Use of the Systemic Immune-Inflammation Index to Predict Treatment Efficacy in Patients with Bladder Pain Syndrome

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ABSTRACT

Objective: To determine the relationship between bladder pain syndrome (BPS) and systemic inflammatory index (SII) and to examine the impact of treatment protocols on it.

Study Design: Observational Study.

Place and Duration of the Study: Department of Urology, Tekirdag Namik Kemal University, Tekirdag, Turkiye, from January 2017 to December 2022.

Methodology: A retrospective analysis was conducted on 30 BPS patients who underwent medical therapy. Upon diagnosis, the patients completed the king's health questionnaire (KHQ), beck depression questionnaire (BDQ), beck anxiety questionnaire (BAQ), and short form (SF-36) quality of life form. Peripheral blood SII was measured. After six months of regular therapy, the SII was recalculated when the patients completed the same forms again. The SII was compared between instances when patients reported more complaints, higher form scores, and instances when they reported fewer and lower scores.

Results: The patients had a mean age of 46.1 ± 13.6 years, with four males and 26 females. The mean follow-up duration was 76.3 ± 24.5 months. Five patients of KHQ subcategories showed statistically significant decreases following therapy (52 to 39.17, 66.66 to 54.16, 54.40 to 41.07, 75.55 to 58.14, and 60.55 to 40.47). All patients of SF-36 components increased ($p = 779$, $p = 0.393$, $p = 0.007$, $p = 0.004$, $p = 0.008$, $p = 0.041$, $p = 0.010$, and $p = 0.767$, respectively). BDQ and BAQ decreased after therapy (11.55 to 11.41 and 11.86 to 11.24, respectively). Lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and SII decreased significantly ($p = 0.001$, 0.019, 0.002 and 0.039, respectively).

Conclusion: SII, lymphocyte count, NLR, and PLR decreased after treatment, similar to BDQ and BAQ. SII is a simple and feasible method for evaluating the treatment efficacy of BPS.

Key Words: *Bladder pain syndrome, Lymphocyte, Neutrophil, Systemic immune inflammation index, Platelet.*

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INTRODUCTION

Bladder pain syndrome (BPS) is defined as persistent or recurrent pain in the urinary bladder region along with at least one other symptom, such as the exacerbation of pain with bladder filling and an increase in daytime and night-time urinary frequency.[1] Its prevalence ranges from 0.01 to 2.3%, with a female predominance.[2] Although the exact pathophysiology of BPS remains unknown, many hypotheses have been proposed to explain its aetiology. A possible aetiology is inflammation. In patients with BPS, diffuse and intense inflammation is noted in the bladder.[3] Moreover, mast cell deposits and inflammatory molecules such as substance P, nerve growth factor, and histamine increase in the urothelium.[4-6]

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The systemic immune-inflammation index (SII) is a simple and feasible marker that is considered to reflect the inflammatory status accurately. Other inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have also been used in studies.[7] The SII can be calculated based on the parameters of a routine complete blood count (CBC) using the formula: Platelet count × neutrophil count/-lymphocyte count.[8]

After treating BPS, the SII may decrease along with a reduction in inflammation. Therefore, the SII could change after treating BPS. The aim of this study was to investigate the connection between BPS and the SII, NLR and PLR and determine if treatment protocols influence them.

METHODOLOGY

With the approval of the Ethics Committee at Tekirdag Namik Kemal University, Tekirdag, Turkiye, 30 patients who were diagnosed as having BPS between January 2017 and December 2022 and underwent regular follow-ups every six months were included in this study. The study's design was retrospective. Because it is so, there are certain limitations, including biases

(e.g., selection, recollection, and confounding), incomplete or inaccurate data, the influence of trends on exposures, and non-representative sample sizes. To standardise the study population, only patients who were solely treated by administering 300 mg of pentosan polysulfate sodium (PPS) daily were included. Patients treated with other medications, including intracavitary medications, and patients with oncological diseases were excluded from the study. According to the authors' clinical follow-up protocol, the patients with BPS were given the king's health questionnaire (KHQ),[9] beck anxiety inventory (BAI),[10] beck depression inventory (BDI),[11] and short form (SF-36) quality of life form[12] at the time of diagnosis and on every routine follow-up visit.[9-12] All the questionnaires were validated in Turkish. Any patient who had lost a minimum of one year of follow-up or had missing data was excluded from the study. The patients who completed the given questionnaires before and after the treatment and had a CBC performed simultaneously were evaluated. Any patient with a concomitant systemic infection and a positive urine culture during the blood testing period was excluded from the study. Based on the CBC parameters, the NLR, PLR, and SII were calculated at the first visit and were recalculated six months after the treatment. The SII values were compared between periods when the patients' complaints were evident before any treatment and periods when the patients' complaints had decreased after the medical treatment.

