Original Article

# Predicting surgical efficacy and diagnosing histological inflammation: the clinical significance of prostate exosome proteins in benign prostatic hyperplasia

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**Background:** Benign prostatic hyperplasia (BPH) is one of the most common causes of lower urinary tract symptoms (LUTS) among the aging male population. Recent studies have shown that histological inflammation (HI) plays a significant role in BPH, with prostatic exosomal protein (PSEP) identified as a potential biomarker for prostate diseases. Therefore, this study aimed to explore the effect of HI on LUTS in patients with BPH, and to further explore the clinical value of PSEP as a diagnostic biomarker of BPH complicated with HI and whether PSEP could be used as an index to predict the improvement of LUTS after operation.

**Methods:** This study was an open-label, cohort study. The study enrolled all patients who were clinical diagnosed as BPH with LUTS and prepared to receive operation of the prostate at the Department of Urology of the Second Hospital of Hebei Medical University. International Prostate Symptom Score (IPSS) were used to evaluate the LUTS of the BPH. And the enrolled patients were divided into four groups, including none, mild HI, moderate HI, and severe HI, based on postoperative pathological results. Then the relationships between HI and IPSS, the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI), as well as PSEP were analyzed. Simple and multiple linear regression analyses were performed on the preoperative IPSS and the difference of IPSS before and after surgery was examined. SPSS software version 26 was used for statistical analysis and Prism 9.0 was used to make violin plots.

**Results:** A total of 69 patients were enrolled in the study. The violin plot results indicated IPSS and NIH-CPSI scores exhibited significant increases in correlation with the severity levels of HI ($P<0.001$; $P<0.001$). Among BPH patients with total prostate-specific antigen (t-PSA) levels higher than 4.0 ng/mL, a significant correlation was observed between PSEP levels and HI ($P=0.04$). Besides, simple and multiple linear regression analysis showed that HI ($P<0.001$) or PSEP ($P=0.03$) was significantly associated with IPSS and improvement of LUTS, assessed by postoperative and preoperative IPSS differences.

**Conclusions:** The study indicated that IPSS and PSEP (when t-PSA >4 ng/mL) were correlated with the severity of HI in patients with BPH. PSEP was linearly correlated with IPSS and the degree of reduction in IPSS after surgery. Consequently, PSEP may serve as a promising predictor for assessing surgical efficacy and diagnosing the severity of HI in patients with BPH.

**Keywords:** Benign prostatic hyperplasia (BPH); lower urinary tract symptoms (LUTS); histological inflammation (HI); prostatic exosomal protein (PSEP)

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## Introduction

Lower urinary tract symptoms (LUTS) are highly common conditions in elderly men, and induce plenty of adverse influences on their well-being and quality of life (QoL) among these patients (1,2). It is well known that benign prostatic hyperplasia (BPH) is one of the most common causes of LUTS among the aging male population (3,4). Meanwhile, with the aging population, the incidence and prevalence of BPH and LUTS are rapidly increasing in China. And thus, China will undoubtedly face a great public health and social economic burden of BPH in the near future. Currently, the main purpose of BPH treatment is to improve LUTS and prevent complications of BPH (5). International Prostate Symptom Score (IPSS) is usually used to assess LUTS, which included seven questions (6). Histological inflammation (HI) is one of the most common chronic urinary disorders with clinical presentations of chronic pelvic pain or discomfort (7), which is also known as type III prostatitis according to the classification of the National Institutes of Health (NIH) in America (8,9). Different from other types of prostatitis, HI is a form of inflammation that can potentially induce long-lasting pain with a lack of objective and specific biological indicators (10,11). Recently, several studies have shown that there was a relationship between HI and BPH (12-14). In particular, those studies indicate HI plays a key role in the development of BPH (15,16). However, limited research has evaluated the relationships of HI and IPSS, and there is a lack of visual evidence.

