RESEARCH ARTICLE

Is the Neutrophil-Lymphocyte Ratio an Indicator of Progression in Patients with Benign Prostatic Hyperplasia?

Serhat Tanik[1]*, Sebahattin Albayrak[1], Kursad Zengin[1], Hasan Borekci[2], Hasan Bakirtas[1], M Abdurrahim Imamoglu[1], Mesut Gurdal[1]

Abstract

Purpose: The aim of this study was to evaluate inflammation parameters and assess the utility of the neutrophil-lymphocyte ratio (NLR) as a simple and readily available predictor for clinical disease activity in patients with nenign prostate hyperplasia BPH. We also aimed to investigate the relationship between inflammatory parameters with α-blocker therapy response, and evaluate the potential association between NLR and the progression of benign prostatic hyperplasia (BPH). Materials and Methods: We examined 320 consecutive patients (July 2013-December 2013) admitted to our outpatient clinic with symptoms of the lower urinary tract at Bozok University. The mean age was 60 (range, 51-75) years. Complete blood count (CBC), prostate-specific antigen (PSA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were assessed. Correlations between PSA, CRP, ESR, prostate volume, International Prostate Symptom Score (IPPS), maximum urinary flow rate (Qmax), and NLR were assessed statistically. Patients were divided into two groups: high and low risk of progression. Results: NLR was positively correlated with IPSS (p=0.001, r=0.265), PSA (p=0.001, r=0.194), and negatively correlated with Qmax (p<0.001, r=-0.236). High-risk patients a had a higher NLR compared with low-risk patients, based on IPSS (p<0.001), PSA (p=0.013), and Qmax (p<0.001); however, there were no significant differences between the groups in terms of age (p>0.05), and prostate volume (p>0.05). Conclusions: NLR can predict BPH progression. We propose that increased inflammation is negatively associated with clinical status in BPH patients and suggest that NLR can give information along with LUTS severity which may be used as a readikly accessible marker for patient follow-up.

Keywords: Benign prostatic hyperplasia - progression - inflammation - neutrophil-lymphocyte ratio

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Introduction

Benign prostatic hyperplasia (BPH) is a common disease in older males. BPH affects 25% of males over 50 years, 33% of those aged ≥60, and 50% of individuals' ≥80 (McVary, 2006). BPH is the most common benign tumor in elderly men (Izmirli et al., 2011). Di Silverio et al. demonstrated that inflammation was correlated with worsened clinical parameters of BPH (Di Silverio et al., 2003). *In vivo* and *in vitro* studies revealed that inflammation plays a role in the development of BPH. Chronic prostatic inflammation is also a risk factor for the development of acute urinary retention during BPH and an increase in prostatic volume (Djavan et al., 2009).

Increased prostate-specific antigen (PSA) levels can be caused by increased prostate volume, but might also be explained by increased release of PSA in to the circulation due to inflammation-induced epithelial damage (Karazanashvili, 2008). It was suggested that immunological events and the response to prostatic inflammation cause BPH and prostate cancer. Cells in the immune system release cytokines, which induce and stimulate other cells to release growth factors. This promotes the replication of stromal cells, which increases the prostate volume. Because of this, anti-inflammatory therapies have been used to treat BPH and successfully improve symptoms. Anti-inflammatory drugs may provide an early response to the symptoms and assist recovery in BPH patients; therefore it is important to determine which patients are likely to respond to therapy. Serum malondialdehyde (MDA), some interleukins, and C-reactive protein (CRP) are currently used to identify patients likely to respond to different therapies (Djavan et al., 2009).

The main medications used to manage BPH are α 1-adrenoreceptor antagonists, which function by inhibiting the effects of endogenously released noradrenaline on prostate smooth muscle cells, thereby reducing prostate tone and obstruction of the bladder outlet (Michel and Vrydag, 2006).

