Original Article

Urinary ATP may be a biomarker for bladder outlet obstruction and its severity in patients with benign prostatic hyperplasia

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Background: Urothelial cells release ATP into the urine in response to bladder stretch. Urinary ATP concentration in benign prostatic hyperplasia (BPH) patients was higher compared with asymptomatic controls. In this study, we aimed to explore the possibility that the urinary ATP level could be a non-invasive biomarker for bladder outlet obstruction (BOO) and its severity in BPH patients.

Methods: We included 117 BPH patients who underwent urodynamic studies and 109 asymptomatic controls. Urine samples at normal desire (from patients and controls), instilled fluids at maximum cystometric capacity (capacity fluid), and voided fluids during a pressure-flow study (only from patients) were collected. The ATP concentration in collected samples was measured using a luciferin-luciferase bioluminescence assay and normalized to urine creatinine (ATP/Cr). The degree of BOO was quantified using the BOO index (BOOI). Correlation between urodynamic parameters and urinary ATP concentration was analyzed in BPH patients.

Results: Urinary ATP concentration of BPH patients was significantly higher compared with controls ($P<0.001$). For BPH patients, a significant positive correlation was found between urinary ATP concentration and BOOI ($P<0.0001$). Although BPH patients with detrusor overactivity or a history of acute urinary retention had increased urinary ATP, a significant positive correlation between ATP and BOOI was also observed in these patients. When BOOI >40 was set as a cutoff point to differentiate BOO from non-BOO patients, the area under the receiver operating characteristic (ROC) curve was 0.77 ($P<0.001$).

Conclusions: BPH patients with BOO released higher amounts of ATP into the urine. Urinary ATP can be used as a non-invasive biomarker of BOO, and its level may also have a predictive value for the degree of obstruction.

Keywords: Lower urinary tract symptoms; benign prostatic hyperplasia (BPH); adenosine triphosphate; bladder outflow obstruction (BOO)

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Introduction

Benign prostatic hyperplasia (BPH) occurs commonly in older men, with historical reports of up to 50% prevalence in men over the age of 50 years (1). An enlarged prostate may anatomically compress the urethra, causing bladder outlet obstruction (BOO). This results in lower urinary tract symptoms (LUTS), which include both voiding and storage symptoms (2). However, studies indicated that the

International Prostate Symptom Scores (IPSS) might not be helpful for diagnosing patients with BOO and predicting its severity (3,4).

A urodynamic study (UDS) is the gold standard to evaluate BOO and the degree of obstruction (5). However, USD is time-consuming and invasive, and it can be expensive for some patients. Additionally, some hospitals may not be able to afford the urodynamic equipment. All of these reasons require a non-invasive and less expensive test or a biomarker to evaluate the existence of BOO and the degree of obstruction in BPH patients.

Traditionally, the urinary bladder urothelium was considered to be a passive membrane, but it has been reported to have sensory neuronal-like properties and it responds to mechanical and chemical stimuli by releasing transmitters or mediators including ATP, ACh, and PGE2 (6,7). Released ATP will activate P2X3 receptors on the suburothelial afferents to trigger the micturition reflex (8,9). Under some pathological conditions, the urothelium releases more ATP into the lumen, and the urinary ATP concentration was found to be increased in patients with overactive bladder (10-12), interstitial cystitis (13), and bladder infection or inflammation (14). Thus, urinary ATP was suggested as a biomarker for these situations.

In addition to the stretch stimulation during bladder filling, intravesical pressure during bladder isometric contraction could further stimulate ATP release from the urothelium (15). In support of this idea, the urinary ATP concentration in BPH patients has been found to be higher than asymptomatic controls and urinary ATP has been suggested to be a non-invasive biomarker of BOO (15). However, because urodynamic tests were not conducted in that study, the authors could not validate the existence of BOO, and thus, the diagnostic value of urinary ATP for BOO could not be verified.

For BPH patients in the compensated stage, the intravesical pressure during voiding would increase as the degree of BOO increases and more ATP may be released. Therefore, the degree of BOO might be inferred by measuring the urinary ATP concentration. In this study, the degree of BOO was quantified using the BOO index (BOOI) in BPH patients who underwent urodynamic exams. We also investigated the possibility that urinary ATP could be a potential non-invasive biomarker of BOO and the degree of BOO by analyzing the correlation between BOOI and urinary ATP.

