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Obesity was an independent risk factor for febrile infection after prostate biopsy

A 10-year single center study in South China

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Abstract

To detect the best antibiotic protocol for prostate biopsy and to assess the potential risk factors postbiopsy in Chinese patients.

A total of 1526 patients underwent biopsy were assessed retrospectively. The effect of 3 antibiotic protocols was compared, including fluoroquinolone (FQ) monotherapy, third-generation cephalosporin combined with FQ and targeted antibiotics according to the prebiopsy rectal swab culture result. Postbiopsy infection (PBI) was defined as fever and/or active urinary tract symptoms such as dysuria or frequency with pyuria and/or leucocytosis, sepsis is defined as the presence of clinically or microbiologically documented infection in conjunction with systemic inflammatory response syndrome. The relationship between infections and clinical characteristics of patients was assessed. Data were first picked out in univariate analysis and then enter multivariate logistic regression.

Thirty-three (2.2%) patients developed febrile infection. The combination antibiotic prophylaxis could significantly decrease the rate of PBI than FQ monotherapy (1.0% vs 4.0%, $P = .000$). The infection rate of the targeted antibiotic group was 1.1%, but there was no significant statistic difference compared with FQ alone ($P = .349$). *Escherichia coli* was the most predominant pathogen causing infection. Rectal swab revealed as high as 47.1% and 36.0% patients harbored FQ resistant and ESBL-producing organisms, respectively. In univariate analysis, overweight (BMI between 25 and 28 kg/m^2), obesity (BMI > 28 kg/m^2), diabetes were picked out as potential risk factors. Obesity remained as risk factor (OR = 12.827, 95% CI: 0.983–8.925, $P = .001$) while overweight and diabetes were close to significance ($P = .052$, .053, respectively).

The combined cephalosporin with FQ prophylaxis could significantly decrease the risk of infectious complications. Obesity was an independent risk factor for PBI.

Abbreviations: BMI = body mass index, BPH = benign prostate hyperplasia, CI = confidence interval, ESBL = extended-spectrum β-lactamase, FQ = fluoroquinolone, MRI = magnetic resonance imaging, PBI = postbiopsy infection, PNB = prostate needle biopsy, PSA = prostate-specific antigen, SIRS = systemic inflammatory response syndrome, UTI = urinary tract infection.

Keywords: body mass index, infection, obesity, prostate biopsy, rectal swab

1. Introduction

With the life style changing close to western country and widespread prostate-specific antigen (PSA) screening in China, the incidence of prostate cancer is rising yearly. More than 100,000 men in China are now diagnosed with prostate cancer every year.[1] Transrectal ultrasound-guided prostate needle biopsy (PNB) is a standard procedure for the diagnosis of prostate cancer. Postbiopsy infection (PBI) which is a common complication after PNB, can be reported as a minor or major course depending on its severity, in rare cases.[2] It is reported that the incidence of urinary tract infection (UTI) after PNB varies from 3% to 11% of patients, while sepsis is between 0.1% and 5%.[3–5]

Thorough review of the literatures reveals that some certain risk factors for PBI have been studied.[4–6] But most articles were based on Caucasian patients in Europe and North America. There are only a few studies focus on PBI in Taiwan and Hong-Kong Chinese patients.[7–9] And there were no systemic reports in mainland Chinese patients yet.

The aim of our study was to detect a more effective antibiotics protocol for prostate biopsy and to identify the potential risk factors for PBI in Chinese patients.

2. Materials and methods

From January 2004 to October 2015, patients underwent transrectal ultrasound-guided PNB in Fujian Provincial Hospital were retrospectively reviewed. The indications of biopsy included: Abnormal digital rectal examination or imagery findings. PSA level higher than 4 ng/mL. Two physicians performed most of the prostate biopsies. Either 6- or 12-core

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biopsies were chosen depending on the discretion of the each ultrasound experts. If extra targeted biopsy (less than 3 cores) was performed depending on the discretion of the ultrasound experts. We used cognitive fusion method to perform the targeted biopsy. A meta-study showed that the diagnostic ability of software-fusion targeted biopsy and cognitive fusion targeted biopsy seems almost comparable, although utility and efficiency both seem to be slightly in favor of the software-based strategy. But our center does not have the equipment for software-fusion targeted biopsy yet.

All patients underwent evaluation of following items, blood analysis, biochemical analysis, urine analysis and culture, PSA.

