Original Research Article

Relationship between the Neutrophil to Lymphocyte Ratio and International Prostate Symptoms Score in Men with a Benign Prostatic Enlargement

Abstract

Introduction: The aim of this study was to investigate whether the neutrophil to lymphocyte ratio (NLR) can be used as a biomarker to evaluate the severity of urinary symptoms in patients with benign prostatic enlargement (BPE).

Methods: This study assessed NLR levels in a cohort of 357 patients with BPE attending to our outpatient clinic from during 2022. We also evaluated other relevant parameters including the International Prostate Symptom Score (IPSS), prostate specific antigen (PSA) level and the maximum urinary flow rate (Qmax). Correlations between NLR and, IPSS, PSA, prostate volume and Qmax were assessed statistically.

Results: The study's findings demonstrated that patients with high IPSS had significantly higher NLR values with positive correlation ($r=0.22$, $p<0.001$). Similar relationship was seen between NLR and PSA ($r=0.33$, $p<0.001$). Positive correlations were also seen between NLR, and age ($r=0.014$, $p=0.79$) and prostate volume ($r=0.134$, $p=0.01$) but there were not statistically significant. Negative correlation between NLR and Qmax was seen ($r= -0.146$, $p=0.006$). The Receiver-Operating Characteristic (ROC) curve analyses showed that NLR of between 1.9 to 2.0 can be used as a parameter to differentiate severe and non-severe symptoms with sensitivity of 74% and specificity of 34% ($p<0.001$).

Conclusion: These findings justifies that NLR can be utilized as a biomarker, in combination with other parameters such as age, Qmax and PSA to accurately and more objectively evaluate the severity of lower urinary tract symptoms in patients with prostate conditions. Further studies required as its potential usage as a marker for monitoring and assessing BPE patients' progression and response to treatment.

Keywords: Benign Prostatic Enlargement, Neutrophil to Lymphocyte Ratio, International Prostate Symptoms Score

Introduction

Benign prostatic enlargement (BPE) has been the most common urological case in our outpatient department for the last decade. It had been considered the result of age-related prostatic gland enlargement. It was the most common benign disease in older men, affecting 25% of males over 50, 33% of those over 60, and 50% of individuals over 80 [1]. However, such a simple explanation was not accepted due to the heterogeneous characteristics of symptoms and their relationships with systemic diseases.

The relationship between inflammation and the biology of BPE has drawn significant academic interest over the past years. Gao et al. have presented evidence from the MTOPS and REDUCE studies that demonstrate a relationship between the risks of experiencing lower urinary tract symptoms (LUTS) as a result of BPE and the infiltration of inflammatory cells within the prostate [2]. The REDUCE trial revealed that chronic inflammation in the prostate was detectable in 77.6% of BPE patients who received prostate biopsies, and several other studies have established a significant association between chronic prostatic inflammation, the severity of LUTS, prostate volume, and an increased likelihood of acute urinary retention [3].

Since not all patients with BPE need to undergo a prostate biopsy, evaluating the influence of chronic prostatic inflammation on BPE is a problem. Some researchers analyzed the association between clinical inflammation and BPE, and the results suggested a positive correlation [4]. In previous research, various inflammatory markers were employed, such as C-reactive protein, neutrophil-lymphocyte ratio (NLR) and total white cell count (TWC).

Objectives

The primary aim of this research was to assess the suitability of NLR as indicator for disease activity in individuals with BPE. It is worth noting that this is the first study of its kind in Malaysia. This study aimed to calculate the value of NLR in all BPE patients attending the urology clinic Hospital Raja Perempuan Zainab II (HRPZ II) by assessing their IPSS and study the correlation between NLR and IPSS. Furthermore, this study aimed at estimating the diagnostic accuracy of NLR, which include sensitivity and specificity of NLR for detecting mild/moderate (non-severe) and severe BPE based on IPSS score and to assess if there is any correlation (strength, direction and significant) between NLR and other secondary parameters such as prostate specific antigen (PSA) and maximum urinary flow rate (Qmax) in patients with BPE.

Methodology

Study design

This is a prospective cross-sectional observational study conducted in the urology clinic HRPZ II from during 2022. The IPSS was obtained during history taking and other

demographic and medical information was also recorded. This includes age, comorbidities, past and current medications and previous prostatic surgeries.

A routine physical examination, which includes a digital rectal examination, was performed to assess the presence of the enlarged prostate clinically. Blood investigations, urinalysis and PSA levels were also performed. All patients underwent uroflowmetry, and the post-voiding residual urine (PVR) was assessed. Formal urinary system ultrasound was done by trained radiologists, mainly looking at the prostate volume and intravesical prostatic protrusion (IPP). The patients were categorized based on the severity of IPSS, distinguishing between mild/moderate (non-severe) and severe symptoms. During the clinic appointment, eligible patients were explained about 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 and analyzed.

