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Original Article

Effect of Bushen Huoxue Decoction combined with moxibustion on inflammation and urinary symptoms in patients with prostate cancer

Junhao Wang, Jianpeng Han, Jianyong Feng, Kuo Guo, Wenbin Chen, Yan Zhou, Yongzhang Li

Department of Urology, Hebei Provincial Hospital of Traditional Chinese Medicine, No. 389, Zhongshan East Road, Shijiazhuang 050011, Hebei, China

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Abstract: Objective: To investigate the efficacy of Bushen Huoxue Decoction (BSHXD) combined with moxibustion on inflammation and urinary symptoms in prostate cancer (PC) patients. Methods: A total of 87 patients with PC admitted to the Hebei Provincial Hospital of Traditional Chinese Medicine from 08/2019 to 12/2021 were collected for this retrospective study. There were 42 patients treated with conventional treatment regimens who were regarded as the control group (CG). The remaining 45 patients treated with BSHXD and moxibustion were considered the experimental group (EG). The quality of survival of patients was assessed through the C30 and PR25 subscales of the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ). Patients' urinary symptom changes were evaluated using the International Prostate Symptom Score (IPSS). The levels of interleukin-6 (IL-6) and tumor necrosis factor α (TNF)-α were measured by Elisa assay before and after the treatment. The maximum urinary flow rate and residual urine volume of the patients were compared before and after the treatment. Logistic regression was used to analyze the risk factors affecting the progression to castration-resistant prostate cancer (CRPC). Results: There was no statistical difference in the total response rate between the two groups of patients ($P>0.05$). Patients in the EG had a higher QLQ-C30 and maximum urinary flow rate scores than those in the CG after the treatment. The residual urine volume, IL-6, TNF-α, QLQ-PR25, and IPSS scores in the EG were lower ($P<0.05$). The multi-factorial regression analysis revealed that the Gleason score and the pre-treatment prostate-specific antigen (PSA) level were independent risk factors for the development of CRPC in patients ($P<0.05$). We plotted the receiver operating characteristic curves for predicting CRPC based on the indicators of patients. The area under the curve for Gleason score and the pre-treatment PSA level were 0.665 and 0.827, respectively, and 0.935 for the combination. Conclusion: BSHXD combined with moxibustion had no effect on patients' progressive values of CRPC and did not enhance their outcomes. It was effective in improving their lower urinary symptoms, inflammation, and quality of life.

Keywords: Bushen Huoxue Decoction (BSHXD), moxibustion, prostate cancer patients, inflammation, urinary symptoms

Introduction

Prostate cancer (PC) refers to the malignant transformation of prostate tissue cells to produce cancer cells. It is a more familiar malignancy in the male reproductive system, with an insidious onset and a high prevalence in older men. It ranks as the second most common male tumor in China [1, 2]. The common age of onset of PC patients in China is over 50 years old. The number of onsets increases with age. PC threatens the life and health of elderly men in China [3]. PC patients are prone to lower urinary symptoms such as straining to urinate, thinning of the urine line, frequent urination, increased nocturia, and incomplete urination. These are the most common clinical manifestations [4]. In severe cases, acute urinary retention, hematuria, and urinary incontinence can occur, causing a great negative impact on the patient's physical and mental health and quality of life [5].

It was found that PC treated with surgical debulking can effectively slow down the progression of the disease with androgen reduction and the appearance of apoptosis. This has been shown to be a proven treatment [6].

Androgens are not completely removed after surgery. The body's adrenal tissue can secrete androgens. Most patients can eventually enter the worse prognosis of the desmoresistant stage. This is the development of castration-resistant prostate cancer (CRPC) [7]. At this time, the tumor enters a rapidly progressive stage, and the patient's quality of life and psychological state are negatively affected [8]. Traditional Chinese medicine has accumulated numerous clinical practice experience and achieved certain efficacy in tumor treatment. Its value and significance in treating PC has been increasingly appreciated. The related mechanism actions are in the active exploration stage [9, 10]. Bushen Huoxue Decoction (BSHXD) is frequently used in the treatment of osteoporosis, endocrine disorders, lumbar disc herniation, uterine adhesions, and diabetic nephropathy, showing good results [11]. Moxibustion is a traditional Chinese medicine specialty that can prevent and treat the adverse effects of chemotherapy by warming the meridians [12]. There are no studies on the combination of the two approaches having an improved effect on PC patients with lower urinary symptoms.

