ORIGINAL RESEARCH

Risk factors for infectious complications following transrectal ultrasound-guided prostate biopsy

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Objective: To explore risk factors of infectious complications following transrectal ultrasound-guided prostate biopsy (TRUSPB).

Methods: We retrospectively analyzed 1,203 patients with suspected prostate cancer who underwent TRUSPB at our center between December 2012 and December 2016. Demographics, clinical characteristics, and data regarding complications were collected, and then univariate and multivariate logistic regression analyses were used to identify independent risk factors for infectious complications after prostate biopsy.

Results: Multivariate logistic analysis demonstrated that body mass index (BMI) (OR=2.339, 95% CI 2.029–2.697, $P<0.001$), history of diabetes (OR=2.203, 95% CI 1.090–4.455, $P=0.028$), and preoperative catheterization (OR=2.303, 95% CI 1.119–4.737, $P=0.023$) were risk factors for infection after prostate biopsy. The area under the receiver operating characteristics curve for infectious complications was 0.930 (95% CI 0.907–0.953, $P<0.001$). BMI=28.196 kg/m^2 was the best cut-off threshold for predicting infection after TRUSPB.

Conclusion: BMI >28.196 kg/m^2, history of diabetes, and preoperative catheterization are independent risk factors for infection after prostate biopsy.

Keywords: body mass index, diabetes mellitus, preoperative catheterization, infectious complications, transrectal ultrasound-guided prostate biopsy

Introduction

Prostate cancer remains the second leading cause of cancer-related death for American men.[1] Prostate cancer incidence rates are rising yearly; in China, >100,000 new patients are diagnosed with prostate cancer annually,[2] making it the seventh most common cancer in 2011 and an important healthcare issue. It has been reported that prostate cancer incidence rates increased nearly 6-fold between 1973 and 2009 in eastern China (from 2.12/100,000 to 12.96/100,000). In addition, the disease-specific mortality of prostate cancer has increased more than 3-fold. However, few studies have focused on infections after prostate biopsy in Chinese men.

Currently, transrectal ultrasound-guided prostate biopsy (TRUSPB) is the gold standard for obtaining pathological specimens to diagnose prostate cancer;[3] however, complications following TRUSPB vary widely and include hematuria, hematospermia, infection, pain, rectal bleeding, urinary retention, lower urinary tract symptoms, erectile dysfunction, and mortality.[4] It has been reported that minor complications such as bleeding and pain are frequent,[5] but worryingly, infectious complications that may lead to death have increased over time.[6,7] Infectious complications after

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TRUSPB are reported in up to 6% of patients,[6–8] and a previous study showed that the hospitalization rate of patients who developed infectious complications ranges from 0% to 6.3%.[4] Chiang et al[9] studied 3,694 Chinese prostate cancer patients and revealed that the rate of complications after prostate biopsy was 1.98%. A retrospective study[10] from China that included 1,130 patients who underwent prostate biopsy demonstrated that the overall infectious complications rate was 4.25% after prostate biopsy. These infectious complications included 26 (2.30%) cases of urinary tract infection, 22 (1.95%) cases of fever, but no cases of sepsis. A 10-year single-center study[11] in southern China that included 1,526 patients who underwent prostate biopsy revealed that the percentage of patients who developed febrile infection was 2.2%.

The use of prophylactic antibiotics plays an important role in reducing complications following prostate biopsy. However, drug choice and treatment course are variable in different Chinese hospitals.[12] Qiao et al[12] studied a Chinese population and reported that 500 mg oral levofloxacin once daily for 3 days could prevent infections after prostate biopsy. Notwithstanding, quinolones remain the most active agent against the bacteria in prostate and feces, and are commonly used to treat urinary tract infections.[9] An 8-year single-center study reported that levofloxacin remained effective and was superior to pipemidic acid-based prophylactic antibiotics. Wang et al[13] demonstrated that quinolones can be used postoperatively as routine antibiotics, and also revealed that carbapenems or teicoplanin can be used for patients with sepsis.

The risk factors for infectious complications after TRUSPB remain controversial. Several studies have demonstrated that recent hospitalization (<1 month prior to TRUSPB), comorbidities (particularly diabetes), history of urinary infections, history of antibiotic use, and year of biopsy were significantly associated with rates of infectious complications after TRUSPB.[8,14,15] This retrospective study aimed to more precisely explore risk factors of infectious complications following TRUSPB.