Prostatic exosomal protein (PSEP), a distinct protein, has been identified within the exosomes released by prostatic epithelial cells and being subsequently excreted in urine (17-19). The detection of PSEP in urine was initially reported in 2004 (20-22). PSEP is considered to carry out a crucial function within the male reproductive system, encompassing the regulation of semen viscosity, safeguarding sperm from harm, and contributing to sperm motility. In recent years, research on PSEP has mainly focused on its application as a biomarker for prostate diseases, such as prostatitis, BPH, and prostate cancer, in male. However, early diagnosis of these diseases remains a big challenge. PSEP has attracted the attention of researchers as a potential biomarker for prostate diseases. Studies have found that the level of PSEP changes significantly in patients with prostate cancers and is closely related to the prostate cancers (23). Therefore, PSEP may serve as an effective tool for early diagnosis and prognosis assessment of prostate diseases. According to these findings, we tried to use urine PSEP to predict the efficacy of transurethral resection of the prostate (TURP) in LUTS. Therefore, the present study aims to investigate the relationship between the PSEP and BPH complicated HI, and further to explore the clinical value of PSEP as the diagnostic biomarker of BPH complicated HI and to investigate whether it can be used as an index to predict the improvement of LUTS after operation. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-655/rc).

### Highlight box

**Key findings**

- Histological inflammation (HI) severity correlates with increased lower urinary tract symptoms (LUTS) in benign prostatic hyperplasia (BPH) patients.
- Higher prostatic exosomal protein (PSEP) levels and HI predict better improvement in LUTS post-surgery, suggesting PSEP as a potential surgical efficacy biomarker.

**What is known and what is new?**

- PSEP is considered a potential biological marker for chronic prostatitis and has become a newer, simpler, non-invasive, and effective method for diagnosing chronic prostatitis.
- This article introduces PSEP as a promising predictor for assessing surgical efficacy and diagnosing the severity of HI in patients with BPH.

**What is the implication, and what should change now?**

- PSEP shows promise as a HI severity biomarker in BPH, especially when total prostate-specific antigen >4 ng/mL.
- Integrating PSEP measurement into routine practice could enhance personalized BPH treatment, potentially improving LUTS management and quality of life.

## Methods

This study was an open-label cohort study. The present cohort study was conducted between March 5, 2021 and February 28, 2022 at the Department of Urology of the Second Hospital of Hebei Medical University in Hebei Province, China. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Second Hospital of Hebei Medical University Ethics Committee (No. 2021-R174), and all participants provided written informed consent.

 

### *Inclusion criteria*

This cohort study enrolled all patients who were clinically diagnosed as BPH with LUTS and prepared to receive an operation. The diagnosis of BPH was based on the diagnostic criteria of the 2019 Chinese Urological Surgery Guidelines for the Diagnosis and Treatment of Malignant Male Diseases. Enrolled patients should be diagnosed with BPH and have moderate (IPSS 8–19 points) or severe (IPSS 20–35 points) LUTS symptoms that significantly affect their QoL. Additionally, only patients aged over 50 years old were eligible.

### *Exclusion criteria*

The exclusion criteria are as follows: firstly, patients who were complicated with positive urine culture and/or leukocyturia. Secondly, patients who were preoperatively diagnosed with or highly suspicious of prostate cancer. Thirdly, patients who were diagnosed with acute prostatitis. Fourthly, patients who were combined with other lower urinary tract diseases, such as urethral stricture, urological tuberculosis, neurogenic bladder, urethral developmental abnormalities, etc. Fifthly, patients with severe psychiatric or behavior complications who were unable to cooperate with the examination and study. Sixthly, patients who were complicated with severe organic dysfunction or critically ill that the safety and efficacy of the study could not be evaluated.

Patients were culled from the study if they were mis-enrolled or misdiagnosed, had severe postoperative complications, had upper urinary tract infections lasting a week or over during a month after the operation, and if the cases were with plenty of missing relevant records.

### *Specimen preparation and classification*

The prostate operative tissues were sent for pathological examination at once after the surgery. And then, they were fixed and embedded in paraffins. After sectioning, the slices were stained with hematoxylin and eosin (HE) and then were observed through a microscope.

