



# Impact of Preoperative Neutrophil to Lymphocyte Ratio in Patients with Benign Prostate Hyperplasia Undergo Open Prostatectomy: A Pilot Study

## Preoperatif Nötrofil Lenfosit Oranının Açık Prostatektomi Yapılan Benign Prostat Hiperplazili Hastalarda Perioperatif Sonuçlara Etkisi

Erhan ATEŞ<sup>1</sup>, Yiğit AKIN<sup>2</sup>, Tümay İPEKÇİ<sup>3</sup>, Eyyüp Sabri PELİT<sup>4</sup>, İltter ALKAN<sup>5</sup>, Halil ÇİFTÇİ<sup>4</sup>, Ercan YENİ<sup>4</sup>

<sup>1</sup>Adnan Menderes University Faculty of Medicine, Department of Urology, Aydın, Turkey

<sup>2</sup>İzmir Katip Çelebi University Faculty of Medicine, Department of Urology, İzmir, Turkey

<sup>3</sup>Başkent University Alanya Practice and Research Center, Department of Urology, Antalya, Turkey

<sup>4</sup>Harran University Faculty of Medicine, Department of Urology, Şanlıurfa, Turkey

<sup>5</sup>Okmeydani Training and Research Hospital, Urology Clinic, Istanbul, Turkey

Correspondence Address

Yazışma Adresi

**Erhan ATEŞ**

Adnan Menderes Üniversitesi  
Tıp Fakültesi, Üroloji Anabilim  
Dalı, Aydın, Turkey

E-mail: drerhanates@yahoo.com

### ABSTRACT

**Objective:** To evaluate preoperative Neutrophil-to-lymphocyte ratio (NLR) in patients who underwent open prostatectomy (OP) for symptomatic BPH.

**Material and Methods:** Our database were investigated for OP between December 2012 and November 2015. Demographic, perioperative, and postoperative data were recorded. Delta haemoglobin was calculated as (preoperative haemoglobin) – (post-operative haemoglobin). Complications was assessed according to Clavien Classification. Significant p was p<0.05.

**Results:** In total, 47 patients enrolled into the study. Mean age was 71.1±4.9 years. Mean Prostate specific antigen 3.7±2.1 ng/dl, Mean delta haemoglobin was 2.4±1.4 and mean duration of drainage was 4.4±1.3 days. Mean NLR was 4±1.6. According to statistical analyses NLR was significant associated with estimated blood loss (EBL) (p=0.005). In multivariate logistic regression analyses, EBL was also associated with operation time (p=0.02) and blood transfusion rate (p=0.05). The most common complication was postoperative fever, in 12 patients (Clavien1). Seven patients needed blood transfusion (Clavien 2).

**Conclusion:** Preoperative NLR may help us to predict EBL and indirectly operation time, in OP patients. There is need more well designed studies with and high numbers of patients on this issue.

**Key Words:** Benign prostatic hyperplasia, Neutrophil to lymphocyte ratio, Operative time, Prostatectomy, Surgical blood loss

### ÖZ

**Amaç:** Çalışmanın amacı semptomatik benign prostat hiperplazisi (BPH) nedeniyle açık prostatektomi yapılan hastalarda preoperatif nötrofil lenfosit oranının (NLO) perioperatif sonuçlar üzerine etkisinin değerlendirilmesidir.

**Gereç ve Yöntemler:** Aralık 2012 ve Kasım 2015 arasında BPH nedeniyle açık prostatektomi olan hastaların demografik, perioperatif ve postoperatif verileri retrospektif olarak değerlendirildi. Demografik özellikler olarak yaş, komorbiditeler, prostat hacmi (ml), PSA (ng/dl), serum nötrofil ve lenfosit değerleri ve oranı; intraoperatif özellikler olarak operasyon süresi (dk.), tahmini kan kaybı (ml), kan transfüzyon oranı; postoperatif özellikler olarak hospitalizasyon süresi ile drenaj kateterinin ve üretral sondanın kalış süresi, kan transfüzyon miktarı ve komplikasyonlar kaydedildi. Delta haemoglobin (Preoperatif Hemoglobin – Postoperatif Hemoglobin) ölçüldü. Komplikasyonlar Clavien sınıflamasına göre değerlendirildi. Anlamli p değeri p<0.05 olarak kabul edildi.

