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Predictive Value of Inflammatory Markers in determining anterior urethral stricture after transurethral resection of prostate

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Abstract
Objective: *To investigate the relationship between preoperative Neutrophil to lymphocyte ratio (NLR) and Platelet to Lymphocyte ratio (PLR) values and post TURP strictures.*
Patients and Methods: *A retrospective review of data regarding preoperative absolute neutrophil, lymphocyte and platelet count were recorded for all patients who underwent TURP for benign prostatic hyperplasia in Urology Department from January 2017 to December 2017. Patients who had posterior urethral strictures, documented active infection at the time of TURP, surgery for any other urethral pathology and previous or ongoing treatment for any cancer and hematologic disorders were excluded. Study group comprised of 285 cases. NLR and PLR were calculated. Diagnosis of urethral stricture was suspected when uroflowmetry showed a maximum flow rate of less than 10 mL per second and was confirmed by both urethrogram and cystoscopyin each stricture patient. Receiver operating characteristic (ROC) curve was drawn to determine the cut off value of PLR and NLR for predicting stricture.*
Results: *Statistically significant differences were observed between the groups in terms of prostate volume, operating time, NLR and PLR. For predicting urethral stricture, the optimal cut-off value of PLR was 111.895, (sensitivity: 1, specificity: 1; AUC=1) and NLR was 2.33 [sensitivity: 0.82; specificity:0.6; AUC=0.721 (0.637 - 0.805)].*
Conclusion: *There is a definite correlation between inflammatory markers and urethral stricture formation. Both PLR and NLR can be used to determine the probability of development of urethral stricture in patients after TURP.*
Keywords: *Inflammatory markers, Neutrophil to lymphocyte ratio (NLR), Platelet to Lymphocyte ratio (PLR), Post-TURP stricture.*

Introduction

With the aging population more and more people are diagnosed to have benign prostatic hyperplasia (BPH) in recent times. The number of people undergoing transurethral resection of prostate (TURP) has also increased proportionately. Though complications after TURP have decreased from yester years, urethral strictures still remain a major bothersome complication. It is widespread and has a substantial impact on the quality of life of the patient.[1] Etiology of strictures have changed over time. During 1960's urethritis was the commonest cause of strictures but by 1980's it was replaced by iatrogenic strictures after TURP.[2] Exact pathology of urethral strictures remains obscure. It has been hypothesized that stricture

develops as a result of inflammation in urethral mucosa and the subepithelial spongy tissue resulting in excessive scar formation.[3] Even though there are many proposed risk factors for stricture disease[4], there is no consensus as to which patients will develop stricture disease after TURP and there is no available predictive marker. The neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are two markers of inflammation that have been found to have prognostic significance in many diseases.[5] Since inflammation is said to play a role in pathogenesis, we aim to investigate the relationship between preoperative NLR and PLR values and post TURP strictures.

Materials and Methods

Data were obtained from all patients who underwent monopolar-TURP between January 2017 and December 2017 in the Department of Urology, Government Medical College Kozhikode after obtaining the permission from the local ethics committee and informed consent from patients. All patients were operated by experienced surgeons of the department. Transurethral resection was performed using a thick loop and by using a standard continuous irrigating resectoscope with a 26 French outer sheath. At the end of the surgery, a 22 Fr three way Foley catheter was left insitu for continuous saline irrigation. The catheters were removed when the urine became clear without continuous saline irrigation. Basic patient profile at the time of surgery would be identified. Routine hematologic analysis in the pre-operative period particularly the absolute neutrophil, lymphocyte and platelet count were recorded. Peri-operative details like prostate size and the operative time were also collected. These patients were followed up for a median period of 9 months. Uroflowmetry pattern were obtained for the patients with symptoms of stricture disease. Diagnosis of urethral stricture was made by uroflowmetry (maximum flow rate of less than 10 mL per second) and confirmed by both urethrogram or cystoscopy. Only anterior urethral strictures were included in the study. The exclusion criteria included

- Posterior urethral strictures
- History of surgery for any other urethral pathology,
- Documented active infection at the time of TURP
- Blood transfusion prior to procedure
- Previous or ongoing treatment for any cancer or hematologic disorders

Based on the presence of anterior urethral stricture patients were allocated to two groups. NLR and PLR were calculated from the preoperative haematological analysis reports. The neutrophil to lymphocyte ratio (NLR) was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. Similarly, PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. The relationship between stricture and the NLR and PLR were studied based on appropriate statistical analysis.

Statistical Method

Statistical analysis was done using SPSS 16.0. Data were expressed as median and inter quartile range (IQR). Comparison between groups was done using Mann-Whitney U test. Receiver operating characteristic (ROC) curve was drawn to determine the cut off value of PLR and NLR for predicting stricture. Area under the curve (AUC) of ROC curve was also calculated. A p value < 0.05 was considered as statistically significant.

