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## ORIGINAL ARTICLE

Prostate Disease

# Prostatic anatomical parameters correlate with clinical characteristics suggestive of benign prostatic hyperplasia

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We conducted the present study to assess the correlation of the prostatic anatomical parameters, especially the ratio of peripheral zone thickness and transitional zone thickness, with clinical and uroflowmetry characteristics suggestive of benign prostate hyperplasia (BPH). A total of 468 consecutive patients with a detailed medical history were identified. All patients were evaluated by scoring subjective symptoms with the International Prostate Symptom Score (IPSS) and quality of life (QoL). The prostatic anatomical parameters were measured using transrectal ultrasonography, and postvoid residual urine and maximum flow rate ( $Q_{max}$ ) values were also determined. Pearson's correlation analysis revealed that both total prostate volume (TPV;  $r = 0.160$ ,  $P < 0.001$ ) and transitional zone volume (TZV;  $r = 0.104$ ,  $P = 0.016$ ) increased with patients' age; however, no correlations were observed of TPV, TZV, transitional zone index (TZI), and transitional zone thickness (TZT) with IPSS or QoL (all  $P > 0.05$ ). Peripheral to transitional zone index (PTI) was found negatively correlated with total IPSS ( $r = -0.113$ ,  $P = 0.024$ ), storage IPSS ( $r = -0.103$ ,  $P = 0.041$ ), and voiding IPSS ( $r = -0.123$ ,  $P = 0.014$ ). As regards the uroflowmetry characteristics, PTI ( $r = 0.157$ ,  $P = 0.007$ ) was indicated to be positively correlated with  $Q_{max}$  and negatively correlated with TZI ( $r = -0.119$ ,  $P = 0.042$ ) and TZT ( $r = -0.118$ ,  $P = 0.045$ ), but not correlated with TPV, TZV, or peripheral zone thickness (PZT) (all  $P > 0.05$ ). Postvoid residual urine (PVR) had not correlated with all the prostatic anatomical variables (all  $P > 0.05$ ). This is the first study that formally proposed the concept of PTI, which is an easy-to-measure prostate anatomical parameter which significantly correlates with total IPSS, storage IPSS, voiding IPSS, and  $Q_{max}$ , suggesting that PTI would be useful in evaluating and managing men with lower urinary tract symptoms (LUTS)/BPH. However, well-designed studies are mandatory to verify the clinical utility of PTI.

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**Keywords:** benign prostatic hyperplasia; lower urinary tract symptoms; peripheral zone thickness; transrectal ultrasound

## INTRODUCTION

Benign prostatic hyperplasia (BPH) is becoming an increasingly common disease as the aged population increases worldwide.<sup>1</sup> Lower urinary tract symptoms (LUTS) secondary to BPH have a major impact on men, their families, health services, and society.<sup>2,3</sup> Although BPH is a commonly reported entity, its pathophysiology is still poorly understood. Both static and dynamic obstructions caused by the enlarged prostate are considered to be responsible for voiding dysfunction. However, men may experience severe symptoms even without a detectably enlarged prostate volume, or, alternatively, no symptoms may be observed even with an evidently enlarged prostate gland.<sup>4,5</sup>

The prostate consists of three glandular regions: the peripheral zone (PZ), central zone, and transitional zone (TZ), which differ in their histology and biology.<sup>6</sup> BPH was classically deemed to originate in the TZ, while the majority of carcinomas develop in the PZ.<sup>7</sup> Indeed, some studies showed that transitional zone volume (TZV) and transitional zone index (TZI) more strongly correlate with measures of BPH severity than total prostate volume (TPV); however, the

correlations between TZV (or TZI) and LUTS or BPH progression are still a matter of debate.<sup>8–10</sup> According to the presumed circle area ratio (PCAR) theory, the normal prostate has a thin triangular shape, which approaches a circle as BPH progresses. When the prostate shape becomes closer to a circle, intraprostatic pressure can increase.<sup>11</sup> Kwon *et al.*<sup>12</sup> believed that the more the TZ grows, the higher the intraprostatic pressure and the thinner the peripheral zone thickness (PZT) becomes. Accordingly, they hypothesized that PZT would inversely correlate with intraprostatic pressure, and demonstrated that it was significantly associated with urinary symptoms. Nevertheless, according to the PCAR theory, the process of dynamic change to prostate morphology involves both the TZ and PZ, and, therefore, consideration of the PZT alone is clearly insufficient. Thus, we propose the new concept of the peripheral to transitional zone index (PTI), which is defined as the ratio of the PZT to the transitional zone thickness (TZT). We believe that the PTI reflects dynamic changes in both the peripheral and transitional zones in the BPH pathological process, and that it might be a useful parameter for patient evaluation.