*[1]Department of Urology, [2]Department of General Surgery, Bozok University, School of Medicine, Yozgat, Turkey, *For correspondence: tanikserhat@gmail.com*

The neutrophil-lymphocyte ratio (NLR) can be calculated easily from complete blood counts and is an easily accessible marker which indicates the state of inflammation in the body. Recently, the neutrophil-to-lymphocyte ratio (NLR) was introduced as a potential biomarker to assess inflammation and to predict outcomes in cancer, cardiac and other disorders (Walsh et al., 2005; Nunez et al., 2008; Tamhane et al., 2008; Halazun et al., 2009; Celikbilek et al., 2013). We can obtain information about two different immune pathways from the NLR. First of all about the neutrophils which are responsible for lasting inflammation and the second about the lymphocytes which demonstrate the regulatory pathway (Celikbilek et al., 2013). Cihan's study patients with BPH had a higher level of neutrophils (Cihan et al., 2013).

The aim of this study was to evaluate inflammation parameters and assess the utility of NLR as a simple and readily available predictor for clinical disease activity in patients with BPH. We also aimed to investigate the relationship between inflammatory parameters with α-blocker therapy response, and evaluate the potential association between NLR and the progression of BPH.

Materials and Methods

Study population

We examined consecutive 320 patients (July 2013-December 2013) admitted to our outpatient clinic with symptoms of the lower urinary tract at Bozok University. The mean age of the patients was 60 (range, 51-75) years. BPH was defined according to BPH clinical study guidelines; age >50 years, International Prostate Symptom Score (IPSS) ≥8 points, prostate volume ≥20cc, maximum urinary flow rate (Qmax) <15mL/second (with a minimum voided volume ≥130ml) and post-void residual volume <100mL (Araki et al., 2013). Patients with acute infections, those who were using anti-inflammatory drugs, acetylsalicylic acid, diuretics, α-blockers, or 5-α reductase inhibitors, and individuals with a history of prostate and urethral surgery, urethral stricture, neurological disease, renal failure, malignancy, and connective tissue diseases were excluded from the study. Acute urinary tract infection was ruled out by a urine culture.

We examined and recorded complete blood counts (CBC), prostate-specific antigen (PSA), erythrocyte sedimentation rate (ESR), and CRP. Qmax and IPSS were evaluated before and 6 weeks after therapy. All patients BPH symptoms were treated with Tamsulosin (0.4mg) after the first diagnosis. The difference between Qmax and IPSS values obtained before and after treatment was calculated (Qmax changes and IPSS changes). The NLR ratio was calculated using the values of neutrophils and lymphocytes obtained from the patients complete blood counts. The correlation between PSA, CRP, ESR, prostate volume, IPSS, IPSS change, Qmax, Qmax change, and NLR was assessed statistically.

In each pretreatment progression criteria's, patients were divided into 2 groups according to Crawford's and Roehrborn's studies: high and low risk of BPH progression. The low risk group was characterized by a PSA <1.6ng/mL, prostate volume <31mL, age <62 years, IPPS <20 points, Qmax ≥10.6mL/second; the high risk group included individuals with a PSA ≥1.6 ng/mL, prostate volume ≥31mL, age ≥62 years, IPPS ≥20 points, and Qmax <10.6mL/second (Crawford et al., 2006; SpringerBasicRoehrborn et al., 2014). NLR was compared between the low- and high-risk groups.

Statistical analysis

Shapiro-Wilk's and Levene's tests were used to test the normality and variance homogeneity of data. Values are expressed as frequencies and percentages, mean±standard deviation or median and 25th-75th percentiles. To compare parametric continuous variables, Student's t-test was used; to compare nonparametric continuous variables, the Mann–Whitney U-test was used. Categorical data were compared by Chi-square distribution. Pearson's test was used for correlation analysis. Receivers operating characteristic (ROC) curve analysis were performed for the N-L ratio. The areas under the ROC curve values

Table 1. Baseline Characteristics of Patients

Variables	Mean±S.D.	N
Prostate-specific antigen (ng/mL)	2.7±0.9	320
Neutrophil-to-lymphocyte ratio	2.25±1.2	320
Erythrocyte sedimentation rate (mm/h)	11±2	320
C-reactive protein (mg/L)	0.63±1	320
Prostate volume (mL)	42.30±9	320
International Prostate Symptom Score	18.5±7	320
International Prostate Symptom Score change	5.3±3	320
Maximum urinary flow rate (mL/second)	12±3	320
Maximum urinary flow rate change	2.1±1.1	320
Age (years)	60.72±8.9	320

