



SIGNIFICANCE OF NON-INVASIVE SONO-MORPHOLOGICAL MARKERS IN THE EVALUATION OF BLADDER OUTLET OBSTRUCTION AND ACUTE URINARY RETENTION SECONDARY TO BENIGN PROSTATIC HYPERPLASIA

Urology

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ABSTRACT

Objectives: To define the diagnostic accuracy of intravesical protrusion of prostate (IPP), bladder wall thickness (BWT) and prostate volume (PV) in diagnosis of bladder outlet obstruction (BOO) and prediction of future acute urinary retention (AUR). **Materials and methods:** A prospective study of 127 patients, presenting with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (BPH) were enrolled with 50 patients among them manifesting AUR. 35 normal persons were selected as control group. After inclusion, all patients underwent transabdominal ultrasound and pressure flow urodynamic study (UDS). UDS parameter, BOO index (BOOI) were used as a reference standard for stratifying the patients into two groups, BOO and non-BOO. The sono-morphological parameters, IPP, BWT and PV were used to compare between these two groups with calculating the diagnostic accuracy for each individual index. **Results:** IPP, BWT and PV had statistically significant difference between group 1 (BOOI < 40) and 2 (BOOI > 40) with strong correlation with BOOI. The Pearson's correlation coefficient (r) for IPP, BWT and PV were 0.762, 0.702 and 0.660 respectively. The AUC for IPP, BWT and PV were 0.824, 0.786 and 0.650 with highest accuracy for IPP (79.2%) at cut-off value of 7 mm. Using the same threshold value, IPP had higher statistical difference than BWT in predicting AUR with similar diagnostic accuracy of IPP and BWT together. **Conclusions:** IPP and BWT in conjunction with PV in place of UDS had good clinical utility in diagnosis of BOO due to BPH and future AUR prediction.

KEYWORDS

Bladder Outlet Obstruction, Intravesical Protrusion Of Prostate, Bladder Wall Thickness, Prostate Volume, Acute Urinary Retention

INTRODUCTION :

Bladder outlet obstruction (BOO) is an important sequel of benign prostatic hyperplasia (BPH) leading to various anatomical & functional changes such as mechanical compression of prostatic urethra, bladder neck elevation, increased prostatic urethral angle & increased smooth muscle tone of prostatic urethra.^[1] It is characterized by increased detrusor pressure & reduced urinary flow with increased incidence in ageing population.^[2] Urodynamic study (UDS) is considered as gold standard modality for determination of BOO,^[3] but is of limited use owing to its invasive nature, patient's discomfort & potential consequences such as dysuria, urinary tract infection, gross haematuria, urinary retention.^[4] Currently, several non-invasive markers have been identified for diagnosis of BOO comprising of symptom score (International prostate symptoms score- IPSS), prostate-specific antigen (PSA), uroflowmetry & ultrasonographic (US) parameters such as prostate volume (PV), bladder wall thickness (BWT), intra-vesical prostatic protrusion (IPP) & post-void residual urine (PVR).^[5,6] The sensitivity and specificity of uroflowmetry parameter, peak urinary flow rate (Qmax), for diagnosis of BOO has limited value depending on its threshold value.^[7] In contrast, anatomical configuration of the prostate in the form of IPP has been found to be strongly correlated with BOO.^[8] IPP is a morphological change caused by the overgrowth of prostatic median lobe & lateral lobes into the bladder leading to voiding dysfunction. It has great capability of predicting clinical progression, efficacy of medical management & success of a trial without catheter (TWOC)^[9] after an episode of acute urinary retention (AUR). Recent studies suggested that BWT might also be useful in predicting BOO.^[10] Therefore, the main aim of our study was to determine the utility of US-derived parameters e.g. IPP, BWT & PV as non-invasive indices of BOO & AUR in patients with symptomatic BPH.

MATERIALS AND METHODS:

Study population:

This study design was a prospective clinical study, which was

conducted from October 2018 to March 2020 in all first-visit patients (>50 years), presenting with lower urinary tract symptoms (LUTS) suggestive of BPH. Total 134 patients were evaluated by physical examination, digital rectal examination (DRE), IPSS with quality of life (QoL) questionnaire, routine urine examination, serum urea, creatinine and PSA measurement. Among them 7 patients were excluded as per our exclusion criteria which were diagnosed case of prostate cancer, urethral stricture, chronic urinary retention, prior prostate surgery (e.g. TURP, open prostatectomy), neurogenic bladder, diabetes mellitus, vesical calculus & patients on LUTS medications. Patients with raised PSA underwent transrectal US guided biopsy to exclude malignancy before inclusion. After meeting inclusion criteria, patients were evaluated by USG, uroflowmetry and UDS. Among rest 127 patients, which were recruited finally, 50 patients presented with AUR & failed at least one episode of TWOC. These AUR patients were asked & recorded of their previous 1 month history of LUTS before onset of AUR. 35 normal individuals were recruited as control group in the non-invasive evaluation part of the study to make the study more reliable and to get normalized value. The ethics review board of our institution approved our study protocol & all patients provided written informed consent before study participation.

