7)	40 (38.1)	
3	76 (19.5)	24 (22.9)	
Preoperative urinary culture positivity, n (%)	46 (11.8)	29 (27.6)	**< 0.001***
Preoperative laboratories, median (min-max)			
Leukocyte (10^9/L)	7.94 (4.24-20.06)	8,65 (4.17-20.96)	**< 0.001****
Neutrophil (10^9/L)	4.84 (1.8-15.84)	6,06 (1.89-16.94)	**< 0.001****
Lymphocyte (10^9/L)	2.08 (0.53-4.86)	1.68 (0.56-3.8)	**< 0.001****
Monocyte (10^9/L)	0.4 (0.12-2.03)	0.45 (0.15-2.04)	**< 0.001****
Platelet (10^9/L)	285.5 (116-632)	290 (108-599)	0.57**
Preoperative inflammatory markers, median (min-max)			
NLR	2.26 (0.44-18.55)	3.81 (0.73-15.91)	**< 0.001****
LMR	5.25 (0.95-16.06)	3.78 (0.78-12.72)	**< 0.001****
PLR	134.56 (52.12-575.47)	171.59 (67.47-688.51)	**< 0.001****
SII	658.53 (121.45-5656.89)	1038.71 (182.85-7353.24)	**< 0.001****

SIRS = systemic inflammatory response syndrome, NLR = neutrophil-lymphocyte ratio, LMR = lymphocyte-monocyte ratio, PLR = platelet-lymphocyte ratio, SII = systemic immune-inflammation index

* Chi-Square Test, **Mann-Whitney U Test

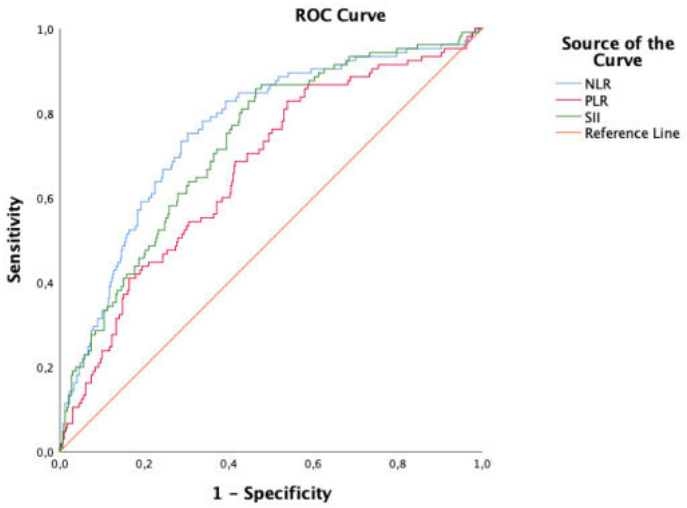

Fig. 1. ROC curve analysis of NLR, PLR and SII according to SIRS.

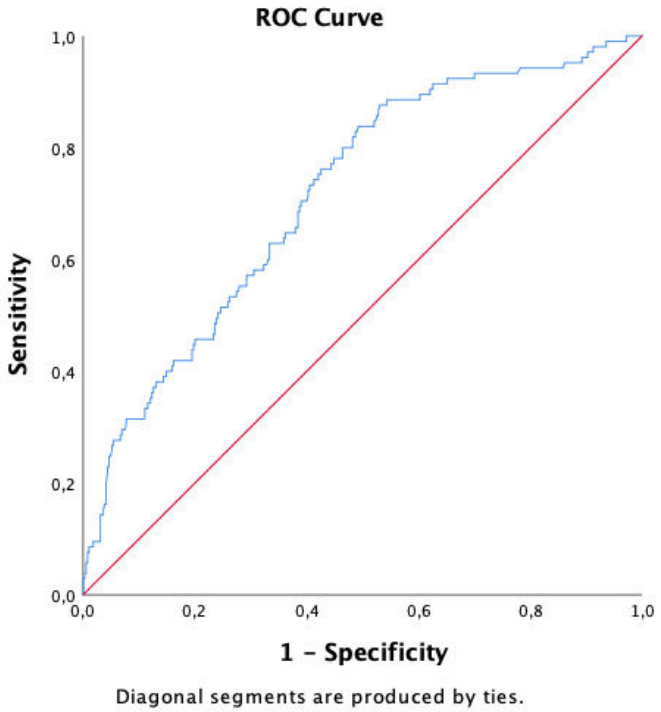

Fig. 2. ROC curve analysis of LMR according to SIRS.