Polyethylene glycol and cleansing enema were given 24 hours, 1 hour before biopsy respectively. If the prebiopsy urine culture is positive, adequate antibiotics were selected according to the result of sensitivity test. Biopsy was postponed until negative repeat urine analysis and culture were obtained.

We compared 3 antibiotic protocols. Group A: oral fluoroquinolone (FQ, such as levofloxacin 0.5 g po Qd or ciprofloxacin 0.5 g po Bid) antibiotics were given 2 hours before to 72 hours after biopsy. Group B: Intravenous use of third-generation cephalosporin (Cefotaxime 1 g iv Q12 h, Ceftriaxone 2 g iv Qd) combined with oral FQ were given 2 hours before to 72 hours after biopsy. Group C: Rectal swabs were collected about 1 to 2 weeks before biopsy and cultured on blood agar, MacConkey agar with 1 μg/mL ciprofloxacin and ChromID extended-spectrum β-lactamase (ESBL) agar. The blood agar was used as control. RS from blood agar plates without growth were considered as inadequate specimen collection. Specimens with growth on blood agar but no growth on selective agars at 48 hours were considered as containing organisms sensitive to FQ and no ESBL producing. Specimens with growth on both agars underwent organism identification and antibiotic sensitivity test. The antibiotics we used included Ceftriaxone 2 g iv Qd, Amikacin 0.5 g iv Q12 h, cefoperazone 1.5 g iv Q12 h, piperacillin 4 g iv Q12 h, etc. The mean duration of antibiotic dosing after biopsy in group C was 4 days (range, 2–7 days) depending on the orders of the urologists. Patients without FQ resistant or ESBL-producing organisms received standard empirical levofloxacin as group A.

PBI was defined as one of the following within 3 weeks: fever and/or active urinary tract symptoms such as dysuria or frequency with pyuria and/or leucocytosis, sepsis is defined as the presence of clinically or microbiologically (blood or urine culture) documented infection in conjunction with systemic inflammatory response syndrome (SIRS).[10] SIRS is characterized by the presence of at least 2 of the following: Body temperature >38°C or <36°C; heart rate > 90 beats/minute; respiratory rate > 20 breaths/minute or $PaCO_2 < 32$ mm Hg; white blood cell (WBC) count > 12,000/μL or <4000/μL or >10% detection of young neutrophils.

Age, body mass index (BMI, divided into 3 groups: normal < 25, overweight 25–28, obesity > 28), smoking history, hypertension, diabetes, prostate volume, biopsy core numbers, PSA level were collected as variables.

The Pearson Chi-square test was used for categorical variables and the Student *t* test and 1-way ANOVA test are used for continuous variables. Variables were first picked out by *P*-value < .10 in univariate analysis and then multivariate logistic regression analysis was used to examine the predictors of post biopsy febrile infection. *P*-values <.05 were considered statistical significant in final model. All analyses were performed by using SPSS 19.0.

2.1. Ethics committee

The study was approved by Fujian province hospital ethics committee Clinical scientific research and experiment for examination and approval (No. K2014-01-001).

3. Results

A total of 1526 patients were enrolled. All patients were Han ethnic. The mean age was 62.2 ± 18.3 years, prostate volume 40.7 ± 26.5 mL, PSA was 11.6 ± 14.5 ng/mL, BMI 23.5 ± 7.6 kg/m^2. The patient characteristics are shown in Table 1.

Table 1

Characteristics of patients in each group.

Characteristic	Group A	Group B	Group C	*P*
n	623	814	89	
Age, y*	62.2 ± 15.9	62.1 ± 18.7	63.5 ± 17.4	.946‡, .057§, .052‖
Prostate volume, mL*	42.6 ± 20.4	39.2 ± 25.9	40.6 ± 26.4	.045‡, .124§, .371‖
PSA, ng/mL*	10.9 ± 13.2	12.6 ± 15.5	8.3 ± 10.3	.111‡, .212§, .012‖
BMI, kg/m^2*	23.4 ± 7.4	23.7 ± 8.5	22.5 ± 6.9	.765‡, .083§, .064‖
Biopsy core numbers				
≤9, %	246 (39.5)	354 (43.4)	38 (42.7)	
≥10, %	377 (60.5)	461 (56.6)	51 (57.3)	.317†
Patients undergo addition biopsy	93 (14.9)	124 (15.2)	13 (14.6)	.907†
Smoking history, %	26 (4.2)	33 (4.1)	4 (4.4)	.978†
Hypertension, %	216 (12.4)	313 (11.5)	109 (9.8)	.786†
Diabetes, %	71 (11.4)	102 (12.5)	11 (12.3)	.804†
Febrile infectious, %	24 (4.0)	8 (1.0)	1 (1.1)	.001†
Sepsis, %	10 (1.6)	3 (0.4)	0 (0)	.003†

Group A: oral fluoroquinolone; Group B: intravenous use of third-generation cephalosporin; Group C: rectal swabs were collected about 1 to 2 weeks before biopsy and cultured on blood agar, MacConkey agar with 1 μg/mL ciprofloxacin and ChromID extended-spectrum β-lactamase (ESBL) agar.