Results

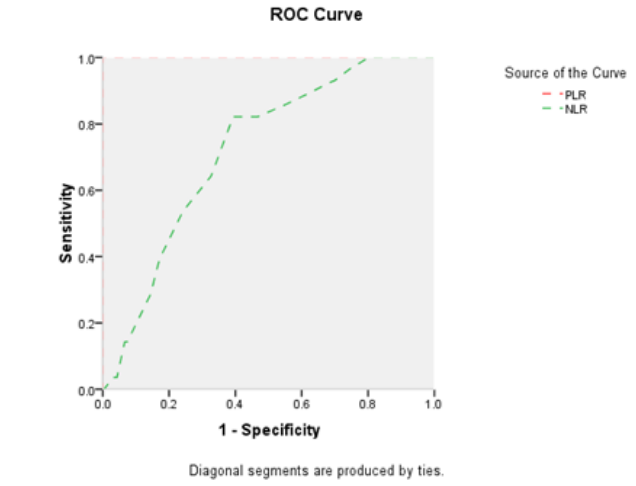
Out of 318 patients, 285 patients meeting the necessary inclusion criteria were included in the present study. 257 patients without urethral stricture were in the control group and 28 with urethral stricture in the study group. The mean age, prostate volume, operation time, NLR and PLR values and also the catheter removal time were evaluated (Table 1). The median follow up after TURP and the median time interval between TURP and recurrence was 9 (range 6-18) and 4.2 months, respectively.

	Patients (n=28)	Controls (n=257)	P value
Age	64 (9)	65 (10)	0.42
Prostate volume	68 (14)	51 (34)	0.001*
Operating time	72.5 (19)	45 (30)	< 0.00001*
PLR	137.75 (40.44)	80.65 (32.02)	< 0.00001*
NLR	2.57 (0.51)	2.13 (0.67)	< 0.00001*
Catheter removal time	3.2(0.4)	3.1(0.8)	0.53

Results are given as median values (inter quartile range).
*Statistically significant at 1% level.

No statistically significant differences were observed between the groups in terms of age. Statistically significant differences were present in the study group related to mean PLR- values, NLR values, prostate volume and operating time.

Receiver Operating Characteristic (ROC) analysis was performed to determine the cut-off value of PLR and NLR to predict urethral stricture, and ROC/area under curve (AUC) was drawn by plotting the sensitivity versus the specificity for different cut-off levels (Figure 1). For predicting urethral stricture, the optimal cut-off value of PLR was 111.895 and NLR was 2.33.



	AUC	P value
PLR	1	<0.00001
NLR	0.721 (0.637 - 0.805)	<0.00001

Result given as area under the ROC curve (95% CI).
For a cut off at 111.895, PLR has 100% sensitivity and specificity.
For a cut off at 2.33, NLR has 82.1% sensitivity and 60.7% specificity

Discussion

Literature review shows that, the incidence of urethral stricture after monopolar TURP varies between 1.5% and 9.8%.[6,7] For bipolar TURP the incidence was even higher and varies between 1.4% and 19%.[6,8] The incidence of stricture disease in our study was 9.8%, which was well comparable to other large series.

The World Health Organization (WHO) defines urethral stricture as a narrowing of the urethral lumen that is secondary to a scarring process that affects the erectile tissue of the corpus spongiosum causing spongiofibrosis. As the time progresses the scar contracts resulting in reduction of the urethral lumen. It becomes a matter of concern, when the lumen is compromised to obstruct the exit flow of urine and the patient develops bothersome voiding symptoms. Urethral strictures can be divided into anterior and posterior ones. Those located in the posterior urethra are invariably the consequence of trauma or TURP.

The matter of concern is why does urethral stricture develop in few and not in many. As per recent literature, role of most of the traditionally established risk factors for development of urethral strictures are debatable. There are both modifiable and non-modifiable risk factors. Size of resectoscope and to and fro movements during the procedure were said to be the prime factors for stricture formation.[9] On the contrary Hart and Fowler reported that, size of the operating sheath, size and material of the catheter, and the presence of an infected urine or even a positive urethral swab did not have a statistically significant correlation to stricture formation.[9]Hammarsten et al. showed that the choice of urethral catheter plays a more important role than other factors during the operative procedure.[10] Bulbous strictures are said to be due to the passage of monopolar current through the sheath due to insufficient lubricant. Another proposed risk factor was the use of high monopolar current resulting in urethral tissue damage.[11,12] Hence to preserve the urethra's normal physiology, urethral manipulation should be minimal, a small calibre resectoscope should be employed, high monopolar current should be avoided, and the postoperative Foley catheter should be used for the least amount

of time possible.[13] All the above mentioned risk factors are modifiable and hence of major concern.