Methods

Patients

All procedures in this study were approved by the Ethics Committees at the Second Hospital of Shandong University as well as Qilu Hospital of Shandong University (Approval number: KYU-2019(LW)018). All patients provided written informed consent before urodynamic examinations, which included consent to use their biological material. BPH patients submitted to urodynamic assessments were randomly recruited between April 2018 and May 2019. The criteria for selecting BPH patients to assess UDS were as follows: male ≥50 years of age; diagnosed with symptomatic BPH; IPSS ≥13; maximum urinary flow rate ≤12 mL/s on a voided volume of ≥150 mL; prostate volume ≥30 mL that was estimated by ultrasound, or with a history of acute urinary retention (AUR). Exclusion criteria were any with a history of malignancy of any sort (including bladder and/or prostate cancer), pelvic radiotherapy, neurologic disease, any systemic or inflammatory condition, active urinary tract infections, or renal impairment (chronic kidney disease stage >2). Initially, 150 BPH patients were recruited, after exclusion of 33 patients, the final number was left 117 (*Figure 1*), the age of these BPH patients is 68.93±0.63 years (range, 51–84 years). One hundred and nine asymptomatic male volunteers (48–75 years of age; mean, 65.33±0.61 years) were recruited from the Health Exam Center at the Second Hospital of Shandong University. Exclusion criteria for volunteers were any urinary tract infection, malignancy, or neurological disease (e.g., diabetes mellitus, prolapsed of intravertebral discs, and spinal trauma). All BPH patients underwent a UDS to differentiate BOO from detrusor underactivity (DU, n=24, *Figure 1*). For patients with AUR, 10–14 days were given to allow bladder function to recover, and these patients could void as usual when urodynamic test was conducted.

Free uroflowmetry measurement

Asymptomatic volunteers were asked to void in accordance with their normal desire into a sterile cup for ATP and creatinine (Cr) determination. BPH patients were asked to void comfortably in accordance with their normal desire in a standing position into a urinary flowmeter. Voided volume was recorded. Midstream urine was taken for ATP and Cr measurement.

