

Relationship between the Neutrophil to Lymphocyte Ratio (NLR) and International Prostate Symptoms Score (IPSS) in Men with Benign Prostatic Enlargement (BPE) in Hospital Raja Perempuan Zainab II (HRPZ II)

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ABSTRACT

This study aimed at investigating the potential use of the Neutrophil to Lymphocyte Ratio (NLR) as a biomarker for assessing the severity of lower urinary tract symptoms in patients with prostate disease. The study included 363 patients with Benign Prostatic Enlargement (BPE) and compared their NLR values with clinical and laboratory parameters, including the International Prostate Symptom Score (IPSS), Prostate-Specific Antigen (PSA) level, and maximum urinary flow rate (Q_{max}).

The results showed that NLR values were significantly higher in patients with more severe lower urinary tract symptoms, as measured by the IPSS score. Furthermore, NLR values were positively correlated with total white cell count and neutrophil count, and negatively correlated with lymphocyte count in BPE patients. The study also found a positive correlation between NLR and PSA levels in BPE patients attending the clinic.

The association between NLR and prostate disease can be explained by the role of inflammation and immune function in the pathogenesis of prostate disease. Chronic inflammation has been linked to the development and progression of BPH and prostate cancer, and neutrophils are one of the key immune cells involved in the inflammatory response. Additionally, lymphocytes play a critical role in the adaptive immune response, which is essential for recognizing and eliminating cancer cells. The study suggests that NLR may be a useful biomarker for assessing the severity of lower urinary tract symptoms in patients with prostate disease. However, the performance of NLR as a predictor of prostate disease may be influenced by external factors such as age, comorbidities, and medication use, and further research is needed to better understand the relationship between NLR and aging. In conclusion, the findings of this study highlight the potential use of NLR as a biomarker for assessing the severity of lower urinary tract symptoms in patients with prostate disease.

Keywords: Chronic inflammation; Prostate disease; Lymphocyte; Comorbidities; Pathogenesis

INTRODUCTION

Benign Prostatic Enlargement (BPE) was the most common urological case seen in our outpatient department for the last decade. It had been considered as the result of age related prostatic gland enlargement. It was the most common benign tumor in elderly men, affecting 25% of males over 50 years, 33% of those aged over 60, and 50% of individuals' more than 80 years old. However, such a simple explanation was not accepted

due to the heterogeneous characteristics of symptoms and their relationships with systemic diseases [1].

The relationship between inflammation and the biology of BPE had drawn significant academic interest for the past years. Evidence from MTOPS and REDUCE studies showed that the risk for Lower Urinary Tract Symptoms (LUTS) due to BPE was correlated with intra-prostatic infiltration of inflammatory cells. The reduce trial showed that chronic prostatic inflammation could be detected in 77.6% of patients with BPE who underwent

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prostate biopsies, and various studies showed a significant link between chronic prostatic inflammation and LUTS severity, prostate volume, and increased risk of acute urinary retention. Since not all the patients with BPE need to undergo a prostate biopsy, it is a problem to evaluate the influence of chronic prostatic inflammation on BPE. So, some researchers analyzed the association between clinical inflammatory and BPE, and the results suggested a positive correlation. The inflammatory markers that had been used in previous studies included Total White Cell count (TWC), Neutrophil-Lymphocyte Ratio (NLR), and C-Reactive Protein (CRP) [2].

Objectives

The main objective of this study was to investigate the potential use of Neutrophil to Lymphocyte Ratio (NLR) as a simple and easily accessible predictor for disease activity in patients with Benign Prostatic Enlargement (BPE). Additionally, the study aimed to explore the relationship between inflammatory parameters and treatment response, as well as to evaluate the possible association between NLR and the progression of BPE. It is worth noting that this is the first study of its kind in Malaysia. Specifically, the study aimed to calculate the value of NLR in all BPE patients attending the urology clinic HPRZ II, assess their IPSS score, and study the correlation between NLR and IPSS score. Furthermore, the study sought to estimate the diagnostic accuracy, sensitivity, and specificity of NLR for detecting mild/moderate and severe BPE based on IPSS score, and to assess the correlation between NLR and other secondary parameters such as PSA, TWC, and Q_{max} in patients with BPE attending the clinic [3].

MATERIALS AND METHODS

Study design

The methodology of the study was a prospective cross-sectional observational study that was conducted in the urology clinic HRPZ II from May 2022 to May 2023. During history taking, the International Prostate Symptom Score (IPSS) was obtained from Benign Prostatic Enlargement (BPE) patients attending the clinic. Other demographic and medical information, such as age, comorbidities, past and current medications, and previous prostatic surgeries, were also recorded.