Study procedure:

USG was done using Philips HD7 model (Bothell, WA, USA) supported with 2-5 MHz abdominal probe and 4-8 MHz transrectal probe. Transabdominal ultrasound (TAUS) was used to measure PVR, IPP & BWT in supine position, but transrectal USG (TRUS) for estimating the PV in left lateral position as TRUS gives more definitive measurements of PV. Both kind of USG were done by a single operator. All the USG scanning was carried out with a bladder volume ~ 150-200 ml filled up in a natural way without retention or by infusion through the indwelling catheter in patients with AUR. IPP can be effectively measured in mid-sagittal plane as the vertical distance (mm) from the tip of the prostate's protrusion to the base of the bladder^[11] (Fig. 1) & was categorized into three grades—grade I - < 5

mm, grade II - 5-10 mm & grade III - >10 mm.^[12]

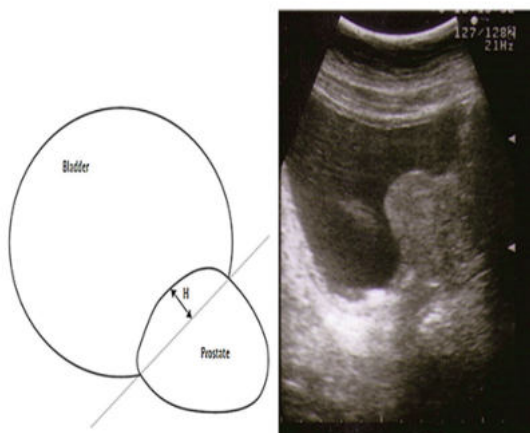


Figure 1: Measurement of intra-vesical prostatic protrusion (IPP). The vertical distance from the tip the protrusion to the base of bladder was measured in sagittal plane by using TAUS

BWT was assessed by the probe in horizontal direction (mm). Bladder wall was seen as three distinct layers identified by inner & outer hyperechogenic layer with middle hypoechoic layer corroborating inner mucosa plus submucosal layer, middle detrusor layer & outer subserosal layer (Fig. 2). We took 3 measurements at 3 different points of the bladder wall & calculated a mean value for further use.



Figure 2: Measurement of bladder wall thickness (BWT) by using TAUS

PV was evaluated at this same bladder volume using ellipsoid formula, $\pi/6 \times \text{prostate width} \times \text{height} \times \text{depth}$. PVR was determined after voiding using the same formula also.

Uroflowmetry was performed after calibration & Qmax was recorded with a voided volume ≥ 150 ml. Patients with Qmax ≥ 15 mL/s were considered as having good flow.

Pressure-flow UDS (PFS) were conducted using Urocomp 2000 model (Status Medical Equipments, India) on all patients. Initial filling phase was executed in semi-recumbent position by filling of bladder with normal saline at a rate of 30 ml/ second till the voiding urge followed by voluntary voiding phase in upright posture. According to ICS recommendations^[13] the extent of BOO was determined by the BOO index (BOOI), also known as Abrams-Griffith score. BOOI > 40 indicates definite obstruction, 20-40 is equivocal & < 20 indicates no obstruction.^[14] The person doing the PFS was blinded to the results of USG. Depending upon the BOOI, all patients were divided into obstructed and non-obstructed groups.

Statistical analysis:

All the data were analyzed by using SPSS version 23 (IBM, Chicago, IL, USA). The data distribution was not normal & non-parametric tests were used. Mann-Whitney U-test was used between inter group comparison. AUR & non-AUR patients were compared using Chi-square & Fisher's exact test with risk estimation as applicable while correlations were quantified using Pearson's correlation co-efficient (r). Receiver operating characteristic (ROC) curves were created for evaluation of area under curve (AUC) & the diagnostic performance of IPP, BWT & PV for BOO. AUC was determined to detect the strength of association (no association when AUC = 0.5 & strong association when AUC = 1). P < 0.05 was considered as statistically significant. Apart from that, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and likelihood ratio (LR) were also determined.