Methods
Patients
This study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University (Fuzhou, China). All patients signed informed consent forms. We retrospectively analyzed 1,252 patients with suspected prostate cancer between December 2012 and December 2016 at the First Affiliated Hospital of Fujian Medical University. We excluded 49 patients who did not meet the inclusion criteria,

and the remaining 1,203 patients who underwent TRUSPB formed the study cohort. All patients underwent digital rectal examination, serum prostate-specific antigen (PSA) testing, Doppler ultrasonography, and MRI.

Indications for TRUSPB were patients with a suspicious finding on digital rectal examination, Doppler ultrasonography, and/or MRI,[16] as well as a PSA >10 ng/mL.[17] Patients with PSA 4–10 ng/mL, a free/total PSA ratio of <0.16,[17] or PSA density >0.15 ng/mL/mL[18] were also included. However, 17 patients with blood coagulation disorders and coagulation function that could not be corrected, 13 patients with alteration of the urinary tract due to infection within 1 month of TRUSPB, five patients with severe organ dysfunction, eight patients with acute prostatitis, and six patients with anal stenosis were excluded from the study.

The definition of febrile urinary tract infections was as follows: fever (≥38.3°C), leukocytes in urine sediment, and tenderness of the prostate during digital rectal examination.[19,20] Fever was defined as body temperature ≥38.3°C, and infectious complications were defined as body temperature ≥38.3°C accompanied by urinary tract infection symptoms.[19,20] Urinary tract infection symptoms were defined as the presence of chilliness, frequency, urgency, and dysuria. Sepsis was defined as the presence of clinically or microbiologically documented infection in conjunction with systemic inflammatory response syndrome.[11,19,20]

TRUSPB
A pre-biopsy enema using glycerin or saline solution was performed 1 hour before the procedure. Patients were instructed to take 200 mg ciprofloxacin 1 hour before TRUSPB, and then 250 mg ciprofloxacin every 12 hours after TRUSPB.[21] All TRUSPB procedures were performed by the same senior urologist under the guidance of color Doppler ultrasonography (Acuson Aspen; Siemens, Erlangen, Germany) with an 18-gage biopsy gun (Max-Core; BARD, Covington, GA, USA). All patients were placed in the left lateral decubitus position with knees and hips flexed and underwent a 12-core biopsy protocol, including six parasagittally and six laterally targeted cores covering the base, mid-zones, and apex.[21]

Statistical analysis
All data were analyzed using SPSS version 18.0 software (SPSS, Chicago, IL, USA). Numerical data that were normally distributed are represented as mean ± SD. Non-parametric numerical data are expressed as median (range) and were analyzed using the Kruskal–Wallis test. Categorical data were analyzed by Pearson's chi-squared test and

Fisher's test. Univariate and multivariate logistic regression analyses were used to determine risk factors for infectious complications. Receiver operating characteristics (ROC) curves were used to evaluate the diagnostic accuracy of the BMI for infection after prostate biopsy. The Youden index (J), defined as the maximum vertical distance between the ROC curve and the diagonal line, serves as another global measure of overall diagnostic accuracy and can be used to choose the optimal cut-off point.[22] The Youden index (J) was calculated using the following formula[23]: J=(sensitivity + specificity)−1. The highest value of J was assumed to be the best cut-off point. Thus, the Youden index was used to determine the cut-off threshold for infectious complications. $P<0.05$ was considered significant for all tests.

Results

In total, 1,203 patients were enrolled in this study after 49 were excluded. The overall complications after prostate biopsy are shown in Table 1. Infectious symptoms were observed within 1 week of prostate biopsy in 99 patients. Patients who developed fever[20] (≥38.3°C) after prostate biopsy were hospitalized and treated with third-generation cephalosporins or quinolones. The eight patients who developed sepsis were treated with carbapenem and teicoplanin. Blood and urine cultures showed that the pathogen was *Escherichia coli* (E. coli). There were no mortalities.