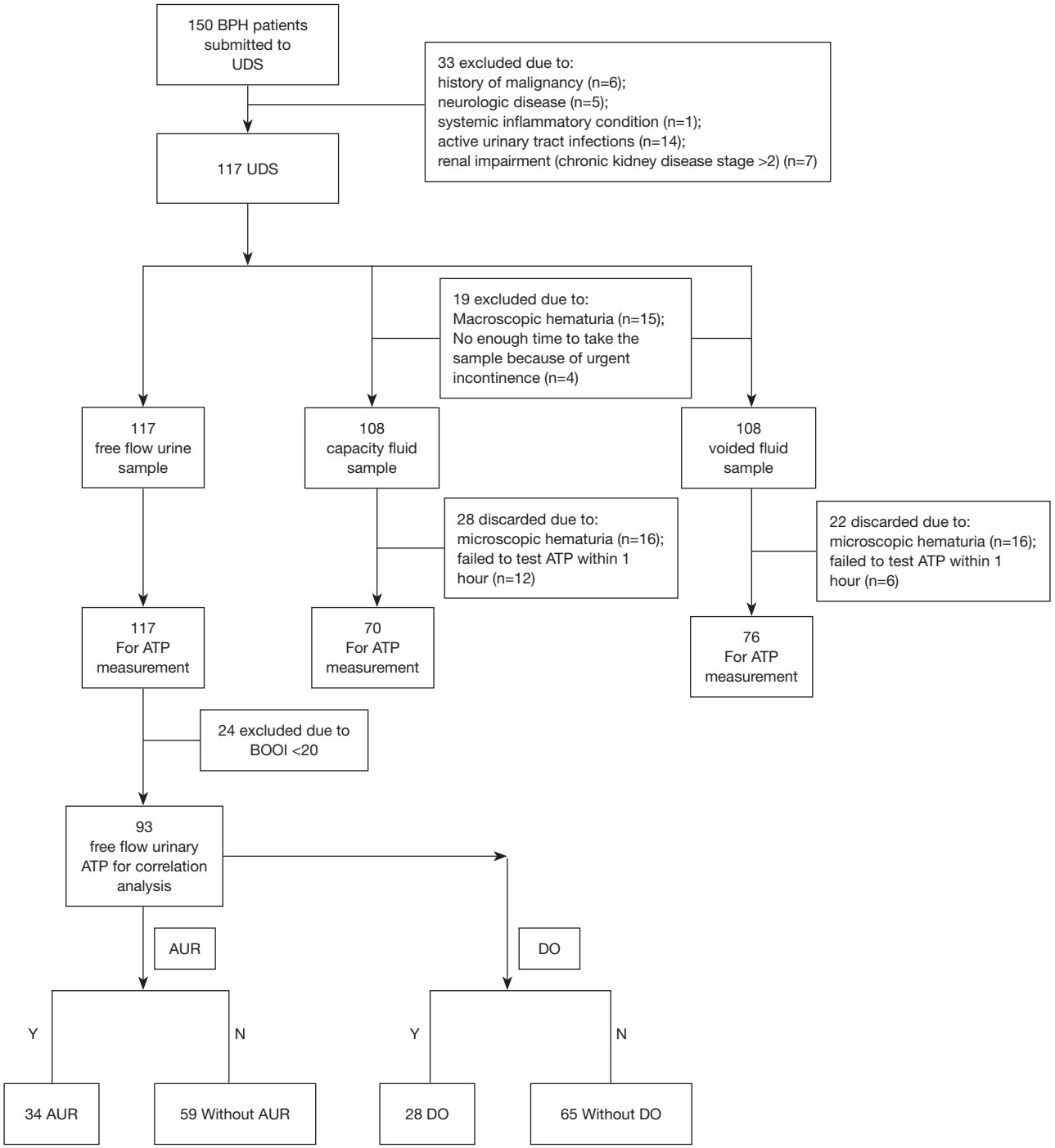

Figure 1 Flowchart of patients' selection and grouping. BPH, benign prostatic hyperplasia; BOOI, BOO index; AUR, acute urinary retention; DO, detrusor overactivity.

Pressure-flow assessment

BPH patients but not asymptomatic volunteers received this assessment. Computer-urodynamic investigation was conducted by one experienced investigator in accordance with the Good Urodynamic Practices Standards (16). Immediately after the free uroflowmetry measurement, the

patient was placed into a semi-reclining position, and a 6-Fr transurethral double-lumen catheter was inserted into their bladder to determine the postvoid residual volume (PVR). The bladder was then filled with room temperature (25 ℃) sterile normal saline at a rate of 30–40 mL/min, and the intravesical pressure was measured. To measure detrusor pressure (Pdet), a 10-F single lumen catheter was inserted into the rectum to measure intra-abdominal pressure. The presence of detrusor overactivity (DO) was identified when Pdet spontaneously increased during the filling phase. When the maximum bladder volume was reached, perfusion was stopped, and an instilled fluid sample was taken from the bladder lumen via a perfusion catheter (this was called the capacity fluid). The patient was asked to void and pressure-flow measurements were recorded. The mid-stream voided fluid was sampled.

Urodynamic parameters analysis

For free uroflowmetry analysis, artifacts need to be manually corrected and the maximum value was selected for maximum urinary flow rate (Qmax). Parameters analyzed include Qmax, voided volume (VV), and PVR.

For pressure-flow parameter analysis, only measurements without straining were considered. Analyzed parameters include maximum Pdet (MaxPdet), Pdet at Qmax (Pdet@Qmax), and bladder obstruction index (BOOI = Pdet@Qmax – 2Qmax). In addition to BOOI, the degree of BOO was also classified into six grades (from 0 to VI) using a Schaefer nomogram.

Measurement of urinary ATP and creatinine

ATP concentrations in urine samples at the normal desire from control or BPH patients as well as in instilled fluids that were taken during the pressure-flow study for BPH patients. These samples were measured immediately (within 1 hour) after they were taken, otherwise, it was discarded (*Figure 1*). Samples were first centrifuged (500 rpm for 5 min) to eliminate dead cells and determine whether microscopic hematuria was present, and then the supernatant was divided into two equal parts, as follows: one for the ATP test and the other for creatinine concentration measurement. Measurement of lactate dehydrogenase (LDH) level, which is a fairly stable intracellular enzyme that is widely used as an indicator of cell integrity revealed no more cell damage after centrifugation. Urinary ATP values were normalized to Cr to limit sample variation or to eliminate the influence of the kidney on ATP levels. The person who analyzed the ATP measurement was blinded to the sample source.

Urine or instilled fluid samples (100 μL) were added to a mixture of luciferin-luciferase (100 μL), in accordance with the manufacturer's instructions using the Promega CellTiter-Glo™ Luminescent Cell Viability Assay Kit (Promega). ATP was measured using the GloMax™ 20/20 luminometer (Promega). Sample bioluminescence was compared with that of standard amounts of ATP that were used in the same concentration range. Standard ATP samples were prepared daily, and all samples were run in duplicate.

The urinary creatinine level was measured using a standard commercial kit (Jiancheng Bioengineering Institute, Nanjing, China) with a spectrophotometer (INFINITE M200PRO, Tecan, China).

Statistical analysis

Statistical analyses were performed using SigmaPlot 10.0 (Systat Software Inc.). Results are reported as the mean ± standard error (SE). The Kolmogorov-Smirnov test was used to check for normality. An unpaired Student's *t*-test was used for statistical analysis between groups. For multiple group comparisons, a one-way ANOVA test with Dunn's post-test modification was used. Correlation between variables was analyzed using the Pearson or Spearman test, and further correlation between variables was analyzed using linear regression analysis. $P<0.05$ (two-tailed) values were considered to be statistically significant. The diagnostic potential of urinary ATP was assessed using receiver operating characteristic (ROC) plots and the area under the curve (AUC).

