RESEARCH ARTICLE

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The Predictive Value of the Systemic Immune-Inflammation Index for the Progression of Lower Urinary Tract Symptoms in Men

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Abstract

Introduction: This retrospective cross-sectional observational study aimed to investigate the predictive value of the systemic immune-inflammation index (SII) for the progression of lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH). **Material and method:** A total of 280 patients diagnosed with LUTS were analyzed, and their demographic characteristics, laboratory results, urological parameters, and SII levels were recorded retrospectively. **Results:** Clinical progression of LUTS was observed in 43.2% of the patients, with 23.9% undergoing surgery and 21.4% progressing to acute urinary retention. The study found that elevated SII levels were significantly correlated with disease progression and worse outcomes. Multivariate analysis revealed that peak urinary flow rate, erectile function scores, and platelet levels were risk factors for predicting clinical progression in LUTS/BPH patients. **Conclusion:** The findings suggest that systemic inflammation and immune dysregulation play a role in BPH pathogenesis and the development of LUTS. Incorporating SII assessment into routine clinical practice could aid in risk stratification, treatment decision-making, and monitoring of disease progression in LUTS/BPH patients.

Keywords: Lower urinary tract symptoms- Benign prostatic hyperplasia- Systemic immune-inflammation index

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Introduction

Benign prostatic hyperplasia (BPH) is defined as a non-malignant enlargement or hyperplasia of prostate tissue and is the most common underlying pathology of lower urinary tract symptoms (LUTS) in ageing men. The histological prevalence of BPH at autopsy series is as high as 50-60% for males at the age of 6th decades and increasing to 80-90% over 7th decades (Roehrborn, 2005). BPH is characterized by stromal and epithelial cell proliferation of the prostate transition zone. As a result, the compression of the urethra and the development of bladder outlet obstruction (BOO), which can cause clinical manifestations of LUTS/BPH may occur (Roehrborn, 2008). Various factors such as metabolic syndrome, obesity, hypertension and genetic factors together with non-modifiable or modifiable risk factors, as well as direct hormonal effects of testosterone on prostate tissue, may contribute to the development of LUTS/BPH (Chughtai et al., 2016). The possible underlying pathophysiological mechanism for obesity and metabolic syndrome includes increased levels of systemic inflammation and increased levels of estrogens (De Nunzio et al., 2012; Furukawa et al., 2017).

There is still debate on the distribution characteristics of inflammatory cells and their mediators in the prostatic tissue that may have effects on the development and clinical progression of the disease. During inflammatory responses, levels of neutrophils, platelets, and acute-phase proteins, such as C-reactive protein and albumin are altered. In recent years, several studies reported that C-reaction protein (CRP), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and monocyte- to-lymphocyte ratio (MLR) as an indicator of inflammation (Colotta et al., 2009; Fukuda et al., 2018; Yang et al., 2019) and the systemic immune-inflammation index (SII), calculated by the formula of neutrophil×platelet/lymphocyte, is a new and promising inflammatory biomarker (Barua et al., 2019; Zhang et al., 2019). When SII is compared to other systemic immune response parameters such as CRP, NLR, MLR and PLR, this parameter includes three types of peripheral blood inflammation and immune response of the body (Li et al., 2021). SII is an easily accessible, reliable and inexpensive

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indicator of the systemic immune response.

We aimed to investigate the predictive value of SII, as an indicator of inflammation, on prognosis in patients suffering from LUTS/BPH.

