A New Nomogram Allowing Physicians to Predict Patients at High Risk of Fever Occurring After Prostate Biopsy

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Background: To facilitate early treatment, we constructed a nomogram to predict risk of postoperative fever before prostate biopsy in patients with high risk of fever.

Material/Methods: We collected information on patients undergoing prostate biopsy from January 2015 to December 2018 from their medical records, including clinical characteristics and laboratory test results. Finally, after strict screening, the prediction model was established in 440 patients who underwent a transrectal prostate biopsy (TRPB). We divided these patients into a training group and validation group at a ratio of 7: 3, respectively. Univariate analysis and multivariate logistic regression analysis were used to select the predictors and to develop the model. Calibration curve and C-index were used to evaluate the accuracy of the nomogram, while DCA was used to assess the clinical value.

Results: The individualized predictive nomogram contained 3 clinical features – Biopsy-positive rate (BPR), Hematuria, and Urine WBC – significantly associated with post-biopsy fever. The nomogram had good discriminating ability in both the training group and validation group – the C-index was 0.774 (95% CI=0.717–0.832) in the training group and 0.808 (95% CI=0.706–0.909) in the validation group. Hosmer-Lemeshow test proved a good calibration curve fit. The DCA curve suggested that the nomogram would have good clinical utility.

Conclusions: This is the first study to develop a nomogram to predict fever after prostate biopsy via Biopsy-positive rate (BPR), Hematuria, and Urine WBC. Use of this nomogram might help prevent fever and infection, and could facilitate individualized medical treatment after prostate biopsy.

MeSH Keywords: Biopsy • Fever • Nomograms • Prostate

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Background

Cancer remains the leading cause of death around the world, and the detection rate of cancer is increasing steadily due to development of medical technology. Cancers of the urinary tract have high incidence and mortality rates. Among these, prostate cancer ranks third in incidence, and it is the second most common cancer in males after lung cancer [1]. It is estimated that 174 650 new cases of prostate cancer were diagnosed in the United States in 2019, resulting in about 31 620 deaths [2].

Prostate biopsy remains the criterion standard for diagnosis of prostate cancer. Transrectal prostate biopsy (TRPB) is one of the main methods widely used in many countries, and it is also recommended by EAU guidelines to diagnose prostate cancer [3]. Although this biopsy technique is considered a mature and safe approach, the associated complications are attracting increasing attention from physicians as the number biopsies performed steadily increases. A report published in 2017 reviewed the complications after prostate biopsy [4], showing that common postoperative complications were pain, bleeding, and voiding dysfunctions, which are usually not fatal and can be quickly cured, and the incidence of postoperative fever and infection was low. Nevertheless, there were adverse events that could be fatal if septicemia develops, which is why prophylactic use of antibiotics was applied during the course of biopsy [5,6]. However, studies from the Global Prevalence Study of Infections in Urology (GPIU) demonstrated that 5% of patients undergoing prostate biopsy still developed infections after prophylactic use of antibiotics [5]. Additionally, recent research shows that, due to increased antibiotic resistance, the use of antibiotics has actually increased the rates of infection instead of decreasing them [7–9]. Therefore, whether antibiotics should be used in prostate biopsy and how to use antibiotics individually have become important issues for clinicians.

Fever is one of the early clinical signs of infection, and a rise in body temperature after a prostate biopsy can suggest a potential infection. Studies have found that biopsy-related infection and fever were associated with various factors, and these can be roughly divided into 2 categories: surgeon-related and host-related [10]. The surgeon-related risks can be controlled and improved via better biopsy methods and surgical procedures, but individual patient differences affect risk of fever and infection, and the relationship between risk of fever and the distribution parameters of related factors needs further study. In the present study, we developed a nomogram to predict fever after prostate biopsy by evaluating host-related risk factors to predict infection.

Material and Methods

Patient enrollment and inclusion criteria

We enrolled patients undergoing prostate biopsy from January 2015 to December 2018 in the First Affiliated Hospital of Anhui Medical University. To obtain more accurate information, we searched the original data from medical records and clinical laboratory information from the laboratory department. We also reviewed data on prostate cancer patients undergoing surgery to search for biopsy information. The search process was approved by the relevant departments.

Inclusion criteria were: (1) first-time prostate biopsy; (2) prostate biopsies were performed by the same team of professional urologists of the First Affiliated Hospital of AHMU; (3) the relevant biopsy records, results of pathology, and information of laboratory test results were complete. Exclusion criteria were: (1) repeat prostate biopsy; (2) indwelling catheter, infections in any part of the body, or any factors which can lead to fever; (3) patients were diagnosed with prostate cancer by TURP; (4) any relevant records were incomplete. The enrollment process is presented in the Supplementary Figure 1.

