ORIGINAL RESEARCH

Retrospective Study of the Etiology and Risk Factors of Systemic Inflammatory Response Syndrome After Systematic Transrectal Ultrasound-Guided Prostate Biopsy

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Objective: To explore the risk factors, pathogenic bacteria distribution and drug resistance of systematic transrectal ultrasound-guided prostate biopsy (TRUS-Bx), 329 cases of TRUS-Bx were collected, retrospectively, in the Second Affiliated Hospital, Army Military Medical University, from April 2017 to October 2019.

Methods: A total of 329 cases were all qualified and grouped into the SIRS group (25 cases) and the non-SIRS group (304 cases). Of all the cases, incidence and risk factors of systemic inflammatory response syndrome (SIRS) were analyzed. Urine and blood samples of patients with SIRS after TRUS-Bx were also collected for bacterial culture and drug sensitivity test.

Results: Multivariate logistic regression analysis showed that BMI $\geq$ 25 kg/m^2 (OR = 1.66, 95% CI = 1.34–2.12, P <0.001), history of diabetes (OR = 5.48, 95% CI = 1.53–19.68, P = 0.008), urinary infection before operation (OR = 9.19, 95% CI = 2.92–20.93, P < 0.001) and erythrocyte sedimentation (ESR) $\geq$ 20 mm/h (OR = 1.04, 95% CI = 1.01–1.08, P = 0.039) were independent risk factors of SIRS after TURS-PB.

Conclusion: The incidence of SIRS and urinary sepsis was 7.59% and 2.13%, respectively, and major pathogens of SIRS after TRUS-Bx were *Escherichia coli* (58.33%), *Klebsiella pneumoniae* (12.5%) and *Pseudomonas aeruginosa* (12.5%). Imipenem, meropenem, tigecycline, piperacillin/tazobactam, teicoplanin, vancomycin, amikacin and cefoperazone/sulbactam had a very strong inhibitory effect to those pathogenic bacteria (sensitivity 85.72% ~100%). Levofloxacin, ciprofloxacin, gentamicin, penicillin G, compound neonomine and second-generation cephalosporins showed less but also worked as a good inhibitor to pathogenic bacteria (42.86%~80.95%).

Keywords: systematic transrectal ultrasound-guided prostate biopsy, systemic inflammatory response syndrome, prostate cancer, risk factors infection, pathogens

Introduction

Prostate cancer (PCa) is one of the most common malignant tumors in men. In Europe and the United States, the incidence rate of PCa ranks first in male cancer and the death rate ranks second.[1,2] In China, there are more than 100,000 new PCa patients every year due to the aging population and the popularization of PCa screening.[1,2] Early diagnosis and treatment of PCa is very important to improve the prognosis of PCa patients.[1,2] Prostate rectal examination, PSA, transrectal ultrasound and MRI are the most commonly used methods to screen PCa.[3–5]

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However, the diagnosis of PCa depends on histological evidence. Therefore, systematic prostate biopsy is the most reliable examination for the diagnosis of PCa.[3–5]

It is suggested that systematic transrectal ultrasound-guided prostate biopsy (TRUS-Bx) is a golden standard for the diagnosis of PCa.[6,7] TRUS-Bx that is usually performed under local anesthesia is considered to be a safe, simple and effective method for the diagnosis of PCa. Moreover, it is well tolerated by patients.[6,7] Nevertheless, TRUS-Bx still has various complications, including acute urinary retention, dysuria, infection, pain, gross hematuria, bloody stool and blood essence.[8,9] Studies suggested that the overall complication rate after TRUS-Bx was as high as 50%, and infection was the most serious complication.[8,9] According to the relevant literature, the incidence of urinary tract infection, sepsis, fever and other infection-related complications after TRUS-Bx is 2.2%–18.23%.[10,11] The pyrogen released from bacteria and virus after TRUS-Bx will cause systemic inflammatory response syndrome (SIRS), by which, if not controlled in time, sepsis would be progressed to and life would be endangered. Therefore, it is of great clinical significance to analyze the risk factors of SIRS after TRUS-Bx for improving the understanding and management ability of SIRS, and formulating the targeted preventive measures.

In this study, we analyzed the clinical data of 329 cases of TRUS-Bx and discussed the incidence, pathogenic characteristics and risk factors of SIRS after TRUS-Bx, so as to provide a basis and reference for clinical prevention.