The aim of this study was to assess the improvement of inflammation and urinary symptoms and survival of PC patients treated with BSHXD combined with moxibustion, and to provide reference for clinical treatment plans.

Methods and materials

Clinical data

A total of 87 patients with PC admitted to the Hebei Provincial Hospital of Traditional Chinese Medicine from August 2019 to December 2021 were collected for a retrospective study. There were 42 patients treated with conventional treatment regimens who were regarded as the control group (CG). The remaining 45 with BSHXD and moxibustion were considered the experimental group (EG). The study was conducted with the approval of the Hebei Provincial Hospital of Traditional Chinese Medicine ethics committee (Ethical lot number: HBZY2021-KY-017).

Inclusion and exclusion criteria

Inclusion criteria: ① Patients who complied with the EAU Guidelines on the Assessment of Non-neurogenic Male Lower Urinary Tract Symptoms including Benign Prostatic Obstruction [13]; ② Patients who met the diagnostic criteria for PC [14]; ③ Patients who had a good tolerance of the diagnosis and treatments, and good compliance during the examinations; ④ Patients or their family members signed an informed consent form; ⑤ Patients who had no other treatments prior to this study.

Exclusion criteria: ① Those who were suffering from severe cardiovascular diseases, with a high risk of cardiovascular accidents assessed preoperatively; ② Those who had severe liver or kidney diseases, or dysfunctions of electrolyte; ③ Those who had severe mental system disorders that do not allow effective cooperation with physicians; ④ Those who had severe coagulation disorders; ⑤ Those who had rectal lesions; ⑥ Those who underwent recent prostate puncture biopsy or endocrine therapy; ⑦ Those who had a history of prostate electrosurgery.

Treatment options

The treatment protocol for patients in the CG was as follows: The healthcare workers conducted health education to encourage patients to drink more water and avoid strong tea or coffee. Patients were encouraged to eat fruits and an easy-to-digest, nutrient-rich diet. Patients were encouraged to avoid cold, greasy, or spicy food. Healthcare workers were to encourage patients to participate in strengthening pelvic floor muscle exercises. Goserelin Acetate Sustained-Release Depot (manufactured by AstraZeneca UK Limited, SFDA Approval No. J20160052) was subcutaneously injected into the anterior abdominal wall, 1 piece/dose, every 28 days. Bicalutamide tablets (manufactured by CORDEN PHARMA GMBH, SFDA Approval No. J20150050) were taken orally, 1 tablet/dose, once daily. The treatment course was 8 weeks.

The treatment protocol for patients in the EG was as follows: The EG was treated with BSHXD + moxibustion. BSHXD consisted of Danshen 10 g, Zeilan 10 g, Safflower 10 g, Red Peony 10 g, frankincense 10 g, Cinnamon 3 g, Radix Rehmanniae 15 g, Cornus officinalis 10 g, Yam 15 g, radix achyranthis bidentatae 15 g, and Astragalus membranaceus 15 g. It was decocted in water for oral dose, 1 dose/d, 3 times/d, for 8 weeks. Moxibustion was performed on Shen Que, Guan Yuan, Qi Hai, and Shenshu Yu (double). The patient first laid in a supine position to expose the local skin. After the moxibus-

Table 1. PSA assessment criteria

Efficacy level	Assessment criteria
Complete remission	Serum PSA decreases to the normal range, i.e., below 4 ng/ml.
Partial remission	Serum PSA decreases to less than 50% of the pre-chemotherapy baseline level.
Stable disease	Serum PSA decreases less than 50% of the baseline level or increases less than 25% of the pre-chemotherapy baseline level.
Progressive disease	Serum PSA elevates above 25% of pre-chemotherapy baseline level.

Note: All indicators were sustained for more than 4 weeks. PSA: Prostate-Specific Antigen.

tion was completed, the patient adjusted to a prone position. After the moxa strips were ignited, moxibustion was carried out at the acupoint 2: 3 cm away from the skin. It was advisable to use local warmth without burning pain, and moxibustion at each acupoint for 5 to 10 min, taking the skin flush as the degree. The above steps were repeated for all acupuncture points in sequence. Moxibustion was applied once every other day for a total of 8 weeks.