RESULTS:

Patients were broadly divided into 2 categories i.e. AUR and non-AUR group. Then non-AUR group was classified into two sub-groups according to BOOI. One group was labelled as group 1 i.e. no BOO comprising of 37 patients and another one as group 2 with BOO including 40 patients. As unobstructed patients with BOOI < 20 (mean - 14.47 $\pm$ 2.98) had no statistically significant difference in age, IPSS, QoL, PSA, Qmax, detrusor pressure at Qmax (Pdet), PV, PVR, IPP & BWT with patients having equivocal (20-40) BOOI (mean - 29.33 $\pm$ 5.89), they were clubbed together to consider as a single group i.e. group 1. We compared all the parameters between control group and two other groups (group 1 and 2) separately and found that all the variables were statistically significant in both groups, but age, QoL, IPP and S.PSA were insignificant in case of group 1. Also, there was significant difference in all variables between group 1 and 2 except PSA (P=0.6) and PVR (P=0.06) (Table 1).

Table 1: Baseline features of control group, patients having BOO, No BOO, AUR, No AUR

Parameters	Control (35) Mean $\pm$ SD (Range)	No BOO (37) Mean $\pm$ SD (Range)	BOO (40) Mean $\pm$ SD (Range)	P *	P †	P ‡	No AUR (77) Mean $\pm$ SD (Range)	AUR (50) Mean $\pm$ SD (Range)	P §
Age (years)	62.3 $\pm$ 3.9 (53-68)	62.8 $\pm$ 4.8 (55-74)	68.98 $\pm$ 8.2 (55-85)	0.8	< 0.001	0.001	66 $\pm$ 7.4 (55-85)	68.9 $\pm$ 8.8 (54-90)	0.08
IPPS _T	4.4 $\pm$ 1.9 (0-7)	15.5 $\pm$ 3.1 (9-21)	18.7 $\pm$ 5.4 (9-28)	< 0.001	< 0.001	0.004	17.2 $\pm$ 4.7 (9-28)	21.3 $\pm$ 6.9 (10-33)	0.001
Q o L	1.22 $\pm$ 0.7 (0-2)	2.1 $\pm$ 0.98 (0-3)	3.03 $\pm$ 1.03 (2-5)	0.1	< 0.001	0.001	2.5 $\pm$ 1.3 (0-6)	5.1 $\pm$ 1.03 (3-6)	< 0.001
PSA	1.7 $\pm$ 0.9 (0.2-3.3)	3.2 $\pm$ 1.6 (0.7-6.4)	3.4 $\pm$ 1.7 (0.8-7.6)	0.05	< 0.001	0.6	3.3 $\pm$ 1.6 (0.7-7.6)	3.6 $\pm$ 1.9 (0.8-8.4)	0.6
PV	41.3 $\pm$ 7.7 (24-55)	46.5 $\pm$ 8.6 (32-62)	59.1 $\pm$ 19.9 (38-95)	0.03	< 0.001	0.02	53 $\pm$ 16.7 (32-95)	76.4 $\pm$ 15.3 (50-122)	< 0.001
PVR	21.5 $\pm$ 10.3 (0-38)	57.8 $\pm$ 28.1 (0-95)	74.8 $\pm$ 26.97 (30-150)	0.004	< 0.001	0.06	66.6 $\pm$ 28.7 (0-150)	325 $\pm$ 63.4 (240-500)	< 0.001
IPP	2.8 $\pm$ 1.4 (0-5.2)	4.2 $\pm$ 3.5 (0-12.4)	10.6 $\pm$ 5.98 (0-25)	0.2	< 0.001	< 0.001	7.5 $\pm$ 5.9 (0-25)	13.97 $\pm$ 8.4 (2-32)	< 0.001
BWT	3.1 $\pm$ 1.1 (1.2-5)	4.5 $\pm$ 1.3 (3-7.7)	6.0 $\pm$ 1.3 (3.5-8.2)	< 0.001	< 0.001	< 0.001	5.3 $\pm$ 1.5 (3-8.2)	6.6 $\pm$ 1.4 (3.6-9)	< 0.001
Qmax	19 $\pm$ 2.4 (16-24)	14.7 $\pm$ 3.9 (8-22)	9.2 $\pm$ 3.7 (4-17)	< 0.001	< 0.001	< 0.001			
Pdet @ Qmax		50.9 $\pm$ 5.3 (40-62)	72.98 $\pm$ 5.03 (64-88)			< 0.001			
BOOI		21.7 $\pm$ 8.9 (8-38)	54.5 $\pm$ 9.6 (42-80)			< 0.001			