According to the degrees of HI, all patients were divided into the following groups.

- Group A, a group of simple BPH: the pathology was consistent with BPH, and no significant infiltration of inflammatory cells was observed;
- Group B, a group of BPH with mild HI: the pathology is consistent with BPH, and scattered inflammatory cell infiltration [<100/4 high-power field (HPF)] can be seen under the microscope;
- Group C, a group of BPH with moderate HI: the pathology conformed to BPH, and inflammatory cells can be seen to fuse into patches (100–500/4 HPF) under the microscope, but there is no tissue destruction or lymph node/follicle formation;
- Group D, a group of BPH with severe HI: the pathology conformed to BPH, and under the microscope, prostate tissue destruction or lymph node/follicle formation can be seen (>500/4 HPF).

### *LUTS and HI symptoms evaluation*

IPSS was used to assess LUTS. IPSS included seven questions, and each question was rated on a 5-point scale, ranging from 0 to 5. The total score is 35 points, and a higher score indicates more severe LUTS. The severity of urinary symptoms is classified as three degrees, including mild (a score of 0–7), moderate (a score of 8–19), and severe (a score of 20–35) (6).

The NIH-Chronic Prostatitis Symptom Index (CPSI) was used to assess the severity of HI. There were a total of nine items to evaluate the patient's pain symptoms, urination symptoms, and their impact on QoL. The higher the score, the more severe the HI symptoms were. A score of 0–9 represented mild symptoms, 10–18 represented moderate symptoms, and 19–31 represented severe symptoms (24).

### *PSEP measurement*

For PSEP measurement, the midstream urine samples were collected in the morning. And then, the samples were sent to the Department of Laboratory Medicine of the Second Hospital of Hebei Medical University for testing as soon as possible. PSEP diagnostic kits (enzyme-linked immunosorbent assay, Onco Biomedical Technology, Suzhou, China) were used to measure PSEP levels. The absorbance values were detected at 450 nm/630 nm through dual-wavelength mode, and the value of PSEP was calculated according to the standard curve.

### *Data collection and outcome measurements*

The demographic characteristics of all enrolled patients were collected, including age, gender, weight, height, comorbidities, prostate-specific antigen (PSA), PSA density

 