Materials and Methods

We designed a retrospective cross-sectional observational study that was conducted between March 2019 and March 2021. A total of 280 patients with the diagnosis of lower urinary tract symptoms (LUTS) were analysed at Izmir Bakircay University, Urology Department. After local ethical committee permission was received (local ethical committee number is 404/384, date 01.12.2021), data from the patients with the diagnosis of LUTS/BPH were recorded retrospectively from the hospital patient record system. Patient's demographic characteristics, laboratory results, maximum flow rate, prostate volume measured by abdominal ultrasonography, post voiding residual urine mounts (PVR), International Prostate Symptom Score (IPSS) and International Erectile Function-5 Turkish validated short form scores (IIEF-5) were recorded. Systemic-immune inflammation index was calculated with the formula of (Neutrophile/Lymphocyte) x Platelet. Patients with acute urinary retention and requiring surgical treatment (including all criteria for BPH surgery such as chronic retention, with or without hydronephrosis, bladder stone, bladder diverticula, recurrent haemorrhage or urinary system infection and unresponsive to medical treatment etc.) were regarded as clinical progression. According to the clinical progression statute, patients are divided into two groups. Group 1 was including patients with no clinical progression (control group) and group 2 was including patients with clinical progression (study group). Patients with urinary tract infection, history of previous lower urinary tract surgery, neuro-muscular disease, psychiatric disease, oncological disease, history of chemotherapy or radiotherapy and using medication to interfere with lower urinary tract were excluded from the study.

All statistical analyses were performed with the SPSS Statistics 26.0 (IBM Inc., Armonk, NY, US) software package programme. Categorical variables were described by frequencies and percentages; continuous variables were described by means and standard deviations. The normality of the distributions was evaluated with Kolmogorov–Smirnov test, and the Mann–Non-parametric test was used to compare groups and quantitative independent data. The qualitative independent data was evaluated with the chi-square test and Spearman's correlation analysis was performed to evaluate the correlation between parameters. Logistic regression models examining the associations between SII levels and LUTS/BPH outcomes were adjusted for age and other potential confounders including age, body mass index, hypertension, and smoking status. Interaction terms were created and were included in the logistic models to examine potential effect modification by third variables. A p-value less than 0.05 was chosen as the criterion for statistical significance.

Results

The mean age of the patients was 60.57±9.59 years and the follow-up period were 39.88±5.36 months. Demographic and laboratory characteristics were summarized in Table 1. Clinical progression of lower

Table 1. Patient's Demographic and Laboratory Characteristics According to the Groups

	Group 1 n=159 (56.8%)	Group 2 n=121 (43.2%)	p value
Age (year), mean±SD.	59.08±9.44	62.74±9.29	0.002
Body Mass Index (kg/m^2), mean±SD	29.13±4.32	28.59±4.59	0.266
Glucose (mg/dl), mean±SD	119.69±67.46	122.76±66.53	0.328
BUN, (mg/dL), mean±SD	37.35±13.49	41.65±33.85	0.834
Creatinine, (mg/dL), mean±SD	0.92±0.32	1.02±0.57	0.016
AST, (IU/L), mean±SD	21.94±8.40	20.93±6.65	0.485
ALT, (IU/L), mean±SD	24.31±12.75	20.98±9.63	0.034
Total Cholesterole, (mg/dL), mean±SD	206.92±42.92	203.07±40.94	0.586
Trigylseride, (mg/dL), mean±SD	160.87±83.31	178.08±120.98	0.484
HDL, (mg/dL), mean±SD	58.21±78.13	63.04±81.14	0.105
LDL, (mg/dL), mean±SD	127.36±38.14	129.05±43.70	0.934
Albumin, (g/dL), mean±SD	4.41±0.29	4.39±0.31	0.692
Neutrophile, (x10^3/uL), mean±SD	4.27±1.24	4.97±1.86	<0.001
Lymphocyte, (x10^3/uL), mean±SD	2.38±1.38	2.25±0.74	0.001
Hemoglobine, (g/dL), mean±SD	14.80±1.24	14.45±1.88	0.152
Platelet, (x10^3/uL), mean±SD	236.81±61.69	296.88±288.59	<0.001
C-reactive protein, (mg/L), mean±SD	1.33±2.86	1.44±2.37	0.001
Systemic immune-inflammation index	468.72±233.66	747.58±1119.75	<0.001

BUN, Blood urea nitrogen; AST, Alanine asetotransferase; ALT, Alanine aminotransferase; HDL, High-density lipoprotein; LDL, Low-density lipoprotein