Mann-Whitney U-test

* Control v/s No BOO

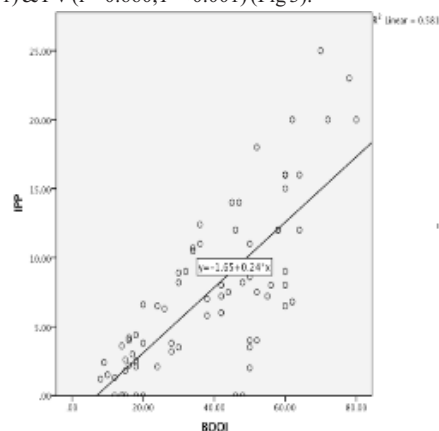
† Control v/s BOO

‡ No BOO v/s BOO

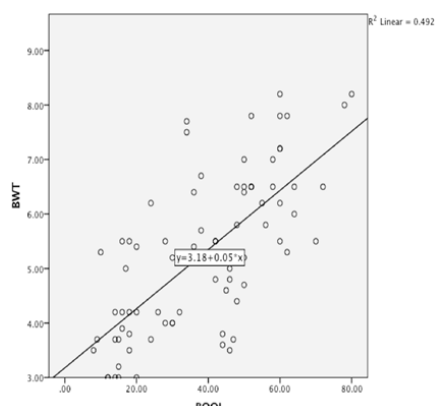
§ No AUR v/s AUR

IPPS_T, International prostate symptoms score Total; Q o L, Quality of Life; PSA, Prostate Specific Antigen; PV, Prostate Volume; PVR, Post-voiding Residue; IPP, intra-vesical prostatic protrusion; BWT, Bladder Wall Thickness; Qmax, Maximum flow rate; Pdet @ Qmax, Detrusor pressure at Qmax; BOOI, Bladder outlet obstruction index.

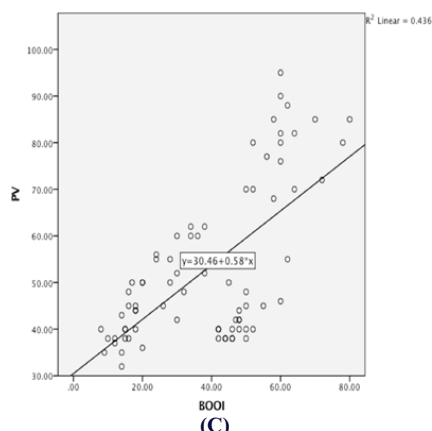
There was significant positive correlation between BOOI and each of the marker IPP, BWT & PV with highest Pearson's correlation coefficient (r) for IPP ($r = 0.762$, $P < 0.001$) followed by BWT ($r = 0.702$, $P < 0.001$) & PV ($r = 0.660$, $P < 0.001$) (Fig 3).



(A)



(B)



(C)

Figure 3: (A) Scatter plot of relationship between BOOI and IPP (mm) ($r = 0.762$) (B) Scatter plot showing relationship between BOOI and BWT (mm) ($r = 0.702$) (C) Scatter plot showing relationship between BOOI and PV (g) ($r = 0.660$)

(BOOI, bladder outlet obstruction index; IPP, intra-vesical prostatic protrusion; BWT, bladder wall thickness; PV, prostate volume)

On ROC analysis for the diagnostic value of IPP, BWT and PV to distinguish BOO, AUC for IPP was 0.824 (95% CI: 0.919 – 0.729; $P < 0.001$); for BWT was 0.786 (95% CI: 0.889 – 0.683; $P < 0.001$) and for PV was 0.650 (95% CI: 0.775 – 0.525; $P = 0.02$) (Fig 4). The best cut-off value for IPP, BWT & PV were 7 mm, 4.2 mm and 40 g respectively.

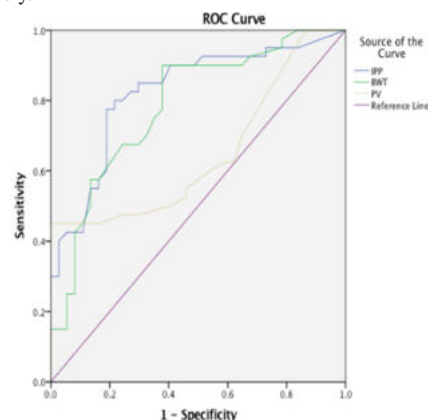


Figure 4: Receiver-operator characteristic curves of IPP, BWT and PV for BOO.