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The purpose of the present study was to assess the correlations of various indices obtained from transrectal ultrasonography (TRUS) with clinical and uroflowmetry characteristics suggestive of BPH, including TPV, TZV, TZI, PZT, TZT, and particularly PTI.

## PATIENTS AND METHODS

### Patients

This retrospective study used data from a prospectively maintained database for patients presenting with LUTS/BPH at Guizhou Provincial People's Hospital, Guiyang, China. A total of 468 consecutive male patients with a detailed medical history who presented between November 2015 and October 2018 were identified. No informed consent was needed due to the retrospective study design, which was approved by the Hospital's Ethics Committee of Guizhou Provincial People's Hospital (No. 2018054).

All patients were evaluated by scoring their subjective symptoms according to the International Prostate Symptom Score (IPSS) and quality of life (QoL) score. In addition, physical examinations including digital rectal examination (DRE), prostate-specific antigen (PSA) level, kidney–bladder ultrasound, TRUS (Philips EPIQ 5 ultrasound machine, Amsterdam, the Netherlands), postvoid residual urine (PVR), and maximum flow rate ( $Q_{max}$ ) values were performed for all patients. Patients suspected of having prostate cancer also received ultrasound-guided transrectal 12-core needle biopsy to confirm the BPH diagnosis.

The exclusion criteria included a previous bladder, prostate, or urethra operation; urethral stricture; IPSS  $\leq 7$ ; prostate or bladder cancer; bladder stones; acute or chronic urinary tract infection; neurogenic bladder dysfunction; uncontrolled diabetes mellitus; and any comorbidities that could affect a patient's voiding function. Patients whose PZT and/or TZT was unmeasurable were also excluded from the study.

### Prostatic anatomical parameters

TPV and TZV were calculated from TRUS measurements of the prostate, using the prostate ellipsoid formula (height  $\times$  width  $\times$  length  $\times \pi/6$ ). The TZI was calculated by dividing the TZV by the TPV. PZT was defined as the longest distance between the outer and inner margins of the peripheral zone when a straight line was drawn from the center of the transitional zone to the outer margin of the peripheral zone on image plains with maximal TZV, as described by Kwon *et al.*<sup>12</sup> TZT was defined according to a straight line passing through the center of the transitional zone from one margin to the other (**Figure 1**). The PTI was calculated by dividing the PZT by the TZT.

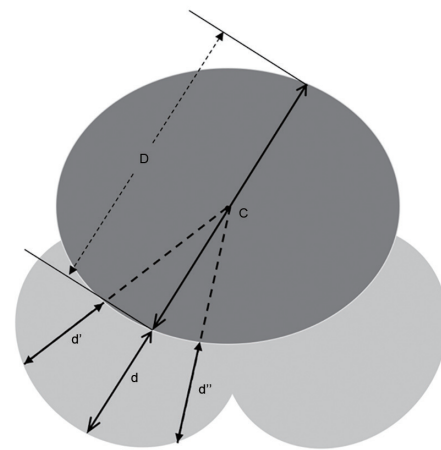
### Statistics

Interobserver agreements in the measurement of prostatic anatomical parameters were verified by intraclass correlation coefficients (ICC) generated with a two-way random-effects model. ICC values of 0.41 to 0.60, 0.61 to 0.80, and 0.81 to 1.00 were considered to correspond with moderate, substantial/good, and excellent agreement, respectively.<sup>13</sup>

Numerical data were reported as the mean  $\pm$  standard deviation (s.d.). Pearson's correlation analysis was used to evaluate associations between the prostatic anatomical parameters and IPSS (including storage IPSS, voiding IPSS, and postmicturitional IPSS domains), QoL,  $Q_{max}$ , and PVR. Statistical analyses were performed using SPSS 22.0 for Windows (Statistical Package for Social Sciences, IBM Corporation, Armonk, NY, USA).  $P < 0.05$  was considered statistically significant.