Patients were then divided into two groups: the infection group (99 patients) and the non-infection group (1,104 patients). Univariate analysis demonstrated that there was no significant relationship between the two groups in terms of age, hypertension, cerebrovascular accident, anticoagulant agents, secondary biopsy, history of transurethral resection of the prostate, pre-biopsy total PSA, prostate volume, core biopsy volume, or pathology. However, there were significant differences between the two arms in terms of BMI, history of

Table 1 Overview of complications following prostate biopsy

Variable	Cases, n (%)
Infectious complications	99 (8.23)
Febrile urinary tract infection	60 (4.99)
Fever	7 (0.58)
Epididymitis	12 (1.00)
Prostatitis	14 (1.16)
Septicemia	8 (0.67)
Hemorrhagic complications	189 (15.71)
Hematuria	154 (12.80)
Hematospermia	21 (1.75)
Rectal hemorrhage	14 (1.16)
Urinary retention	16 (1.33)
Pain	19 (1.58)

diabetes, chronic prostatitis, preoperative catheterization, and history of urinary infection ($P<0.05$) (Table 2). Multivariate logistic regression analysis demonstrated that BMI, history of diabetes, and preoperative catheterization were risk factors for infection after TRUSPB (Table 3). The area under the ROC curve for infectious complications was 0.930 (95% CI 0.907–0.953, $P<0.001$). BMI=28.196 kg/m^2 was the best cut-off threshold for predicting infection after TRUSPB.

Among the 99 patients with infections after prostate biopsy, 98 had blood cultures and 99 had urine cultures. These results demonstrated that 48 patients had positive blood cultures and 61 had positive urine cultures. Among the 109 positive cultures (blood or urine), *E. coli* was the most frequent pathogen (n=98, 89.9%), followed by *Klebsiella* (n=8, 7.34%), and *Bacteroides fragilis* (n=3, 2.75%). Quinolone resistance was observed in 72 (66.06%) cultures (Table 4).

Discussion

While complications following TRUSPB are common, infectious complications are some of the most severe that face this patient population.[4] Mortality after TRUSPB is extremely rare, and most reported deaths are caused by septic shock.[24] Batura and Gopal Rao[25] reported that ~2.15%–3.6% of patients who underwent TRUSPB in England and Wales were readmitted with infectious complications. Simsir et al[26] showed that there was a 3.06% chance of sepsis after TRUSPB, while Wagenlehner et al[27] reported that 3.5% of patients had febrile urinary infections and 3.1% required hospitalization after TRUSPB. Carignan et al[8] reported that chronic obstructive pulmonary disease, diabetes, and recent hospitalization were risk factors for infectious complications, while Simsir et al[26] reported that diabetes, benign prostatic hyperplasia, the presence of a catheter, more biopsy cores, and repeat biopsies were also associated with infectious complications after TRUSPB.

To the best of our knowledge, most studies investigating infections after prostate biopsy have been based on patients from North America and Europe.[28,29] The genetic and physiological characteristics of Chinese men are significantly different from those of Western populations; however, studies pertinent to Chinese patients are lacking.[11] Chiang et al[9] studied a total of 3,694 Chinese patients and revealed that the rate of complications after prostate biopsy was 1.98%. A retrospective study[10] from China including 1,130 patients who underwent prostate biopsy demonstrated that the overall infectious complications rate was 4.25% after prostate biopsy. These infectious complications included 26 (2.30%) cases of urinary tract infection, 22 (1.95%) cases of fever, and