European organization for research and treatment of cancer core quality of life questionnaire (EORTC QLQ) [15]

The EORTC QLQ-PR55 scale developed by the European Organization for Research and Treatment of Cancer was used. The scale combined the Chinese version of the Quality-of-Life Core Scale LQ-C30 (V3.0) and the Prostate Cancer Quality of Life Specific Scale QLQ-PR25. The QLQ-C30 (V3.0) was divided into 15 subscales with a total of 30 entries. The QLQ-PR25 was divided into 4 domains with a total of 25 entries. The raw scores for each of the QLQ-C30 (V3.0) and QLQ-PR25 were converted into scores from 0 to 100 points by a linear formula. Higher scores on the total health and functioning subscales indicated a better quality of life.

Enzyme linked immunosorbent assay (Elisa)

Peripheral blood was collected from patients before and after the treatment and centrifuged at 1500 rpm for 10 min to obtain serum. The levels of interleukin-6 (IL-6) (PI330) and tumor necrosis factor α (TNF)-α (PT518) in the serum of patients were tested by Elisa kits provided by Shanghai Beyotime Biotechnology.

International prostate symptom score (IPSS) [16]

Changes in urinary symptoms before and after the treatment were assessed in patients through the IPSS. It included a total of 7 symptom score entries in the total symptom score of the storage phase (difficulty in holding urine, nocturia) and the score of the voiding phase (feeling of incomplete urination, intermittent urination, frequency, several starts and interruptions of urination, and thinning of the urine line). Each item was added to the total symptom score, with 0-7 points being mild, 8-19 points being moderate, and 20-35 points being severe.

Outcome measures

Main outcome measures: The clinical efficacy of both groups of patients after the treatment was compared. The assessment criteria is shown in **Table 1**. The total response rate was calculated: total response rate = (complete remission + partial remission)/total number of patients × 100%. IPSS changes before and after the treatment was assessed. The quality of life of patients was compared through the EORTC QLQ-PR55 scale. The maximum urine flow rate before and after the treatment was measured using a Labree (UROCAP-III) urine flow rate meter. The residual urine volume of the patients before and after the treatment was tested using a Meike bladder scanner (PBSV4.1).

Secondary outcome measures: The changes in serum levels of IL-6 and TNF-α in both groups before and after the treatment was compared. The time to develop CRPC after the treatment was counted in both groups and the risk factors were analyzed. The differences in clinical data between both groups of patients were assessed.

Statistical methods

The collected data were statistically analyzed through SPSS 20.0 (SPSS Ltd., Chicago, USA) medical statistical analysis software. Pictures

Table 2. Analysis of clinical data

Factors	Control group (n=42)	Experiment group (n=45)	t/X^2 value	*P* value
Age (years)	60.57±11.42	60.46±10.48	0.044	0.964
BMI (kg/m^2)	20.96±2.05	21.66±1.99	1.617	0.109
Occupation (manual/non-manual)	20/22	25/20	0.548	0.459
Education (≥ high school/< high school)	30/12	37/8	1.430	0.232
History of hypertension (yes/no)	12/30	17/38	0.828	0.362
History of diabetes (yes/no)	19/23	25/20	0.925	0.336
T stage (T1 + T2/T3 + T4)	26/16	25/20	0.361	0.547
Lymph node metastasis (transferred/not transferred)	15/27	15/30	0.054	0.815
Gleason score (≤6/7/≥8)	15/18/9	17/20/8	0.185	0.911
Pre-treatment PSA level (μg/L)	66.27±33.95	66.06±34.83	0.028	0.977

BMI: Body Mass Index.

Table 3. Efficacy assessment

Groups	Complete remission	Partial remission	Stable disease	Progressive disease	Overall response rate
Control group (n=42)	20 (47.61)	10 (23.80)	10 (23.80)	2 (4.79)	30 (71.43)
Experiment group (n=45)	23 (51.11)	11 (24.44)	8 (17.78)	3 (6.67)	34 (75.56)
X^2 values					0.190
P value					0.662

were drawn by the GraphPad Prism 8 (GraphPad Software Co., San Diego, USA). The counting data were expressed as rate (%) and assessed using the Chi-square test, marked by X^2. The measured data were represented as mean ± standard deviation (mean ± SD) and compared using the independent samples t-test for inter-group comparisons. The paired t-test was used for intra-group comparisons. The rank-sum test was used for ranked data. Risk factors for the development of CRPC in the patients were assessed using logistics regression. The Receiver Operating Characteristic (ROC) Curve was conducted to predict indicators of CRPC. P<0.05 was considered statistically significant.

