Diagnosis of Chronic Prostatitis by Noninvasive Methods in Elderly Patients with Benign Prostatic Hyperplasia in China

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Research article

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Abstract

Background: Chronic prostatitis is hard to be identified in benign prostatic hyperplasia (BPH) patients in clinical works. This study aimed to diagnose chronic prostatitis in BPH patients by noninvasive methods.

Methods: The research was carried out on the BPH patients who received transurethral resection of prostate at Xinhua hospital from January 2014 to Jul 2015. Before operation, patients were asked for medical history and required to receive physical examination, serum sample collection including PSA, sex hormones, inflammatory cytokines, metabolic panel and transrectal ultrasonography. According to histological results, the patients were divided into 2 group of BPH with/without prostatitis. Logistic regression was used to find the risk factors of chronic prostatitis.

Results: As a result, 181 men with an average age of 72.15±8.41 years were enrolled in this study, including 116 patients with prostatitis and 65 patients without prostatitis. The storage sub-score (9.24±1.55 vs 8.52±1.63, \( p = 0.009 \)), PSA (8.23±7.69 vs 4.92±3.84, \( p = 0.005 \)) and IL-2R (531.96±200.75 vs 434.11±153.54, \( p = 0.001 \)) were significantly higher in patients with prostatitis than those without prostatitis. Based on logistic regression analysis, the above three parameters were also the risk factors of BPH with prostatitis. The diagnostic model was calculated as: 0.317* storage sub-score+0.092* PSA+0.003* IL-2R-4.296. The AUC was 0.725.

Conclusions: Histological prostatitis in BPH patients can be diagnosed by the combination of serum IL-2R, PSA and storage sub-score. Identification of chronic prostatitis among patients with BPH is beneficial for medical decisions, which can more efficiently alleviate urinary symptoms and reduce the risk of disease progression.

Background:

Chronic prostatitis (CP) is one of the most common urogenital diseases in adult males. The prevalence of CP in men between 25 and 50 years old is 13.4% in Italy [1] while about 25.3% of men over the age of 40 have CP in China [2]. Moreover, 35–50% of men were reported to be likely affected by associated symptoms during their lifetime [3]. Indeed, the prevalence of asymptomatic inflammatory prostatitis may even higher than chronic prostatitis/chronic pelvic pain syndrome. Most of benign prostatic hyperplasia (BPH) patients have concomitant CP. In a study carried by Morote et al, chronic inflammation was found in 68.3% (194/284) of the enrolled BPH patients underwent sextant prostate biopsy [4]. In the past few years, it has been revealed that inflammation plays a key role in etiology of BPH [5]. In addition, the degree of inflammation in prostate has been shown significantly correlated with the severity of BPH [6]. However, in BPH patients, CP is hard to be identified in clinical works, as urinary symptoms of CP are often concealed by BPH to a great extent. Furthermore, the existence of inflammation in prostate made α1-blockers and 5α reductase inhibitors (5-ARIs) insufficient to improve the urinary symptoms [7]. The objective of the current study is to analyze the efficacy of noninvasive methods in diagnosis of chronic prostatitis in BPH patients.
Methods:

This clinical study was carried out on the BPH patients who received transurethral resection of prostate (TURP) at Xinhua hospital from January 2014 to Jul 2015. All of the enrolled patients without the history of chronic prostatitis were diagnosed as bladder outlet obstruction (BOO) by clinical symptoms, cystoscopy or urodynamic study. Urinary symptoms of these patients didn’t show improvement after at least one year of medical treatment. Patients with acute urinary retention history within one month, concurrent catheterization, urinary infection, bladder stone, hydronephrosis or renal dysfunction, history of neurogenic lower urinary tract dysfunction or malignant tumor, history of pelvic or prostate operation, positive digital rectal examination (DRE) result, and histological diagnosis of prostate cancer post-operation were excluded from the study.