Table 2 Patient characteristics between the infection and non-infection groups

Variable	Total	Infection group	Non-infection group	*P*-value
Cases, n	1,203	99	1,104	
Age (years)	66 (43–88)	68 (43–88)	66 (43–88)	0.263
BMI (kg/m²), mean ± SD	24.06±2.61	30.97±2.65	25.74±2.48	<0.001*
Diabetes, n (%)	166 (13.80)	23 (23.23)	143 (12.95)	0.004*
Hypertension, n (%)	153 (12.72)	14 (14.14)	139 (12.59)	0.657
Cerebrovascular accident, n (%)	102 (8.48)	10 (10.10)	92 (8.33)	0.545
Chronic prostatitis, n (%)	164 (13.63)	20 (20.20)	144 (13.04)	0.047*
Anticoagulant agents, n (%)	115 (9.56)	7 (11.11)	104 (9.42)	0.584
Preoperative catheterization, n (%)	172 (14.30)	23 (23.23)	149 (13.49)	0.008*
History of urinary infection, n (%)	352 (29.26)	38 (38.38)	319 (28.89)	0.048*
Secondary biopsy, n (%)	212 (17.62)	16 (16.16)	196 (17.75)	0.690
History of TURP, n (%)	60 (4.98)	6 (6.06)	54 (4.89)	0.627
t-PSA (ng/mL), mean ± SD	17.74±8.24	18.86±8.45	17.64±8.22	0.158
Prostate volume (mL), mean ± SD	52.30±13.85	53.63±15.49	52.18±13.69	0.316
Prostate volume >45 mL, n	851	68	783	0.639
Pathologically confirmed malignancy, n (%)	623 (51.79)	54 (54.55)	569 (51.54)	0.566

Note: *$P<0.05$.
Abbreviations: BMI, body mass index; TURP, transurethral radical prostatectomy; t-PSA, total prostate-specific antigen.

Table 3 Multivariate logistic regression analysis of risk factors for infection after prostate biopsy (n=1203)

Variable	OR (95% CI)	*P*-value
BMI	2.339 (2.029–2.697)	<0.001*
History of diabetes	2.203 (1.090–4.455)	0.028*
Chronic prostatitis	1.405 (0.665–2.968)	0.373
Preoperative catheterization	2.303 (1.119–4.737)	0.023*
History of urinary infection	1.653 (0.921–2.967)	0.092

Note: *$P<0.05$.
Abbreviation: BMI, body mas index.

Table 4 Antibiotic susceptibility in patients who underwent blood or urine cultures

Antibiotic	Sensitive, n (%)	Medium, n (%)	Resistant, n (%)
Amikacin	74	6	0
Ampicillin	66	10	4
Piperacillin/tazobactam	62	12	6
Cefoperazone	76	2	2
Gentamycin	54	24	2
Ciprofloxacin	21	6	62
Levofloxacin	20	7	72
Imipenem	76	4	0
Sulfamethoxazole	70	8	2
Vancomycin	78	2	0
Aztreonam	78	2	0
Nitrofurantoin	78	1	1

no cases of sepsis. A 10-year single-center study[11] in South China including 1,526 patients who underwent prostate biopsy revealed that the percentage of patients who developed febrile infection was 2.2%.

In this study, the rate of infectious complications following TRUSPB was 8.23% (99/1,203). Febrile urinary tract infections were the most common symptom in patients with infections (n=60), followed by prostatitis (n=14), fever (n=7), and severe sepsis (n=8). The risk factors for infectious complications and effective preventive strategies for dealing with infectious complications after TRUSPB were identified. Multivariate logistic regression analysis demonstrated that BMI, history of diabetes, and preoperative catheterization increased the risk of infection after prostate biopsy.

Our multivariate logistic regression analysis demonstrated that elevated BMI increased the risk of infectious complications after TRUSPB. Choi et al[19] reported that 3.3% (39/1,195) of patients developed febrile urinary tract infections, and that BMI >25 kg/m² was associated with this complication

in univariate analysis. After adjusting for core number in the multivariate analysis, BMI >25 kg/m² was still significantly correlated with febrile urinary tract infections in their study. Semins et al[30] also reported that obese patients were more likely to be vulnerable to infection, as the obese were nearly five times more likely to be diagnosed with pyelonephritis than those with a BMI in the normal range. Wu et al[11] reported that obesity (BMI >28 kg/m²) was an independent risk factor for post-biopsy infection (OR=3.383, 95% CI 1.327–8.626). In this study, we found that elevated BMI increased the risk of infectious complications after TRUSPB in Chinese patients (OR=2.339, 95% CI 2.029–2.697).