(BOOI, bladder outlet obstruction index; IPP, intra-vesical prostatic protrusion; BWT, bladder wall thickness; PV, prostate volume)

When we computed performance status of cut-off values of IPP, BWT & PV between group 1 & 2 (Table 2), the sensitivity was 77.5%, 90% and 70%; specificity was 81.1%, 62.2% and 35.1%; the PPV was 81.6%, 72% and 53.9%; the NPV was 77%, 85.2% and 52%; the positive LR was 4.1, 2.4 and 1.1; the negative LR was 0.28, 0.16 and 0.85; the accuracy was 79.2%, 76.6% and 53.3% respectively.

Table 2: Evaluation of accuracy of IPP, BWT and PV for detecting BOO

Variables	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR +	LR -	Accuracy (%)
IPP	7 mm	77.5	81.1	81.6	77	4.1	0.3	79.2
BWT	4.2 mm	90	62.2	72	85.2	2.4	0.2	76.6
PV	40 g	70	35.1	53.9	52	1.1	0.9	53.3

PPV, positive predictive value; NPV, negative predictive value; LR+ positive likelihood ratio; LR- negative likelihood ratio.

IPP, intra-vesical prostatic protrusion; BWT, Bladder Wall Thickness; PV, Prostate Volume

The third group consisted of 50 patients presenting with AUR & was compared with non-AUR group (Table 1). There was significant difference between all the parameters except age ($P = 0.08$) and PSA ($P = 0.6$) while Table 3 clearly establishes high statistical significance in IPP ($P = 0.001$) followed by BWT ($P = 0.004$) with similar high statistical significance in combined IPP and BWT ($P = 0.001$) in prediction of future AUR.

Table 3: Distribution of sono-morphologic indices (IPP and BWT) between patients with and without AUR

Variables	No AUR (77)	AUR (50)	P*	Odds ratio (95% CI)
IPP (mm)-				
≤ 7	39 (50.6%)	10 (20%)	0.001	0.398
> 7	38 (49.4%)	40 (80%)		0.220-0.721
BWT (mm)-				
≤ 4.2	27 (35.1%)	6 (12%)	0.004	0.388
> 4.2	50 (64.9%)	44 (88%)		0.183-0.827
Combined IPP & BWT-				
Absent-	44 (57.1%)	13 (26%)	0.001	0.431
Present-	33 (42.9%)	37 (74%)		0.255-0.730

*Fisher's Exact test.

IPP, intra-vesical prostatic protrusion; BWT, Bladder Wall Thickness; AUR, Acute urinary retention

DISCUSSION:

BPH is a very common pathophysiologic cause of BOO in men older than 50 years presenting with LUTS which is the main reason for seeking treatment. Before treating a patient, it is mandatory to exclude other possible causes masquerading as BPH and to assess the severity of the symptoms. So that urologist can easily select appropriate treatment strategy and avoid overtreatment of patients with mild BOO or LUTS secondary to other causes. However, LUTS does not have good correlation with severity of BPH as proved in most of the studies.^[15,16] IPSS is a simple tool in evaluation of BPH; but its poor correlation with BOO is a major drawback.^[17,18] Though PVR is widely used non-invasive marker and reflects the severity of LUTS, but presence of intrinsic bladder dysfunction may mislead to decide optimal treatment option.^[19] For complete evaluation of LUTS, UDS is necessary for accurate diagnosis of BOO by calculating Pdet, Qmax and BOOI. But owing to its higher cost, invasive nature, delicate features and associated complications, its routine use has been limited in regular clinical practice.^[20] Now-a-days, patients with LUTS are initially prescribed empirical treatment protocol and PFS is advised only before the surgical intervention or in case of failed medical therapy. In this way, there is always a high chance of overtreatment of the patients with mild symptoms or symptoms due to other causes of LUTS. Even, it is very difficult to predict which patients will silently progress to AUR in near future, as with this conservative treatment, patient may become asymptomatic within a few days. So, our aim was to establish certain sono-morphologic indices of bladder and prostate which can replace conventional UDS for precise diagnosis of BOO and future AUR.