Results

Comparison of clinical data

Clinical data between both groups revealed no statistical differences in age, body mass index, occupation, education, history of hypertension, history of diabetes, T stage, lymph node metastasis, Gleason score, and pre-treatment prostate-specific antigen (PSA) level (P>0.05, **Table 2**).

Clinical efficacy assessment

The clinical efficacy of patients revealed that there was no statistical difference in the total response rate after the treatment (P>0.05, **Table 3**).

Changes in prostate symptoms and quality of life before and after the treatment

We compared the changes in prostate symptoms and quality of life before and after the treatment in both groups of patients. We found that the QLQ-C30 scores increased in both groups after the treatment compared to before the treatment, but the QLQ-PR25 and IPSS scores decreased (P<0.05). Another analysis revealed that the QLQ-C30 score was higher, but the QLQ-PR25 and IPSS scores were lower after the treatment in the EG than those in the CG (P<0.01, **Figure 1**).

Changes in maximum urinary flow rate and residual urine volume before and after the treatment

In this study, we compared the changes in the maximum urinary flow rate and the residual

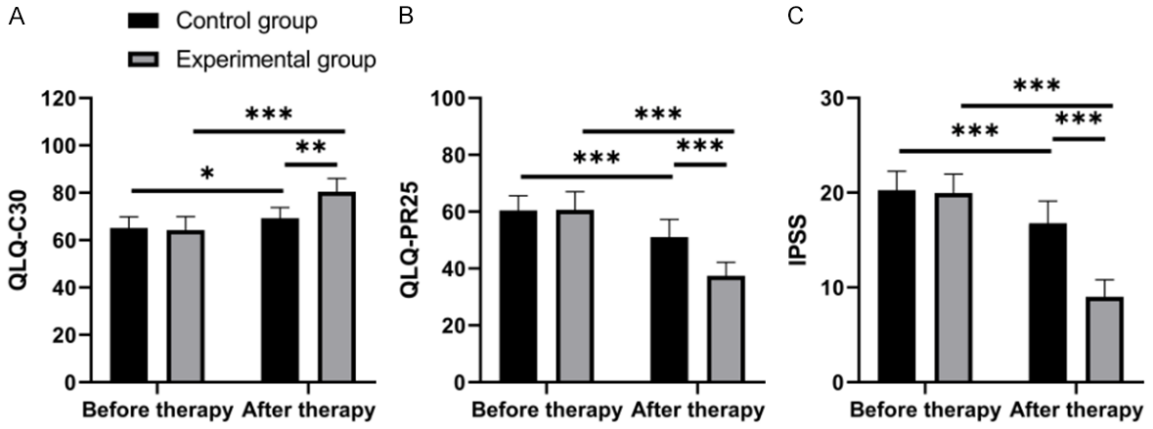

Figure 1. Changes in prostate symptoms and quality of life before and after treatment. A. Changes in QLQ-C30 scores before and after treatment. B. Changes in QLQ-PR25 scores before and after treatment. C. Changes in IPSS scores before and after treatment. Note: *P<0.05, **P<0.01, ***P<0.001, QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-PR25: Quality of Life Prostate Cancer-specific Module; IPSS: International Prostate Symptom Score.

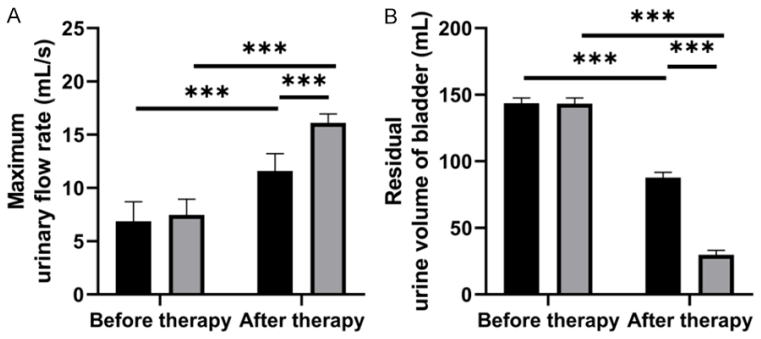

Figure 2. Changes in maximum urinary flow rate and residual urine volume before and after treatment. A. Changes in maximum urinary flow rate of patients before and after treatment. B. Changes in residual urine volume of patients before and after treatment. Note: ***P<0.001.