Methods
Clinical Case Collection
The clinical data of 329 cases of TRUS-Bx in our hospital from April 2017 to October 2019 were collected retrospectively. TRUS-Bx inclusion criteria: abnormal nodule found on digital rectal examination (DRE); abnormal nodule of prostate found by transrectal ultrasound or abnormal signal of prostate found by MRI; PSA > 10 μg/L; and patients with PSA 4–10 μg/L, a free/total PSA ratio < 0.16, or PSA density > 0.15 ng/mL were also included. Patients need to meet one of the above indicators. When abnormal nodule was found on DRE or abnormal nodule of prostate was found by transrectal ultrasound or abnormal signal of prostate was found by MRI, the prostate-specific antigen level may not be considered, and TRUS-Bx must be performed. TRUS-Bx exclusion criteria: patients with severe cardiopulmonary

insufficiency were intolerable; patients with severe immune system diseases; patients with abnormal coagulation function; patients with acute urinary tract infection; patients with other organ infections and febrile diseases; and other patients who were not suitable for invasive examination. This study was approved by the ethics committee of the Second Affiliated Hospital of the Army Medical University. Informed consent was signed by all patients included in the study.

Preoperative Preparation and STRUTS-PB Steps
The specific operation steps and methods of TRUS-Bx are as reported in the previous literature.[11–13] All patients were treated with 0.5 g levofloxacin prophylactic antibiotic 1 day before operation and cleaning enema 30 minutes before operation. After TRUS-Bx, patients were instructed to take a liquid diet and take 0.5 g levofloxacin daily for 3 days. If SIRS occurs, further blood routines, urine routines, blood cultures and urine cultures are performed, and levofloxacin was replaced with intravenous broad-spectrum antibiotics for anti-infective treatment. TRUS-Bx is guided by BK ultrasonic scanner 1202. The prostate automatic puncture gun and disposable BARD 18 G biopsy needle produced by Bard company in the United States were used for systematic 12-needle puncture biopsy. During the process of puncture, the puncture gun, biopsy needle and puncture frame are all required to be sterile. The ultrasound probe is covered with sterile latex to reduce the incidence of iatrogenic infection.

Clinical Data Collection and SIRS Diagnostic Criteria
The following indicators were collected for the study patients: 1) general clinical data: age, BMI, comorbidity, PSA, prostate volume, erythrocyte sedimentation rate (ESR), urea, creatinine, EGFR, postoperative pathological type, etc; 2) perioperative conditions: whether the catheter is retained before operation; whether there is urinary tract infection and the number of TRUS-Bx punctures before operation; TURP operation history; antibiotic use within the last 3 months, etc; and 3) the data of bacterial culture and drug sensitivity test in urine and blood of patients with SIRS after TRUS-Bx operation were collected and analyzed. The diagnostic criteria for SIRS are as follows: 1) body temperature < 38 °C or > 38 °C; 2) pulse > 90 beats/min; 3) breathing > 20/min; and 4) WBC > 12×10^9/L or

WBC $< 3 \times 10^9$/L; any two of these can be diagnosed as SIRS. The diagnosis of sepsis refers to previous research reports, the main diagnosis points of sepsis are: pathogenic bacteria infection evidence in conjunction with SIRS.[11–13] The diagnostic criteria of urinary tract infection before operation were as follows: 1) there are symptoms of urinary tract infection such as frequency of urination, urgency of urination and pain of urination; 2) the bacterial colony count of the urine in the middle of cleaning is more than 10^5/mL; 3) the number of leukocytes in centrifuged urine was more than 5/HP; and 4) the result of urine bacterial culture was positive. Those who meet one or more of the above conditions can be diagnosed with a preoperative urinary tract infection.

Statistical Analysis
SPSS 20.0 software was used for data analysis. Numerical data that were normally distributed were represented as mean ± SD. Nonparametric 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 analyze the statistical significance of the indicators and calculate the regression coefficient (β), relative odds ratio (OR) and 95% confidence interval.

Result
Univariate Analysis of General Clinical Data in the Two Groups
A total of 329 patients were included in the study, including 25 cases in the SIRS group and 304 cases in the non-SIRS group. The incidence of SIRS after TRUS-Bx was 7.59%. In 25 SIRS patients, 7 patients developed sepsis, and the overall incidence of sepsis was 2.13%. As shown in Table 1, univariate analysis demonstrated that there was no significant difference between the two groups in age, history of hypertension, history of coronary heart disease, PSA, f-PSA, f-PSA/PSA, urea, creatinine, eGFR, prostate volume, preoperative indwelling catheter rate, TURP operation history, secondary biopsy rate and diagnosis rate of PCa ($p > 0.05$). However, there were significant differences between the two groups in BMI ≥ 25 kg/m^2 (84.00% vs 31.57%, $p < 0.001$), history of diabetes (56.00% vs 10.52%, $p < 0.001$), ESR ≥ 20 mm/h (52.00% vs 20.72%, $p = 0.001$), preoperative urinary tract infection (56.00% vs 14.14%, $p < 0.001$) and

antibiotic abuse within the last 3 months (48.00% vs 15.46%, $p < 0.001$).