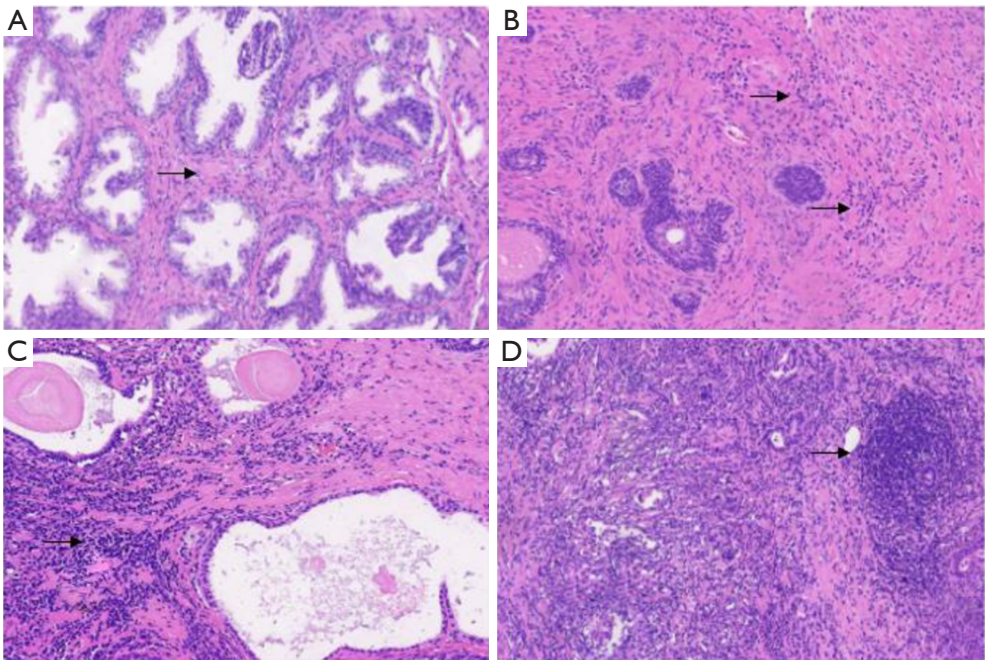


**Figure 1** Histopathological changes of prostate in each group (HE, ×100). (A) No inflammatory cells in the interstitial tissue. (B) Scattered lymphocytes in the interstitial tissue. (C) Lymphocytes aggregated in the interstitial tissue. (D) Nodular regeneration of lymphoid tissue. The arrows point to the lymphocyte. HE, hematoxylin and eosin.

(PSAD), the maximum urinary flow rate (Qmax), residual urine, and pathological characteristics. Body mass index (BMI) was calculated from weight and height for each patient. IPSS and NIH-CPSI were conducted before and 3 months after surgery in each patient to evaluate the LUTS and HI symptoms. Postoperative complications were defined as any condition occurring while the patient was hospitalized following surgery. Postoperative mortality was defined as the death within 30 days of the initial surgery regardless of its cause.

### *Statistical analysis*

Continuous variables are represented by means and standard deviations. Categorical variables are represented by proportions. Data with high skew were presented as medians [interquartile ranges (IQRs)]. Kruskal-Wallis test, and analysis of variance were used to determine differences. And Kendall's tau-b correlation analysis was used for the correlation analysis of PSEP. Simple and multiple linear regression analyses were applied to identify factors that might affect preoperative IPSS and IPSS difference of before and after the surgery. All statistical analyses were conducted by the SPSS package (SPSS v.26.0 software, IBM Corp., Armonk, NY, USA). And GraphPad Prism (Prism v.9.3.1 software, GraphPad Software LLC., La Jolla, CA, USA) was used to create the violin plots. Differences were considered to be statistically significant if the P value <0.05 (two-sided).

## Results

### *Clinical and pathological characteristics and the impacts on preoperative LUTS (IPSS and NIH-CPSI) of patients*

According to the inclusion and exclusion criteria, a total of 69 BPH patients were enrolled in the present study, including nine cases in no inflammation group (Group A), 12 cases in mild inflammation group (Group B), 40 cases in moderate inflammation group (Group C), and eight cases in severe inflammation group (Group D). The degrees of HI are presented in *Figure 1*. Among all the included cases, 60 cases were complicated with HI, accounting for 87.0%. There were no significant differences in age (P=0.71) and BMI (P=0.36) among each group. Significant differences were observed in IPSS (P<0.001) and NIH-CPSI (P<0.001) among each group. No significant differences were

 

**Table 1** Demographic and clinicopathologic characteristics of the enrolled patients

| Characteristics | Group A (n=9) | Group B (n=12) | Group C (n=40) | Group D (n=8) | P value |
|---|---|---|---|---|---|
| Age (years) | 68 [60–75] | 69 [67–74.75] | 68.5 [64–72.75] | 67 [65–69.5] | 0.71 |
| BMI (kg/m$^2$) | 25.09±2.24 | 23.66±2.58 | 25.32±3.38 | 24.03±3.29 | 0.36 |
| t-PSA (ng/mL) | 6.71 [3.42–12.33] | 4.48 [2.17–9.20] | 5.07 [3.52–10.46] | 6.96 [1.91–14.03] | 0.38 |
| f-PSA/t-PSA (%) | 16.5 [7.85–30.92] | 13.02 [7.74–32.36] | 17.39 [11.64–19.75] | 9.78 [2.98–20.92] | 0.68 |
| PSAD (ng/mL/cm$^3$) | 0.14 [0.11–0.30] | 0.081 [0.31–0.24] | 0.06 [0.05–0.10] | 0.11 [0.03–0.28] | 0.11 |
| Qmax (mL/s) | 6.56±2.64 | 6.40±3.30 | 6.72±2.85 | 6.48±2.83 | 0.68 |
| Residual urine (mL) | 102 [56–450] | 185.5 [37.75–520.25] | 138.5 [51–318.25] | 249 [127.75–635.25] | 0.49 |
| PSEP (ng/mL) | 4.53 [4–5.04] | 3.39 [2.89–4.76] | 4.43 [3.8–4.89] | 4.76 [3.77–5.22] | 0.79 |
| IPSS | 19 [13–22.5] | 26 [25–28] | 26 [25–28] | 30 [29–31] | <0.001 |
| NIH-CPSI | 19.78±3.15 | 23±2.7 | 24±3.2 | 26.13±2.36 | <0.001 |