Results

Urinary ATP in BPH patients was higher compared with asymptomatic controls

Comparison of urinary ATP concentration

The clinical characteristics of BPH patients (n=117) and male asymptomatic controls (n=109) were listed in *Table 1*), There was no significant difference in age between the control and BPH patients (65.33±0.61 *vs.* 68.93±0.63 years, $P>0.05$). BPH patients had significant higher IPSS (21.33±1.85) than asymptomatic volunteers (3.53±0.7, $P<0.001$). Urinary ATP concentration in BPH patients (118.54±7.18 nM) was significantly higher compared with normal controls (47.67±2.42 nM; *Figure 2A*). This was also

Table 1 Characteristics of BPH patients and asymptomatic controls

Parameters	Patients, n=117, mean ± SD	Control, n=109, mean ± SD	P value
Age	68.93±0.63	65.33±0.61	>0.050
IPSS	21.33±1.85	3.53±0.70	<0.001
PV (cc)	75.58±13.63	–	–
Qmax (mL/s)	8.13±0.47	–	–
PVR (mL)	22.07±9.47	–	–
Urinary ATP (nM)	118.54±7.18	47.67±2.42	<0.001
Cr (mg/dL)	95.49±9.92	93.28±13.85	>0.050
ATP/Cr (pmol/mg)	126.20±7.99	51.80±2.63	<0.001

IPSS, the international Prostate Symptom Scores; PV, prostate volume; Qmax, maximum urinary flow rate; PVR, postvoid residual volume; Cr, creatinine.

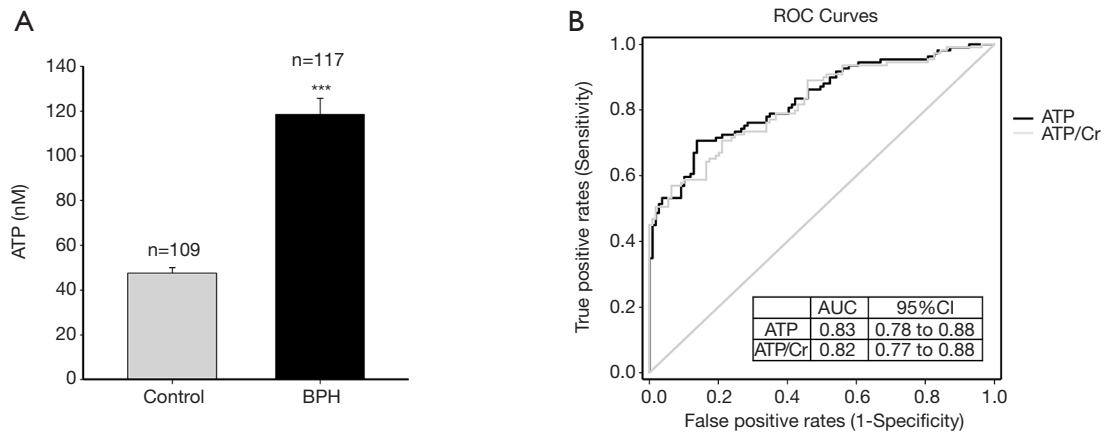

Figure 2 The diagnostic value of urinary ATP to distinguish between BPH patients and normal people. (A) Comparison of urinary ATP concentration between BPH patients and asymptomatic controls. There was a significant difference between the two groups (***, P<0.001). (B) ROC curves of urinary ATP concentration. ATP (black line) and the results corrected for urinary creatinine levels (ATP/Cr, grey line) were plotted as continuous variables to distinguish between true-positive and false-positive rates among BPH patients and controls. AUC was 0.83 for ATP and 0.82 for ATP/Cr, and both results were significant (P<0.001). There were no differences (P>0.05) between the two variables (ATP *vs.* ATP/Cr). BPH, benign prostatic hyperplasia; ROC, receiver operating characteristic; AUC, area under the curve.

true when urinary ATP was normalized to urine creatinine levels (ATP/Cr, 126.20±7.99 *vs.* 51.8±2.63 pmol/mg, P<0.0001). There was no significant difference in the urinary creatinine level between the two groups (95.49±9.92 *vs.* 93.28±13.85 mg/dL, P>0.05). Thus, unless stated, we used the ATP concentration (nM) without normalization for most of the following analyses.

ROC curve

To assess the diagnostic value of urinary ATP for BPH, the ROC curves (*Figure 2B*) for urinary ATP concentration (ATP, black line) and ATP/Cr (grey line) were plotted for all BPH patients and controls. The AUC value was 0.83 for ATP (95% CI: 0.78–0.88, P<0.001) and 0.82 for ATP/Cr (95% CI: 0.77–0.88, P<0.001). There was no difference between the two variables (P>0.05).

