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ORIGINAL RESEARCH

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Evaluation of the non-invasive indicators in predicting detrusor underactivity in individuals with small-volume prostatic hyperplasia and lower urinary tract symptoms

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Abstract

This study was aimed to retrospectively analyze the potential of non-invasive serum biomarkers in clinically predicting the detrusor underactivity (DU) in benign prostatic hyperplasia (BPH) patients with lower urinary tract symptoms (LUTS) and low prostate volume (PV). The study enrolled 196 patients with BPH and LUTS at our hospital in the period from January 2018 to October 2023. The patients were divided into two groups based on the projected isovolumetric pressure (PIP): the DU and the control groups. The patients included in the study had PV of less than 50 mL. A total of 93 and 103 cases were placed in the DU and control groups, respectively. Univariate analysis exhibited that the age was associated with DU occurrence (p = 0.004), and the serum prostate specific antigen (PSA) might act as DU protective factor (p = 0.001). However, there was no statistically significant relation between pre-selected serum hematological parameters and the DU diagnosis accuracy. Multivariate analysis suggested that only the age (OR (odds ratio) 1.07, 95% CI (confidence interval) 1.03–1.12, p = 0.001) and PSA (OR 0.79, 95% CI 0.69–0.90, $p < 0.001$) were the independent predictors of DU. In this study, it was observed that the pre-selected serum hematological parameters had no relevance in diagnosing DU in low PV male patients. Nonetheless, it was found that the age and PSA could be the independent non-invasive predictors of male patients with LUTS and low PV, who were unable to undergo urodynamic examinations.

Keywords

Prostatic hyperplasia; Lower urinary tract symptoms; Detrusor underactivity; Serum hematological parameters

1. Introduction

Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) are prevalent and globally impact the life quality of elderly males [1]. LUTS arise from factors including BPH, neurogenic bladder, bladder outlet obstruction (BOO), overactive bladder (OAB), and detrusor underactivity (DU) [2]. There is a reduction in the strength or duration of detrusor contractions in DU which results in the prolonged bladder emptying [3]. DU is challenging for the healthcare professionals and affected individuals. Presently, the pharmacological interventions are lacking in managing DU [4]. Parasympathomimetics in combination with alpha-adrenoreceptors antagonists are the common pharmacotherapies of DU, however their therapeutic impacts are limited. Potential pharmacological targets for treating DU may involve bombesin receptors, prostaglandins, adenosine triphosphate (ATP), nitric oxide (NO), calcitonin gene related peptide (CGRP), substance P (SP), nerve growth factor (NGF) and agrin-dependent pathways [5]. However, the successful treatment approaches for DU are lacking.

It is clinically imperative to precisely diagnose DU. Kim *et al.* [5] observed that DU pathophysiology might encompass abnormal tissue inflammation, fibrosis, denervation and apoptosis of bladder muscle tissue [6]. Vascular endothelial injury is a risk factor contributing to the development of arteriosclerosis and hypertension. Inadequate blood supply to the pelvic tissues can occur in pelvic vascular injury to result in the localized tissue fibrosis and potentially necrosis. This vascular impairment can be an underlying factor in DU occurrence [7]. Inflammation can harm the structural integrity of vascular endothelium which may impair the vascular endothelium and subsequent local tissue ischemia. This, in turn, exacerbates the organs dysfunction [8].

DU is diagnosed by the urodynamic studies, however widely accepted diagnostic criteria are lacking. Several approaches contribute to the diagnosis, wherein most assess the detrusor contraction strength, although this is one aspect of urination [9]. The projected isovolumetric pressure (PIP) determination is based on Schafer's nomogram which assesses the detrusor pressure during bladder isovolumetric contraction. PIP formula is PIP = Pdet@Qmax + 5Qmax for men, and the

PIP between 100 and 150 is the normal contractility range [10]. DU is found in 48% of men with over 70 years age compared to 9–28% in men under 50 years. In Korea, the DU prevalence is 40.2% in men with LUTS of above 65 years age. DU prevalence is recorded as 23% in an Australian study [10, 11]. The prevalence and clinical significance of DU in elderly population remains unknown because of no standard measurement techniques or quantitative diagnostic criteria. It is important to note that this examination is invasive and can cause discomfort and pain for certain patients. Herein, the objective is to utilize easily measurable serum hematological parameters or other indicators for enhancing the diagnostic precision of DU in male patients with BPH and LUTS who are unwilling or unable to undergo urodynamic examinations.