BMI = body mass index, PSA = prostate-specific antigen.

* Data are presented as the mean ± standard error and compared by 1-way ANOVA test.

† Chi-square test.

‡ Group A vs B.

§ Group A vs C.

‖ Group B vs C.

PBI totally occurred in 33/1526 (2.2%) cases after PNB, including UTI in 20 (60.6%) patients and sepsis in 13 (39.4%) patients. Three (9.1%) patients were admitted to the intensive care unit because of septic shock. One patient (In group A) developed cardiac arrest but there was no biopsy related death. Urine and blood culture came back positive in 20, 13 of these 33 patients respectively. Eight patients were both positive on urine and blood culture. *Escherichia coli* was both the most common pathogen on urine and blood culture (n=16, 80.0%; n=9, 69.2%, respectively).

Rate of PBI in 3 groups was 24/623 (4.0%), 8/814 (1.0%), 1/89 (1.1%), respectively. The combined third-generation of cephalosporin with FQ prophylaxis could significantly reduce the risk of PBI (Chi-square, $P<.001$). Though the infection rate of targeted antibiotics seem obviously lower than FQ monotherapy (1.1% vs 4.0%), but Chi-square test show there was no significant difference ($P=.349$). There was also no significant difference of the PBI rate in group B and C (1.0% vs 1.1%, Chi-square $P=.572$).

In group A, 16/24 (66.7%) infectious patients had positive microbiological evidence. Fifteen infections were caused by FQ resistant organisms, including one ESBL-producing *E coli* and only one was caused by FQ sensitive organisms. The rest of patients with no growth on urine and blood culture and diagnosed-infection by clinical manifestation (fever, LUTS) accompanied with pyuria, leukocytosis. In group B, 8 infections were all caused by ESBL-producing organisms with resistance to FQ, including *E coli* (n=5), *Pseudomonas aeruginosa* (n=2), Klebsiella pneumonia (n=1). In group C, 42/89 (47.2%) patients were found to harbor FQ resistant organisms, whereas 32/89 (36.0%) patients were found to harbor ESBL-producing organism. In total, from these 89 patients, 60 FQ-resistance or ESBL-producing pathogens colonies were isolated. *E coli* was the most common pathogen (n=52, 86.7%), followed by Klebsiella pneumonia (n=5, 8.3%), *P aeruginosa* (n=2, 3.3%), *Enterococcus faecalis* (n=1, 1.7%). The resistance pattern of the isolated pathogens is shown in Fig. 1. All these patients received targeted antibiotic prophylaxis and only 1 patient whose rectal swab culture result was FQ resistant *E coli* suffered from infection due to amikacin resistance *E faecalis* which was sensitive to FQ.

Table 2 shows univariate analysis the potential risk factors predisposing to febrile infection related to PNB. Overweight, obesity, diabetes were picked up as potential risk factors (Chi-square, $P=.035$, .000, .036, respectively). On multivariable logistic regression (Table 3), obesity (OR=12.827, 95% CI: 8.931–18.423, $P=.001$) remained as risk factor while overweight and diabetes were close to significance ($P=.052$, .053, respectively).

Table 2

Univariable analysis of potential risk factors predisposing to PBI.

Variable	Infection	No infection	*P*
Age, y*	63.3±15.5	62.5±16.7	.216†
Prostate volume, mL*	43.8±21.3	40.6±25.3	.177†
PSA, ng/mL*	11.2±12.8	11.6±13.9	.786†
Body mass index, n			**<.001**‡
Normal (<25), %	6 (0.7)	844 (99.3)	
Overweight (25–28), %	10 (2.1)	468 (97.9)	**.035**‡,§
Obesity (>28), %	17 (8.6)	181 (91.4)	**<.001**‡,§
Biopsy core numbers			
6 cores+, %	18 (2.4)	729 (97.6)	
12 cores+, %	15 (1.8)	797 (98.2)	.484‡
Smoking history, n			
No, %	28 (2.1)	1307 (97.9)	
Yes, %	5 (2.6)	186 (97.4)	.595‡
Hypertension, n			
No, %	26 (2.0)	1241 (98.0)	
Yes, %	7 (2.7)	252 (97.3)	.156‡
Diabetes, n			
No, %	24 (1.8)	1293 (98.2)	
Yes, %	9 (4.3)	200 (95.7)	**.036**‡
Antibiotic protocol, n			**.001**‡
Group A: Empirical, %	24 (3.9)	599 (96.1)	
Group B: Combined, %	8 (1.0)	806 (99.0)	**<.001**‡,‖
Group C: Targeted, %	1 (1.1)	88 (98.9)	.349‡,‖, .572‡,¶