Multivariate Logistic Regression Analysis of Risk Factors of SIRS After TRUS-Bx
As shown in Table 2, the results of multivariate logistic regression analysis revealed that BMI ≥ 25 kg/m^2 (OR = 1.66, 95% CI = 1.34–2.12, $P < 0.001$), history of diabetes (OR = 5.48, 95% CI = 1.53–19.68, $P = 0.008$), preoperative urinary tract infection (OR = 9.19, 95% CI = 2.92–20.93, $P < 0.001$) and ESR ≥ 20 mm/h (OR = 1.04, 95% CI = 1.01–1.08, $P = 0.039$) are the independent risk factors of SIRS after TRUS-Bx, while antibiotic abuse within the last 3 months ($P = 0.133$) is not related to the occurrence of SIRS after TRUS-Bx.

Distribution and Drug Resistance of Blood and Urine Bacteria in Patients with SIRS
In all 25 SIRS patients the positive rate of blood and urine bacterial culture is 28% (7/25) and 68% (17/25) respectively. As shown in Table 3, of the 24 positive specimens, 14 were *Escherichia coli* (58.33%), 3 were *Klebsiella pneumoniae* (12.5%), 3 were *Pseudomonas aeruginosa* (12.5%), 2 were *Enterococcus faecalis* (8.33%), 1 was *Staphylococcus epidermidis* (4.17%) and 1 was *Enterobacter cloacae* (4.17%). As shown in Table 4, in the susceptibility analysis of pathogenic bacteria, we found that the main sensitive drugs of pathogenic bacteria were imipenem, meropenem, tigecycline, piperacillin/tazobactam, teicoplanin, vancomycin, amikacin, cefoperazone/sulbactam, etc. However, levofloxacin, ciprofloxacin, gentamycin, penicillin G, sulfamethoxazole and the second-generation cephalosporins showed a strong drug resistance rate (42.86%~80.95%).

Discussion
In China, with the improvement of PSA screening and the people's health awareness, more and more patients are receiving TRUS-Bx.[14,15] However, TRUS-Bx is an invasive procedure with complications such as infection, bleeding, pain and retention of urine. Among all of these complications, the most serious one is infection.[16,17] It is suggested that the incidence of infection after TRUS-Bx is about 2%-11.5%, of which nearly 30.50% are associated with bacteremia, and about 1.22% of bacteremia patients progress to severe sepsis.[6,18] The wound that is exposed to

Table 1 Patients Characteristics in the SIRS Group and Non-SIRS Group

Parameters		SIRS Group (n = 25)	Non-SIRS Group (n = 304)	P value
Age (years)		70.08 ± 7.27	69.59 ± 9.23	0.797
BMI (kg/m^2)	≥25	21 (84.00%)	96 (31.57%)	
	<25	4 (16.00%)	208 (68.43%)	<0.001
Diabetes (n, %)	Yes	14 (56.00)	32 (10.52)	
	No	11 (44.00)	272 (89.47)	<0.001
Hypertension (n, %)	Yes	7 (28.00)	85 (19.08)	
	No	18 (72.00)	219 (72.02)	0.997
coronary heart disease (n, %)	Yes	2 (8.00)	23 (7.57)	
	No	23 (92.00)	281 (92.43)	0.937
PSA (μg/L)		32.73 ± 27.78	30.55 ± 37.57	0.777
f-PSA (μg/L)		4.03 ± 2.49	7.37 ± 10.99	0.131
fPSA/PSA		0.15 ± 0.11	0.17 ± 0.12	0.517
Erythrocyte sedimentation rate (mm/h)	≥20	13 (52.00)	63 (20.72%)	
	<20	12 (48.00)	241 (79.28%)	0.001
Urea (mmol/L)		6.51 ± 3.43	6.31 ± 2.45	0.699
Creatinine (μmol/L)		110.67 ± 75.27	91.24 ± 46.37	0.356
eGFR (mL/min/L)		76.85 ± 22.28	78.94 ± 18.92	0.602
Prostate volume (mL)		50.75 ± 20.66	59.62 ± 41.98	0.297
Preoperative urinary tract infection (n, %)	Yes	14 (56.00)	43 (14.14)	
	No	11 (44.00)	264 (85.86)	<0.001
Preoperative indwelling catheter (n, %)	Yes	4 (52.00)	99(14.14)	
	No	21(48.00)	205 (85.86)	0.086
Secondary biopsy (n, %)	Yes	3 (12.00)	15 (4.93)	
	No	22 (88.00)	288 (94.73)	0.137
History of TURP surgery (n, %)	Yes	1 (4.00)	19 (6.25)	
	No	24 (96.00)	285 (93.75)	0.651
Antibiotic abuse within the last 3 months (n, %)	Yes	12 (48.00)	4 (15.46)	
	No	13 (52.00)	259 (85.19)	<0.001
Pathologically confirmed malignancy (n, %)	Yes	16 (64.00)	195 (64.15)	
	No	9 (36.00)	109 (35.85)	0.988