## RESULTS

A total of 397 patients diagnosed with BPH were finally included in the current analysis. **Table 1** presents the patient characteristics for the entire study population.



**Figure 1:** Schematic diagram of PZT and TZT measurement (C: the center of the transitional zone). PZT (d) is defined as the maximum distance of the line across the peripheral zone ( $d > d'$  and  $d > d''$ ), and TZT (D) is defined as the distance of the reverse extending line of PZT across the transitional zone. PZT: peripheral zone thickness; TZT: transitional zone thickness.

**Table 1: Clinical characteristics of the patients with benign prostate hyperplasia (n=397)**

Variable	Mean $\pm$ s.d.
Age (year)	71.9 $\pm$ 7.6
PSA (ng ml <sup>-1</sup> )	5.77 $\pm$ 4.97
Urinary Symptom Questionnaire	
IPSS, total	21.9 $\pm$ 7.7
IPSS, storage	9.9 $\pm$ 3.6
IPSS, voiding	8.7 $\pm$ 4.1
IPSS, postmicturitional	3.3 $\pm$ 1.8
QoL	4.6 $\pm$ 1.2
$Q_{max}$ (ml s <sup>-1</sup> )	7.4 $\pm$ 4.1
PVR (ml)	74.3 $\pm$ 109.4
TRUS	
TPV (ml)	55.2 $\pm$ 31.7
TZV (ml)	27.4 $\pm$ 23.6
TZI	0.44 $\pm$ 0.18
PZT (cm)	1.33 $\pm$ 0.63
TZT (cm)	3.45 $\pm$ 1.03
PZT/TZT	0.46 $\pm$ 0.31

Data are presented as mean $\pm$ s.d. PSA: prostate-specific antigen; IPSS: International Prostate Symptom Score;  $Q_{max}$ : maximum flow rate; QoL: quality of life; PVR: postvoid residual; PZT: peripheral zone thickness; TZT: transitional zone thickness; TRUS: transrectal ultrasonography; TPV: total prostate volume; s.d.: standard deviation; TZV: transitional zone volume; TZI: transitional zone index

### Interobserver variability

Interobserver reproducibility was evaluated for the four morphological variables of TPV, TZV, PZT, and TZT using the data of all patients. The values of the above-mentioned variables measured by the two independent examiners were in excellent agreement, with ICCs of 0.898 (95% confidence interval [CI]: 0.847–0.936,  $P < 0.0001$ ), 0.905 (95% CI: 0.862–0.934,  $P < 0.0001$ ), 0.881 (95% CI: 0.866–0.901,  $P < 0.0001$ ), and 0.913 (95% CI: 0.898–0.924,  $P < 0.0001$ ), respectively (**Table 2**).

### Change in prostatic anatomical variables according to patient age

Pearson's correlation analysis showed that both TPV ( $r = 0.160$ ,  $P < 0.001$ ) and TZV ( $r = 0.104$ ,  $P = 0.016$ ) increased with increasing patient age (**Figure 2** and **Table 3**); however, there was no statistically significant correlation between age and TZI ( $r = 0.047$ ,

**Table 2: Interobserver reproducibility in the measurement of prostatic morphological parameters**

Variable	ICC	95% CI	P
Prostate volume	0.898	0.847–0.936	<0.0001
Transitional zone volume	0.905	0.862–0.934	<0.0001
PZT	0.881	0.866–0.901	<0.0001
TZT	0.913	0.898–0.924	<0.0001

ICC: intraclass correlation coefficient; CI: confidence interval; PZT: peripheral zone thickness; TZT: transitional zone thickness

$P = 0.279$ ). Although PZT was not significantly correlated with age ( $r = -0.037$ ,  $P = 0.393$ ), TZT showed a positive correlation with age ( $r = 0.118$ ,  $P = 0.007$ ), but PTI indicated a negative correlation with age ( $r = -0.089$ ,  $P = 0.039$ ).

### Correlation of prostatic anatomical variables with clinical characteristics in patients with BPH

Table 3 shows that no correlations were observed between the TPV and IPSS domains (including total IPSS, storage IPSS, voiding IPSS, and postmicturitional IPSS domains), QoL score, TZV, TZI, and TZT (all  $P > 0.05$ ). However, PZT was negatively correlated with total IPSS ( $r = -0.126$ ,  $P = 0.012$ ) and PTI was negatively correlated with total IPSS ( $r = -0.113$ ,  $P = 0.024$ ), storage IPSS ( $r = -0.103$ ,  $P = 0.041$ ), and voiding IPSS ( $r = -0.123$ ,  $P = 0.014$ ), but was not significantly correlated with the other clinical characteristics (Figure 3).