2. Methods

2.1 Patients

This study was retrospectively conducted at our hospital. A complete urodynamic evaluation was necessary to understand the pathophysiology underlying in men with LUTS (patients with International Prostate Symptom Score, International Prostate Symptom Score (IPSS) assessment >7). A urodynamic study was conducted by following the basic LUTS evaluation including Qmax, PdetQmax, PIP and post-void residual (PVR). BPH/LUTS patients from the Department of Urology at our hospital were recruited between January 2018 and October 2023. Inclusion criteria: (1) subjects voluntarily signing the informed consent form; (2) between 18 and 100 years old, conscious, compliant, ability to express feelings and independently complete symptom questionnaire; (3) diagnosis made through physical examinations, PV measurement by abdominal ultrasound, urodynamic examination by following the International Continence Society (ICS) guidelines, and DU defined with the PIP <100. Exclusion criteria: (1) patients of PV >50 mL; (2) individuals with the history of prostate surgery, prostate biopsy, medication (including antimuscarinic, beta3 agonists, alpha1-antagonists, alpha5-reductase inhibitor, intravesical injection Botulinum Neurotoxin A and hyaluronic acid), and acute and chronic prostatitis; (3) patients with urethral stricture, radical pelvic surgery, neurologic disease, overactive bladder, urinary incontinence, diabetes and no other periferic neurologic condition to explain DU (Tarlov cyst, severe lumbar hernia, pelvic trauma). A total of 201 patients were considered, however 5 were excluded (3 due to refusal of participation, and 2 because of the history of lower urinary tract surgery), leaving 196 patients.

The collected clinical data included age, height, weight, body mass index (BMI), hypertension, diabetes mellitus, cardiovascular disease, hyperlipidemic status and smoking habit. Furthermore, the prostate specific antigen (PSA) and PV were also assessed. PV = $\pi/6 \times$ length $\times$ width $\times$ height [12]. The prognosis nutrition index (PNI), systemic immune inflammation index (SII), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and systemic inflammation response index (SIRI) were calculated as follows: PNI = albumin (g/L) + 5 $\times$ total lymphocyte counts (10^9/L); SII = platelet $\times$ neutrophil/lymphocyte counts; NLR = neutrophil/lymphocyte counts; PLR = platelet/lymphocyte counts; LMR = lymphocyte/monocyte counts; and SIRI = neutrophil $\times$ monocyte/lymphocyte [13].

2.2 Statistical analysis

SPSS 27 (SPSS Inc., Chicago, IL, USA) was employed to statistically analyze the data. Mean $\pm$ Standard Deviation (SD) represented the continuous variables while qualitative variables like hypertension, diabetes, cardiovascular disease and bladder stone were described by frequency/percentages. The two independent sample *t*-test compared the two groups when data was normally distributed. The non-parametric Mann-Whitney U test was employed if the data was not normally distributed. A univariate logistic regression was performed to predict DU in our cohort. A multivariate logistic regression analysis was performed by employing all the variables analyzed in univariate logistic regression (independent of their significant or insignificant association). Only the variables independently associated with DU were shown in multivariate analysis. Chi-square test was used to compare the binary variables, univariate and multivariate regression analysis to select the independent risk factors, and receiver operating characteristics (ROC) to analyze the specificity and sensitivity of independent risk factors. Areas under the ROC curves were estimated and compared by chi-square test. The optimal cutoff (Youden index) was selected to maximize the sum of sensitivity and specificity for evaluating the value effectiveness [14]. The $p < 0.05$ was considered statistically significant.