FQ=fluoroquinolone, PBI=postbiopsy infection, PSA=prostate-specific antigen.
* Data are presented as the mean value±standard error.
† Student *t* test.
‡ Chi-square test.
§ Overweight and Obesity group compared with Normal group, respectively.
‖ Group B and C compared with group A, respectively.
¶ Group C compared with group B.
The bold representation of a difference is statistically significant.

4. Discussion

Magnetic resonance imaging (MRI) is a useful tool for prostate cancer diagnosis and disease staging. It is widely used to assess the location and border of tumors as well as to determine the level of infiltration to adjacent tissues.

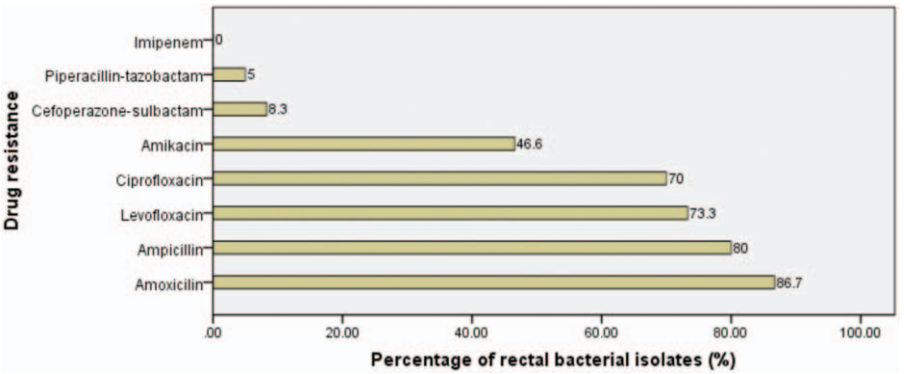

Figure 1. Antibiotic resistance pattern of isolated bacteria. The isolates bacteria displayed high level of resistance to the commonly used antibiotics. The highest rates of resistance were for amoxicillin (86.7%) and ampicillin (80%). Resistance to fluoroquinolone was observed in 73.3%, 70% for levofloxacin and ciprofloxacin, respectively. On the other hand, all isolates were universally susceptible to the carbapenems, and there were just a few isolates which were resistant to β-lactamase inhibitor.

Table 3

Multivariable logistic regression to indentify independent risk factor PBI.

Variable	Infection	No infection	Odds ratio (95% CI)	*P*
Body mass index, n				
Normal (<25), %	6 (0.7)	844 (99.3)		
Overweight (25–28), %	10 (2.1)	468 (97.9)	2.962 (0.983–8.925)	.052
Obesity (>28), %	17 (8.6)	181 (91.4)	12.827 (8.931–18.423)	**.001**
Diabetes, n				
No, %	24 (1.8)	1293 (98.2)		
Yes, %	9 (4.3)	200 (95.7)	1.332 (0.993–1.786)	.053
Antibiotic protocol, n				
Group A: Empirical, %	24 (3.9)	599 (96.1)		
Group B: Combined, %	8 (1.0)	806 (99.0)	4.037 (1.801–9.048)	**.001**
Group C: Targeted, %	1 (1.1)	88 (98.9)	3.526 (0.471–26.390)	.220

CI = confidence interval, PBI = postbiopsy infection.

The bold representation of a difference is statistically significant.

MRI can be performed either before or after prostate biopsy. We prefer MRI before prostate biopsy because there are several advantages. First, it can avoid the postbiopsy artifact caused by hemorrhage will lead to better local staging accuracy, while determining more accurately the disease burden. MRI after prostate biopsy is likely to be confounded by hemorrhage artifact, which manifests as low-signal areas on t2w sequences, and are indistinguishable from cancer. Artifact can lead to overestimation of cancer burden in 20% of cases manifest as errors in local staging and requires 2 to 4 months to resolve.[11] Second, the use of MRI before a biopsy can serve as a triage test in men with raised serum PSA levels, in order to select those for biopsy with significant cancer that requires treatment. This strategy could avoid biopsy, and hence unnecessary treatment, in those with no disease or insignificant cancer.[12] Third, MRI before biopsy can provide more information to perform the cognitive or software fusion targeted biopsy.