Informed consent was signed by all patients. Patient clinical data were obtained including age, current and past history, medical conditions, International Prostate Symptom Score (IPSS) were collected. IPSS consists of seven questions, and all patients were required to complete the questions independently. The storage sub-score was the sum of question 2, question 4 and question 7 while the voiding sub-score was the sum of question 3, question 5 and question 6. In addition, fasting blood sample for analysis of prostate specific antigen (PSA), free PSA (fPSA), serum inflammatory cytokines (interleukin (IL)-6, IL-8, IL-2R and tumor necrosis factor (TNF)α), serum sex hormone (Luteinizing hormone(LH), follicle stimulating hormone (FSH), prolactin (PRL), testosterone (T), estradiol (E2) and progesterone (P)), serum metabolic panel (total proteins, albumin, triglyceride (TG), cholesterol (TC), high density lipoprotein (HDL), low density lipoprotein (LDL), creatinine (CR), fast blood glucose (Glu) and glycohemoglobin (HbA1c)) were collected at 6 am before DRE and operation.

Meanwhile, patients received transrectal prostate ultrasonography (TRUS), through which ultrasonic images were obtained with the patient in the left decubitus position. Total prostate volume (TPV), transitional zone volume (TZV) and intravesical prostatic protrusion (IPP) were measured by a certified ultrasonologist. All the patients were subsequently underwent TURP. During TURP, deep random tissue specimens (weighing 1–2 g) were collected under sterile conditions through resectoscope and transported to pathology laboratory in sterile saline. The specimens were then fixed in 10% neutral-buffered formalin and embedded in paraffin following routine histologic procedures. Tissue sections (5 µm) were stained with hematoxylin and eosin. Inflammatory cell infiltration in the glandular and/or stromal was defined as prostatitis by an experienced pathologist.

The data were analyzed by Statistical package for social science, version 21.0. Results were presented as mean ± SD. Independent t-test was used to evaluate the numerical parameters of the two groups for statistic difference when the parameter was consistent with normal distribution and Mann-Whitney U test was used when the parameter was consistent with nonparametric distribution. Multivariate logistic regression was used to identify the risk factor of chronic prostatitis in BPH patients. For all statistic tests, \( p < 0.05 \) was considered to be statistically significant.
Results:

A total of 181 patients were recruited in our study and the mean age was 72.15 ± 8.41 years old. According to the pathological results, 116 patients were diagnosed with histological prostatitis while 65 patients showed no pathological prostatitis. Table 1 showed the comparison of clinical parameters and serum examination results between BPH patients with prostatitis and BPH patients without prostatitis. Serum PSA level (8.23 ± 7.69 vs 4.92 ± 3.84, \( p = 0.005 \)), serum IL-2R level (531.96 ± 200.75 vs 434.11 ± 153.54, \( p = 0.001 \)) and storage sub-score (9.24 ± 1.55 vs 8.52 ± 1.63, \( p = 0.009 \)) in the prostatitis group were significantly higher than those in BPH alone group. The other results between two groups had no significant difference.
Table 1