Data are presented as median [range] or mean ± SD. Group A: a group of simple BPH; Group B: a group of BPH with mild HI; Group C: a group of BPH with moderate HI; Group D: a group of BPH with severe HI. BMI, body mass index; t-PSA, total prostate-specific antigen; f-PSA, free prostate-specific antigen; PSAD, prostate-specific antigen density; Qmax, maximum urinary flow rate; PSEP, prostatic exosomal protein; IPSS, International Prostate Symptom Score; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index; HI, histological inflammation; SD, standard deviation.

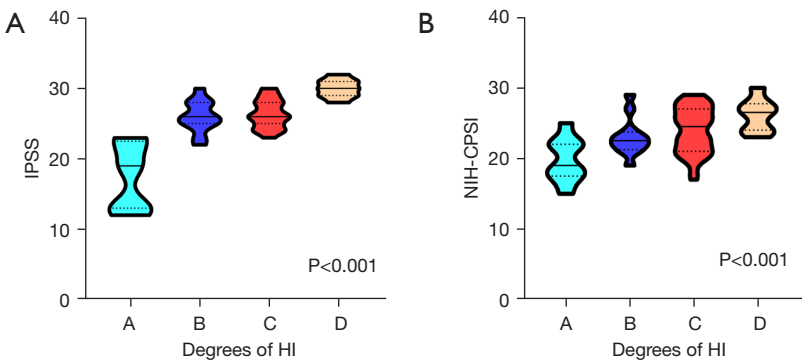


**Figure 2** Violin plots of IPSS and NIH-CPSI with HI. Solid lines represent medians and dotted lines represent quartiles. (A) Relationship between preoperative IPSS and HI. (B) Relationship between preoperative NIH-CPSI and HI. Group A: a group of simple BPH; Group B: a group of BPH with mild HI; Group C: a group of BPH with moderate HI; Group D: a group of BPH with severe HI. IPSS, International Prostate Symptom Score; HI, histological inflammation; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index.

identified in total PSA (t-PSA), free PSA (f-PSA)/t-PSA, PSAD, Qmax, residual urine, and PSEP (P>0.05). The detailed demographic and clinicopathologic characteristics are provided in *Table 1*.

The violin plot results indicated a progressive rise in preoperative IPSS corresponding to the severity degrees of HI. The difference was significant (P<0.001). Besides, the results showed that the NIH-CPSI scores exhibited a significant increase in correlation with the severity levels of HI (P<0.001). All these represented that preoperative LUTS gradually worsened with the increasing degrees of HI according to the violin plot results. The details are presented in *Figure 2A*,*2B*.

### *Correlation analysis of PSEP*

The correlation analysis revealed that PSAD, preoperative IPSS, and the difference between preoperative and

 

postoperative IPSS were all significantly correlated with PSEP levels (P=0.02, P=0.03, and P=0.03). The detailed results are provided in *Table 2*.

There were no significant correlations between the PSEP and HI (P=0.79) among all the patients. However, among patients with total t-PSA levels higher than 4.0 ng/mL, a significant correlation was observed between PSEP levels and HI (P=0.04). Notably, among those patients with t-PSA levels higher than 4.0 ng/mL and HI, a strong correlation was found between PSEP levels and the degree of HI (P=0.02). The results are presented in *Figure 3A*,*3B*.