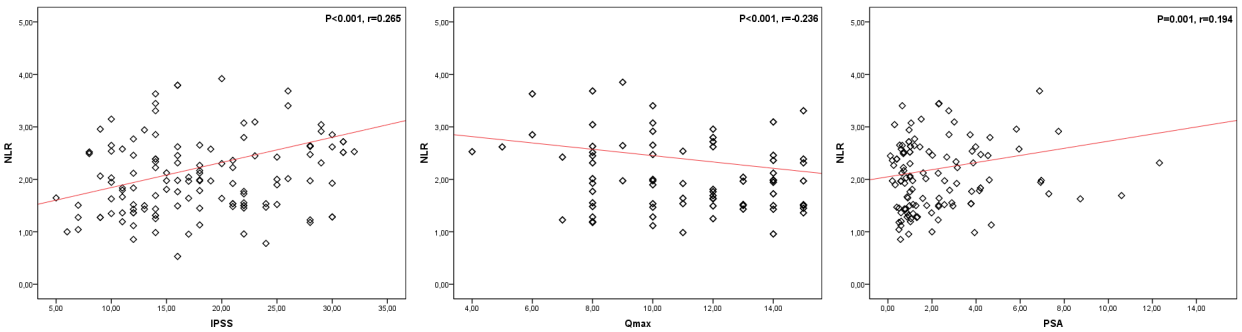

Figure The Correlation of A Neutrophil-Lymphocyte Ratio between International Prostate Symptom Score (IPSS), Maximum Urinary Flow Rate (Qmax), and Prostate-Specific Antigen (PSA)

Table 2. Parameters of Progression According to the NLR

Neutrophil-to-lymphocyte ratio		N	Mean±S.D.	p value
Prostate volume	<31ml	125	2.14±0.89	
	≥31ml	195	2.32±1.46	0.212
IPSS	0-19	178	1.99±0.72	
	20-35	142	2.58±1.71	<0.001
Qmax	<10.6	143	2.73±1.92	
	≥10.6	177	2.00±0.73	<0.001
Age (y)	<62	191	2.22±1.38	
	≥62	129	2.29±0.97	0.610
PSA	<1.6	156	2.04±0.7	
	≥1.6	164	2.43±0.9	0.013

*Abbreviations: International prostate symptom score (IPSS) points, maximum urinary flow rate (Qmax) (mL/second), prostate-specific antigen (ng/mL)

Table 3. Receiver-operating Characteristic (ROC) Curve Analyses Results According to Neutrophil-to-Lymphocyte Ratio

Variables	NLR cut-off	SEN (95% CI)	SPE (95% CI)	p values
Prostate-specific antigen (ng/mL)	1.96	54	44	0.018
Prostate volume (mL)	1.96	57	47	0.606
International prostate symptom score	1.93	55	37	0.002
Maximum urinary flow rate (mL/second)	1.99	62	57	0.001
Age (years)	1.99	52	52	0.245

*SEN: Sensitivity; SPE: Specifity; NLR: Neutrophil-to-lymphocyte ratio

with 95% CIs were calculated and compared with each other. Optimal cut-off values were determined, sensitivity, specify were calculated with (95% CI). Statistical analyses were performed using the statistical package SPSS, version 15.0 (SPSS Inc., Chicago IL, USA); a value of $p<0.05$ was used to define statistical significance.