ated under elective conditions ($p = 0.001$). There were significant differences in serum leukocyte, neutrophil, lymphocyte and monocyte counts and NLR, LMR, PLR and SII values between the two groups ($p < 0.001$ in all) (Table 1). In the ROC curve analysis (Figs. 1 and 2), the optimal cut-off (AUC, sensitivity, specificity) values for SII, NLR, LMR and PLR were found to be 816.16 (0.73, 66.7%, 65.1%), 2.98 (0.76, 73.3%, 71.3%), 4.5 (0.72, 64.8%, 63.8%), and 152.02 (0.67, 60%, 61.5%), respectively (Table 2). Besides, multivariate logistic regression analyses showed that age (OR 1.022, 95% CI 1.003-1.04; $p = 0.02$), cardiovascular disease (OR 2.684, 95% CI 1.335-5.397; $p = 0.006$), preoperative urinary culture positivity (OR 2.919, 95% CI 1.588-5.366; $p < 0.001$), and NLR (OR 6.347, 95% CI 2.976-13.537; $p < 0.001$) were found to be independent risk factors for the development of postoperative SIRS (Table 3).

DISCUSSION

Today, the most commonly used procedure in the treatment of ureteral stones is URS. Although URS is among the minimally invasive procedures, it is associated with many complications. Infective complications may present with clinical presentations ranging from bacteremia to sepsis. Although sepsis and septic shock are very rare, they are closely associated with perioperative mortality [9]. Therefore, there is a need for biomarkers to predict postoperative infective complications. Until now, many predictive factors have been studied in the definition of infective complications after URS. Studies with large series have shown

Table 2. ROC curve analysis for NLR, PLR, SII and LMR

	AUC	Sensitivity	Specificity	Cut-off	*p* value
NLR	0.76	73.3	71.3	>2.98	**< 0.001**
PLR	0.67	60	61.5	>152.02	**< 0.001**
SII	0.73	66.7	65.1	>815.16	**< 0.001**
LMR	0.72	64.8	63.8	<4.5	**< 0.001**

AUC = area under curve, NLR = neutrophil-lymphocyte ratio, LMR = lymphocyte-monocyte ratio, PLR = platelet-lymphocyte ratio, SII = systemic immune-inflammation index

Table 3. Multivariate analysis of factors that predict SIRS

Multivariate logistic regression analyses		
	OR (CI 95%)	***p* value**
Age	1.022 (1.003-1.04)	**0.02**
Diabetes mellitus	1.243 (0.682-2.263)	0.38
Cardiovascular disease	2.684 (1.335-5.397)	**0.006**
Outpatient type	1.415 (0.692-2.895)	0.37
Preoperative urinary culture positivity	2.919 (1.588-5.366)	**< 0.001**
NLR	6.347 (2.976-13.537)	**< 0.001**
PLR	1.076 (0.586-1.975)	0.81
SII	0.842 (0.389-1.823)	0.66
LMR	1.264 (0.702-2.274)	0.44

NLR = neutrophil-lymphocyte ratio, LMR = lymphocyte-monocyte ratio, PLR = platelet-lymphocyte ratio, SII = systemic immune-inflammation index

that comorbidities such as preoperative pyuria, preoperative urine culture positivity, prolonged operation time, high Charlson Comorbidity index, and diabetes mellitus are associated with postoperative fever and SIRS [10-12]. In our study, a relationship was found between age, diabetes mellitus, cardiovascular disease, preoperative urine culture positivity and the development of SIRS. Among these, age, cardiovascular disease, and preoperative urine culture positivity were found to be independent predictors for the development of postoperative SIRS in multivariate analysis.

Atherosclerosis, the main underlying pathology for ischemic heart diseases, is a chronic inflammatory process initiated and maintained by leukocytes infiltrating the subendothelial space. The accumulation of pro-inflammatory leukocytes drives progression of atherosclerosis. Many studies with animal experiments support this theory [13]. The fact that cardiovascular disease was an independent risk factor for the development of SIRS in our study may be related to this inflammatory background.

Although it could not be shown in the multivariate analysis, the risk of developing SIRS was higher in patients who were evaluated and operated in the emergency outpatient clinic compared to elective patients. This association may possibly be related to higher preoperative urine culture positivity in emergency patients compared to elective patients (16.8% vs. 29.4%).

URS is not applied to any patient whose urine culture is not sterile in our clinic. We found a significantly higher rate of postoperative SIRS in patients who received treatment for urinary tract infection in the preoperative period. Although preoperative urine culture positivity was found to be higher in women compared to men in previous studies, no such difference was found in our study. The propensity for infection in female gender in the population may be related to the higher incidence of phosphate stones in women, which are directly related to postoperative infection [14, 15]. Parallel to this, while female gender has been reported as a risk for the development of SIRS in the literature, such a relationship could not be shown in our study. This difference may be related to many factors such as ethnicity, geography and genetics.