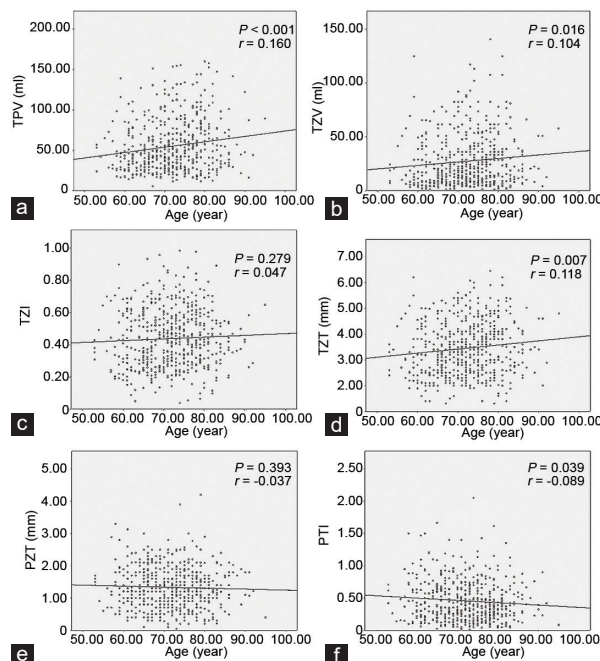
### Correlation of prostatic anatomical variables with uroflowmetry characteristics in patients with BPH

Finally, we investigated the relationship of the prostatic anatomical variables and the uroflowmetry characteristics ( $Q_{\max}$  and PVR).  $Q_{\max}$  was negatively correlated with TZI ( $r = -0.119$ ,  $P = 0.042$ ) and TZT ( $r = -0.118$ ,  $P = 0.045$ ) and positively correlated with PTI ( $r = 0.157$ ,  $P = 0.007$ ), but not significantly correlated with TPV ( $r = -0.072$ ,  $P = 0.218$ ), TZV ( $r = -0.064$ ,  $P = 0.273$ ), or PZT ( $r = 0.109$ ,  $P = 0.063$ ). PVR was not significantly correlated with any of the prostatic anatomical variables (all  $P > 0.05$ ; Table 3).

## DISCUSSION

The present study assessed correlations between prostatic anatomical parameters measured using transrectal ultrasonography and clinical and uroflowmetry characteristics of LUTS/BPH patients. Our study revealed no significant relationship between TPV (or TZV) and clinical or uroflowmetry characteristics. TZI and TZT showed correlations of borderline significance with  $Q_{\max}$ , but did not show significant correlations with other parameters. PZT was negatively correlated with total IPSS, but not with any other characteristics. However, PTI demonstrated significant correlations with total IPSS, storage IPSS, voiding IPSS, and  $Q_{\max}$ .

Although pressure flow studies have been the gold standard for the diagnosis of bladder outlet obstruction in patients with LUTS/BPH, they are subject to some disadvantages, such as their invasiveness, high cost, and the potential for complications. Therefore, many investigators have evaluated the correlations of symptom severity,  $Q_{\max}$ , and bladder outlet obstruction with prostatic anatomical parameters obtained using reliable noninvasive ultrasound imaging techniques. It is well known that BPH develops in the transitional zone of the prostate. Thus, several studies focused on the TZV and TZI, and indicated that TZV and TZI may be more accurate predictors of BPH progression and response to medicinal or surgical therapies than TPV.<sup>14</sup> Kaplan *et al.*<sup>15</sup> reported that TZI measured by TRUS was highly correlated with clinical symptoms,



**Figure 2:** Correlation between age and (a) TPV, (b) TZV, (c) TZI, (d) TZT, (e) PZT, and (f) PTI. TPV: total prostate volume; TZV: transitional zone volume; TZI, transitional zone index; TZT: transitional zone thickness; PZT: peripheral zone thickness; PTI: peripheral to transitional zone index.

objective parameters, and bladder function in patients with BPH, regardless of the TPV or TZV. However, such findings are not consistent throughout the literature, with St Sauver and colleagues<sup>8</sup> finding that changes in TZV and TZI correlated only weakly with changes in peak urinary flow rate and urinary symptoms. Lepor *et al.*<sup>16</sup> indicated that TPV, TZV, and TZI were not directly related to the patients' symptom scores, and were only weakly related to peak flow rate. Consistent with these results, we also found that TPV, TZV, and TZI were either not or only marginally correlated with both objective and subjective symptom indicators.