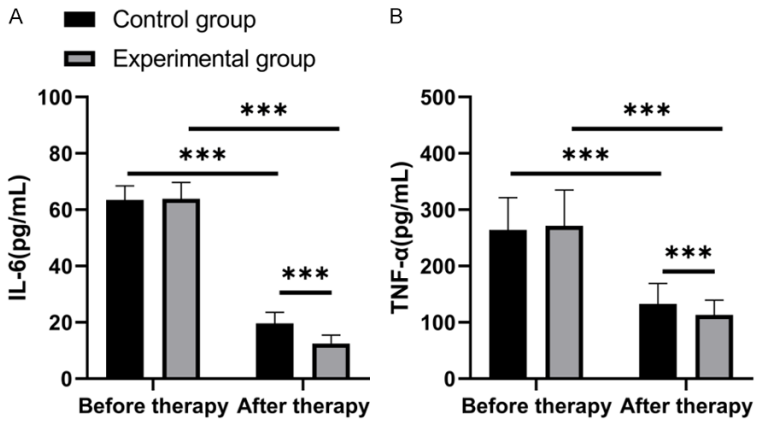

Figure 3. Changes in IL-6 and TNF-α in patients before and after treatment. A. Changes in IL-6 in patients before and after treatment. B. Changes in TNF-α in patients before and after treatment. Note: ***P<0.001, interleukin-6 (IL-6) and tumor necrosis factor α (TNF)-α.

urine volume before and after the treatment in both groups of patients. We found that the maximum urinary flow rate increased, and the residual urine volume decreased after the treatment, compared with those before the treatment in both groups (P<0.001). Another analysis revealed that the maximum urinary flow rate was higher, and that the residual urine volume was lower after the treatment in the EG than those in the CG (P<0.001, **Figure 2**).

Changes in inflammatory factor levels before and after the treatment

We compared the changes of IL-6 and TNF-α before and after the treatment in both groups of patients. We discovered that IL-6 and TNF-α were lower in both groups after the treatment compared with those before the treatment (P<0.001). Another analysis denoted that IL-6 and TNF-α were lower in the EG than in the CG after the treatment (P<0.001, **Figure 3**).

Table 4. Single-factor analysis

Factor	Occurrence group (n=32)	Non-occurrence group (n=55)	t/X^2 value	*P* value
Age (year)	61.59±12.10	59.89±10.17	0.701	0.484
BMI (kg/m^2)	21.20±2.03	21.40±2.06	0.417	0.677
Occupation (manual/non-manual)	15/17	30/25	0.476	0.489
Education (≥ high school/< high school)	25/7	42/13	0.035	0.850
History of hypertension (yes/no)	9/23	20/35	0.617	0.431
History of diabetes (yes/no)	19/13	27/28	0.858	0.354
T stage (T1 + T2/T3 + T4)	12/20	39/16	9.309	0.002
Lymph node metastasis (transferred/not transferred)	17/15	13/42	7.787	0.0015
Gleason score (≤6/7/≥8)	8/12/12	24/26/5	10.712	0.004
Pre-treatment PSA level (μg/L)	90.53±29.61	51.98±28.35	6.016	0.001
Treatment protocol (control/experimental)	18/14	24/31	1.289	0.256

BMI: Body Mass Index; PSA: Prostate-Specific Antigen.

Table 5. Assignment table

Factor	Assignment
T stage	T1 + T2=0, T3 + T4=1
Lymph node metastasis	Not transferred =0, transferred =1
Gleason score	≤6=0, 7=1, ≥8=0
Pre-treatment PSA level (μg/L)	≥77.88=1, <77.88=0
CRPC	Occurrence group =1, Non-occurrence group =0

PSA: Prostate-Specific Antigen; CRPC: Castration-Resistant Prostate Cancer.