The routine physical examination, including a digital rectal examination to assess the prostate clinically, was performed. Blood investigations, urinalysis, and Prostate Specific Antigen (PSA) levels were also performed. All patients underwent uroflowmetry, and the Post-Voiding Residual urine (PVR) was assessed. Formal ultrasound of the urinary system was done by trained radiologists mainly looking at the prostate volume and Intravesical Prostatic Protrusion (IPP). The patients were divided into two groups based on IPSS, mild/moderate (non-severe) and severe symptoms [4].

During the clinic appointment, eligible patients were explained regarding the study and offered participation. Once agreed and they had understood, written consent was obtained. IPSS was calculated during the interview and recorded in patients' files

and study proforma. Later they underwent uroflowmetry, and blood investigation and ultrasound of the kidney, ureter, bladder, and prostate were arranged. The results were reviewed when the investigation results were ready typically between two to four weeks.

Statistical analysis

The study utilized various statistical tests to analyze the data collected from the patients. The Shapiro-Wilk's and Levene's tests were used to determine the normality and variance homogeneity of the data. The data was presented using different formats, such as frequencies and percentages, and mean and standard deviation, to compare different types of continuous variables, either independent sample t-test was used for dichotomous variables and one way ANOVA was used for multi-categorical variables [5].

Categorical data were compared using the *Chi-square* distribution test. The correlation analysis was conducted using Pearson's test. The study also employed the Receiver Operating Characteristic (ROC) curve analysis to determine the usefulness of the NLR ratio. The area under the ROC curve was calculated for different values along with their respective 95% Confidence Intervals (CIs). Optimal cut-off values were also determined, and the sensitivity and specificity of the test were calculated along with their 95% CIs [6].

RESULTS

The sample consisted of 363 individuals. The age variable ranges from 41 to 93 years, with a mean value of 70.68 and a standard deviation of 8.131.

Out of the 357 individuals in the sample, 53 people (14.8%) have a mild IPSS grade, 195 people (54.6%) have a moderate IPSS grade, and 109 people (30.5%) have a severe IPSS grade. (14.8%) have had past prostate surgery. (11.2%) have a prostate volume less than 30 g and are while 316 people (88.8%) have a prostate volume greater than 30 g. 29.7% have not been diagnosed with an IPP while 251 people (70.3%) have been diagnosed with an IPP [7].

Out of the 357 individuals in the sample, 103 people (28.9%) do not have an IPP and are categorized as no IPP among the 254 individuals who have an IPP, 151 people (42.3%) have an IPP grade of less than 5, 94 people (26.3%) have an IPP grade between 5 and 10, and 9 people (2.5%) have an IPP grade greater than 10.

30.5% of the patients had a Q_{max} greater than 10, while 69.5% had a Q_{max} less than 10. The total number of valid responses was 357, with 109 patients reporting a Q_{max} greater than 10, and 248 patients reporting a Q_{max} less than 10. Of those, 205 cases (56.5% of the valid responses) had a PVR < 50 mL. 122 cases (33.6% of the valid responses) had a PVR between 50 mL-100 mL. The IPSS score variable ranges from 3 to 29, with a mean value of 15.73 ± 6.215 . The total white cell count ranges from 2.90 to 14.20, with a mean value of $7.5065 \pm SD \pm 1.95792$. The neutrophil count ranges from 1.32 to 40.50, with a mean value of $4.5476 SD \pm 2.45975$. The lymphocyte count ranges from

0.93 to 45.70, with a mean value of 2.1807 and a standard deviation of 2.38992 [8].

The NLR ranges from 0.69 to 43.20, with a mean value of 2.3535 SD±2.31086. The PSA variable ranges from 0.3 to mean value of was (M=6.849, SD=7.7894).

Table 1: Descriptive characteristics.

	Mean ± SD	N
Age	70.68 ± 8.1	357
IPSS score	15.73 ± 6.2	357
Neutrophil count	4.55 ± 2.5	357
Lymphocyte count	2.18 ± 2.4	357
NLR	2.35 ± 2.3	357
PSA	6.85 ± 7.8	357
Creatinine	102.92 ± 43.3	357
Prostate volume	53.42 ± 26.7	357
Maximum urinary flow		
Rate	8.62 ± 2.7	357
PVR	45.72 ± 36.8	356

IPSS had positively correlated with age ($r=0.282$, $p<0.001$), neutrophil count ($r=0.210$, $p<0.001$), neutrophil to lymphocyte ratio ($r=0.220$, $p<0.001$), and prostate volume ($r=0.163$, $p=0.002$). It was negatively correlated with maximum urinary flow rate (Q_{max}) ($r=-0.653$, $p<0.001$).