Although elevated BMI has been correlated as an increased risk factor for surgical infections in several surgical settings,[31,32] the mechanisms whereby obesity contributes to

increased infectious complications during prostate biopsy remain unknown. Diabetes is a known risk factor for infectious complications, and diabetic patients often present with an elevated BMI. Thus, diabetes may be treated as a confounder when determining the effects of obesity on infectious complications after TRUSPB. Prolonged hospital stays caused by difficulties in early ambulation after biopsy in obese patients may also contribute to the increased rate of infectious complications.[33] Further studies are needed to validate whether a cause-and-effect relationship exists between elevated BMI and increased risk of infections. However, this finding should be used as guidance for urologists when treating obese patients.[30]

The increased risk of infectious complications following TRUSPB in diabetic patients has been observed in some centers.[8,26] In this study, multivariate logistic regression analysis demonstrated that a history of diabetes increased the risk of infection after prostate biopsy. Consistent with previous studies, a history of diabetes was an independent risk factor for infection after prostate biopsy. Carignan et al[8] reported a case-controlled study from a Canadian tertiary-care center that showed that diabetes was also an independent risk factor for infectious complications following prostate biopsy in a distinct geographic region. This finding was also demonstrated in a European randomized trial conducted by Loeb et al.[29] Tsu et al[34] reported that diabetes was associated with infection after TRUSPB. This was consistent with our study. However, a 10-year single-center study[11] in the same region as our study revealed that diabetes was not an independent predictor of infection after TRUSPB, which was inconsistent with our study.

We also found correlations between infectious complications following TRUSPB and the use of preoperative catheterization. Preoperative catheterization increases the risk of introducing pathogenic microorganisms. In this study, the infection group included 23 patients (23.23%) who underwent preoperative catheterization, while only 149 patients (13.49%) underwent preoperative catheterization in non-infection group. Thus, there was a significant difference between the infection and non-infection groups, which was consistent with previous studies. Aus et al[35] revealed that patients with preoperative catheterization were at a 2.3-fold increased risk of infection after prostate biopsy than those without preoperative catheterization. In this study, patients with preoperative catheterization showed a 2.303-fold increased risk of infection after prostate biopsy compared with those without preoperative catheterization. It has been reported that a catheter in the urinary tract may be treated as a foreign object that facilitates the proliferation of pathogenic microorganisms.[36] Patients who underwent preoperative catheterization were often accompanied by urological diseases, including urinary retention, urinary incontinence, benign prostatic hyperplasia, and bladder calculi, which were significantly associated with a high risk of infectious complications after TRUSPB.

Choi et al[19] reported on the incidence rate of infectious complications, and their data suggested that quinolone resistance has been increasing in recent years. Steensels et al[37] also showed that quinolone-resistant infections after TRUSPB are on the rise. It has been reported that quinolones are the most frequently used prophylactic antibiotic before TRUSPB.[8] To date, adequate studies of Chinese prostate cancer patients have not been conducted.[11] A prospective study[34] that enrolled 371 Chinese patients who underwent TRUSPB reported on the prevalence of fluoroquinolone-resistant bacteria and the relationship between microbiology and post-biopsy infection rates. This study also revealed that 150 (40.4%) Chinese patients had fluoroquinolone-resistant bacteria. Tsu et al[34] reported a high prevalence of antimicrobial resistance (40.4%), although few patients (2.4%) developed infections (eight with fever and one with septic shock) after prostate biopsy. Furthermore, all infections were successfully managed with carbapenems. In this study, *E. coli* was the most frequent pathogen. Thus, alternative prophylactic agents should be preoperatively determined by rectal swab cultures for patients with a history of urinary infection and chronic prostatitis, to reduce the rate of infections after prostate biopsy. However, at our center, pre-biopsy rectal swab cultures[38] are not routine for patients undergoing TRUSPB.

This study had several limitations. First, the sample size was limited by the low incidence of infectious complications after TRUSPB. Second, this was a retrospective study using data derived from a single center. Third, the conditions of blood-glucose control and diabetes treatments, and previous histories of quinolone use were not considered in this study. A large-scale, multicenter, prospective study is needed to confirm these results.

Conclusion

Our data show that BMI, history of diabetes, and preoperative catheterization are independent risk factors for infection after prostate biopsy.

Data sharing statement

All data generated or analyzed during this study are included in this published article.

Acknowledgments

Author contributions

YPW, XDL, and ZBK wrote the manuscript. SHC, PZC, and YW analyzed the results and revised the paper. JBH and XLS collected and analyzed clinical information on the patients. XYX, QSZ, and NX designed the study, analyzed the results, and revised the paper. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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