| Parameter                          | BPH without prostatitis (n = 65) (mean ± SD) | BPH with prostatitis (n = 116) (mean ± SD) | P value |
|------------------------------------|---------------------------------------------|---------------------------------------------|---------|
| Age                                | 71.82 ± 8.306                               | 72.34 ± 8.504                               | 0.686   |
| IPSS                               | 20.05 ± 3.189                               | 20.53 ± 3.163                               | 0.322   |
| Storage sub-score                  | 8.52 ± 1.631                                | 9.24 ± 1.553                                | 0.009** |
| Voiding sub-score                  | 11.52 ± 2.652                               | 11.28 ± 2.280                               | 0.523   |
| Nocturia                           | 3.78 ± 0.944                                | 4.03 ± 0.946                                | 0.084   |
| PSA (ng/ml)                        | 4.92 ± 3.841                                | 8.23 ± 7.694                                | 0.005** |
| %fPSA                              | 0.2282 ± 0.1416                             | 0.2196 ± 0.1382                             | 0.540   |
| Estradiol (pmol/l)                 | 170.35 ± 76.353                             | 175.75 ± 86.01                              | 0.674   |
| FSH (IU/l)                         | 16.198 ± 12.047                             | 17.238 ± 11.394                             | 0.353   |
| LH (IU/l)                          | 8.880 ± 10.627                              | 8.543 ± 5.242                               | 0.345   |
| Prolactin (mIU/l)                  | 285.97 ± 127.14                             | 283.66 ± 127.11                             | 0.955   |
| P (nmol/l)                         | 2.376 ± 1.331                               | 2.364 ± 1.394                               | 0.954   |
| T (nmol/l)                         | 12.686 ± 4.661                              | 12.102 ± 3.915                              | 0.370   |
| TC (mmol/l)                        | 3.8542 ± 1.4484                             | 3.9097 ± 1.2416                             | 0.558   |
| TG (mmol/l)                        | 1.5648 ± 0.8357                             | 1.3935 ± 0.8454                             | 0.084   |
| HDL (mmol/l)                       | 1.3552 ± 0.3870                             | 1.3041 ± 0.3444                             | 0.361   |
| LDL (mmol/l)                       | 2.5651 ± 0.6580                             | 2.4678 ± 0.4026                             | 0.362   |
| Cr (µmol/l)                        | 81.32 ± 33.221                              | 78.32 ± 28.072                              | 0.726   |
| Total protein (g/l)                | 65.597 ± 5.2337                             | 64.557 ± 5.4873                             | 0.215   |
| Albumin (g/l)                      | 38.440 ± 3.1898                             | 37.479 ± 3.4087                             | 0.081   |
| Glu (mmol/l)                       | 5.6654 ± 1.3127                             | 5.4688 ± 1.3366                             | 0.266   |
| HbA1c (%)                          | 6.1708 ± 1.0580                             | 5.9828 ± 1.2931                             | 0.170   |
| IL-2R (U/ml)                       | 434.11 ± 153.54                             | 531.96 ± 200.75                             | 0.001** |
Table 2 showed the results of multivariate logistic regression. Storage sub-core (OR 1.373, 95%CI 1.096–1.719, p = 0.006), serum PSA level (OR 1.097, 95%CI 1.023–1.176, p = 0.007) and serum IL-2R level (OR 1.003, 95%CI 1.001–1.005, p = 0.010) were the three independent risk factors for BPH with chronic prostatitis. The model: 0.317* storage sub-core + 0.092* PSA (ng/ml) + 0.003* IL-2R (U/ml) - 4.296 established on the results of multivariate logistic regression could be used to diagnose whether the BPH patients have concomitant chronic prostatitis. The AUC of the model was 0.725 (Fig. 1). The optimal sensitivity, specificity and positive predictive value (PPV) was 69.0%, 66.2% and 78.4%, respectively.

**Discussion:**
The diagnosis of chronic prostatitis in BPH patients is of great clinical significance. The first reason is that long-term inflammation in prostate tissue may have association with malignant tumor, though it is still controversial until now. Approximately 20% of human malignant tumors can be caused by chronic inflammation or chronic infection [8]. In De Marzo's study which found a connection between atrophic area of human prostate tissue and the co-existing of inflammatory cell infiltration, under the condition called "proliferative inflammatory atrophy (PIA)", atypical cells were observed in the area of proliferative inflammatory atrophy [9]. In addition, the hypothesis that inflammatory reaction could lead to cancer has also been confirmed in the adult animal model [10].

The second reason is based on the hypothesis founded by several studies that inflammation is an obstacle to effective treatment in BPH patients. Roehrborn et al concluded that chronic prostatitis played an important role in promoting disease progression and increasing the risk of acute urinary retention in benign prostatic hyperplasia [11]. Moreover, 5-ARIs may lose their efficacy upon chronic inflammation. Presence of inflammation in prostate is able to stimulate IL-6 and IL-8 production which could activate androgen receptors without dihydrotestosterone (DHT), as well as increase releasing in growth factors. Therefore, lymphocyte infiltration could maintain prostate cell proliferation despite the presence of 5-ARIs [7]. Additionally, the efficacy of α1-blocks may also decrease in the condition of prostatitis. A1-adrenoceptors and some inflammatory mediators such as thromboxane A2 (TXA2) share common intracellular mediators to induce smooth muscle contraction in the prostate [12, 13]. Thus, blocking only α1-adrenoceptors would be insufficient for complete prevention of prostatic contraction. This might explain why the effect of α1-blocks is limited during inflammatory status in prostate. Furthermore, Kwon et al observed that the combination use of α1-blocks and 5-ARIs could also be insufficient to reduce symptom severity in patients with high-grade prostatic inflammation in a 1-year-follow-up prospective study [14]. Therefore, for the BPH patients with chronic prostatitis, nonsteroidal anti-inflammatory drugs (NSAIDs) (especially cyclooxygenase-2 inhibitors), vitamin D receptor agonists, extracts of Serenoa repens, Eviprostat or other herbal medicine [7, 15] may be the better choice.