3. Results

A total of 196 BPH/LUTS patients were included for the urodynamic assessment where 93 were diagnosed with DU and 103 had no DU. The average age of patients' cohort was 69.0 $\pm$ 7.3 years, wherein 70 (35.7%) individuals had hypertension and 25 (12.8%) had diabetes. Additionally, 32 (16.3%) patients had a history of cardiovascular disease while 24 (12.2%) of bladder stone. Besides, 78 (39.8%) patients had hyperlipidemic status, and 54 (27.6%) had smoking habits. Thirteen (6.6%) patients required clean intermittent catheterization (CIC). No significant differences were observed between the groups pertaining to BMI, testosterone, prostate volume, hypertension, diabetes, cardiovascular disease, bladder stone, hyperlipidemic states, smoking habits, CIC, NLR, PNI, SII, LMR or SIRI. The patients in DU group had higher age and lower PSA compared to those without DU. The baseline clinical characteristics of the cohort had been presented in Table 1. The multivariate analysis revealed that the age had an odds ratio (OR) equal to 1.06, 95% confidence interval (CI) 1.02–1.11, $p = 0.004$. The value of 1.06 was not that big compared to 1, but it was too strong to affirm that the age was an independent factor. Furthermore, high PSA level was a protective factor (OR 0.81, 95% CI 0.72–0.92, $p = 0.001$) (Table 2). As shown in Fig. 1, ROC curve for age yielded an Area Under Curve (AUC) value of 0.71. The optimal age cutoff was calculated as 66.5 years with sensitivity of 0.72 and specificity of 0.46. ROC curve

TABLE 1. Characteristics of the study cohort.

	All patients N = 196	DU N = 93 (47.4)	Non-DU N = 103 (52.6)	*p*
Age (yr), mean ± SD	69.0 ± 7.3	70.7 ± 6.9	67.6 ± 7.4	0.003*
BMI, mean ± SD	24.1 ± 4.0	23.7 ± 3.3	24.4 ± 4.5	0.268
PSA, mean ± SD	3.1 ± 2.8	2.4 ± 2.0	3.7 ± 3.2	0.001*
Testosterone, mean ± SD	4.3 ± 1.4	4.4 ± 1.4	4.1 ± 1.3	0.441
Prostate volume, mean ± SD	37.4 ± 7.8	37.1 ± 7.5	37.6 ± 8.2	0.646
Hypertension, N (%)				
No	126 (64.3)	55 (59.1)	71 (68.9)	0.180
Yes	70 (35.7)	38 (40.9)	32 (31.1)	
Diabetes, N (%)				
No	171 (87.2)	81 (87.1)	93 (90.3)	0.505
Yes	25 (12.8)	12 (12.9)	10 (9.7)	
Cardiovascular Disease, N (%)				
No	164 (83.7)	74 (79.6)	90 (87.4)	0.176
Yes	32 (16.3)	19 (20.4)	13 (12.6)	
Bladder stone, N (%)				
No	172 (87.8)	83 (89.2)	89 (86.4)	0.664
Yes	24 (12.2)	10 (10.8)	14 (13.6)	
Hyperlipidemic status, N (%)				
No	118 (60.2)	55 (59.1)	63 (61.2)	0.884
Yes	78 (39.8)	38 (40.9)	40 (38.8)	
Smoking habitude, N (%)				
No	142 (72.4)	66 (71.0)	76 (73.8)	0.749
Yes	54 (27.6)	27 (29.0)	27 (26.2)	
CIC, N (%)				
No	183 (93.4)	88 (94.6)	95 (92.2)	0.575
Yes	13 (6.6)	5 (5.4)	8 (7.8)	
Before UDS laboratories				
Serum albumin, mean ± SD, g/L	41.2 ± 3.6	40.8 ± 3.5	41.5 ± 3.7	0.570
Serum leukocyte, mean ± SD, 10^9/L	5.8 ± 1.5	5.9 ± 1.4	5.8 ± 1.5	0.698
Serum neutrophil, mean ± SD, 10^9/L	3.6 ± 1.4	3.6 ± 1.2	3.6 ± 1.5	0.777
Serum lymphocyte, mean ± SD, 10^9/L	1.7 ± 0.5	1.8 ± 0.5	1.7 ± 0.6	0.104
Serum monocyte, mean ± SD, 10^9/L	0.37 ± 0.11	0.37 ± 0.12	0.37 ± 0.1	0.680
Serum platelet, mean ± SD, 10^9/L	191.0 ± 42.2	195.2 ± 41.8	187.3 ± 42.4	0.192
NLR, mean ± SD	2.3 ± 1.4	2.2 ± 1.0	2.4 ± 1.7	0.240
PLR, mean ± SD	122.3 ± 50.8	121.0 ± 57.6	123.4 ± 44.1	0.747
LMR, mean ± SD	4.8 ± 1.8	5.0 ± 2.0	4.7 ± 1.6	0.285
SII, mean ± SD	446.1 ± 287.8	437.2 ± 243.8	454.1 ± 323.4	0.682
SIRI, mean ± SD	0.86 ± 0.57	0.82 ± 0.44	0.89 ± 0.67	0.386
PNI, mean ± SD	49.7 ± 4.9	49.2 ± 5.0	50.1 ± 4.8	0.219
Urodynamic study				
Qmax, mean ± SD, mL/s	8.9 ± 4.9	4.4 ± 1.2	13.0 ± 3.0	<0.001*
PdetQmax, mean ± SD, cmH_2O	41.4 ± 13.0	32.7 ± 7.8	49.3 ± 11.6	<0.001*
PIP, mean ± SD	86.0 ± 31.3	54.5 ± 8.6	114.5 ± 8.9	<0.001*
PVR, mean ± SD	80.6 ± 42.8	117.0 ± 30.4	47.8 ± 19.2	<0.001*