Results

Baseline characteristics of patients were summarized in (Table 1). The mean age of the patients was 60 (range, 51-75) years. PSA was positively correlated with prostate volume ($p<0.001$, $r=0.475$), patient age ($p=0.001$, $r=0.181$), and NLR ($p=0.001$, $r=0.194$) negatively correlated with Qmax ($p=0.035$, $r=-0.128$). Prostate volume was positively correlated with IPSS ($p=0.02$, $r=0.177$), change in IPSS ($p=0.03$, $r=0.172$), and patient age ($p<0.001$, $r=0.291$), negatively correlated with Qmax ($p=0.002$, $r=-0.187$), but not with change in Qmax. IPSS was positively correlated with NLR ($p<0.001$, $r=0.265$), patient age ($p<0.001$, $r=0.277$), and ESR ($p=0.03$, $r=0.251$), negatively correlated with Qmax ($p<0.001$, $r=-0.655$). Qmax was negatively correlated with NLR ($p<0.001$, $r=-0.236$), patient age ($p<0.001$, $r=-0.350$). High-risk patients according to IPSS, PSA and Qmax values had a higher NLR compared with low-risk patients, based on IPSS ($p<0.001$), PSA ($p=0.013$), and Qmax ($p<0.001$); however, there were no significant differences between the groups in terms of age ($p>0.05$), and prostate volume ($p>0.05$) (Table 2).

Receivers operating characteristic (ROC) analyses showed that the cut-off value for NLR as an indicator of progression according to Qmax was 1.99, with a specificity and sensitivity of 57 and 62%, respectively (Table 3).

Discussion

In this study, IPSS, which is related to clinical status in BPH patients, was positively correlated with prostate volume, age and inflammatory parameters including ESR and NLR. Also NLR were higher in all high risk groups but it is not statistically significant in prostate volume and age groups. Additionally, IPSS, Qmax, and PSA were statistically significant.

Previous studies demonstrated that an increasing number and activity of inflammatory cells in tissues are detected during the histological examination of nodular hyperplasic prostate gland; lymphocytes can be seen in the interstitium and around the ductus. This may be the result, rather than the cause, of hyperplasia (McVary, 2006). There are two hypotheses to explain the chronic inflammation observed with BPH. One is infections and infection-related events. The other is an autoimmune response to bacteria and viruses, both of which are commonly identified in specimens of BPH tissue and chronic prostatitis. Sauver et al. demonstrated that prostatitis may be a risk factor for the development of BPH (St Sauver et al., 2008). Increasing evidence suggests an important role for chronic inflammation in bacterial infections, urine reflux, the response to dietary factors and hormones, and the autoimmune response during the development and progression of benign and malignant prostatic disorders (De Marzo et al., 2007; Fibbi et al., 2010; De Nunzio et al., 2011). PSA might be affected by prostate volume, the grade and stage of neoplasms, patient age, and ethnicity (Partin et al., 1990). Several studies reported that the extent and grade of inflammation were correlated positively with serum PSA levels (Kandirali et al., 2007; Ozden et al., 2007). We also reported that PSA levels were positively correlated with NLR which confirms the association of inflammation and PSA. Also PSA was positively correlated with prostate volume and age, consistent with previous studies.

In the current study, Qmax, IPSS and IPSS changes were correlated with prostate volume, which is associated with the clinical status of patients. Therefore, patients with high-grade prostatic inflammation and IPSS had a significantly greater prostate volume (Mishra et al., 2007). As the prostate volume or PSA levels increase, so do the likelihood of symptom deterioration, the risk of acute urinary retention (AUR), and the possible need for BPH-related surgery (Roehrborn et al., 1999; Madersbacher et al., 2007; Emberton et al., 2011).Compatible with these findings , according to our results, NLR was associated with IPSS, Qmax and clinical status of patients. In addition, PSA, and IPSS were positively correlated, and Qmax were negatively correlated with NLR; NLR ($p<0.001$, $r=0.265$) was more strongly positively correlated with these parameters than with ESR ($p=0.03$, $r=0.251$) and CRP ($p>0.05$, $r=0.068$). NLR can be obtained easily during routine CBC, and may predict disease severity more accurately than ESR and CRP.

In our study, only prostate volume predicts the response to α-blocker therapy but inflammatory parameters and other parameters are not. Therefore, prostate volume, which affects the response to α-blocker therapy, could

be used to predict the response of patients to treatment.