**Table 2** Correlations analyses results of PSEP

| Variables | P value |
|---|---|
| Age | 0.61 |
| BMI | 0.91 |
| t-PSA | 0.33 |
| f-PSA/t-PSA | 0.11 |
| PSAD | 0.02 |
| Qmax | 0.24 |
| Residual urine | 0.13 |
| Preoperative IPSS | 0.03 |
| Preoperative NIH-CPSI | 0.13 |
| Preoperative and postoperative IPSS differences | 0.03 |
| Complicated with HI | 0.79 |

PSEP, prostatic exosomal protein; BMI, body mass index; t-PSA, total prostate-specific antigen; f-PSA, free prostate-specific antigen; PSAD, prostate-specific antigen density; Qmax, maximum urinary flow rate; IPSS, International Prostate Symptom Score; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index; HI, histological inflammation.

In addition, univariate linear regression analysis indicated that HI was significantly associated with preoperative IPSS (P<0.001). Furthermore, multiple linear regression was performed on the statistically significant factors from simple linear regression (HI) and potential preoperative and postoperative IPSS difference-related factors (t-PSA and PSEP). And the results revealed that both PSEP level (P=0.003) and HI (P<0.001) were significantly associated with preoperative IPSS. The detailed results were presented in *Tables 3*,*4*.

Besides, univariate linear regression analysis revealed that HI (P<0.001) was significantly associated with postoperative and preoperative IPSS difference, too. Additionally, multiple linear regression was performed on the statistically significant factors from simple linear regression (HI) and potential preoperative and postoperative IPSS difference-related factors (t-PSA and PSEP). And the results revealed that PSEP level (P=0.03) and HI (P<0.001) were significantly associated with postoperative and preoperative IPSS differences. Details were presented in *Tables 5*,*6*.

## Discussion

BPH—also called benign prostatic hypertrophy or benign

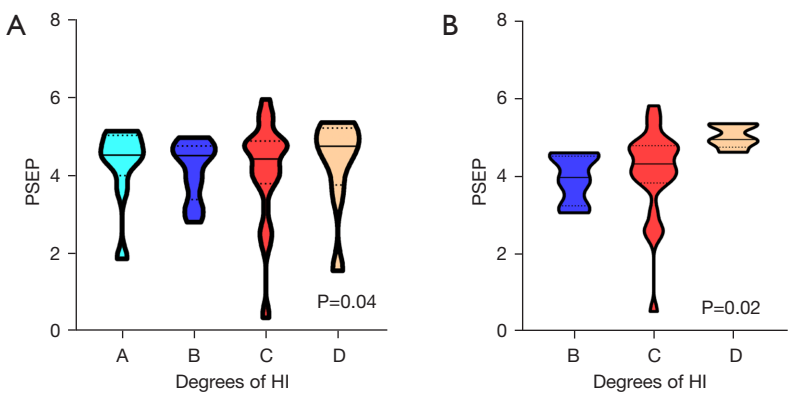


**Figure 3** Relationship between the PSEP and HI among patients with t-PSA >4 ng/mL. Solid lines represent medians and dotted lines represent quartiles. (A) Relationship between PSEP and HI among all patients with t-PSA >4 ng/mL. (B) Relationship between PSEP and HI among patients with t-PSA >4 ng/mL. Group A: a group of simple BPH; Group B: a group of BPH with mild HI; Group C: a group of BPH with moderate HI; Group D: a group of BPH with severe HI. PSEP, prostatic exosomal protein; HI, histological inflammation; t-PSA, total prostate-specific antigen.