Statistical analysis

The research employed multiple statistical tests to analyze the patient data, including the Shapiro-Wilk's tests to assess normality. In order to compare different types of continuous variables, the study utilized either independent sample t-tests for dichotomous variables or one-way ANOVA for multi-categorical variables

The Chi-square distribution test to compare categorical data and Pearson's test for correlation analysis. The Chi-square distribution test is a widely used statistical method for analyzing categorical data, which we used in comparing the observed frequencies of different variable categories with their expected frequencies. On the

other hand, Pearson's test was used asses the strength and direction of the linear relationship between two continuous variables in our study.

In addition, the study utilized the Receiver Operating Characteristic (ROC) curve analysis to evaluate the usefulness of the NLR in assessing symptoms severity of BPE patients. We calculated the area under curve (AUC) for different values of the NLR and their respective 95% confidence intervals. The optimal cutoff values were also determined, which can be used to classify patients as having a severe or non-severe symptoms. Moreover, the sensitivity and specificity of the test were calculated, along with their 95% confidence intervals, which provide an estimate of the precision and reliability of the test.

Results

The sample consisted of 357 individuals. The age variable ranges from 41 to 93 years, with a mean value of 70.68 and a standard deviation of 8.13.

Out of the 357 individuals in the sample, 53 patients (14.8%) had mild symptoms based on IPSS, 195 patients (54.6%) had moderate symptoms and 109 patients (30.5%) had severe symptoms. 11.2% of patients had prostate volume of less than 30 grams, while 316 people (88.8%) had prostate volume of more than 30 grams. 29.7% of patients did not have IPP, while 251 patients (70.3%) had IPP. 30.5% of the patients had a Qmax greater than 10mls/s, while 69.5% had a Qmax less than 10mls/s. 250 patients (56.5%) had a PVR less than 50mls, 152 patients (33.6%) had a PVR between 50 to 100mls. The IPSS ranges from 3 to 29, with a mean value of 15.73 ± 6.21.

The white cell count ranges from 2.90 to 14.20 (Mean = 7.50, SD=1.96). The mean value (±SD) for neutrophil count is 4.55±2.46, lymphocyte count is 2.18±2.39. The NLR and PSA mean values (±SD) are 2.35±2.31 and 6.85±7.79 respectively. The mean value

(±SD) for Qmax and PVR are 8.62±2.68 and 45.72±36.81 respectively.

The results of the study suggest that there are significant correlations between NLR, IPSS, PSA and Qmax in patients with BPE. Age, NLR and prostate volume were found to be positively correlated with IPSS, while Qmax was negatively correlated with IPSS. PSA was found to be positively correlated with NLR and prostate volume. Prostate volume was positively correlated with PSA ($r=0.555, p<0.001$), IPSS ($r=0.163$, $p=0.002$), and NLR ($r=0.134$, $p = 0.011$).

The study found no significant correlation between prostate volume and age ($r = -0.013$, $p =0.805$) or Qmax ($r=-0.128$, $p=0.015$). However, a significant positive correlation was observed between prostate volume and PVR ($r =0.193$, $p <0.001$).

There is a weak negative correlation ($r=-0.226$) between age and Qmax, which is statistically significant ($p<0.001$). There is a strong negative correlation ($r=-0.653$) between the IPSS and Qmax, which is statistically significant ($p<0.001$).
The results of the study showed that there were various correlations between Qmax and other variables. There was a weak negative correlation between Qmax and the NLR ($r=-0.146$, $p<0.001$). A weak negative correlation was also observed between Qmax and PSA but not statistically significant ($r=-0.097$, $p=0.068$). However, a strong negative correlation was found between Qmax and PVR ($r=-0.336$, $p<0.001$).

The main focus of this study, we found a positive correlation between NLR and IPSS which was statistically significant (r=0.22, p<0.001). NLR values are significantly lower in individuals with Qmax of greater that 10mls/s than those with Qmax less than 10mls/s (p<0.001). There is no significant difference in NLR values between individuals with a prostate volume less than 30 grams and those with a prostate volume more than 30 gram (p=0.473). There is a trend toward 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 than those younger than 62 (p-value=0.015).

The results of the ROC curve analysis indicated that, based on NLR, a cutoff value of 1.99 was found to be optimal for PSA level equal or more than 1.6. At this cutoff value, the test demonstrated a sensitivity of 57% and a specificity of 32% (p=0.009).

The optimal NLR cutoff value for prostate volume more than 30 grams was 2.01, with a sensitivity of 51% and a specificity of 28% but was not statistically significant (p=0.113)

The study identified the optimal NLR cutoff value for the non-severe and severe symptoms base on IPSS was 1.9, with a sensitivity of 74% and a specificity of 34% (p<0.001). The NLR cutoff value for Qmax of less than 10mls/s was 1.94, with a sensitivity of 34% and a specificity of 70% (p<0.001).