There was no significant correlation between IPSS and lymphocyte count ($r=-0.021$, $p=0.694$), PSA ($r=0.102$, $p=0.054$), or creatinine ($r=0.046$, $p=0.390$). Additionally, post-voiding residual urine was positively correlated with IPSS ($r=0.297$, $p<0.001$).

PSA was positively correlated with neutrophil to lymphocyte ratio ($r=0.330$, $p<0.001$) and prostate volume ($r=0.555$, $p<0.001$).

There was no significant correlation between PSA and age ($r=-0.060$, $p=0.259$), IPSS score ($r=0.102$, $p=0.054$), creatinine ($r=-0.036$, $p=0.499$), maximum urinary flow rate (Q_{max}) ($r=-0.097$, $p=0.068$), or post-voiding residual urine ($r=0.094$, $p=0.076$).

Prostate volume was positively correlated with PSA ($r=0.555$, $p<0.001$), IPSS score ($r=0.163$, $p=0.002$), and neutrophil to lymphocyte ratio ($r=0.134$, $p=0.011$) [10].

There was no significant correlation between prostate volume and age ($r=-0.013$, $p=0.805$), creatinine ($r=-0.020$, $p=0.711$), or maximum urinary flow rate (Q_{max}) ($r=-0.128$, $p=0.015$). However, there was a significant positive correlation between prostate volume and post-voiding residual urine ($r=0.193$, $p<0.001$).

The Q_{max} mean value was 8.620 and a standard deviation of 2.6809. The PVR variable ranges from 0 to 172, with a mean value of 45.72 and a standard deviation of 36.810 (Table 1) [9].

There is a weak negative correlation (-0.226) between age and maximum urinary flow rate (Q_{max}), which is statistically significant ($p=0$). There is a strong negative correlation (-0.653) between the International Prostate Symptom Score (IPSS) and Q_{max} , which is statistically significant ($p<0.000$).

There is a weak negative correlation (-0.146) between Neutrophil to Lymphocyte Ratio (NLR) and Q_{max} , which is statistically significant ($p=0.006$) [11].

There was a weak negative correlation (-0.097) between Prostate-Specific Antigen (PSA) and Q_{max} , which is not statistically significant ($p=0.068$). There was a weak negative correlation (-0.032) between creatinine levels and Q_{max} , which is not statistically significant ($p=0.55$). There is a strong negative correlation (-0.336) between post-voiding residual urine and Q_{max} , which is statistically significant ($p<0.000$). There is a positive correlation between NLR and total white cell count with a Pearson correlation coefficient of 0.121 and a p-value of 0.022 (Figure 1) [12].

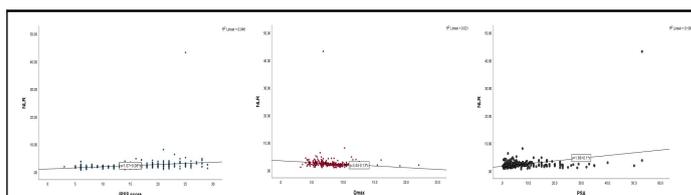


Figure 1: Positive correlation between NLR and total white cell count.

NLR values are significantly lower in individuals with Q_{max} greater than 10 compared to those with Q_{max} less than 10 ($p=0.007$). There is no significant difference in NLR values between individuals with prostate volume less than 30 g and those with prostate volume greater than 30 g ($p=0.473$). There is a trend towards higher NLR values in individuals with PSA greater than or equal to 1.6 compared to those with PSA less

than 1.6, but the difference is not statistically significant (p -value=0.077). NLR values are significantly higher in individuals older than 62 years compared to those younger than 62 years (p -value=0.015) (Tables 2 and 3) [13].

Table 2: Parameters of progression according to the NLR.