Correlation of urinary ATP with urodynamic parameters in BPH patients

ATP concentration in urine and urodynamic fluids

For BPH patients, ATP concentrations in urine taken

Table 2 Correlation of urinary ATP with age and urodynamic parameters in BPH patients

Parameters	Mean	Std. Error	Coefficient	P value
Age	68.927	0.630	0.0983	0.309
Free uroflowmetry				
Qmax (mL/s)	8.134	0.466	–0.177	0.123
VV (mL)	180.128	12.101	–0.276	0.006
PVR (mL)	22.071	9.466	–0.00511	0.960
Pressure-flow				
Pdet@Qmax	75.264	2.787	0.379	<0.001
MaxPdet	80.949	3.116	0.301	0.002
BOOI	64.059	2.510	0.566	<0.001
Degree of obstruction (Schaefer nomogram)	3.218	0.143	0.380	<0.001

Analysis was based on 93 BPH patients with BOOI >20. BPH, benign prostatic hyperplasia; Qmax, maximum urinary flow rate; VV, voided volume; PVR, postvoid residual volume; Pdet@Qmax, Pdet at Qmax; MaxPdet, maximum Pdet; BOOI, bladder obstruction index (BOOI = Pdet@Qmax – 2Qmax).

at free uroflow (free flow urine), instilled fluids taken at maximum bladder volume (capacity fluid), and fluids taken at voiding during the pressure-flow study (voided fluid) were measured. The ATP concentration in free-flow urine (118.54±7.18 nM, n=117) was not significantly different from that of the capacity fluid (109.99±12.45 nM, n=70, P>0.05) or from that of the voided fluid (135.26±14.64 nM, n=76, one-way ANOVA, P>0.05). The ATP concentration in voided fluid tended to be higher compared with the capacity fluid, but it did not reach significance (P>0.05).

Correlation with urodynamic parameters

Based on the results above, the ATP concentration in free uroflow urine was used in the following analysis to explore the potential correlation with urodynamic parameters for BPH patients with BOOI >20 (n=93). Pearson correlation analysis was performed, and analysis results were summarized in *Table 2*. Void volume (VV, 180.1±12.1 mL) in BPH patients showed an inverse correlation with urinary ATP levels (P=0.006), while the BOOI (64.06±2.51, P<0.001), Pdet@Qmax (75.26±2.79 cmH_2O, P<0.001), and MaxPdet (80.95±3.12 cmH_2O, P=0.002) showed a positive correlation with the urinary ATP. Qmax (8.13±0.47 mL/s) tended to be correlated with urinary ATP, but it did not reach significance (P>0.05). Age and PVR showed no correlation.

Linear regression analysis of urinary ATP with BOOI

To examine the possibility of urinary ATP as a non-invasive biomarker for the severity of BOO, further correlation tests were performed (*Figure 3*). As expected, linear regression analysis showed a significant positive correlation between BOOI and urinary ATP in BPH patients with BOOI >20 (r=0.5441, P<0.0001; *Figure 3A*).

To examine the diagnostic value of urinary ATP for BOO, BOOI >40 was set as a cutoff point to differentiate BOO from non-BOO patients (16,17). ROC curves showed a high AUC for both ATP and ATP/Cr (*Figure 3B*), which was 0.77 (95% CI: 0.67–0.87) for ATP and 0.76 (95% CI: 0.66–0.87) for ATP/Cr. Both were statistically significant (P<0.001).

Situations that influence the urinary ATP level and its correlation with BOOI

Urinary ATP in patients with DO or a history of AUR

Situations such as a history of AUR or the presence of DO may influence the urinary ATP concentration (10-12). In this study, the urinary ATP concentration of BPH patients with DO (169.38±20.64 nM, n=28) was significantly higher compared with patients without DO (114.46±8.75 nM, n=65, P=0.006; *Figure 4A*); it was also significantly higher in patients with a history of AUR (162.35±18.47 nM, n=34) compared with those without AUR (112.92±8.79 nM, n=59, P=0.006; *Figure 4B*).To note, AUR patients have a significantly larger BOOI than patients without AUR (162.35±18.47 *vs.* 112.92±8.79, P=0.019).