**Bulgular:** Toplam 47 hasta çalışmaya dahil edildi. Ortalama yaş 71,1±4,9 yıl, ortalama PSA değeri 3,7±2,1 ng/dl, ortalama prostat hacmi 89,3±4,7 ml, ortalama delta haemoglobin değeri 2,4±1,4, drenaj kateterinin ortalama kalış süresi 4,4±1,3 gün ve ortalama NLO 4±1,6 idi. Tahmini kan kaybı ile NLO arasında istatistiksel olarak anlamlı bir ilişki vardı (p=0,005). Multivariate lojistik regresyon

Received \ Geliş tarihi : 19.11.2017

Accepted \ Kabul tarihi : 27.11.2017

Elektronik yayın tarihi : 05.01.2018

Online published

DOI: 10.17954/amj.2018.105

analizinde tahmini kan kaybı ile operasyon süresi ( $p=0,02$ ) ve kan transfüzyon oranı ( $p=0,05$ ) arasında ilişki tespit edildi. En yaygın komplikasyon postoperatif ateşi (Clavien 1). Yedi hastada kan transfüzyon ihtiyacı oldu (Clavien 2).

**Sonuç:** Preoperatif NLO açık prostatektomi yapılan hastalarda tahmini kan kaybı ve indirekt operasyon süresi için bir prediktör faktör olabilir. Bu etkinin tam olarak açıklığa kavuşturulabilmesi için daha geniş serilerle ileri çalışmalara gereksinim vardır.

**Anahtar Sözcükler:** Benign prostat hiperplazisi, Nötrofil lenfosit oranı, Operasyon süresi, Prostatektomi, Cerrahi kan kaybı

## INTRODUCTION

Benign prostate hyperplasia (BPH) is one the most frequent diseases in the aging male (1). The BPH include cellular growth and enlargement (2). Thus, it can cause to lower urinary tract symptoms (LUTS). These can decrease quality of life and may lead to loss human power (3). However, the size of prostate may disproportionate to the severity of LUTS (4). Nonetheless, BPH can effect men over 40 years and one of three men have BPH between 50-65 years old (5). Furthermore, inflammation and its association with BPH is recently a hot topic (6). Enlarged prostate may be associated with higher inflammation in prostate (7). The quantity of inflammation may indirectly affect treatment strategies in course of BPH. At this point, neutrophil to lymphocyte ratio (NLR) can be one of the markers of inflammation and its clinical relations (8).

A stepped therapy is recommended for LUTS due to BPH (9). The conservative treatment includes watchful waiting, behavioural and dietary modifications, and practical considerations (10). The second step is medical management and of course alpha blockers, notably alpha receptor specific ones, are the essential for treatment of BPH (11). The size of prostate size does not affect efficacy of alpha blocker which can be more effective in patients with smaller prostates ( $< 40$  mL) (12,13). Combination of medical therapy in term of 5alpha reductase inhibitors and alpha blockers are recently used for patients with prostate bigger than 40ml (14). Additionally, muscarinic receptor antagonists in case of predominant over active bladder (15) and/or phosphodiesterase 5 inhibitors in case of erectile dysfunction with/without LUTS (16) are the other components of combination therapies for BPH.

Surgical treatment options come into question when there is no response to medical treatment or increasing LUTS under medical treatment. Transurethral resection of prostate is the gold standard endoscopic treatment option (17). However, European Association of Urology guidelines on BPH recommended open prostatectomy (OP) in patients with enlarged glands ( $> 80-100$  mL) (18).

A handful of published studies on relationship between BPH and NLR. However, there is no study on effects of NLR and surgical treatment modalities in BPH.

We here focused on effects of preoperative NLR in patients who were scheduled for OP. The evaluations were

performed under statistical analyses, in this pilot study. According to our best knowledge, this is the first study that impact of preoperative NLR was investigated in OP patients.

## MATERIAL and METHOD

### Study Design

This study presents retrospective view of prospectively collected data. Three centres provided data for present study. Institutional approval was gained and all procedures performed in studies involving human participants 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. All patients read and understand the aim of the study. Then, informed consent was obtained from all individual participants included in the study. Patients with a prostate volume greater than 80 ml and who did not benefit from combined therapy consisting of an alpha blocker and a 5-alpha reductase inhibitor were included in the study. Excluding criteria were having prostate cancer, previous prostate operations, active and chronic cystitis, co-morbidity including inflammatory and autoimmune diseases such as rheumatologic and others, any other cancer, urinary and other infections, and nephrolithiasis. Additionally, patients who has atypical small acinar proliferation (ASAP) and high-grade prostatic intraepithelial neoplasia (HGPIN) in pathology report were excluded. All patients were performed physical examinations including digital rectal examinations (DRE). The patient, who has abnormal DRE findings and elevated prostate specific antigen (PSA), underwent prostate biopsy.