As BPH is the amalgamation of different morphological alterations in vesico-prostatic level,^[1] we tried to quantify these morphological parameters by USG in our study. IPP is caused by enlargement of median and lateral prostatic lobes along the path of least resistance resulting in BOO by ball-valve mechanism^[6] and imparts various anatomical configurations as described by Randall in pathological specimens.^[21] Hence, IPP measurement is a very good indicator in predicting the causal relationship with BOO. In our study, IPP had good diagnostic power as AUC of ROC curve was 0.824 and at a cut-off value of 7 mm, sensitivity, specificity, PPV and NPV were 77.5%, 81.1%, 81.6% and 77% with good accuracy 79.2%. It has also positive correlation with the severity of BOO with $r = 0.762$, $P < 0.001$. These results were in accordance with previous studies^[6,22] evaluating relation of IPP with BOO. Keqin *et al.*^[23] reported that IPP threshold at 7.5 mm has good sensitivity and specificity i.e. 75.5% and 82.6% which was greater than our threshold value of 7 mm. Lim *et al.*^[5] also supported our study findings as they showed AUC for IPP was 0.772 while Franco *et al.*^[10] calculated AUC for IPP as 0.835 with lower sensitivity and specificity than our study; but their study was conducted at a threshold value of 12 mm which was higher than the present study.

Using the same threshold value i.e. IPP of > 7 mm, patients with AUR were 40 out of 50 (80%) having significant association as depicted by odds ratio and 95% CI in table 4. These results are corroborative with the earlier studies,^[5,23] where IPP grade III (> 10 mm) was found in 71% of patients with AUR in the study conducted by Lim *et al.* (5) and 67% in the study by Tan and Foo.^[23]

BWT is a very attractive parameter to diagnose BOO because after induction of BOO in experimental animals, it was proved that bladder weight and wall thickness had been increased simultaneously.^[24] However, the optimal cut-off value remains controversial in different studies.^[1,25,26,27,10] There was significant variability in threshold value for diagnosis of BOO as reported by Oelke *et al.*^[1] (2 mm), Guzel *et al.*^[25] (3.25 mm), Manieri *et al.*^[26] (5 mm), Kessler *et al.*^[27] (2.9 mm) and Franco *et al.*^[10] (6 mm) whereas in our study it was found to be optimum at 4.2 mm to diagnose BOO with sensitivity of 90%, specificity of 62.2% and accuracy of 76.6%. This difference was mainly due to different method of measurement and stretchability of bladder wall with different level of bladder filling. The AUC of ROC curve for BWT was 0.786 with good positive correlation ($r = 0.702$, $P < 0.001$).

Also, 88% of patients with AUR presented with BWT > 4.2 mm which was in accordance with study done by Oelke *et al.*^[28] Kessler *et al.*^[27]

calculated sensitivity of 92%, specificity of 68% at a cut-off value of 2.9 mm which was smaller than our cut-off value. With increasing threshold value, sensitivity and specificity were reduced which has been proved in our present study.

PV is a good predictor of disease progression, gradual deterioration of flow rate, AUR^[29] and requirement of surgery.^[30] In our study, PV had significant positive correlation with BOOI with $r = 0.660$, $P < 0.001$ and AUC of ROC curve was 0.650. Sensitivity and specificity were 70% and 35.1% at a cut-off value of 40 g with PPV of 53.9% and NPV of 52% which corroborated with the conclusion of the study by Lim *et al.*^[5]

Owing to high diagnostic accuracy and easy determination of these sono-morphologic variables by non-invasive TAUS, one can effectively and easily diagnose BOO and AUR without using UDS.

Although, it is a prospective study, there are certain limitations also present in our study. Effect of symptom duration, impact of pre-void bladder volume on the non-invasive variables and degree of BOO were not evaluated. Moreover, we did not include asymptomatic patients in our study. So, this study results could not be generalized to patients with asymptomatic obstruction caused by BPH.

CONCLUSION:

Though UDS is a gold standard diagnostic tool, our study proves that USG parameters IPP, BWT and PV provide good non-invasive alternatives to UDS for evaluation of BOO due to BPH and decision-making in offering treatment options. Also, its easy applicability makes it acceptable to both urologists and patients. Even, we figured out the optimum threshold values of these indices to make it more standardized and clinically useful. The combination of IPP and BWT are also very good indicator for predicting AUR with higher sensitivity, specificity and accuracy than each individual marker. Thus, IPP and BWT can be used confidently to identify the patients at increased risk of AUR and to guide early surgical intervention.

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