Table 2 Multivariate Logistic Regression Analysis of Risk Factors for SIRS After TRUS-BX

Parameters	OR (95% CI)	P value
Diabetes	5.48 (1.53–19.68)	0.008
BMI ≥ 25 kg/m^2	1.66 (1.34–2.12)	<0.001
Preoperative urinary tract infection	9.19 (2.92–20.93)	<0.001
Antibiotic abuse within the last 3 months	2.77 (0.71–10.58)	0.133
Erythrocyte sedimentation rate ≥ 20 mm/h	1.04 (1.01–1.08)	0.039

bacteria and other pyrogens after TRUS-Bx may be infected and SIRS would be caused. If SIRS cannot be controlled in time, SIRS will progress to urinary sepsis, which seriously endangers the patient's life.[19,20] In this study, we found that the incidence of SIRS and sepsis was 7.59% and 2.13%, respectively, and the results are very close to the previous literature.[6,18–20] Previous studies have also shown that almost all deaths after TRUS-Bx were caused by sepsis with septic shock and multiple organ failure.[19,20] Therefore, the risk factors of SIRS

Table 3 Distribution of Bacterial Strains in 24 Positive Specimens

Pathogenic bacteria	Proportion
Escherichia coli	14 (58.33%)
Klebsiella pneumoniae	3 (12.5%)
Pseudomonas aeruginosa	3 (12.5%)
Enterococcus faecalis	2 (8.33%)
Staphylococcus epidermidis	1 (4.17%)
Enterobacter cloacae	1 (4.17%)

Table 4 Drug Sensitivity Analysis of Bacterial Strains in 24 Positive Samples

Antibiotics	Sensitive	Medium	Resistance
Imipenem	90.48%	0%	9.52%
Meropenem	95.24%	0%	4.76%
Tigecycline	100%	0%	0%
Teicoplanin	100%	0%	0%
Amikacin	87.50%	0%	12.50%
Piperacillin/tazobactam	85.72%	4.76%	9.52%
Cefoperazone/sulbactam	80.95%	0%	19.05%
Ceftazidime	66.71%	4.72%	28.57%
Ampicillin	19.05%	0%	80.95%
Cefuroxime	38.89%	0%	61.11%
Cefoperazone	47.62%	4.76%	47.62%
Piperacillin	31.58%	0%	68.42%
Tetracycline	28.57%	0%	71.43%
Cefepime	47.62%	9.52%	42.86%
Ciprofloxacin	48.00%	0%	52%
Levofloxacin	52.38%	0%	47.62%
Sulfamethoxazole	40%	0%	60%
Ampicillin/sulbactam	27.78%	22.22%	50.00%
Gentamicin	68.18%	0%	31.82%
Vancomycin	95.46%	0%	4.54%

after TRUS-Bx should be fully understood to avoid severe complications such as septic shock and multiple organ failure. In our study, the SIRS and sepsis patients in this study were cured and discharged after close monitoring and active treatment.

Currently, some studies indicate that age, BMI ≥ 25 kg/m², diabetes mellitus, preoperative catheter, prostate volume, multiple punctures, history of hypertension, history of antiplatelet drugs, preoperative antibiotics and clean perfusion are risk factors for infection after TRUS-Bx.[12,21–25] However, some other scholars suggest that age, prostate volume, history of hypertension, PSA, fPSA/PSA, history of antiplatelet drugs, history of coronary heart disease and pathological results are not risk factors of infection after TURS-PB.[11,23] In this study, we found that age, hypertension, indwelling catheter, prostate volume, PSA, fPSA/PSA, pathological type

and antibiotic use history were not independent risk factors of SIRS after TRUS-Bx.