Neutrophil to lymphocyte ratio		N	Mean	p-value
Q_{max} and gt	<10 (no)	248	2.5 ± 2.7	0.007
	>10 (yes)	109	2.0 ± 0.8	
Prostate volume more 30 g	<30 g	40	2.2 ± 1.0	0.473
	>30 g	316	2.4 ± 2.4	
Prostate Specific Antigen (PSA)	<1.6	59	2.1 ± 0.8	0.077
	≥1.6	298	2.4 ± 2.5	
Age range	<62	68	2.0 ± 0.5	0.015
	>62	289	2.4 ± 2.6	

Table 3: Receiver-Operating Characteristic (ROC) curve analyses results according to neutrophil to lymphocyte ratio.

Cutoff	SEN	SPE	p-value	
PSA (mg/ml)	1.99	57	32	0.009
Prostate volume (ml)	2.01	51	28	0.113
IPSS	1.9	74	34	0
Maximum urinary				
Flow rate (ml/second)	1.94	34	70	0

The Receiver-Operating Characteristic (ROC) curve analyses according to the Neutrophil-to-Lymphocyte Ratio (NLR) showed that Prostate-Specific Antigen (PSA), the optimal cutoff value was 1.99 ng/mL, with a sensitivity of 57% and a specificity of 32%. The p-value for the ROC analysis was significant ($p=0.009$).

The optimal cutoff value for prostate volume was 2.01 mL, with a sensitivity of 51% and a specificity of 28%. However, the p-value for the ROC analysis was not significant ($p=0.113$).

The optimal cutoff value for the International Prostate Symptom Score (IPSS), was 1.9, with a sensitivity of 74% and a specificity of 34%. The p-value for the ROC analysis was significant ($p=0.000$). The cutoff value for maximum urinary flow rate (Q_{max}), was 1.94 mL/second, with a sensitivity of 34% and a specificity of 70%. The p-value for the ROC analysis was significant ($p<0.000$) [14].

DISCUSSION

The results indicate that IPSS score was correlated with age, neutrophil count, NLR, and prostate volume, while negatively correlated with maximum urinary flow rate (Q_{max}). These findings are consistent with previous studies that have identified age, prostate volume, and Q_{max} as significant predictors of BPE severity and symptoms.

The results of this study suggest that there is significant difference in the mean NLR values between patients with Q_{max} values greater than 10 (yes) compared to those with Q_{max} values less than 10 (no).

The difference in mean NLR values between patients with Q_{max} values greater than 10 compared to those with Q_{max} values less than 10 suggests that there is an association between NLR and the severity of urinary symptoms in patients with prostate disease.

One possible explanation for this association is that the inflammatory response plays a role in the pathogenesis of prostate disease. According to Thapa, and Ghosh chronic inflammation has been linked to the development and progression of BPH and prostate cancer, and neutrophils are one of the key immune cells involved in the inflammatory response.

Also neutrophil to lymphocyte ratio may be a surrogate marker of immune function. Lymphocytes play a critical role in the adaptive immune response, which is essential for recognizing and eliminating cancer cells, a lower lymphocyte count and a higher neutrophil count may indicate a weakened immune response, which could contribute to the development and progression of prostate disease.

One of the hallmarks of immune-senescence is a shift in the balance of immune cells, with a decrease in the number and function of T cells and an increase in the number and function of innate immune cells, such as neutrophils. This shift may contribute to the development of chronic inflammation and age related diseases, including cancer.

The lower NLR values in younger patients may reflect a more robust and balanced immune response, while the higher NLR values in older patients may reflect a shift towards a more inflammatory and less effective immune response. However, it's important to note that age is just one factor that can affect NLR values, and further research is needed to better understand the relationship between NLR and aging.

The correlation between IPSS score and NLR is that the inflammatory response contributes to the development and progression of lower urinary tract symptoms. Chronic inflammation has been implicated in the pathogenesis of BPH and other prostate diseases, and it's possible that neutrophils and other immune cells contribute to the inflammation and tissue damage that underlie these conditions.

The relatively modest performance of NLR in predicting certain parameters related to prostate disease, such as PSA levels and maximum urinary flow rate, could be due to a number of factors.

Firstly, prostate disease is a complex and multifactorial condition, with a wide range of factors contributing to its development and progression. As such, it is unlikely that any single parameter or biomarker, such as NLR, would be able to predict all aspects of the disease with high accuracy.

Secondly, the performance of NLR may be influenced by a number of external factors, such as age, comorbidities, and medication use, which can affect both neutrophil and lymphocyte counts, and hence the NLR ratio. For example, older age has been shown to be associated with higher NLR, which could impact its performance as a predictor of prostate disease in older populations.

The performance of NLR as a predictor of prostate disease may be influenced by differences in study populations, such as variations in disease severity, treatment status, and underlying comorbidities.