*BMI: body mass index; PSA: prostate-specific antigen; NLR: neutrophil to lymphocyte ratio; PLR: platelets to lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune inflammation index; LMR: lymphocyte to monocyte ratio; SIRI: systemic inflammation response index; PIP: projected isovolumetric pressure; PVR: post-void residual; DU: detrusor underactivity; CIC: clean intermittent catheterization; SD: standard deviation; UDS: urodynamics. *Statistically significant.*

TABLE 2. Univariate and multivariate analysis for the DU prediction.

	Univariate analysis			Multivariate analysis		
Variables	OR	95% CI	*p*	OR	95% CI	*p*
Age (yr)	1.06	1.02–1.11	0.004*	1.07	1.03–1.12	0.001*
BMI	0.96	0.89–1.03	0.270			
PSA	0.81	0.72–0.92	0.001*	0.79	0.69–0.90	<0.001*
Testosterone	1.15	0.93–1.43	0.203			
Prostate volume	0.99	0.96–1.03	0.641			
NLR	0.88	0.71–1.09	0.250			
PLR	0.99	0.99–1.01	0.746			
LMR	1.09	0.93–1.27	0.285			
SII	1.00	0.99–1.00	0.681			
SIRI	0.80	0.47–1.34	0.391			
PNI	0.96	0.91–1.02	0.219			

*BMI: body mass index; PSA: prostate-specific antigen; NLR: neutrophil to lymphocyte ratio; PLR: platelets to lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune inflammation index; LMR: lymphocyte to monocyte ratio; SIRI: systemic inflammation response index; OR: odds ratio; CI: confidence interval; *Statistically significant.*