Statistical variables were analysed using SPSS 26.0 (IBM Corp.). Continuous variables were summarised as means and standard deviations, and categorical variables were summarised as frequencies and percentages. The categorical variables in the study groups were compared using the Shapiro-Wilk test, and the continuous variables were compared using the Wilcoxon test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 30 patients with BPS were included in the study. Four (13.3%) patients were male and 26 (87.7%) were female. The patients' mean age was 46.07 ± 13.6 (24-71) years. The patients were under a standard follow-up protocol; their mean follow-up period was 36.3 ± 14.5 (12-70) months. The general health perception, physical limitation, social limitation, emotion, and sleep/energy level subunit scores in the KHQ, significantly decreased after the treatment ($p = 0.021$, 0.018, 0.039, 0.041, and 0.017, respectively, Table I). Among the patient population, 25 (83.3%) stated that they felt much better with the treatment. Additionally, 22 (73.3%) of them stated that there were improvements in their sleep patterns, and 20 (66.7%) people stated that they felt more energetic with the treatment. In addition, significant increases were noted in the scores of all five parts of the SF-36 (Table II). It was determined that in half of the patients, there was a decrease in pre-existing perineal pain with treatment.

The patients' mean BAI and BDI scores before the treatment were 11.86 ± 10.8 and 11.55 ± 9.2, respectively. The scores slightly decreased after the treatment, but the reductions were insignificant ($p = 0.745$ and 0.807, respectively). The mean platelet, neutrophil, and lymphocyte counts did not change significantly after the treatment (Figure 1 and 2). However, the NLR, PLR, and SII significantly decreased after the treatment ($p = 0.019$, 0.002, and 0.039, respectively) (Table III, Figure 1 and 2).

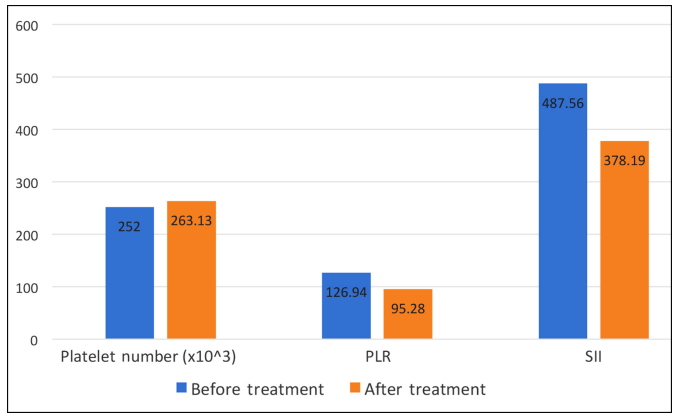

Figure 1: Comparison of platelet number, PLR and SII before and after treatment.

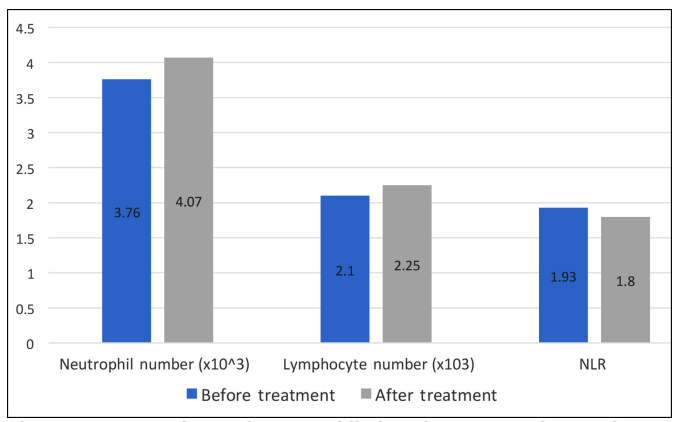

Figure 2: Comparison of neutrophil, lymphocyte number and NLR before and after treatment.