In the current study, the prevalence of chronic prostatitis in BPH patients was 64.09% (116/181 patients), which was similar to that in Morote's study (68.3%) [4]. The established model to diagnose chronic prostatitis in BPH patients was composed of serum PSA level, storage sub-score and serum IL-2R level. As mentioned above, The PSA release is elevated due to the activation of androgen receptors stimulated by inflammatory cytokines [7]. The study of Agnihotri et al suggested that significant inflammation of the prostate resulted in spurious rise in serum PSA level [16]. This conclusion was also confirmed in young men [17]. Effective treatment for prostatitis could significantly reduce serum PSA level in aging men [18]. Therefore, relatively high serum PSA level is an important manifestation of chronic prostatitis in BPH patients.

The data from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial showed the evidence of a relationship between the degree of lower urinary tract symptoms (LUTS) and the degree of chronic inflammation. IPSS score, especially storage sub-scores were obviously higher in the group of patients with histological chronic inflammation compared with those without chronic inflammation [19].
In our study, the storage sub-scores of the patients with chronic prostatitis were significantly higher than those without prostatitis, which was similar to the result of REDUCE trial. However, no significant difference was detected between two groups in regards to IPSS and voiding sub-score in this study, which was probably due to the different timing of IPSS collection. The data of REDUCE trial was collected before medical intervention while the data of patients in our study was collected after medical treatment. The result of our study suggested that medical treatment for BPH alone could relieve voiding symptoms but not storage symptoms.

A great number of scholars tend to verify the important role of the immune factors in the pathogenesis of chronic prostatitis. Engelhardt et al found the increasing expression of IL-2R, IL-6 and TNF-α in prostate tissue of patients with BPH and chronic prostatitis [20, 21]. Korrovits et al observed elevation of seminal IL-6 level in patients with chronic prostatitis [17]. Significant increase in seminal IL-1β and TNF-α level was observed in patients with chronic prostatitis according to the study of Nadler et al [22]. Several studies revealed that IL-8 may be a reliable biomarker of inflammation in BPH patients because its level was significantly higher in both seminal plasma and expressed prostatic secretion (EPS) in BPH patients with chronic prostatitis [23, 24]. However, seminal IL-8 level was associated with not only prostatitis, but also inflammation in other organs, such as seminal vasculitis and epididymitis. In addition, seminal IL-8 level was also closely related to prostate cancer. Moreover, seminal IL-8 level was inversely related to volume per ejaculate [25]. All of the above greatly limit the diagnostic value of seminal IL-8 level in BPH patients with prostatitis.

IL-2 is a pleiotropic cytokine which can promote the growth of T cells, enhance the activity of NK cell lysis, induce regulatory T cell differentiation, mediate activation and induce cell death, and plays a key role in immune response [26]. IL-2 activated lymphocytes increased the number of membrane-bound IL-2R. In the meantime, they release a soluble form of interleukin-2 receptor (sIL-2R) into blood. The role of sIL-2R is to bind excess IL-2 and release it later. B and T lymphocytes are activated in this process. They can subsequently activate the production of interleukin, interferon and tumor necrosis factor, and stimulate the cytotoxic cells and lymphokine activated killer cells, as well as the cytotoxicity of macrophages [20].