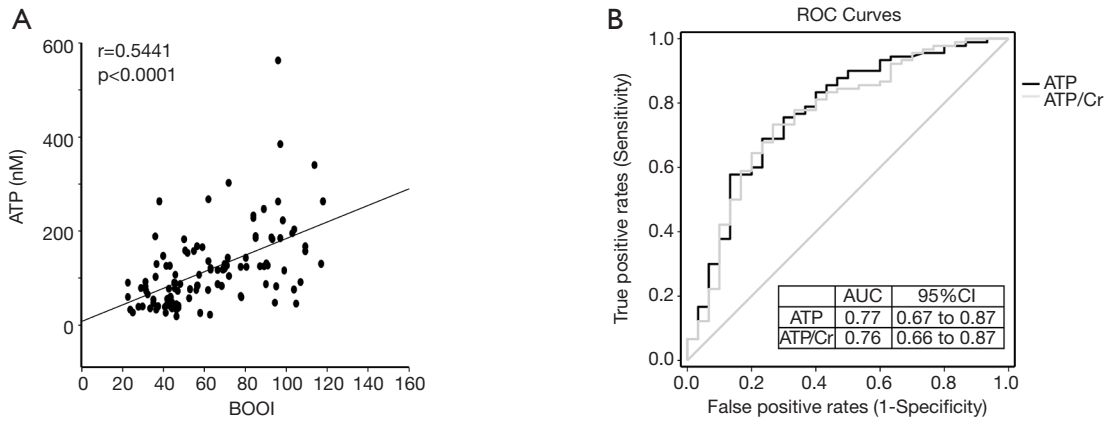

Figure 3 The diagnostic value of urinary ATP for BOO. (A) Linear regression analysis of urinary ATP concentration with BOOI for BPH patients. There was a significant positive correlation of urinary ATP with BOOI (r=0.5441, P<0.0001) for all BPH patients. (B) ROC curves of urinary ATP concentration among BPH patients. With the cut-off value of BOOI at 40, BPH patients were divided into two groups: with BOO (BOOI >40) and without BOO (BOOI <40). ATP (black line) and ATP/Cr (grey line) were plotted as continuous variables to distinguish between true-positive and false-positive rates. The AUC was 0.77 for ATP and 0.76 for ATP/Cr, which were both statistically significant (P<0.001). ROC, receiver operating characteristic; AUC, area under the curve; BOOI, BOO index; BPH, benign prostatic hyperplasia.

Impact of DO and AUR on the correlation

Despite the influence of DO or AUR on urinary ATP (*Figure 4A*,*B*), when the linear regression analysis was performed separately (*Figure 4C*,*D*,*E*,*F*), there was a significant positive correlation between urinary ATP and BOOI either in patients with DO (r=0.4413, P=0.0187, *Figure 4C*) or without DO (r=0.5965, P<0.0001, *Figure 4E*) and in patients with AUR (r=0.3813, P=0.0261, *Figure 4D*) or without AUR (r=0.5688, P<0.0001, *Figure 4F*).

Discussion

In this study, we confirmed the finding that urinary ATP is higher in BPH patients compared with asymptomatic controls (15). We also quantified the degree of BOO using the BOOI in BPH patients who underwent urodynamic studies, and we found that the urinary ATP concentration was positively correlated with BOOI. Moreover, this correlation was not affected by the presence of DO or a history of AUR. When BOOI >40 was set as a cutoff point to differentiate BOO from NO-BOO patients, a high area under the ROC curve (0.77 for ATP; 0.76 for ATP/Cr) was noted. Our results suggest that the urinary ATP level in BPH patients might be used as a non-invasive biomarker for BOO as well as its severity.

Although it is hard to confirm the origin of urinary ATP, most studies have suggested that it is mainly from the urothelium (18). We and other researchers (15) propose that in addition to stretch-induced ATP release during filling, increased wall tension produced by intravesical pressure would further enhance ATP release from the urothelium. This view could be supported by the following evidence from us and others: (I) ATP concentrations in voided fluids tend to be higher compared with capacity fluids; (II) a significant positive correlation was found between MaxPdet or Pdet@Qmax and the ATP level as well as between the BOOI and the ATP level (*Table 2*); (III) urinary ATP concentration in BPH patients was higher compared with normal controls (15) and urothelium strips from BPH patients released five-times more ATP compared with preparations from normal controls (19); and (IV) in BPH patients, after treatment with an alpha-adrenergic receptor antagonist to reduce urethral resistance, the urinary ATP level was decreased accordingly (19). In addition to increased ATP release from the urothelium (20), decreased ATP catabolism (21), enhanced ATP-induced ATP release (13), and increased ATP release from parasympathetic nerves (22). All these factors occurred in the BPH bladder and they may also contribute to the higher urinary ATP concentration.