### Patient selection and creation the database

Our database was investigated for OP patients between December 2012 and November 2015, retrospectively. Demographic included, age (years), comorbidities, prostate volume (ml), PSA (ng/dl), serum neutrophil and lymphocyte with NLR. Intraoperative data included operation time (min.), estimated blood loss (EBL) (ml), amount of blood transfusion. Postoperative data included hospital stay, duration of drainage catheter and urethral catheter, amount of blood transfusion, and complications.

Delta haemoglobin was calculated as (preoperative haemoglobin)-(post-operative haemoglobin). Complications

was assessed according to Clavien Classifications (19). We performed similar surgical technique for transvesical OP that was described before (20,21).

The retroperitoneal drain was removed 4 days after surgery and urethral catheter was removed 8-10 days after prostatectomy.

### Statistical analyses

The data of all patients were prospectively recorded in a Microsoft Excel data sheet. The Statistical Package for the Social Sciences (SPSS) for Windows 16.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. Paired-T tests were used to compare differences between groups. Univariate and multivariate logistic regression analyses were performed. The p value was accepted significant when  $p < 0.05$ .

## RESULTS

Mean follow-up was  $17.7 \pm 4.4$  months. In total, 47 patients enrolled into the study. Mean age was  $71.1 \pm 4.9$  years. Mean PSA  $3.7 \pm 2.1$  ng/dl. Mean preoperative NLR was  $4 \pm 1.6$ . Mean delta haemoglobin was  $2.4 \pm 1.4$  and mean duration of drainage was  $4.4 \pm 1.3$  days. All of these were summarized in Table I.

Univariate regression analyses were performed and according to analyses NLR was significant associated with EBL ( $p=0.005$ ) (Table II). In multivariate logistic regression analyses, the EBL was positive associated with operation time ( $p=0.02$ ) and blood transfusion rate ( $p=0.05$ ) (Table III).

The most common complication was postoperative fever and was observed in 12 patients (Clavien 1). It was managed by administering antipyretic (paracetamol). Seven patients needed blood transfusions (Clavien 2). A patient had bladder neck sclerosis and needed endoscopic intervention under regional anaesthesia (Clavien 3b). There was no complication Clavien 4 and over.

## DISCUSSION

Elevated levels of NLR was found (mean  $4 \pm 1.6$ ) in our study group. Additionally, the NLR was significant associated with EBL that was related with operation time. Thus, the higher NLR might associated with higher EBL and might indirectly associated with blood transfusion rate, in patients underwent OP.

The neutrophil count is one of the inflammation marker in serum (22). The inflammatory process and its effects are recently published for BPH (23). Additionally, the neutrophil count but not the NLR has been used for determining prostate cancer and its prognosis, by Fujita et al (24) At this point, Kaplan reported role of inflammation in enlarged prostate in the course of BPH (7) In view of these

**Table I:** Demographic data on study group.

Parameter	Mean value $\pm$ SD
Age (years)	$71.1 \pm 4.9$
PSA (ng/dl)	$3.7 \pm 2.1$
Prostate volume (ml)	$89.3 \pm 4.7$
NLR	$4 \pm 1.6$
Delta haemoglobin	$2.4 \pm 1.4$

**Abbreviations:** NLR: Neutrophil to lymphocyte ratio, PSA: Prostate specific antigen, SD: Standard deviation.

**Table II:** Univariate analysis of parameters for association with neutrophil to lymphocyte ratio.

Parameter	P value
Age (years)	0.7
Prostate volume (ml)	0.4
PSA (ng/dl)	0.6
Delta haemoglobin	0.1
EBL (ml)	0.005*
Operation time (min)	0.1
Blood transfusion rate	0.06
Postoperative complications	0.3
Duration of drainage catheter	0.5
Duration of Urethral catheter	0.09

**Abbreviations:** PSA: Prostate specific antigen, EBL: Estimated blood loss.

\*Statistical significant P value.