DISCUSSION

The exact pathology of BPS is unknown. A possible aetiological factor is inflammation within the bladder. Various factors, such as some microbial infections, disruption of the bladder mucosa, autoimmunity, and ischaemia, induce inflammation and cause irritative symptoms.[13] PPS is the only Food and Drug Administration (FDA)-approved oral therapeutic agent for BPS. Its mechanism involves adhering to the bladder mucosal membrane and preventing irritants, which may cause irritation and inflammation, from reaching submucosal cells.[14] It also exhibits an anti-inflammatory effect on mast cells by reducing histamine secretion.[15] The administration of PPS has been shown to be efficacious in the management of bladder pain and discomfort in people diagnosed with BPS. This may be attributed to its capacity to repair damaged glycosaminoglycans (GAG) layers and exert anti-inflammatory properties.[16] In general, the studies indicate that PPS exhibits anti-inflammatory properties *via* several pathways, such as the preservation of renal function, decreased inflammatory responses, urothelial repair, inhibition of leukocyte activity, and suppression of inflammatory mediators and enzymes.

Table I: Comparison of king's health questionnaire scores before and after treatment.

	Before treatment (%)	After treatment (%)	p-value
General health perception	52.00 ± 17.35 (46.7-59.9)	39.17 ± 20.43 (34.9-49.7)	0.021
Incontinence impact	77.00 ± 28.31 (68.7-90.3)	70.23 ± 35.53 (61.0-87.7)	0.374
Role limitations	62.07 ± 30.18 (53.3-76.2)	54.76 ± 31.70 (46.3-70.4)	0.208
Physical limitations	66.66 ± 31.18 (56.9-81.5)	54.16 ± 31.63 (44.5-69.6)	0.018
Social limitations	54.40 ± 34.42 (44.1-69.6)	41.07 ± 33.24 (30.2-57.0)	0.039
Personal relationships	54.48 ± 36.07 (39.9-69.1)	51.92 ± 35.06 (37.8-66.1)	0.693
Emotions	75.55 ± 24.66 (65.9-84.6)	58.14 ± 37.33 (54.4-79.8)	0.041
Sleep/energy level	60.55 ± 30.48 (51.0-74.6)	40.47 ± 28.12 (31.8-54.1)	0.017
Severity measures	25.05 ± 19.24 (17.6-33.1)	18.80 ± 16.44 (12.8-26.2)	0.290

**Mean ± standard deviation (SD), confidence intervals. **Shapiro–Wilk test, Wilcoxon test.*

Table II: Comparison of short form-36 questionnaire scores before and after treatment.

	Before treatment (%)	After treatment (%)	p-value
Physical functioning	65.34 ± 30.47 (53.8-76.9)	67.24 ± 29.54 (65.5-84.1)	0.779
Role limitations due to physical health	44.83 ± 43.0 (28.5-61.1)	50.0 ± 43.85 (32.7-67.3)	0.393
Role limitations due to emotional problems	46.66 ± 33.45 (35.8-60.8)	67.78 ± 34.45 (50.5-77.8)	0.007
Energy/fatigue	39.0 ± 19.80 (32.6-47.4)	54.83 ± 21.48 (43.5-58.4)	0.004
Emotional well-being	56.27 ± 20.50 (50.0-65.0)	70.00 ± 19.42 (59.8-73.6)	0.008
Social functioning	50.0 ± 23.86 (40.9-59.1)	64.81 ± 27.52 (53.9-75.7)	0.041
Pain	42.08 ± 28.54 (33.0-54.1)	61.0 ± 29.3 (46.3-69.3)	0.010
General health	41.03 ± 18.19 (34.1-48.0)	44.48 ± 23.81 (32.9-47.8)	0.767

**Mean ± standard deviation (SD), confidence intervals. **Shapiro–Wilk test, Wilcoxon test.*

Table III: Comparison of beck anxiety inventory (BAI) and beck depression inventory (BDI) scores and haematological parameters before and after treatment.

	Before treatment (%)	After treatment (%)	p-value
BECK-A score	11.86 ± 10.8 (8.1-16.8)	11.24 ± 9.02 (8.1-15.4)	0.745
BECK-D score	11.55 ± 9.24 (8.5-15.8)	11.41 ± 9.88 (7.5-15.3)	0.807
Platelet number ($x10^3$)	252.0 ± 34.58 (238.6-266.4)	263.13 ± 50.03 (239.0-279.2)	0.276
Neutrophil number ($x10^3$)	3.76 ± 1.33 (3.1-4.1)	4.07 ± 0.84 (3.7-4.3)	0.150
Lymphocyte number ($x10^3$)	2.10 ± 0.62 (1.8-2.3)	2.25 ± 0.58 (2.07-3.1)	0.546
NLR	1.93 ± 0.94 (1.5-2.3)	1.45 ± 0.36 (1.3-1.6)	0.019
PLR	126.94 ± 40.48 (112.1-145.4)	95.28 ± 23.72 (83.8-100.8)	0.002
SII	487.56 ± 264.44 (372.7-591.4)	378.19 ± 114.14 (322.8-415.3)	0.039