The relationship between NLR and these secondary parameters can be explained by the underlying biology of BPE. Inflammation is known to be associated with an increase in the number of neutrophils and a decrease in the number of lymphocytes. Therefore, it is not surprising that NLR is positively correlated with total white cell count and neutrophil count, and negatively correlated with lymphocyte count in BPE patients.

Moreover, prostate inflammation and infection can increase PSA levels. NLR is known to be a marker of inflammation, and previous studies have shown that NLR is associated with an increase in PSA levels. Therefore, the positive correlation between NLR and PSA in BPE patients attending the clinic can be explained by the fact that NLR is a marker of prostate inflammation and infection, both of which can increase PSA levels.

CONCLUSION

In conclusion, the findings of this study suggest that NLR may be a useful biomarker for assessing the severity of lower urinary tract symptoms in patients with prostate disease. However, further research is needed to better understand the relationship between NLR and prostate disease, and to determine the optimal cutoff values for NLR in different populations and clinical settings. Additionally, the performance of NLR as a predictor of prostate disease may be improved by combining it with other biomarkers or clinical parameters, such as age, prostate volume, and Q_{max} . Ultimately, a better understanding of the underlying biology of prostate disease and the role of inflammation and immune function in its development and progression may lead to the development of more effective diagnostic and treatment strategies for this common and debilitating condition.

REFERENCES

1. Abidi SH, Bilwani F, Ghias K, Abbas F. Viral etiology of prostate cancer: Genetic alterations and immune response. A literature review. *Int J Surg*. 2018;52:136-140.
2. Carruba G. Estrogen and prostate cancer: An eclipsed truth in an androgen dominated scenario. *J Cell Biochem*. 2007;102(4):899-911.
3. de Nunzio C, Presicce F, Tubaro A. Inflammatory mediators in the development and progression of benign prostatic hyperplasia. *Nat Rev Urol*. 2016;13(10):613-626.
4. Elmusrati A, Wang J, Wang CY. Tumor microenvironment and immune evasion in head and neck squamous cell carcinoma. *Int J Oral Sci*. 2021;13(1):24.
5. Erbay G, Ceyhan G. Association between hyperlipidemia and prostatic enlargement: A case-control study. *Urologia*. 2022;89(1): 58-63.
6. Gao Y, Xue J, Zhang L, Wang Z. Synthesis of bio-based polyester elastomers and evaluation of their *in vivo* biocompatibility and biodegradability as biomedical materials. *Biomater Sci*. 2022;10(14): 3924-3934.
7. Izmirli M, Arıkan B, Bayazit Y, Alptekin D. Associations of polymorphisms in *HPC2/ELAC2* and *SRD5A2* genes with benign prostate hyperplasia in Turkish men. *Asian Pac J Cancer Prev*. 2011;12(3):731-733.

8. Robert G, Descazeaud A, Allory Y, Vacherot F, de la Taille A. Should we investigate prostatic inflammation for the management of benign prostatic hyperplasia?. *Eur Urol Suppl.* 2009;8(13):879-886.
9. Thapa D, Ghosh R. Chronic inflammatory mediators enhance prostate cancer development and progression. *Biochem Pharmacol.* 2015;94(2):53-62.
10. Majnaric LT, Guljas S, Bosnic Z, Seric V, Wittlinger T. Neutrophil to lymphocyte ratio as a cardiovascular risk marker may be less efficient in women than in men. *Biomolecules.* 2021;11(4):528.
11. Wu Y, Chen Y, Yang X, Chen L, Yang Y. Neutrophil to Lymphocyte Ratio (NLR) and Platelet to Lymphocyte Ratio (PLR) were associated with disease activity in patients with systemic lupus erythematosus. *International immunopharmacol.* 2016;36:94-99.
12. Yan H, Kuroiwa A, Tanaka H, Shindo M, Kiyonaga A, Nagayama A. Effect of moderate exercise on immune senescence in men. *Eur J Appl Physiol.* 2001;86(2):105-111.
13. Yan X, Li F, Wang X, Yan J, Zhu F, Tang S, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: A retrospective cross-sectional study. *J Med Virol.* 2020;92(11):2573-2581.
14. Kim DS, Shin D, Lee MS, Kim HJ, Kim DY, Kim SM, et al. Assessments of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in Korean patients with psoriasis vulgaris and psoriatic arthritis. *J Dermatol.* 2016;43(3):305-310.