 

**Table 3** Univariate linear regression analysis results of IPSS in BPH patients

| Variables | P value |
|---|---|
| Age | 0.73 |
| BMI | 0.98 |
| t-PSA | 0.68 |
| f-PSA/t-PSA | 0.51 |
| PSAD | 0.32 |
| Qmax | 0.29 |
| Residual urine | 0.78 |
| PSEP level | 0.15 |
| Complicated with HI | <0.001 |

IPSS, International Prostate Symptom Score; BPH, benign prostatic hyperplasia; BMI, body mass index; t-PSA, total prostate-specific antigen; f-PSA, free prostate-specific antigen; PSAD, prostate-specific antigen density; Qmax, maximum urinary flow rate; PSEP, prostatic exosomal protein; HI, histological inflammation.

**Table 4** Multivariate linear regression analysis results of IPSS in BPH patients

| Variables | Beta value | 95% CI | P value |
|---|---|---|---|
| PSEP level | 0.233 | 0.297–1.402 | 0.003 |
| Complicated with HI | 0.778 | 7.717–11.386 | <0.001 |

IPSS, International Prostate Symptom Score; BPH, benign prostatic hyperplasia; CI, confidence interval; PSEP, prostatic exosomal protein; HI, histological inflammation.

**Table 5** Univariate linear regression analysis results of postoperative and preoperative IPSS difference in BPH patients

| Variables | P value |
|---|---|
| Age | 0.95 |
| BMI | 0.90 |
| t-PSA | 0.28 |
| f-PSA/t-PSA | 0.59 |
| PSAD | 0.17 |
| Qmax | 0.24 |
| Residual urine | 0.74 |
| PSEP level | 0.15 |
| Complicated with HI | <0.001 |

IPSS, International Prostate Symptom Score; BPH, benign prostatic hyperplasia; BMI, body mass index; t-PSA, total prostate-specific antigen; f-PSA, free prostate-specific antigen; PSAD, prostate-specific antigen density; Qmax, maximum urinary flow rate; PSEP, prostatic exosomal protein; HI, histological inflammation.

**Table 6** Multivariate linear regression analysis results of postoperative and preoperative IPSS difference in BPH patients

| Variables | Beta value | 95% CI | P value |
|---|---|---|---|
| PSEP level | 0.233 | 0.297–1.402 | 0.03 |
| Complicated with HI | 0.778 | 7.717–11.386 | <0.001 |

IPSS, International Prostate Symptom Score; BPH, benign prostatic hyperplasia; CI, confidence interval; PSEP, prostatic exosomal protein; HI, histological inflammation.

prostatic obstruction—is one of the commonest diseases in aging men in which the prostate gland is enlarged but not malignant, resulting in LUTS and bladder outlet obstruction usually (25). Patients with BPH complicated with HI are prone to have larger prostate volumes, more severe LUTS, and a higher probability of acute urinary retention than those without HI (14,15). In this study, we discovered that patients with more severe HI were more likely to have severe LUTS, as evidenced by higher and increasing IPSS and NIH-CPSI scores, among those diagnosed with BPH. Moreover, we found that PSEP levels were correlated with degrees of HI among patients with complicated BPH and t-PSA levels greater than 4.0 ng/mL. Additionally, we observed a correlation between PSEP level or HI and the difference between preoperative and postoperative IPSS.

The severity of HI is strongly linked to LUTS, as evidenced by IPSS and NIH-CPSI scores. As inflammation increases, the intensity of LUTS also intensifies, which is reflected in higher IPSS and NIH-CPSI scores. This result is consistent with previous studies (10,26). However, our study differs from previous studies in that we assessed the severity of HI through pathological results, resulting in a more objective and dependable outcome.