In fact, the development of SIRS in patients with sterile preoperative urine cultures may seem confusing, but several mechanisms may be explanatory. In the presence of a ureteral stone that does not allow urinary passage, the infection may not be detected in a urethral sample and may cause infective complications after URS. In a study by Singh *et al*. [16], the fact that intraoperative renal pelvic urine culture taken during the percutaneous nephrolithotomy (PCNL) operation was found to be associated with postoperative SIRS also supports this view. In the aforementioned study, the correlation of preoperative urine culture with intraoperative pelvic urine culture and stone culture was found in only 18% of cases [16]. Most stones are known to carry bacteria under their layers. These bacteria that emerge with the lithotripsy procedure can be a source of infection. In a study evaluating patients who underwent PCNL, it was reported that infective complications that occur when urine cultures are sterile are due to bacteria released during lithotripsy [17]. In our study, no relationship was found between stone size and postoperative SIRS. This finding may be associated with less stone burden in those who underwent URS compared to those who underwent PCNL. In the literature, long operation time has also been found to be associated with infective complications. These complications are usually attributed to a longer duration of irrigation fluid reflux [18]. However, long operation time may be associated with excessive stone

burden. Increased stone burden may also cause more bacteria to emerge and infective complications.

It is known that high neutrophil and low lymphocyte count in the circulation prepare a suitable environment for kidney stone formation via inflammatory mediators [4]. On the other hand, vascular permeability factors arising from activated platelets also contribute to the inflammatory response by causing leukocyte chemotaxis [5]. The relationship between this inflammatory response, which predisposes to stone formation, and postoperative infective complications is not clear. So far, NLR, LMR and PLR have been studied to evaluate the development of SIRS after stone surgery. The predictive value of these markers in the development of SIRS after both URS and PCNL surgery has been demonstrated [4, 5, 19]. Hu *et al*. [20] first described a new inflammatory index, the SII, defined as platelet, which includes absolute blood counts. In the same study, it was found to be a prognostic indicator for poor outcome in patients with hepatocellular carcinoma [20]. It has also been shown to have prognostic significance for other gastrointestinal cancers and prostate cancer in subsequent studies [6, 7]. SII as an inflammatory marker have not been used so far to assess the risk of developing SIRS after URS. Our study is the first research in the literature in this respect. Preoperative SII, NLR, and PLR value were found to be significantly higher and LMR value significantly lower in the group of patients who developed SIRS. In the ROC analysis, we revealed that SII, NLR, LMR and PLR have predictive value for the development of postoperative SIRS. When these inflammatory markers were categorically grouped according to their cut-off values and evaluated by multivariance analysis, only NLR was detected as an independent risk factor. If the cut-off value for NLR is taken as > 2.98, we can predict the development of postoperative SIRS with 73.3% sensitivity and 71.3% specificity. With this result, it can be thought that preoperative NLR may help the clinician to predict high-risk patients. Therefore, patients with a high preoperative NLR value should be closely monitored for postoperative infective complications. Although previous studies have reported that SII and LMR are independent risk factors for the development of postoperative SIRS, our study reveals that they cannot be used alone as independent predictors. It can be thought that these, along with other clinical and laboratory variables, contribute to the development of postoperative SIRS.

Limitations

Unfortunately, our study has some limitations. First of all, our regional patient population may not reflect the whole society due to its single-center nature. In addition, due to its retrospective nature, we could not obtain data that could contribute to our study such as operation time, perioperative urine culture and stone culture.

CONCLUSION

Our study revealed that only NLR among inflammatory markers is an independent risk factor for the development of postoperative SIRS. Although SII has been reported to be an independent risk factor in some other diseases, we found no such relationship in terms of postoperative SIRS development in patients who underwent ureteroscopy. Elderly patients, patients with cardiovascular disease, patients receiving urinary infection treatment in the preoperative period, and patients with high preoperative NLR values should be closely monitored for postoperative infective complications. Especially, patients receiving preoperative infection treatment have a high risk of encountering infective complications even if the urine culture is sterile. It should be ensured that these patients receive adequate antibiotic therapy. Larger-scale, prospective, multicenter studies may provide more precise information to support the predictive value of inflammatory markers in the future.

Authors' Contribution

Study Conception: SY, KC; Study Design: SY, KC, AD; Supervision: SY; Funding: N/A; Materials: SY, KC; Data Collection and/or Processing: KC; Statistical Analysis and/or Data Interpretation: SY; Literature Review: SY, KC; Manuscript Preparation: SY and Critical Review: SY, KC.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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