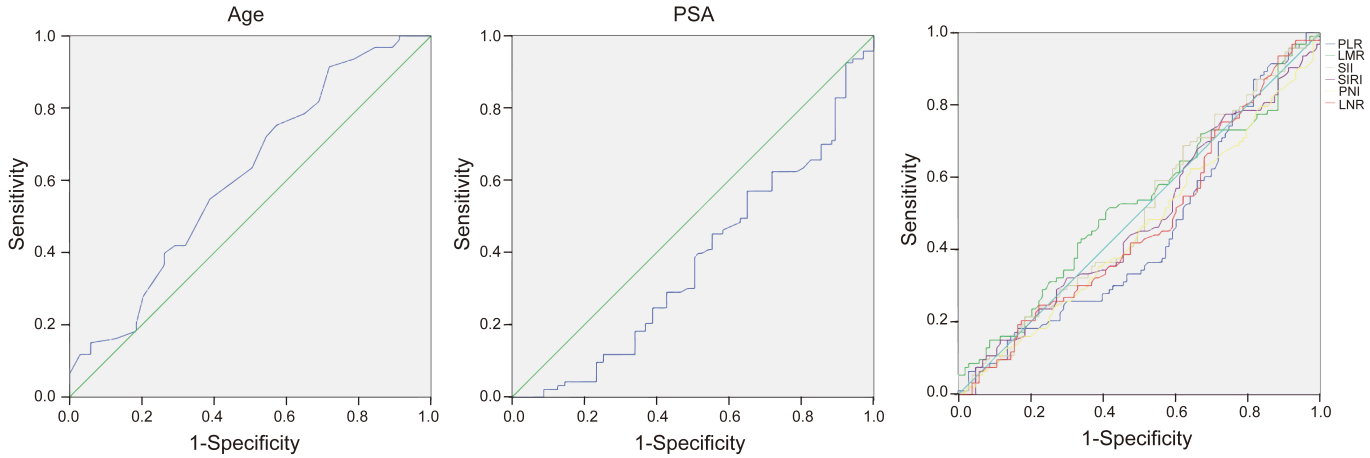

FIGURE 1. ROC curves for the DU prediction. ROC: receiver operating characteristic; AUC: area under the curve; PSA: prostate-specific antigen; PLR: platelets to lymphocyte ratio; LMR: lymphocyte to monocyte ratio; SII: systemic immune inflammation index; SIRI: systemic inflammation response index; PNI: prognostic nutritional index; NLR: neutrophil to lymphocyte ratio.

for PSA yielded an AUC value of 0.37 which indicated poor discrimination. The optimal age cutoff was calculated as 2.90 ng/mL with sensitivity of 0.30 and specificity of 0.49. It was poorly discriminated according to its accuracy performance.

4. Discussion

According to ICS, the underactive bladder (UAB) had a slow urinary stream, hesitancy and straining to void, with or without the feeling of incomplete bladder emptying, sometimes with storage symptoms. DU referred to the low detrusor pressure or short detrusor contraction time in combination with low urine flow rate, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying in normal time span as measured *via* the urodynamic assessment. DU thus referred to the urodynamic finding of impaired bladder contraction, whereas UAB was defined as the combination of associated symptoms [15, 16]. The gold standard for diagnosing DU in clinical practice remained the urodynamic examination despite the associated risks of hematuria and urinary tract infection. No effective non-invasive index could be discovered to enhance DU diagnosis accuracy. The timely identification of DU was a challenge in the clinical management of BPH/LUTS patients. This study represented a convenient approach in investigating the prognostic significance of inflammation in BPH/LUTS patients with small PV. The objective was to identify potential independent factors for accurately predicting the DU presence. In this small-scale study, it was discovered that PSA could forecast the DU presence but with poor discrimination. Only a few pre-selected factors tested in complete