**Table III:** Multivariate analyses of parameters for association with estimated blood loss.

Parameter	P value
Age (years)	0.8
Prostate volume (ml)	0.9
PSA (ng/dl)	0.7
Delta haemoglobin	0.04
NLR	0.06
Operation time (min)	0.02*
Blood transfusion rate	0.05*
Postoperative complications	0.1
Duration of drainage catheter	0.4
Duration of Urethral catheter	0.8

**Abbreviations:** PSA: Prostate specific antigen, NLR: Neutrophil to lymphocyte ratio.

\*Statistical significant P value.

above, to evaluate the NLR in BPH patients underwent OP was logical. However, it will be more useful and beneficial to evaluate the molecular mechanisms. This will be subject of another future study.

The OP is associated with higher EBL, notably in enlarged prostate (25). However, more EBL will adversely affect patients in terms of risk of adverse events of blood transfusions (26). The EBL can be related changing multiple reasons such as surgical technique, type of anaesthesia, experience of surgeon, modifications of anatomic structures, type of surgical approach, characteristics of the patients including prostate volume, body mass index (27). All centres of the present study performed similar surgical technique retropubic prostatectomy, for OP (21). Additionally, surgeons are experienced at least 6 years in urology and open surgical procedures of prostate. On the other hand, the impact of NLR on EBL has not been studied yet. According to results of our study, NLR was significantly associated with EBL, regardless of prostate volume in BPH patients who underwent OP. These results show that elevated inflammation might be predictor of EBL in BPH patients who are being scheduled OP. Furthermore, the EBL was associated with operation time in multivariate analyses, in the present study. Of course more bleeding may cause to extend operation time, during OP. Nonetheless, surgeons can inform patients more accurately for predicted EBL and operation time before surgical session, by measuring NLR. Moreover, clinicians can make provisions for high amount of EBL in BPH patients with higher level of NLR. There is of course needed more studies on this issue including more factors for predicting EBL before operation.

The most common complication was post-operative fever and it was managed by antipyretics. Seven patients with higher NLR needed blood transfusions. Additionally, their drainage catheter was removed later than other patients. Thus, their hospital stay was at least one day longer than the others. In view of all these above, NLR should be more investigated in BPH patients.

There are limitations in this study. The low numbers of patients and retrospective pattern are some of them. However, this is a pilot study and according to our best knowledge this was the first study that impact of NLR was investigated in BPH patients underwent OP, in the published literature.

Finally, we think that elevated levels of NLR may predict EBL in BPH patient who would be scheduled for OP. Additionally NLR may indirectly affect operation time in OP. In addition to all these, molecular studies are still lacking on this issue.

## CONCLUSIONS

The NLR may indicate inflammation in BPH. It can be higher and may independently predict EBL, in BPH patients who would be scheduled for OP. Additionally, the NLR may indirectly related with operation time, in OP. The importance of NLR should be demonstrated with molecular studies in the course of BPH.

## DISCLOSURE

The authors declare no conflict of interest.

## REFERENCES

1. Agarwal A, Eryuzlu LN, Cartwright R, Thorlund K, Tammela TL, Guyatt GH, Auvinen A, Tikkinen KA. What is the most bothersome lower urinary tract symptom? Individual- and population-level perspectives for both men and women. *Eur Urol* 2014; 65: 1211-7.
2. Michel MC, Vrydag W. Alpha1-, alpha2- and beta-adrenoceptors in the urinary bladder, urethra and prostate. *Br J Pharmacol* 2006; 147 Suppl 2: S88-S119.
3. Akin Y, Gulmez H, Ucar M, Yucel S. The effect of first dose of tamsulosin on flow rate and its predictive ability on the improvement of LUTS in men with BPH in the mid-term. *Int Urol Nephrol* 2013; 45: 45-51.
4. Oelke M, Baard J, Wijkstra H, de la Rosette JJ, Jonas U, Höfner K. Age and bladder outlet obstruction are independently associated with detrusor overactivity in patients with benign prostatic hyperplasia. *Eur Urol* 2008; 54: 419-26.
5. Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: Benign prostatic hyperplasia. *J Urol* 2008; 179: S75-S80.
6. Ficarra V, Rossanese M, Zazzara M, Giannarini G, Abbinante M, Bartoletti R, Mirone V, Scaglione F. The role of inflammation in lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and its potential impact on medical therapy. *Curr Urol Rep* 2014; 15(12):463.
7. Kaplan SA. The role of inflammation in lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and its potential impact on medical therapy. *J Urol* 2016; 195: 689-92.
8. Gregory AD, Houghton AM. Tumor-associated neutrophils: New targets for cancer therapy. *Cancer Res* 2014; 71: 2411-6.
9. Thorpe A, Neal D. Benign prostatic hyperplasia. *Lancet* 2003; 36: 1359-67.