Table 6. Multi-factor analysis

Factor	β	SE	X^2	*P* value	HR	95% CI	
						Lower limit	Upper limit
T stage	-0.929	0.606	2.348	0.125	0.395	0.12	1.296
Lymph node metastasis	1.085	0.602	3.251	0.071	2.959	0.91	9.624
Gleason scores	1.243	0.441	7.946	0.005	3.467	1.461	8.229
Pre-treatment PSA levels	2.723	0.624	19.021	<0.001	15.22	4.478	51.737

PSA: Prostate-Specific Antigen.

CRPC risk factor analysis

By June 2022, we queried patients' electronic medical records and outpatient review records and found that 37 of 87 patients had CRPC. The patients were divided into an occurrence group (n=32) and a non-occurrence group (n=55) according to the occurrence of CRPC after the treatment. The patients' clinical data were collected for univariate analysis. T-stage, lymph node metastasis, Gleason score, and pre-treatment PSA level were found to be risk factors for CRPC development (P<0.01, **Table 4**). We assigned the data (**Table 5**) and used multivariate regression analysis to find that the Gleason score and pre-treatment PSA level were independent risk factors for CRPC development (P<0.01, **Table 6**). We plotted the ROC curves for predicting CRPC based on the indicators of the patients. The area under the curve for Gleason score and pre-treatment PSA level were 0.665 and 0.827, respectively, and 0.935 for the combination (**Figure 4**; **Table 7**).

Discussion

"Bushen" in BSHXD means tonifying kidney, and "Huoxue" means promoting blood circulation. BSHXD is a general term for a series of Chinese herbal formulas that have the effect of

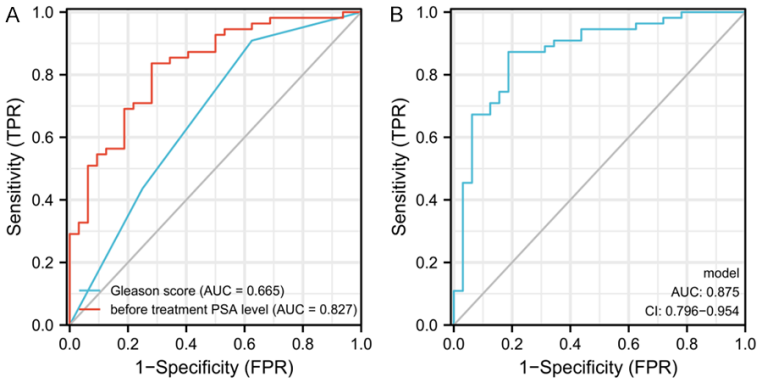

Figure 4. Area under the curve of predictors of CRPC. A. Gleason score and pre-treatment PSA levels for predicting the occurrence of CRPC in patients. B. The combination of Gleason score and pre-treatment PSA levels for predicting the occurrence of CRPC in patients. PSA: Prostate-Specific Antigen; CRPC: Castration-Resistant Prostate Cancer.

Table 7. Receiver operating characteristic parameters

Predictive variables	Gleason score	before treatment PSA level	Combined
Sensitivity	0.909	0.836	0.836
Specificity	0.375	0.719	0.906
Youden index	0.284	0.555	0.743
Area under curve	0.665	0.827	0.910
Confidence interval	0.550-0.780	0.738-0.915	0.847-0.974

tonifying the kidney and invigorating the blood [17]. Recent research has found that BSHXD promotes the proliferation of metaphase stromal cells in unexplained recurrent miscarriages through the PI3K/AKT pathway [18]. Another research showed that BSHXD ameliorated cognitive decline in rats with cerebral hypoperfusion [19]. Moxibustion is a treatment like acupuncture, but involves the use of heat to stimulate acupuncture points. Recent studies reported that moxibustion was effective in the treatment of post-stroke urinary incontinence, stress urinary incontinence, and overactive bladder disorder. It was also effective in the prevention of prolapse and difficult urination after hemorrhoid surgery [20]. Traditional Chinese medicine believes that PC patients accompanied by lower urinary symptoms are suffering from Qi and Blood deficiency and Spleen and Kidney Yang deficiency. BSHXD with moxibustion has the effect of invigorating blood stasis, unblocking the meridians, strengthening the spleen, and tonifying the kidneys [21, 22]. There are no studies on whether the combination of the two can improve the condition of PC patients with lower urinary symptoms. In the current study, we found that BSHXD combined with moxibustion did not enhance patient outcomes during the treatment. This suggested that BSHXD combined with moxibustion does not have an efficacy on PC.