Although not a life-threatening situation like prostate, symptomatic BPH produce severe influence on quality of life and evidently requires urgent therapeutic interventions (Konwar et al., 2010). Benign prostatic hyperplasia is also a progressive disease, mainly characterized by a deterioration of lower urinary tract symptoms (LUTS) over time, and in some patients by the occurrence of serious outcomes such as acute urinary retention (AUR) and need for BPH-related surgery (Roehrborn, 2008). The role of inflammation in BPH is well defined. Nevertheless, a more affordable and readily available marker is needed to predict the progression of BPH. NLR was higher in patients at high risk of progression compared with those at low risk. Our results suggest that NLR was associated with BPH progression. A previous study compared the pathology specimens of 374 patients who underwent transurethral resection of the prostate (TURP) for either LUTS or urinary retention. They reported that 70% of males with urinary retention had acute and/or chronic inflammation compared with 45% of males without LUTS. These data support the hypothesis that anti-inflammatory therapies may relieve BPH symptoms and condition the growth of prostate tissue (Sebastiano et al., 2012).

A previous study showed that the primary outcome was time to overall clinical progression of BPH, defined as either a confirmed 4-point or more increase in American Urological Association Symptom Score, acute urinary retention, incontinence, renal insufficiency, or recurrent urinary tract infection. Baseline total prostate volume, PSA, Qmax, post void residue and age were important predictors of the risk of clinical progression of BPH (Crawford et al., 2006). According to our results, NLR, with a cut-off value of 1.99, can be used in conjunction with other parameters in predicting the progression of BPH.

In a double-blinded, randomized study, Falahatkar et al. assessed the effect of Celecoxib on nocturia and IPSS; the frequencies of nocturia and IPSS were lower in the Celecoxib-treated group than in the control group (Falahatkar et al., 2008). NLR could be an important measure of systemic inflammation as it is cost effective, readily available (Karaman et al., 2013). However, the current study failed to demonstrate that pre-treatment NLR was predictive of the response to therapy. This may be because this study was retrospective, and anti-inflammatory therapies were not used. A future randomized trial may be able to demonstrate such an effect using combined treatment with anti-inflammatory agents and α-blockers. The concurrent use of anti-inflammatory agents and α-blockers may increase the therapeutic response.

In conclusion, NLR can predict the BPH progression. We propose that the increased inflammation was negatively associated with clinical status in BPH patients. We suggest that NLR can give information along with LUTS severity and may be used as an easily accessible marker for patients follow-up.

References

Araki T, Monden K, Araki M (2013). Comparison of 7 alpha(1)-adrenoceptor antagonists in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia:a short-term crossover study. *Acta Med Okayama*, **67**, 245-51.

Celikbilek M, Dogan S, Ozbakir O, et al (2013). Neutrophil-lymphocyte ratio as a predictor of disease severity in ulcerative colitis. *J Clin Lab Anal*, **27**, 72-6.

Cihan YB, Arslan A, Ergul MA (2013). Subtypes of white blood cells in patients with prostate cancer or benign prostatic hyperplasia and healthy individuals. *Asian Pac J Cancer Prev*, **14**, 4779-83.

Crawford ED, Wilson SS, McConnell JD, et al (2006). Baseline factors as predictors of clinical progression of benign prostatic hyperplasia in men treated with placebo. *J Urol*, **175**, 1422-6; discussion 6-7.

De Marzo AM, Platz EA, Sutcliffe S, et al (2007). Inflammation in prostate carcinogenesis. *Nat Rev Cancer*, **7**, 256-69.

De Nunzio C, Kramer G, Marberger M, et al (2011). The controversial relationship between benign prostatic hyperplasia and prostate cancer: the role of inflammation. *Eur Urol*, **60**, 106-17.

Di Silverio F, Gentile V, De Matteis A, et al (2003). Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis. *Eur Urol*, **43**, 164-75.

Djavan B, Eckersberger E, Espinosa G, et al (2009). Complex mechanisms in prostatic inflammatory response. *Eur Urology Supplements*, **8**, 872-8.

Emberton M, Fitzpatrick JM, Rees J (2011). Risk stratification for benign prostatic hyperplasia (BPH) treatment. *BJU Int*, **107**, 876-80.

Falahatkar S, Mokhtari G, Pourreza F, et al (2008). Celecoxib for treatment of nocturia caused by benign prostatic hyperplasia: a prospective, randomized, double-blind, placebo-controlled study. *Urology*, **72**, 813-6.