10. Brown CT, van der Meulen J, Mundy AR, O'Flynn E, Emberton M. Defining the components of a self-management programme for men with uncomplicated lower urinary tract symptoms: A consensus approach. *Eur Urol* 2004; 46: 254-62.
11. Michel MC, Mehlburger L, Bressel HU, Goepel M. Comparison of tamsulosin efficacy in subgroups of patients with lower urinary tract symptoms. *Prostate Cancer Prostatic Dis* 1998; 1: 332-5.
12. Roehrborn CG. Three months' treatment with the alpha1-blocker alfuzosin does not affect total or transition zone volume of the prostate. *Prostate Cancer Prostatic Dis* 2006; 9: 121-5.
13. Boyle P, Robertson C, Manski R, Padley RJ, Roehrborn CG. Meta-analysis of randomized trials of terazosin in the treatment of benign prostatic hyperplasia. *Urology* 2001; 58: 717-22.
14. Andriole G, Bruchofsky N, Chung LW, Matsumoto AM, Rittmaster R, Roehrborn C, Russell D, Tindall D. Dihydrotestosterone and the prostate: The scientific rationale for 5alpha-reductase inhibitors in the treatment of benign prostatic hyperplasia. *J Urol* 2004; 172(4 Pt 1): 1399-1403.
15. Abrams P, Kaplan S, De Koning Gans HJ, Millard R. Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. *J Urol* 2006; 175: 999-1004.
16. Gacci M, Corona G, Salvi M, Vignozzi L, McVary KT, Kaplan SA, Roehrborn CG, Serni S, Mirone V, Carini M, Maggi M. A systematic review and meta-analysis on the use of phosphodiesterase 5 inhibitors alone or in combination with  $\alpha$ -blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. *Eur Urol* 2012; 61: 994-1003.
17. Reich O, Gratzke C, Stief CG. Techniques and long-term results of surgical procedures for BPH. *Eur Urol* 2006; 49:970-8.
18. [http://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/#note\\_180](http://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/#note_180). (accessed 16 May 2016)
19. Dindo D, Clavien PA. Interest in morbidity scores and classification in general surgery. *Cir Esp* 2009; 86:269-71.
20. Jepsen JV, Bruskewitz RC. Recent developments in the surgical management of benign prostatic hyperplasia. *Urology* 1998; 51 Suppl 4A: 23-31.
21. Yassin M, Prasad SM, Hashim H. Surgery for benign prostatic obstruction. In: Keane TE, Graham SDJR, eds. *Glenn's urologic surgery*. 7th ed. Philadelphia: Wolters Kluwer, 2010; 166-74.
22. Wright HL, Moots RJ, Bucknall RC, Edwards SW. Neutrophil function in inflammation and inflammatory diseases. *Rheumatology (Oxford)* 2010; 49: 1618-31.
23. Vignozzi L, Gacci M, Maggi M. Lower urinary tract symptoms, benign prostatic hyperplasia and metabolic syndrome. *Nat Rev Urol* 2016; 13: 108-19.
24. Fujita K, Imamura R, Tanigawa G, Nakagawa M, Hayashi T, Kishimoto N, Hosomi M, Yamaguchi S. Low serum neutrophil count predicts a positive prostate biopsy. *Prostate Cancer Prostatic Dis* 2012; 15: 386-90.
25. Ngugi PM, Saula PW. Open simple prostatectomy and blood transfusion in Nairobi. *East Afr Med J* 2007; 84 Suppl 9: S12-S23.
26. Spence RK. Emerging trends in surgical blood transfusion. *Semin Hematol* 1997; 34 Suppl 2: 48-53.
27. Chang SS, Duong DT, Wells N, Cole EE, Smith JA Jr, Cookson MS. Predicting blood loss and transfusion requirements during radical prostatectomy: The significant negative impact of increasing body mass index. *J Urol* 2004; 171: 1861-5.