Besides, univariate and multivariate linear regression analyses showed that BPH concomitant with HI was significantly correlated with higher IPSS. Thus, all these results support the idea that BPH patients complicated with HI often have severe LUTS. And, those patients usually have high PSEP levels. These results showed that BPH patients with HI often have elevated PSEP levels and more severe LUTS. Several previous studies have reported the

 

relationship between PSEP levels and inflammation as well as the relationship between PSEP levels and prostate cancer (27-29). However, for the first time, we focused on the characteristics of PSEP in patients with BPH. Although our study results showed that there was no correlation between PSEP levels and inflammation in all BPH patients, interestingly, we found that PSEP levels were correlated with HI among patients with t-PSA >4 ng/mL. We analyzed for the reason why PSEP levels were not correlated with HI in the overall population. Our enrolled patients were all diagnosed as BPH, and BPH patients generally had PSA elevation and prostatitis. After controlling variables, we found that PSEP levels were correlated with inflammation among patients with t-PSA >4 ng/mL. Thus, this conclusion may be more relevant to the characteristics of BPH patients. In addition, in a previous study (27), it was found that when t-PSA levels were 4–10 ng/mL, PSEP levels were negatively correlated with prostate cancer, that is, lower PSEP levels were associated with higher prostate cancer risk. However, our study found that when t-PSA >4 ng/mL (in fact, our patients' t-PSA levels were mostly below 10 ng/mL), PSEP levels were positively correlated with BPH combined with HI. It is well known that PSA has been widely used as a diagnostic marker for prostate cancer in clinical practice (30-32). When PSA >10 ng/mL, a high clinical suspicion of prostate cancer is present, when PSA <4 ng/mL, a low possibility of prostate cancer is considered, and when PSA is between 4 and 10 ng/mL, it is in the clinical grey area. Based on the findings of this article and previous study, we believe that when PSA is between 4 and 10 ng/mL, PSEP levels increase simultaneously, which is more likely to be BPH combined with HI, while decreasing PSEP levels should prompt to the consideration of prostate cancer. Therefore, in the gray area, PSEP may be a very valuable diagnostic and differential diagnostic indicator. Of course, we need to further explore the relationship between PSEP levels and HI and prostate cancer.

In addition, we found that preoperative and postoperative IPSS differences were related to PSEP in the correlation analysis. Moreover, we also found that the difference between preoperative and postoperative IPSS were related to PSEP or HI in the multivariate linear regression analysis. All these results indicated that surgical treatment can achieve better therapeutic effects for BPH patients. A high PSEP level or HI could serve as a good biomarker for predicting the efficacy of surgical treatment in alleviating LUTS among BPH patients. For these patients, surgical treatment can effectively relieve LUTS, improve urinary flow rate, and enhance QoL. Currently, the objectives of BPH treatment include: (I) relieving symptoms, such as frequent urination, urgent urination, nocturia, etc.; (II) improvement of urodynamic parameters, such as maximum flow rate and average flow rate; (III) prevention of complications, such as repeated urinary tract infections, bladder stones, etc.; (IV) improving the QoL. And the treatment methods include drug and surgical therapy (4,33). There are plenty of side effects and risks of surgical therapy, such as bleeding, infection, urinary incontinence, frequent urination, urethral stricture, erectile dysfunction, etc. (34,35). However, for some BPH patients, surgery cannot effectively relieve LUTS. Now, accurately identifying patients who will benefit from surgery is a key issue that needs to be solved urgently. Our study provided a promising predictor for the surgical efficacy of BPH and better surgical IPSS relief. Thus, according to the present study, higher PSEP is more likely to have better IPSS relief, and it is more inclined to perform surgery.

There are several limitations in our study. First of all, although our study is a cohort study, it is a single-center study. Secondly, the sample size is small in each group in our study. Thirdly, although we found that the combination of PSEP and t-PSA could be used to predict the efficacy of surgery among BPH patients, we did not provide a recommended cutoff value for this method. Lastly, larger prospective studies are needed to further confirm the findings.

## Conclusions

The study indicated that IPSS and PSEP (when t-PSA >4 ng/mL) were correlated with the severity of HI in patients with BPH. PSEP was linearly correlated with IPSS and the degree of reduction in IPSS after surgery. Consequently, PSEP may serve as a promising predictor for assessing surgical efficacy and diagnosing the severity of HI in patients with BPH.

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## Footnote

*Reporting Checklist:* The authors have completed the

 

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*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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Second Hospital of Hebei Medical University Ethics Committee (No. 2021-R174), and all participants provided written informed consent.



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