Fibbi B, Penna G, Morelli A, et al (2010). Chronic inflammation in the pathogenesis of benign prostatic hyperplasia. *Int J Androl*, **33**, 475-88.

Halazun KJ, Hardy MA, Rana AA, et al (2009). Negative impact of neutrophil-lymphocyte ratio on outcome after liver transplantation for hepatocellular carcinoma. *Ann Surg*, **250**, 141-51.

Izmirli M, Arikan B, Bayazit Y, et al (2011). Associations of polymorphisms in HPC2/ELAC2 and SRD5A2 genes with benign prostate hyperplasia in Turkish men. *Asian Pac J Cancer Prev*, **12**, 731-3.

Kandirali E, Boran C, Serin E, et al (2007). Association of extent and aggressiveness of inflammation with serum PSA levels and PSA density in asymptomatic patients. *Urology*, **70**, 743-7.

Karaman H, Karaman A, Erden A, et al (2013). Relationship between colonic polyp type and the neutrophil/ lymphocyte ratio as a biomarker. *Asian Pac J Cancer Prev*, **14**, 3159-61.

Karazanashvili G (2008). Editorial comment on: the relationship between prostate inflammation and lower urinary tract symptoms: examination of baseline data from the REDUCE trial. *Eur Urol*, **54**, 1383-4.

Konwar R, Manchanda PK, Chaudhary P, et al (2010). Glutathione S-transferase (GST) gene variants and risk of benign prostatic hyperplasia: a report in a North Indian population. *Asian Pac J Cancer Prev*, **11**, 1067-72.

Madersbacher S, Marszalek M, Lackner J, et al (2007). The long-term outcome of medical therapy for BPH. *Eur Urol*, **51**, 1522-33.

McVary KT (2006). BPH: epidemiology and comorbidities. Am *J Manag Care*, **12**, S122-8.
Michel MC, Vrydag W (2006). Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. *Br J Pharmacol*, **147**, 88-119.
Mishra VC, Allen DJ, Nicolaou C, et al (2007). Does intraprostatic inflammation have a role in the pathogenesis and progression of benign prostatic hyperplasia? *BJU Int*, **100**, 327-31.
Nunez J, Nunez E, Bodi V, et al (2008). Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. *Am J Cardiol*, **101**, 747-52.
Ozden C, Ozdal OL, Guzel O, et al (2007). The correlation between serum prostate specific antigen levels and asymptomatic inflammatory prostatitis. *Int Urol Nephrol*, **39**, 859-63.
Partin AW, Carter HB, Chan DW, et al (1990). Prostate specific antigen in the staging of localized prostate cancer: influence of tumor differentiation, tumor volume and benign hyperplasia. *J Urol*, **143**, 747-52.
Roehrborn CG (2008). BPH progression: concept and key learning from MTOPS, ALTESS, COMBAT, and ALF-ONE. *BJU Int*, **101**, 17-21.
Roehrborn CG, Boyle P, Bergner D, et al (1999). Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group. *Urology*, **54**, 662-9.
Sebastiano C, Vincenzo F, Tommaso C, et al (2012). Dietary patterns and prostatic diseases. *Front Biosci*, **4**, 195-204.
SpringerBasicRoehrborn CG, Barkin J, Tubaro A, et al (2014). Influence of baseline variables on changes in International Prostate Symptom Score after combined therapy with dutasteride plus tamsulosin or either monotherapy in patients with benign prostatic hyperplasia and lower urinary tract symptoms: 4-year results of the CombAT study. *BJU Int*, **113**, 623-35.
St Sauver JL, Jacobson DJ, McGree ME, et al (2008). Longitudinal association between prostatitis and development of benign prostatic hyperplasia. *Urology*, **71**, 475-9; discussion 9.
Tamhane UU, Aneja S, Montgomery D, et al (2008). Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. *Am J Cardiol*, **102**, 653-7.
Walsh SR, Cook EJ, Goulder F, et al (2005). Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. *J Surg Oncol*, **91**, 181-4.