Discussion

The results indicate that the IPSS was positively correlated with age, NLR and prostate volume, while negatively correlated with Qmax. These findings are consistent with previous studies that have identified age (more than 60), prostate volume (more than 30 grams) and Qmax (less than 10mls/s) as significant predictors of BPE severity and risk factors for disease progression.

Thapa & Ghosh proposed a potential explanation for the observed associations, suggesting that the inflammatory response could be involved in the pathogenesis of prostate disease. Chronic inflammation has been previously linked to the development and advancement of both benign prostatic hyperplasia (BPH) and prostate cancer. Neutrophils, which are crucial immune cells involved in the inflammatory response, have been identified as playing a role [8]

Also, the NLR may be a surrogate marker of immune function [7]. Lymphocytes play a critical role in the adaptive immune response, essential for recognizing and eliminating cancer cells [9]. 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 position of innate immune cells, such as neutrophils [10]. This shift may contribute to the developing 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. In comparison, the higher NLR values in older patients may reflect a shift toward a more inflammatory and less effective immune response [11]

The correlation between the IPSS and NLR is that the inflammatory response contributes to the development and progression of lower urinary tract symptoms. Mounting evidence suggests that chronic inflammation plays a crucial role in the pathophysiology of BPH and other prostate diseases. In particular, it has been postulated that neutrophils and other immune cells are implicated in the complex interplay of molecular and cellular events that underlie the initiation and progression of these conditions. By contributing to the recruitment and activation of other immune cells, secreting proinflammatory cytokines and reactive oxygen species, and inducing tissue damage and remodeling, neutrophils may act as key mediators of the inflammatory response in the prostate gland [12].

The relatively modest performance of NLR in predicting specific parameters related to prostate disease, such as PSA levels and Qmax, could be due to several factors. Firstly, prostate disease is a complex and multifactorial condition, with many factors contributing to its development and progression [13]. As such, it is unlikely that any single parameter or biomarker, such as NLR, could predict all aspects of the disease with high accuracy.

Secondly, the performance of NLR may be influenced by several external factors, such as age, comorbidities, and medication use, which can affect both neutrophil and lymphocyte counts, and hence the NLR [5]. For example, older age is associated with higher NLR, which could impact its performance as a predictor of prostate disease in older populations.

Differences may influence the performance of NLR as a predictor of prostate disease in study populations, such as variations in disease severity, treatment status, and underlying comorbidities.

The observed relationship between NLR and the secondary parameters can be explained by the underlying biology of BPE. Inflammation has been associated with an elevation in the number of neutrophils, which are a type of white blood cell, and a reduction in the number of lymphocytes, which are another type of white blood cell. Therefore, it is unsurprising 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 a well-known marker of inflammation, and previous research has indicated that there is a significant association between NLR and elevated levels of PSA [6]. 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, which can increase PSA levels.

Conclusion

The findings of this study suggest that NLR may be a useful biomarker in assessing the severity of LUTS in individuals with prostate disease. However, further research is needed better to understand the relationship between NLR and prostate disease and to determine the optimal cutoff values for NLR in different populations and clinical settings. In this study, NLR cutoff value of 1.9 seems to be optimal to be used for

differentiating between severe and non-severe BPE patients. It maybe potential to be used as a marker for monitoring disease progression and response to BPE treatments. The utilization of NLR in BPE progression may be improved by combining it with other parameters such as age, prostate volume and Qmax. 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 more effective diagnostic and treatment strategies for this common and debilitating condition. Furthermore, treatment with anti-inflammatory drugs maybe an option BPE patients considering their pathophysiology discussed above.

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Table 1. Descriptive Characteristics

	Mean+/-SD	N
Age	70.68±8.1	357
IPSS score	15.73±6.2	357
Total white cell	7.51±2.0	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

Table 2. Parameters of Progression According to the NLR

	Neutrophil-to-lymphocyte ratio	N	Mean	p-value
Qmax	<10	248	2.5±2.7	0.007
	>10	109	2.0±0.8	
Prostate volume	<30g	40	2.2±1.0	0.473
	>30g	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	<62	68	2.0±0.5	0.015
	>62	289	2.4±2.6	

Table 3. Summary of the results of the receiver-operating characteristic (ROC) curve analyses, according to the 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
IPPS	1.9	74	34	0.000
Maximum urinary Flow rate (ml/second)	1.94	34	70	0.000

Figure 1. The Correlation of A Neutrophil-Lymphocyte Ratio between International Prostate Symptom Score (IPSS), Maximum Urinary Flow Rate (Qmax), and Prostate-Specific Antigen (PSA)