Table 2. Clinical Characteristics of Patients According to the Groups

	Group 1 n=159 (56.8%)	Group 2 n=121 (43.2%)	p value
PSA, (ng/mL), mean±SD	2.14±2.53	3.18±3.67	0.007
Total testosterone, (ng/mL), mean±SD	4.82±2.01	4.57±2.03	0.298
Prostate volume, (mL), mean±SD	40.63±19.45	52.94±32.91	<0.001
Q max, (mL/s), mean±SD	23.34±9.11	11.39±6.03	<0.001
PVR, (mL), mean±SD	40.81±39.96	87.21±155.20	<0.001
IPSS, (point), mean±SD	12.77±7.62	18.93±12.25	<0.001
IIEF-5, (point), mean±SD	17.96±5.65	13.21±6.14	<0.001

PSA, Prostate specific antigen; Q max, maximum urine flow; PVR, post voided urine mounts; IPSS, International Prostate Symptome score; IIEF-5, International index of erectile function-5.

Table 3. Spearman Correlation Analyses Results

	Clinical progression	Age	Neutrophile	Lymphocyte	Platelet	CRP	PSA	Total testosterone	Prostate volume	Q max	PVR	IPSS	IIEF-5	SII
Clinical progression		0.184**	0.215**	-0.079	-0.271**	0.093**	0.161**	-0.062	0.243**	-0.721**	0.283**	0.321**	-0.377**	0.318**
Age			0.091	-0.310**	-0.190**	0.05	0.362**	0.113	0.429**	-0.246**	0.286**	0.174**	-0.349**	0.142**
Neutrophile				0.128*	0.276**	0.130*	0.11	-0.091**	0.032	-0.160**	0.117	0.215**	-0.132*	0.705**
Lymphocyte					0.266**	0.08	-0.086	-0.098	-0.096	0.056	-0.019	-0.001	0.024	-0.336**
Platelet						0.145*	0.183**	-0.163**	0.041	-0.160**	0.018	0.173**	-0.082	0.534**
CRP							0.095	-0.178**	0.141*	-0.309**	0.170**	0.196**	-0.189**	0.109
PSA								-0.018	0.403**	-0.148*	0.200**	0.186**	-0.214**	0.230**
Total testosterone									-0.018	0.026	-0.059	-0.163**	0.11	-0.096
Prostate volume										-0.277**	0.333**	0.214**	-0.333**	0.095
Q max											-0.371**	-0.462**	0.435**	-0.206**
PVR												0.433**	-0.466**	0.065
IPSS													-0.647**	0.216**
IIEF-5														-0.137*
SII														

CRP, C reactive protein; PSA, Prostate specific antigen; Q max, maximum urine flow; PVR, post voided urine mounts; IPSS, International Prostate Symptome score; IIEF-5, International index of erectile function-5; SII, Systemic immune-inflammation index. Correlation is significant at the 0.01 level (2-tailed).** Correlation is significant at the 0.05 level (2-tailed).*

Table 4. Univariate and Multivariate Analyse Results of the Study

	Univariate analyse	Multivariate analyse	
	p value	OR (CI 95%)	p value
PSA	0.007	0.95 (0.42-2.14)	0.909
Prostate volume	<0.001	0.64 (0.34-1.24)	0.165
Q max	<0.001	55.83 (12.76-244.33)	0.001
PVR	<0.001	1.19 (0.40-3.52)	0.748
IPSS	<0.001	0.67 (0.33-1.39)	0.292
IIEF-5	<0.001	2.63 (1.22-5.63)	0.013
SII	<0.001	0.67 (0.35-1.28)	0.233
Neutrophile	<0.001	1.38 (1.15-1.65)	0.001
Lymphocyte	0.001	0.85 (0.63-1.13)	0.265
Platelet	<0.001	1.00 (1.00-1.01)	0.001