Pathogenesis of stricture formation is reported to be due to extravasation of urine which results in inflammation and scar formation. There are two hypotheses regarding the inciting event leading on to urine leak. Some investigators proposed that a mucosal injury caused direct leakage of urine[4] while others suggested that the damaged urethral epithelium changes to stratified squamous epithelium which is less resilient to pressure changes and normal urethral distention and results in frequent urine extravasation. Trauma to the urethra is undoubtedly a significant factor. On urethroscopy several days after resection, isolated erythematous areas in the urethral mucosa can be visualized.[14] Metaplasia of the urethral epithelium from its normal pseudo-stratified columnar type to stratified squamous epithelium[15] which is a more fragile epithelium, results in fissures and ulcers and tends to split when distended during voiding. These fissures or ulcers in the epithelium lead to focal extravasation of urine on voiding. The pathologic change associated with urethral stricture disease is fibrosis of the epithelial-lined cavernous tissue.[16] Nielsen and Nordling also underlined the role of urine extravasation into the subepithelial space causing increased inflammation and subsequent fibrosis.[17]

Microscopic foci of fibrosis form and coalesce over a period of years to form macroscopic plaques, which may then constrict the urethra if they coalesce around the circumference of the urethra to form a complete ring. This process is progressive and becomes a vicious cycle with the non-distensible, nonelastic fibrotic tissue further damaged from the hydrostatic pressure of voiding leading to further leakage across the mucosal barrier causing worsening fibrosis.[18]

Metaplastic change occurs not just at the site of mucosal injury but also occurs proximal to the site of stricture, due to chronic distension under pressure during voiding. The proximal epithelium gets a wash leather appearance after it undergoes metaplasia but this metaplasia seems reversible after relieving the obstruction.

Myofibroblasts are probably responsible for the formation of the stricture, and giant cells may be involved in continued collagen synthesis. Unlike stricture at other sites, urethral strictures have unusually high proportion of type 1 collagen compared with type 3, which usually predominates in a scar.

As inflammation and subsequent scar formation are said to be the driving events in the development of stricture, many investigators have tried anti-inflammatory drugs to reduce the incidence of strictures. Some of the drugs that have been tried are COX2 inhibitors[19], steroids like triamcinolone[4], and corticosteroids[20], colchicine[21] and mitomycin-c[22].

In our study, we tested the role of NLR and PLR to predict the development of post-TURP urethral strictures. During systemic inflammation there is predominant neutrophilia and associated lymphopenia. NLR and PLR were introduced as novel markers of inflammation in many scenarios.[23,24] Both NLR and PLR values showed significant changes in urethral stricture patients.

A typical blood specimen comprises 93% red blood cells, 6% platelets, and 1% white blood cells. Neutrophils are the most abundant type of WBC's and are the first cell types to travel to the site of an infection. Platelets are small discoid cells with a life span of about 7 to 10 days and responsible for hemostasis, construction of new connective tissue and revascularization. Activation of these two types of cells result in release of many growth factors which result in a cascade of events which might end in fibrosis. Neutrophils secrete vascular-endothelial growth factor (VEGF) and basic fibroblast growth factor(b-FGF).[25]Activation of platelets results in secretion of platelet-derived growth factor (PDGF), vascular-endothelial growth factor (VEGF), insulin-like growth factor (IGF), epidermal growth factor (EGF) and transforming growth factor-β (TGF-β).[26] All these factors in particular the profibrotic factors -TGF-β1 and b-

FGF have been shown to play a crucial role in the pathophysiology of fibrotic diseases such as pulmonary fibrosis, oral submucosal fibrosis, systemic sclerosis, renal fibrosis and Peyronie's disease.[27,28] Besides, TGF-β1 was proven to create fibrosis of the urethra in several animal studies.[29] Neutrophils have receptors for TGF B1 and play a major role in their functioning.[30]Statistically significant differences were present in the study group related to mean PLR- values and NLR values.

Prostate size and longer resection time are two other factors which have been found to be decisive in stricture development. A larger gland implies a longer resection time and a longer resection time may perhaps be due to its correlation with unfavorable surgical events including hemorrhage, poor vision, more fluid leakage/absorption and urethral mucosal impairment, all of which are potential reasons of urethral stricture. The lubricant gel should be applied carefully in the urethra and along the shaft of the resectoscope. The lubricant must be reapplied in cases of longer resection time to prevent stricture formation.[11]

The present study has some limitations. First, the study was designed as a retrospective study. Second, we didnot investigate the b-FGF and TGF-β1 levels and we assumed that the higher the NLR and PLR values the higher would be the levels of b-FGF and TGF-β1.

Conclusion

The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) can be used to determine urethral stricture as a cost-effective, common, and simple biomarker in patients after TURP. Further studies are needed in order to evince these inflammatory markers as preoperative predictors for urethral stricture that may facilitate institution of appropriate therapy and reduce morbidity and cost.

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