A meta-study showed that the diagnostic ability of software-fusion targeted biopsy and cognitive fusion targeted biopsy seems almost comparable, although utility and efficiency both seem to be slightly in favor of the software-based strategy.[13] But our center does not have the equipment for software-fusion targeted biopsy yet.

Although generally considered a safe and well-tolerated procedure, infectious complications related to transrectal PNB can sometimes occur and even lead to life-threatening sequelae. FQ is the most widely used antibiotic before PNB as recommended by the American Urological Association.[14] Randomized controlled trials have demonstrated their efficacy in decreasing the risk of sepsis after PNB.[15,16] However, it is reported that the incidence of post-PNB infection has an increasing trend in several centers in North America and Europe due to significantly increased prevalence of FQ resistant bacteria these years.[3,17–19] Indeed the trend of increasing FQ-resistant bacteria was also reported in Asian area.[20,21]

We observed that the total incidence of PBI was 33/1526 (2.2%), and was close to prior studies from the western countries. However, the infection rate in 3 groups was 4.0%, 1.0%, 1.1%, respectively. The rate of PBI was obviously high in group A. and most of them (15/24) were caused by FQ resistant organisms. This result seems to be consistent with prior reports, suggesting a rising rate of infectious complications because of increasing FQ resistant organisms. We also note that the rate of harboring FQ resistant organisms in Chinese patients (47.1% in group C) seems significantly higher than western countries, which indicates Asian ethnicity may be a risk factor for PBI as prior reports.[7,22,23] There are some possible explanations for this. First, the antibiotics abuse causes a selection pressure favoring the resistant organisms. Especially in China, the use of antibiotics is rapidly increasing and is nonstandardized. Second, patients can easily get antibiotics without a prescription in China. Third, environmental pollution getting worse.[24,25] Fourth, regional difference in antibiotic use in the food supply, and different genetic makeup may also play a role.

Despite routinely use of prophylactic antibiotics, the rate of PBI was still increasing. The first reaction was to add more antibiotics to the empiric treatment when BPI occurred. Most studies added one type of cephalosporins or aminoglycoside or other antibiotic treatment. Many studies have reported that FQ resistant organisms were sensitive to cephalosporins or aminoglycosides, using combined antibiotics prophylaxis can reduce the incidence of infectious complications, the rate of fever and hospitalization.[26,27] Similar to prior reports, our results showed that the combined third-generation cephalosporins combined with FQ can significantly reduce the rate of infectious complication. But there were still two problems for combined antibiotics. First, it may rise the cost. Although using combined antibiotics represents a greater cost for single patient, it may be more cost-effective for patients involved as a whole. Second, the most serious concern lies in inducing the drug resistance. Taylor reported 4.6% of their patients harbored ESBL-producing organisms in their rectums.[28] James reported as high as 41.0% of ESBL-producing rectal flora in Hong-Kong population and using antibiotic within 6 months was an independent risk factor for producing drug resistance organism.[7]

We found that all of the infections were caused by ESBL-producing organisms in group B. It seems combined antibiotics may make too strong selective pressure favoring the multidrug resistant organisms. If the strategy do not improve bacterial resistance some day, will it be necessary to add more kinds of drugs or use the most powerful drug such as imipenem? The alternative antibiotic prophylaxis was under exploring. But Chao reported patient population harbored organisms with heterogeneous phenotypic susceptibility, and universal prophylaxis would not provide optimal coverage for patients undergoing transrectal ultrasound-guided prostate biopsy.[29]