blood count did not reflect that inflammation markers were not important in relation to DU. In future studies, the patient CRP, cytokines and other markers would be incorporated for examination. Based on multivariate analysis, the age and PSA were emerged as independent predictors of DU diagnosis through urodynamic studies in the patients of low PV (<50 mL). Among this subgroup of patients, the older individuals and those with lower PSA levels faced higher DU risk. DU was a prevalent condition associated with LUTS. DU etiology remained poorly understood despite its high prevalence. Additional investigations were thus imperative to explore the key risk factors contributing to DU presence [14]. Reem *et al*. [16] compiled the risk factors associated with DU. The study identified DU predictors including age, congenital factors, neurogenic factors and BOO. Furthermore, it highlighted that individuals with diabetes were at elevated risk of developing DU [16]. However, in this study, no significant association was observed between the diabetes and risk of developing DU. Luo *et al*. [6] posited that PV as a predictor could enhance the precision of diagnosing DU with optimal cutoff of 46 mL. However, in this study, the patients of low PV did not exhibit statistically significant difference in PV upon comparing DU group to the control. The data could not be compared to this study as the population herein differed—our patients were older with lower PV and PSA values. Contrary to the findings of their study, this work suggested that PSA could be regarded as a predictor having independent influence on DU occurrence. This study revealed that PSA had a role in DU diagnosis. Moreover, the non-DU group exhibited elevated PSA levels compared to those of DU. A positive correlation was observed between the levels of inflammation in prostate and PSA concentration in the bloodstream. An increase in prostate inflammation was associated with higher PSA values. Therefore, the etiology of LUTS in individuals without DU was associated with prostate inflammation. LUTS in DU group was linked to the bladder detrusor dysfunction, although with insufficient evidence. There might be an inverse relationship between inflammation and DU occurrence. Several studies had established a strong correlation between age and detrusor contractility, however the disagreement remained in the academic community. Ameda *et al*. [17] demonstrated no correlation between maximum detrusor pressure and age in LUTS patients. Conversely, Kullmann *et al*. [18] argued that detrusor contractility was weakened as age increased. In this research, ROC curve analysis revealed that 66.5 years age had the highest Youden index value. Kim *et al*. [7] developed a DU rat model by inducing chronic bladder ischemia through arterial damage. This model provided evidence that vascular endothelial damage was a contributor to DU [19]. Inflammation had detrimental effects on the vascular endothelium. It was thus hypothesized that the presence of inflammatory markers in bloodstream might be associated with chronic bladder ischemia which contributed to the DU presence. Previous works had investigated the correlation between inflammatory markers including NLR, PLR, SII, SIRI and PNI, and the incidence and prognosis of various tumor types [20, 21]. These indicators reflected the extent of systemic inflammation in the organism.

Shortcomings of this study included the limited number of participants and incomplete incorporation of inflammation markers. Increasing the sample size and including the healthy individuals would make the results more authentic. Besides, it would be meaningful to include investigations of inflammatory markers such as C-reactive protein (CRP) and cytokines. The hematological markers chosen for this study were oversimplified and did not provide comprehensive representation of patient's condition. The objectives of this study were evident, and the obtained results were practical.

5. Conclusions

The diagnosis and underlying causes of DU remain unclear. The utilization of invasive diagnostic techniques in clinical settings may lead to adverse complications for patients. Our investigations have identified the age and PSA as the indicators for predicting DU presence in low PV patients. The inflammation factors can serve as the predictors to enhance DU diagnostic accuracy. Their absence in our findings can be attributed to the limited sample size. Therefore, further research is necessary to explore the association between inflammation and the risk of DU occurrence.

AVAILABILITY OF DATA AND MATERIALS

All data during this research process are included in this published article.

AUTHOR CONTRIBUTIONS

YYW, JQ and ZPW—protocol development, manuscript writing. YDH and SW—data analysis. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study along with the associated procedures was conducted according to the World Medical Association Declaration of Helsinki, and the Guidelines for International Council on Harmonization and Good Practice (ICH-GCP). Protocol review, study coordination, data management, and safety monitoring were carried out through the hospital's Clinical Research Unit. The trial was approved from the Ethics Committee of Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (Ethics No. XHEC-C-2021-106-1). All the patients signed an informed consent form prior to any examination.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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