Consistent with Silva-Ramos's study (15), we found that urinary ATP concentration in BPH patients was significantly higher compared with asymptomatic controls (*Figure 2A*). Additionally, also consistent with their study, ROC curves showed a large AUC for ATP and ATP/

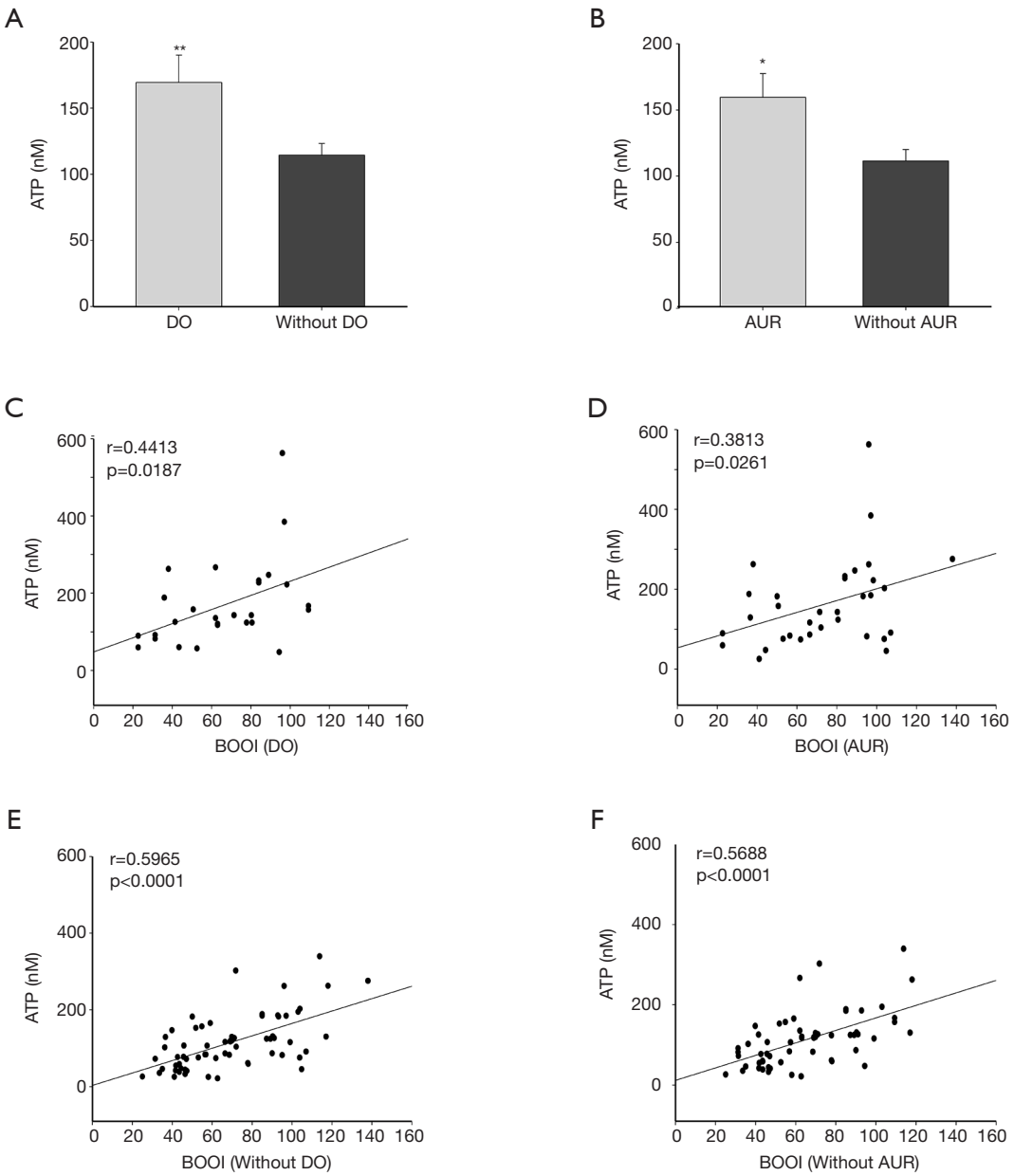

Figure 4 Urinary ATP concentration in BPH patients with and without DO, or with and without AUR (A,B) and its further correlation with BOOI. (A) The urinary ATP concentration was higher in BPH patients with DO compared with those without DO (P=0.006), (B) it was significantly higher in BPH patients with a history of AUR compared with those without AUR (P=0.019). *, P<0.05; **, P<0.01. There was a significant positive correlation of urinary ATP with BOOI for BPH patients with DO (C) or without DO (E). A significant positive correlation was also present when the analysis was performed separately in patients with AUR (D) and without AUR (F). BPH, benign prostatic hyperplasia; DO, detrusor overactivity; AUR, acute urinary retention; BOOI, BOO index.

Cr (*Figure 2B*), which were both significantly different (P<0.001). This suggests that urinary ATP is an excellent factor to use to distinguish between asymptomatic controls and BPH patients.