The PZT and PTI measurements used in our study are based on the PCAR theory, which was introduced as a new BPH concept by Watanabe<sup>11</sup> in 1998. The PCAR is the ratio of the area of the maximum horizontal section of the prostate to the area of a presumed circle with a circumference equal to the circumference of the maximum horizontal section. Simply stated, the PCAR represents the roundness of the prostate, *i.e.*, how closely the shape of a prostate section approaches a circle on axial TRUS imaging. The greater the intraprostatic pressure, the rounder the shape becomes, and the more the pressure extends over the circumference of the urethra causing urinary disturbance.

PCAR evaluation is complicated and requires specialized software. Matsugasumi *et al.*<sup>17</sup> reported on the relationships of PZT and PCAR with magnetic resonance imaging (MRI)-determined peripheral zone morphology. They found compression of PZT that was attributable to an enlarged transitional zone. The greater the increase in the TZV, the thinner the peripheral zone becomes. Furthermore, there were no age-related changes in PZV without racial differences. They interpreted their results as indicating that a growing TZV increases intraprostatic pressure, making the PZT thinner, which is in accord with the PCAR theory. Kwon *et al.*<sup>12</sup> suggested that PZT was a valid alternative to the PCAR parameter because PZT was significantly associated with urinary symptoms, and measuring the PZT is much easier than measuring the

Table 3: Correlation summary of Urinary Symptom Questionnaire, maximum flow rate, and postvoid residual urine with morphological parameters

Variable	Urinary Symptom Questionnaire parameters					Q <sub>max</sub> (ml s <sup>-1</sup> )	PVR
	Age (year)	IPSS, total	IPSS, storage	IPSS, voiding	IPSS, postmicturitional		
TPV (r, P)	0.160, <0.001*	0.039, 0.441	0.022, 0.666	0.021, 0.653	0.073, 0.147	-0.072, 0.218	-0.003, 0.955
TZV (r, P)	0.104, 0.016*	0.069, 0.167	0.032, 0.529	0.065, 0.196	0.085, 0.091	-0.064, 0.273	-0.013, 0.824
TZI (r, P)	0.047, 0.279	0.094, 0.061	0.058, 0.251	0.090, 0.072	0.081, 0.109	-0.119, 0.042*	-0.036, 0.531
PZT (r, P)	-0.037, 0.393	-0.126, 0.012*	-0.093, 0.065	-0.095, 0.059	-0.073, 0.148	0.109, 0.063	0.018, 0.762
TZT (r, P)	0.118, 0.007*	0.067, 0.186	0.045, 0.376	0.050, 0.316	0.080, 0.111	-0.118, 0.045*	0.030, 0.603
PTI (r, P)	-0.089, 0.039*	-0.113, 0.024*	-0.103, 0.041*	-0.123, 0.014*	-0.083, 0.101	0.157, 0.007*	0.030, 0.602

\*P<0.05. IPSS: International Prostate Symptom Score; Q<sub>max</sub>: maximum flow rate; PVR: postvoid residual; QoL: quality of life; PVR: postvoid residual; PTI: peripheral to transitional zone index; TZI: transitional zone thickness; PZI: peripheral zone thickness; TZI: transitional zone index; TZV: transitional zone volume; TPV: total prostate volume

PCAR. However, none of the above studies treated the prostate as a whole, and they focused on either the TZ or PZ independently, rather than both together.

The rationale of the PCAR theory suggests that as the TZ grows, it exerts pressure on the surrounding surgical capsule, including the PZ as well as the prostate capsule. Matsugasumi *et al.*<sup>17</sup> indicated that as the TZ grows, the PZ becomes thinner. We confirmed relationships between prostatic morphological parameters and age, consistent with the PCAR theory. To our knowledge, this is the first study to formally propose the concept of the PTI, which is also based on the PCAR theory. Calculation of the PTI considers both the TZ and PZ, and, in the present study, PTI demonstrated the highest correlation coefficient with both clinical and uroflowmetry characteristics. We showed that PTI was significantly negatively correlated with total IPSS, storage IPSS, and voiding IPSS and positively correlated with Q<sub>max</sub>, which indicates that PTI is potentially a better parameter than TZV, TZI (negatively correlated with Q<sub>max</sub> only), and PZT (negatively correlated with total IPSS only).