urinary tract symptoms was observed in 121 (43.2%) patients. 82 (23.9%) of patients underwent surgery and 60 (21.4%) of patients progressed to acute urinary retention. Mean SII, IPSS and IIEF-5 scores were calculated as 589.22±767.67, 15.43±10.33, and 15.91±6.31, respectively. The mean prostate volume of the patients was 45.95±26.78 cc (range 14-288). Mean Q max flow was 18.18±9.89 ml/sn and PVR was 63.16±108.92 cc. The clinical characteristics of the patients were summarized in table 2. Statistical significant differences was observed between groups in terms of PSA (p=0.015), SII (p=0.037), prostate volume (p=0.036), Q max flow (p<0.001), PVR (p<0.001), IPSS (p<0.001) and IIEF-5 (p<0.001). Spearman correlation test demonstrated that there was positive correlation between clinical progression and age (r=0.184; p=0.002), neutrophile (r=0.215; p<0.001), platelet (r=0.271; p<0.001), CRP (r=0.193; p=0.001), PSA (r=0.161; p=0.007), prostate volume (r=0.243; p<0.001), PVR (r:0.283; p<0.001), IPSS (r:321; p<0.001), SII (r:0.318; p<0.001), while negative correlation between clinical progression and Q max (r: -0.721; p<0.001), IIEF-5 (r: -0.377 ;p<0.001). Table 3 summarized the correlation coefficient results according to the Spearman correlation analyse. Univariate and multivariate analyse results were summarized in table 4. According to the multivariate analysis, peak urinary flow rate (Qmax), IIEF-5 scores and platelet levels were risk factors to predict the clinical progression of patients with LUTS/BPH. Figure-1 summarized the ROC analysis for the sub-parameters of the formula of SII. According to the ROC analysis, lymphocyte levels (AUC:0.454; p=0.185) were not associated with the clinical progression of patients with LUTS/BPH, but neutrophile and platelet levels were related to clinical progression (AUC:626, p=0.001; AUC:0.658, p=0.001).

Discussion

This cross-sectional retrospective observational study revealed that the findings of our study provide valuable insights into the association between SII levels and clinical progression in patients with LUTS/BPH. We observed that elevated SII levels were significantly correlated with disease progression and worse outcomes. This supports the hypothesis that inflammation and immune dysregulation play a role in the pathogenesis of BPH and the development of LUTS.

Systemic inflammatory biomarkers that can be measured from a blood test may indicate systemic inflammation. Up to date, the association between SII and many kinds of cancers are investigated. Preoperative high SII levels were found associated with an advanced pathological stage for any kind of cancer such as colorectal, bladder, breast, hepatocellular and pancreatic cancers (Chen et al., 2020; Murray et al., 2020; Shui et al., 2021; Zhao et al., 2019). But there are limited studies that investigate the association between LUTS/BPH and systemic inflammation.

The underlying causes of prostatic inflammation remain unclear. Inflammation is likely to play a role in the development and progression of BPH, as evidenced by the strong links between BPH and histological inflammation in specimens from prostate biopsies and BPH surgery. A strong correlation in the development of BPH between histological inflammation, clinical symptoms, prostate volume, and inflammation have been reported (Robert et al., 2009). Furthermore, several studies reported that inflammatory cytokines are over-expressed in BPH tissues (Di Silverio et al., 2003; Nickel et al., 1999). Inflammation has been implicated as the primary stimulus for prostate carcinogenesis, and BPH may represent a pathway of non-malignant, unregulated prostate growth promoted by oxidative stress, inflammatory mediators, and insulin-like growth factors (Lim, 2017). The Olmsted cohort study reported that the risks of both low urine flow rate and prostate volume enlargement were significantly reduced in men with lower urinary tract symptoms with daily use of nonsteroidal anti-inflammatory drugs (NSAIDs) or statins (St Sauver et al., 2006; St Sauver et al., 2011). However, other large cohort studies investigating the effects of NSAIDs on lower urinary tract symptoms found no association between NSAI use and a reduced risk of clinical BPH (Schenk et al., 2012; Sutcliffe et al., 2012). In the study of Meng including 76 patients who underwent transurethral resection of the prostate for BPH, they reported that all patients with hyperplasic prostate had inflammatory cell infiltration, especially in the periglanduler zone. And also, the characteristics of this inflammation was different from chronic prostatitis. The extent of inflammation in hyperplasic prostatic tissue was mostly multifocal, scarcely focal or diffuse infiltration which is different from that of chronic prostatitis. Although T lymphocyte and macrophage infiltration is increased in glandular infiltration, T lymphocyte and B lymphocyte infiltration was increased in the periglandular infiltration (Meng et al., 2020). Furthermore, our study evaluated the correlation between individual components of SII and clinical progression. The analysis revealed that neutrophil and platelet levels were significantly associated with clinical progression, while lymphocyte levels did not show a significant correlation. These findings suggest that neutrophils and platelets play a more prominent role in the inflammatory processes contributing to BPH progression. Inflammation was associated with the LUTS/

BPH development and progression, but we used SII as an indicator of systemic inflammation. We could not show the prostatic inflammation histopathologically.