**Mean ± standard deviation (SD), confidence intervals. **Shapiro–Wilk test, Wilcoxon test.*

In addition to exhibiting anti-inflammatory effects, PPS effectively reduce BPS-related symptoms. In a recent meta-analysis, oral PPS treatment exhibited a statistically significant positive effect over the placebo in patients with BPS.[17] In another study, PPS successfully reduced pelvic pain, urinary urgency, pollakiuria, and nocturia symptoms by 37%, 28%, 54%, and 48%, respectively.[18] In addition to causing symptomatic improvement, the authors found that PPS treatment increased the general health perception, physical limitation, social limitation, emotion, and sleep/energy level scores in the KHQ. The KHQ is a good indicator of the general health of patients with bladder problems. Some subunit scores in this questionnaire significantly increased in the patients with BPS after PPS treatment. Nickel *et al.* found that PPS treatment improved sleep dysfunction and physical and mental health-related quality of life.[19] Oral PPS treatment can improve the physical and psychological status of patients with BPS by reducing the sensation of discomfort around the bladder. Similarly, the SF-36 provides a multidimensional measure of patients' health-related quality of life with BPS, with lower scores representing more pain. PPS treatment improved scores related to emotional role limitations, energy levels, social functioning, and pain. The pain around the bladder may affect emotion- and energy-related subscale scores. PPS treatment diminishes the pain around the bladder, increases patients' sense of comfort, and makes patients feel happier and more active. Similarly, both anxiety and depression scores decrease with the PPS treatment.

Because BPS is associated with bladder inflammation, the SII may be a helpful indicator of BPS and may decrease after treatment. The study of novel biomarkers as indicators of inflammation has recently drawn increasing attention. Neutrophils, lymphocytes, and platelets may contribute to inflammatory processes.[20] In a recent study, the normal range of NLR was found to be 1-2.[20] The present authors found that even at the time of diagnosis, the NLR of patients with BPS was higher than that of the healthy population; thus, it is an indicator of high inflammation in the body. The SII has recently been claimed to be more predictive than the NLR and PLR.[21] In this study, all these parameters decreased after treating BPS with PPS, suggesting that PPS exhibits a strong anti-inflammatory effect.

This is the first study to demonstrate the relationship between BPS and increased SII, NLR, and PLR. The researchers revealed the relationship between BPS and inflammation and that inflammation can be reduced in patients with BPS after medical treatment. It was demonstrated that the SII can be used in the follow-up of patients with BPS when inflammation is predominantly involved. Moreover, the relationship of BPS with the SII, NLR, and PLR was also demonstrated.

This study has some limitations. First, it had a retrospective design. Second, this study's population was relatively small because only those patients with BPS were included who were using a particular medication (PPS) and undergoing regular follow-ups. Generalising the findings to all patients with BPS was challenging due to the unique patient population involved. Nevertheless, more research is necessary to see if the SII can aid in the diagnosis or act as a possible indicator for other treatments used for BPS. There is a need for randomised controlled prospective studies with a large patient population to investigate whether other drugs used in treating BPS, such as amitriptyline, have similar effects, or the effects of different doses of PPS. Future research is also required to clarify the inflammatory basis of BPS. Third, some published literature indicates that the SII and NLR are affected by many factors, including age, medication use, coronary heart disease, stroke, diabetes, obesity, anaemia, and stress.[22] However, it was not possible for the authors to assess these factors for each patient. Therefore, the authors had to ignore these situations for this unique disease.

CONCLUSION

In patients with BPS, inflammatory markers, depression, anxiety scores, and perineal pain decreased, and quality of life and energy levels increased after the appropriate PPS treatment. The SII, NLR, and PLR as inflammatory markers could be used as predictors of the efficacy of PPS treatment.

ETHICAL APPROVAL:

This study protocol was reviewed and approved by the Ethical Committee of Tekirdag Namik Kemal University. (Approval no: 2022.61.04.11, Dated: 26.04.2022). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

PATIENTS' CONSENT:

A written informed consent was obtained from all the participants (for the ones under age 18, a written informed consent was obtained from their parent/legal guardian/next of kin) to participate in the study. Each patient who participated in the study has given written consent to have their data join the Tekirdag Namik Kemal University Urology Department Urodynamics and Functional Urology database. Another written consent was also obtained for the use of the data for retrospective analysis.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

MA, CD: Substantial contribution to conception and design, acquisition, analysis, and interpretation of data.
EE, AM: Pathological laboratory works.
CY, MFS: Drafting and revision of the manuscript critically for important intellectual content.
All authors approved the final version of the manuscript to be published.

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