One concern in ultrasound measurement of prostate parameters is the potential for high inter-examiner variability. To assess inter-observer reproducibility, two investigators performed all ultrasound parameter measurements independently, and the values obtained were in excellent agreement. Other studies have also suggested that TRUS can provide valid prostate parameters in patients with LUTS/BPH, comparable in quality to those obtained on MRI.<sup>17,18</sup>

There are some limitations to the current study. First, some parameters such as intravesical prostatic protrusion (IPP) were not evaluated, and further studies are required to analyze such parameters. Second, the patients in our study represented a highly selected population, consisting of men who visited the clinic for LUTS with an IPSS ≥8; therefore, the study cohort may not represent the general population, especially men with no or only mild symptoms of BPH. Third, heterogeneity in the patients' medication history was not evaluated. 5α-reductase inhibitors were deemed to alter the prostate zone anatomy because these drugs target glandular epithelial tissue. Dutasteride decreased transitional and peripheral zone volume equally, however, the PTI data were not presented.<sup>19</sup> Kwon *et al.*<sup>12</sup> found similar PZT and clinical variable correlations in BPH patients between those with and without medication history.

## CONCLUSIONS

To the best of our knowledge, this is the first study to formally propose the concept of the PTI, which is based on the PCAR theory. The main finding of the present study is that PTI is an easy-to-measure prostate anatomical parameter, which significantly correlates with total IPSS, storage IPSS, voiding IPSS, and Q<sub>max</sub>. These results suggest that PTI would be useful for evaluating and managing men with LUTS/BPH. However, well-designed studies to elucidate the clinical utility of PTI are mandatory.

## COMPETING INTERESTS

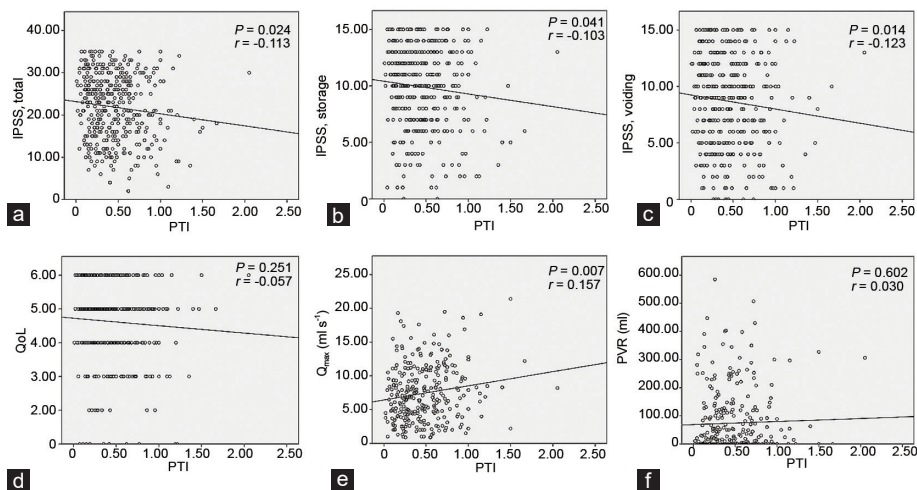
All authors declared no competing interests.

## AUTHOR CONTRIBUTIONS

YT and SJX conceived the study. YT, BY, and HML collected and analyzed the clinical data and drafted the manuscript. GH, SJX, and FS designed the study and participated in critical revision of the manuscript. ZLS and SJX assisted with detailed statistical analysis. YT and XSY interpreted the clinical data. All authors read and approved the final manuscript.







**Figure 3:** Correlation between PTI and (a) IPSS, total; (b) IPSS, storage; (c) IPSS, voiding; (d) QoL, (e)  $Q_{max}$ , and (f) PVR. PTI: peripheral to transitional zone index; IPSS: International Prostate Symptom Score;  $Q_{max}$ : maximum flow rate; QoL: quality of life; PVR: postvoid residual.

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