C-reactive protein (CRP) is one of the non-specific markers of systemic inflammation. Association between CRP and LUTS/BPH is investigated in several studies. The study of Sauver and colleagues including 2,115 men reported that although patients with increased CRP levels were not statistically associated with LUTS/BPH, increased CRP levels were associated with rapid changes in LUTS/BPH. They also showed that CRP>3.0 mg/L was the cut-off level for the rapid changes in LUTS/BPH such as 2 times more likely to increase irritative symptoms and 2.5 times more likely to decrease peak urinary flow rates. Additionally, high BMI, being a smoker and the presence of hypertension were patients with high BMI, smokers and had hypertensions were has increased CRP levels (St Sauver et al., 2009). Another study including 2,337 men reported that CRP may be an indicator of intraprostatic inflammation. Patients with serum CRP>0.30 mg/dL had 1.47 times more likely to have 3 or 4 symptoms, but these results were not statistically significant (Rohrmann et al., 2005). We observed increased CRP levels in patients who clinically progressed, but we could not find statistical significance in logistic regression analyse. These associations could be related to being the non-specific marker for systemic inflammation. CRP levels may be influenced by other parameters such as BMI, diabetes and hypertension. Additionally, there was no association between clinically progression and BMI in our study, and also, BMI was lower in patients who clinically progressed contrary to studies in the literature, although there was no statistical significance.

Although we know that the inflammation may result in the development and progression of the LUTS/BPH, most the patients with LUTS/BPH do not receive prostate biopsy or prostate surgery to indicate the inflammation (Liao et al., 2020). To indicate the inflammation of prostate tissue, several studies investigate some biomarkers such as interleukin-8 in seminal plasma and inducible T lymphocyte co-stimulatory in the urine (Liu et al., 2009; Robert et al., 2009). But, these biomarkers are expensive and not easy to use in daily clinical practice. So, we considered the possibility of using inflammation markers such as SII which is cheap, safe and can be measured from the peripheric blood test. Because using it in clinical practice is easy. Although we could not observe a statistical relationship between the clinical progression of patients with LUTS/BPH with SII, we observed increased levels in patients who progressed clinically, but this progression risk may be associated with the neutrophile and platelet levels which is the part of the formula.

The implications of our study are twofold. First, the association between SII levels and clinical progression highlights the potential utility of systemic immune-inflammatory markers as prognostic indicators in patients with LUTS/BPH. Incorporating SII assessment into routine clinical practice could aid in risk stratification, treatment decision-making, and monitoring of disease progression. Second, the identification of Qmax, IIEF-5 scores, and platelet levels as risk factors underscores the multifactorial nature of disease progression in LUTS/BPH. Comprehensive evaluation of these factors could enhance our ability to predict and manage clinical outcomes effectively.

While our study provides valuable insights, there are some limitations that should be acknowledged. The retrospective nature of the study introduces inherent biases and limits our ability to establish causality. Additionally, the study was conducted at a single center, which may limit the generalizability of the findings. Further multicenter prospective studies with larger sample sizes are warranted to validate our results and explore the underlying mechanisms linking systemic inflammation, urological parameters, and clinical outcomes in LUTS/BPH.

In conclusion, our study demonstrates that elevated SII levels are associated with clinical progression and worse outcomes in patients with LUTS/BPH. The findings suggest that systemic inflammation and immune dysregulation may contribute to disease pathogenesis and highlight the potential utility of SII as a prognostic indicator. Furthermore, our study identifies additional risk factors, including urological parameters and erectile function, that can aid in predicting disease progression. These findings provide valuable insights for risk stratification and personalized management of patients with LUTS/BPH.

Author Contribution Statement

All authors contributed equally in this study.

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Conflict of interest
The authors declared no conflict of interest.

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