In our study, we found that the free uroflow urinary ATP concentration was similar to that in urodynamic fluids. This result establishes that free uroflow urinary ATP could be a good alternative biomarker when urodynamic exams are not

available. However, we found that the ATP concentration in voided fluid during the pressure-flow test tends to be higher compared with capacity fluids, suggesting that increased Pdet during micturition would further increase the ATP release.

In this study, no significant correlation was found between age and urinary ATP concentration for BPH patients (*Table 2*) or for normal subjects (data not shown). In terms of the age effect, some reports showed that urinary ATP increases with age (23), while others found a negative correlation (15) or no age effect (14,24). The reasons for these inconsistent results remain unclear.

Consistent with Silva-Ramos's study (15), there was a non-significant trend toward an inverse correlation between Qmax and urinary ATP in our study. Additionally, in agreement with their study, we did not find a correlation between PVR and urinary ATP. However, in contrast to their report that VV has a positive correlation with ATP, we found a significant inverse correlation of VV with ATP (*Table 2*). A significant inverse correlation of ATP with the maximum bladder capacity has was found in normal women and women with overactive bladder (OAB) (11,12). The reasons for this inconsistency between the studies remains unclear. One reason may come from the different subpopulations between Silva-Ramos's study and our study. Compared with patients in their study, our patients had more severe LUTS, for example, IPSS of our patients is larger than theirs (21.33±1.85 *vs.* 15.07±0.73), we had more patients with a history of AUR (34 of 117). We suggest that two opposite effects of VV or bladder volume on ATP concentration should be considered. On the one hand, a larger bladder capacity would enhance more ATP release by producing a greater extent of stretch, while on the other hand, a larger bladder volume may have a dilution effect on ATP.

The presence of DO during bladder filling would evoke an urgency sensation and OAB symptoms. Several studies indicated that urinary ATP is increased in OAB patients with DO, which is either neurogenic or idiopathic (10,12,25), and thus, urinary ATP may be a biomarker for DO. In our study, the incidence of DO in BPH patients was 24% (28/117). This is consistent with published results (10,12,25), and the urinary ATP concentration was higher in our BPH patients with DO compared with those without DO (*Figure 4A*).

BPH patients may progress to AUR in the late stages. However, AUR patients who were included in our study could void during the pressure–flow study and during the free uroflowmetry test after 10–14 days of recovery. We found that the urinary ATP concentration was higher in BPH patients who had a history of AUR compared with non-AUR patients. The explanation for this remains unclear. A higher degree of BOO in AUR patients might explain the difference. Additionally, urinary catheter-induced irritation might not be the cause. In three AUR patients, we collected urine samples on 5 consecutive days from the urinary catheter, and no significant differences were found among the ATP concentrations on these 5 days (data not shown).

The most important finding in our study was that urinary ATP concentration is positively correlated with BOOI. BOOI is a continuous variable, and it is usually used to quantify the degree of BOO (26). Based on the BOOI value, the patients were classified into obstructed (BOOI >40), equivocal (BOOI 20–40), and unobstructed (<20) (27). In some reports, equivocal (BOOI 20–40) has been considered to be obstructed (28,29). Thus, to fully evaluate the correlation of urinary ATP with BOOI, we included BPH patients with equivocal BOOI scores (*Figures 3A* and *4*). However, when the diagnostic value of urinary ATP for BOO was determined using ROC curves (*Figure 3B*), only the obstructed BPH patients were selected (BOOI >40).

In addition to BOOI, two other voiding parameters (MaxPdet and Pdet@Qmax) were also found to be positively correlated with urinary ATP (*Table 2*). Our findings showed that, besides stretching during bladder filling, increased intravesical pressure during voiding is another stimulus that promotes further urothelial ATP release. These findings are in contrast to one study in healthy women or OAB patients that showed no correlation between Pdet and urinary ATP (11). In that study, OAB patients who had Pdet > 60 cmH_2O were excluded, and thus, it is impossible to obtain the complete picture of Pdet correlation with ATP. The inconsistent reports might also indicate that there is a sex difference.

Patients with BPH released higher amounts of ATP into the urine, and the amount increased with the increasing degree of BOO. A significant positive correlation of urinary ATP with BOOI and the high AUC of the ROC curve indicated the value of urinary ATP as a non-invasive biomarker to identify BOO and to predict its severity in BPH patients. Compared with the invasive and expensive features of USD, urinary ATP measurement is simple, non-invasive, inexpensive, and reliable, and it might be an alternative method to evaluate BOO.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau.2020.02.18). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures in this study were approved by the Ethics Committees at the Second Hospital of Shandong University as well as Qilu Hospital of Shandong University (Approval number: KYU-2019(LW)018). All patients provided written informed consent before urodynamic examinations, which included consent to use their biological material.

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