In China, the incidence of moderate to severe lower urinary symptoms is as high as 93.2% in PC patients, including locally progressive and distant metastatic PC [23]. The etiology of lower urinary symptoms due to PC is unclear. It can be related to tumor invasion of the prostatic urethra, bladder, neurovascular bundle, or to fibrosis of the bladder neck, and overactivity of the detrusor muscle [24, 25]. Research has found that severe lower urinary symptoms have many adverse effects on both quality of life and treatment, but there are no guidelines for the treatment of PC combined with lower urinary symptoms [26]. The Chinese version of the EORTC QLQ-PR55 is the main scale for assessing the quality of life in Chinese PC patients, with good reliability, validity, and responsiveness [27]. The IPSS score is an essential scale used to assess the severity of lower urinary symptoms in patients with prostatic hyperplasia. The higher scores indicated more severe lower urinary symptoms [28]. In the present study, we found that IL-6, TNF-α, residual urine volume, IPSS score, and QLQ-PR25 score were much lower. The maximum urine flow rate and QLQ-C30 score were much higher in the EG after the treatment. He et al. [29] found effective relief of lower urinary symptoms, increased the maximum urinary flow rate, reduced the urine volume, and decreased the IPSS scores by treprostinil in patients with advanced PC. Another study [30] found that IL-6 and TNF-α levels were suppressed in patients with cancer weakness after the treatment by moxibustion. BSHXD and moxibustion were both effective in improving the patients' lower urinary symp-

toms, quality of life, and inflammation *in vivo*. Kidney tonics improve blood rheology, inhibit platelet aggregation, and enhance hematopoiesis. Promoting blood circulation improves kidney function, inhibits kidney thrombosis, and preserves potassium and diuresis. The remedy contains Dihuang (a kidney tonic). Dihuang polysaccharide, the main chemical component of Dihuang, improves the hematopoietic function, especially on white blood cells and platelets. Cornus officinalis (blood invigorating herb) can tonify the kidneys and has a blood invigorating effect. It was found that the Cornus officinalis injection dramatically inhibited platelet aggregation in a dose dependent manner. Moxibustion has analgesic, anti-inflammatory, and immunomodulatory effects. It can improve the body's immune capacity and resistance to disease. This suggested that the combination effectively inhibits the inflammation in patients, improves their lower urinary symptoms, and enhances their quality of life.

We analyzed the risk factors affecting the development of CRPC. The lymph node metastasis, Gleason score, and pretreatment PSA levels were found to be risk factors for CRPC. The Gleason scoring system is considered an important prognostic indicator for PC. A study on the correlation between survival time and the Gleason score of patients found that this scoring system measured the degree of tissue differentiation of PC and had a strong correlation with their prognosis [31]. PSA is highly organ-specific, representing tumor load and tumor sensitivity to androgens. Its elevated PSA levels in PC patients after minimization of endocrine therapy are a crucial indication of progression to CRPC [32]. Early screening of high-risk patients and development of individualized treatment strategies are important to guide the treatment of PC. We found that the Gleason score combined with preoperative PSA level had high clinical value in predicting CRPC in patients by ROC curve analysis.

The present study had some limitations. As a retrospective study, we had limited access to the number of patients presenting with CRPC and were unable to follow them over time as in a prospective study. The sample size was small. It was not guaranteed that the sample was homogeneous in all randomized controlled studies. This can cause bias in the results. We did not build a prediction model and validate it. We will carry out a prospective study and build predictive models to refine our findings.

In conclusion, BSHXD combined with moxibustion had good therapeutic efficacy in PC patients. It improved patients' urinary symptoms and inflammation levels with a low incidence of adverse effects.

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Disclosure of conflict of interest

None.

Address correspondence to: Yan Zhou and Yongzhang Li, Department of Urology, Hebei Provincial Hospital of Traditional Chinese Medicine, No. 389, Zhongshan East Road, Shijiazhuang 050011, Hebei, China. E-mail: hbszzhouyanyan@163.com (YZ); hbszliyongzhang@163.com (YZL)

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