In our study, serum IL-2R levels (soluble IL-2R) were significantly higher in BPH patients with chronic prostatitis. It indicates that inflammatory cells were activated by IL-2 to participate in the inflammatory response, which is consistent with the infiltration of lymphocytes, monocytes and plasma cells in the histology of chronic prostatitis. Moreover, Poutahidis et al found that there was also a higher expression of IL-2 in prostate cancer, which further confirmed the relationship between prostatitis and prostate cancer [27].

The subjects of our study were mainly elderly men, among whom the average age is over 65. It is hard to acquire enough semen or EPS from each elderly people while serum sample is convenient to collect. The Meares-Stamey 4-glass test is the standard method of assessing inflammation and the presence of bacteria in the lower urinary tract in men presenting with the chronic prostatitis syndrome. However, most urologists do not use it in daily practice because of the time and difficulty in performing it, as well as the test is not suitable for diagnosis of nonbacterial prostatitis. Several researches revealed that LUTS could
be evaluated by serum inflammatory cytokines, such as serum hyper-sensitivity C-reactive protein (hsCRP) concentration [28]. Choi et al suggested that serum hsCRP levels may indicate the severity of LUTS in aging men [29]. Additionally, another evidence showed that serum hsCRP, TNF-α, and soluble e-selectin had significant moderating effects on the development of storage LUTS [30]. However, up to now, the consistence of serum IL-2R and semen or urine IL-2R has not been reported, in which further investigation is needed.

AUC of the diagnostic model established by us was 0.724. The sensitivity and specificity were considered fair, which may be related to the small sample size in our study. However, the optimal PPV was up to 78.4%, which meant approximately 80% of the patients diagnosed with chronic prostatitis by the current model were really suffered from prostatitis diagnosed by histological results. The accuracy rate would be considered satisfactory for both urologists and patients on condition that the model has been validated in other studies.

The limitation of this study is that the prostatitis was not classified according to the grading system. Further multicenter study will be carried out to establish a more accurate model.

**Conclusions:**

In conclusion, the model consisting of serum PSA level, serum IL-2R and storage sub-score could assist in diagnosing chronic prostatitis from BPH patients. Identification of chronic prostatitis among patients with BPH is beneficial for medical decisions, which can more efficiently alleviate urinary symptoms and reduce the risk of disease progression.

**List Of Abbreviations:**

BPH: benign prostatic hyperplasia

CP: chronic prostatitis

5-ARIs: 5α reductase inhibitors

TURP: transurethral resection of prostate

BOO: bladder outlet obstruction

DRE: digital rectal examination

IPSS: International Prostate Symptom Score

PSA: prostate specific antigen

IL: interleukin
TNF: tumor necrosis factor
LH: Luteinizing hormone
FSH: follicle stimulating hormone,
PRL: prolactin
T: testosterone
E2: estradiol
P: progesterone
TG: triglyceride
TC: cholesterol
HDL: high density lipoprotein
LDL: low density lipoprotein
CR: creatinine
Glu: fast blood glucose
HbA1c: glycohemoglobin
TRUS: transrectal prostate ultrasonography
TPV: Total prostate volume
TZV: transitional zone volume
IPP: intravesical prostatic protrusion
PPV: positive predictive value
PIA: proliferative inflammatory atrophy
TXA2: thromboxane A2
DHT: dihydrotestosterone
NSAIDs: nonsteroidal anti-inflammatory drugs
REDUCE: Reduction by Dutasteride of Prostate Cancer Events
LUTS: lower urinary tract symptoms
EPS: expressed prostatic secretion
hsCRP: hyper-sensitivity C-reactive protein

**Decrelations:**

**Ethics approval and consent to participate:**

Informed consent was signed by all patients. The research was approved by Ethics Committee of Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine (XHEC-D-2015-167).

**Consent for publication:**

Not applicable

**Availability of data and materials:**

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:**

The authors declare that they have no competing interests

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**Authors' contributions:**

QC: Manuscript writing
YW: Data collection
WG: Data analysis
YZ: Data analysis
Acknowledgements:

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Figures

![ROC curve](image-url)
Figure 1

the ROC curve of diagnostic model established by the current study (AUC=0.725)
the ROC curve of diagnostic model established by the current study (AUC=0.725)