Recent studies have demonstrated using targeted antibiotic prophylaxis based on rectal swab might be more effective in reducing the rate of infection.[30] Tim reported a totally of 3.83% reduction in infection rate when comparing targeted antibiotic prophylaxis with empirical prophylaxis in his meta-analysis.[31] The benefits of rectal swab before PNB include use narrow

spectrum antibiotic, reduce the occurrence of drug resistance, low down the overall cost of for patients. It was reported 27 men would need to receive targeted antibiotic prophylaxis to prevent one infective complication and the total cost was obviously lower (£810 vs £4260).[31] In present study, we noted the effect of targeted antibiotic prophylaxis was not superior to FQ monotherapy (1.0% vs 4.0%, $P=.349$), but there was also no significant difference when comparing with combined antibiotic prophylaxis (1.0% vs 1.1%, $P=.572$). It is most probably because the sample size was too small to provide statistical significance. Meanwhile, the mean dose duration after biopsy in group C was a bit longer than the other groups (4 days vs 3 days) which may also cause statistical bias. So further studies with larger volume and same antibiotic dose duration were warranted. Interestingly, in group C there was only 1 patient whose prebiopsy rectal swab culture was *E coli* which was FQ resistant. So we chose amikacin as prophylaxis. And the infection was caused by *E faecalis*, which was sensitive to FQ but resistant to amikacin. Therefore, we deduce there might be a potential disadvantage in targeted antibiotic strategy. In common case we select relatively narrow spectrum antibiotics according to the result of rectal swab culture by using FQ resistant selective medium. It may ignore the other organisms which were sensitive to FQ but resistant to the using drug and let them be the main pathogens of infection. In this situation, shall we add more selective mediums to ensure the effect of using drug or just choosing wider spectrum antibiotics?

In present study, we found obesity ($BMI > 28\,kg/m^2$) was the only independent risk factor for PBI (OR = 12.827 95% CI: 8.931–18.423, $P=.001$). Obesity is one of the fastest growing health problems nowadays. It has direct association with increasing the risk of diabetes, cardiovascular atherosclerotic diseases, and other metabolic diseases, which will lead to a preinflammatory state.[32] It is also reported that obesity and as a component of Metabolic Syndrome possibly play a role in the pathogenesis of benign prostate hyperplasia (BPH) and prostate cancer. On histopathologic and molecular pathologic level, obesity possibly increases insulin resistance, oxidative stress, and releasing inflammatory cytokines (IL 1b, 6, 8, and TNFα) from adipose tissue to cause hypoxia, fibrosis and macrophage, neutrophil infiltration in prostatic tissues.[33,34] Therefore these changes caused by obesity may play a role in occurrence of infectious complications. Meanwhile, obesity was also related with poor wound healing, tissue dehiscence, prolonged inpatient-time which may further increase the risk of infectious complications.[5] As a result, it will not be false to claim obesity could play a certain role in the occurrence of PBI. Through review of the literatures, there was only 1 study had explored the relation between obesity and prostate biopsy infection, and found $BMI > 25\,kg/m^2$ was a risk factor, but the author did not conduct further discussion for the possible reason.[35]

Several studies reported that diabetes mellitus was a definitive risk factor for post biopsy septicemia. The exact mechanism for diabetes increasing the risk of infection was unclear. The hypothesis may include diabetes lead to endothelial dysfunction, atherosclerosis, impairing blood supply and causing chronic ischemia resulting in urinary tract dysfunction and lower systemic resistance.[36] We also noted diabetes was close to significance in multivariate analysis ($P=.053$), which may be caused by relatively limited sample size. The rest factors we evaluated were not significantly associated with infectious complication.

There were several limitations in our study. First, comparing with prior studies, it seemed we had used "too much" additional modalities for preparing biopsy. Such as more form of bowel preparation, intravenous using combined antibiotic, relatively longer duration of antibiotic dosing, etc. Second, the retrospective nonrandomized design makes the patients numbers in the groups are quite different. And there was no standard criterion how physicians choose empirical, combined and targeted prophylaxis. It may lead to selection bias. Third, the relatively small sample size and the incidence of PBI was too low to provide statistical reliability. Fourth, the different antibiotic duration used in group C was different from Group A or B may cause statistical bias. Fifth, we did not consider a previous history of any antibiotic use, as some studies had reported prior antibiotic exposure may be a risk factor and associated with increasing the rate of drug-resistance organisms harbored in rectum.[6,7] And Chinese patients were more easily to have exposure history during their daily lives. Last, the study is lacking a cost-effect analysis for we may have "over done" the preparing work.

5. Conclusion

Our study demonstrated a high incidence of harboring FQ-resistant in Chinese patients. The combined cephalosporin with FQ prophylaxis could significantly decrease the risk of infectious complications related to prostate biopsy. And obesity was an independent risk factor for PBI.

6. Author contributions

Help to collect the raw data: Chenbo Ye, Tao Li, Le Lin, Liefu Ye, Xiangxun Gao.

Performed the statistical analysis: Xiang Wu and Chenbo Yu.

Draft the manuscript: Xiang Wu.

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