However, in our study, we found that BMI ≥ 25 kg/m², diabetes history, preoperative urinary tract infection and ESR ≥ 20 mm/h were independent risk factors of SIRS after TRUS-Bx. Obesity and diabetes are risk factors for SIRS after TRUS-Bx. The possible reason is that obesity and diabetes are chronic endocrine and metabolic diseases. Obese and diabetic patients have weak immune regulation ability and defense ability against external stimuli (especially in elderly patients), and insufficient postoperative stress ability, which leads to a significant increase in SIRS risk after TRUS-Bx. Preoperative urinary tract infection is an independent risk factor for SIRS after TRUS-Bx. The possible cause is that patients with urinary tract infection before surgery already have bacteria in their urine. During the TRUS-Bx process, bacteria can enter the blood vessels to spread along the channel formed after puncture, further causing bacteremia and SIRS. By now, the study of ESR ≥ 20 mm/h is an independent risk factor for SIRS after TRUS-Bx has not been reported. Under normal circumstances, ESR is generally less than 20 mm/h, and increases in infection, malignant tumor, injury, immune system disorders and other diseases.[26] The acceleration of ESR is mainly caused by changes in the proportion of various protein components in the plasma, especially macromolecular proteins such as fibrinogen, immunoglobulin and macroglobulin, etc.[27] Elevated ESR in TRUS-Bx patients before operation indicates that the immune system of patients is abnormally activated, and after TRUS-Bx surgery, SIRS is more likely to occur, due to injury, stress, bacteria and other pyrogen release.

It is suggested that the main bacteria causing infection after TRUS-Bx are *Escherichia coli* (75%).[28–30] *Escherichia coli* is a normal intestinal flora. It mainly enters the blood directly from the puncture needle through the intestine, or spreads into the blood after latent entering the prostate tissue. Antibiotics, prophylactic, can inhibit the spread of this bacteria. With the use of prophylactic antibiotics, the incidence of infection after TRUS-Bx was significantly reduced. However, with the increase of *Escherichia coli* resistance and the emergence of new bacteria, the incidence of infection, SIRS and sepsis increased significantly after TRUS-Bx.[28–30] In this study, we also found that the major pathogens causing SIRS after TRUS-Bx were *Escherichia coli* (58.33%), but the infection rates of *Klebsiella pneumoniae* (12.5%), *Pseudomonas aeruginosa* (12.5%) and *Enterococcus faecalis* (8.33%) were increasing.

Previous quinolone antibacterials have been widely used for TURS-PB preoperative prevention.[28–30] Unfortunately, in recent years, studies have found that the pathogenic bacteria *Escherichia coli* after TURS-PB resistance to quinolone antibiotics is as high as 80–90%.[29,31,32] In this study, we found that SIRS pathogens after TRUS-Bx showed strong resistance to levofloxacin, ciprofloxacin, gentamycin, penicillin G, compound Xinnuoming and the second-generation cephalosporins, with a resistance rate of 42.86%–80.95%. Therefore, we suggest that the preventive use of levofloxacin may need to be adjusted. In addition we also found that the resistance of pathogenic bacteria to β-lactam combined enzyme inhibitors (piperacillin/tazobactam) and aminoglycoside antibiotics (amikacin) was 9.52%−12.50%. Therefore, for mild to moderate infections, β-lactam combination enzyme inhibitors (piperacillin/tazobactam) and aminoglycoside antibiotics (amikacin) are highly recommended and can be used as the preferred drugs. Aminoglycoside antibiotics (amikacin) should be used with caution due to nephrotoxicity and ototoxicity. SIRS pathogens, in this study, were highly sensitive (90.48%–100%) to carbapenems (meropenem, imipenem), glycyltetracyclines (tigecycline), glycopeptide antibiotics (teicoplanin, vancomycin), etc. Therefore, for severe infections, we recommend the use of such restricted antibiotics for anti-infective treatment in the absence of pathogenic susceptibility results. This study still has some limitations: First, it is a retrospective study and is not a double-blind randomized controlled trial in design. Second, the sample size of this study is small, and the research results need a larger sample to verify. Third, the results of this study can only represent the situation of the population of the unit, and there may be differences in the results of the study for other populations and units.

Conclusion

Diabetes, BMI ≥ 25 kg/m², preoperative urinary tract infection and ESR ≥ 20 mm/h are independent risk factors for SIRS after TRUS-Bx. Therefore, active control of body weight and ESR, correction of blood glucose and preoperative urinary tract infection are important measures to prevent SIRS after TRUS-Bx. *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are the major pathogens of SIRS. The pathogenic bacteria have a high resistance rate to antibacterial drugs such as quinolones, first- and second-generation cephalosporins. But it is sensitive to amikacin, β-lactam combined enzyme inhibitor complex preparation and carbapenems.

Disclosure

The authors declare no conflicts of interest for this work.

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