Clinical characteristics

In this retrospective analysis, ethics approval was obtained and the informed consent requirement was waved. We collected the following clinical data on all enrolled patients: age, height, weight, presence of diabetes or hematuria, and history of alcohol consumption. Results of laboratory tests performed before biopsy were also recorded, including routine blood tests, blood biochemistry, TPSA, and routine urine tests. Body mass index (BMI, weight divided by height squared, kg/m^2), NLR (neutrophil-to-lymphocyte ratio), and A/G (albumin/globulin) were calculated to describe the general condition of the patients, biopsy-positive rate (BPR, the positive numbers divided by the total cores), and Gleason score were used to describe the results of biopsy. To find more potential cases of fever, we defined fever as axillary temperature rising above 37°C after prostate biopsy.

Preparation of biopsy

Standard procedures were performed in accordance with the European Association of Urology Guidelines. The same team of professional urologists performed strict preoperative and intraoperative preparation, including: (1) the oral antibiotics cefdinir and metronidazole were given to patients 3 days before the biopsy, and all anticoagulant and vasodilator drugs were stopped; (2) patients had a fasting blood test on the morning of the biopsy, and then electrocardiography and chest X-ray were performed to exclude patients with contraindications;

(3) patients were asked to fast on the day of the biopsy and underwent a rectal-cleaning enema; (4) digital rectal examination before biopsy; (5) intrarectal iodine perfusion and skin disinfection around the anus; (6) intrarectal instillation of local anaesthesia.

Statistical analysis

STATA 15.0 for Windows (StataCorp, TX, USA) and R version 3.5.1 (R Foundation for Statistical Computing) were used to execute the statistical analysis. In univariate analysis, the Mann-Whitney U test was used to examine ordinally-distributed and continuous variables, while the chi-squared test and Fisher's exact test were used for categorical variables. We performed logistic regression analysis for multivariable analysis, and used the likelihood ratio test with Akaike's information criterion as the stopping rule to execute stepwise regression [11]. To establish the best model, some significant factors from the univariate analysis were also forced into the development of the model and validated. The nomogram was constructed using the "rms package" of R software version 3.5.1, according to the results of the logistic regression analysis. Evaluations of sample size and power analysis were performed in GPower version 3.1.9.2.

To evaluate the nomogram, the following validations were applied. We used the area under the receiver operating characteristic (ROC) curve and calibration curve to assess the sensitivity. The Hosmer-Lemeshow goodness-of-fit test was used to assess fit. All tests were two-tailed, and significant results were considered at P values <0.05. Factors with P value <0.1 were also assessed to explore potential predictors.

Clinical use

Decision curve analysis was conducted to determine the clinical usefulness of the fever-predicting nomogram by quantifying the net benefits at different threshold probabilities in the validation dataset [12]. The optimal threshold was determined by the maximal point of the sum of sensitivity and specificity.

Results

Clinical data and univariate analysis

Through strict criteria screening, we included 440 patients who underwent a prostate biopsy in compliance with the Chinese safety consensus [13]. Patient ages ranged from 46 to 88 years, and the median age was 70 years. Fever developed after biopsy in 72 (16.36%) patients. BRP, Gleason score, Hematuria, Urine WBC, and TPSA were found to be significantly associated with fever ($p<0.01$). In the fever group, the median biopsy-positive

ratio was 0.7, compared with 0.3 in the non-fever group, and the median of TPSA was 25.6 in the fever group, compared with 17.5 in the non-fever group. In terms of Gleason score, patients with ≥7 points accounted for the highest proportion in both groups (80.6% in the fever group and 49.7% in the non-fever group). There were 18 cases each of hematuria and WBC-positive urine in the fever group, accounting for 25% and 26.4% of patients, respectively. Detailed clinical data are shown in Table 1.

With a ratio of 7: 3, all cases were divided into a training group and a validation group via the random split-sample method implemented by "sample" instruction in STATA, including 308 and 132 cases, respectively, and the details are presented in Table 2. There were significant correlations between BPR and fever in the training group ($p<0.01$), compared with the same P value in the validation group. In terms of Hematuria and Urine WBC, their P values were less than 0.01 in both the training group and validation group, as shown in Table 1. Additionally, the P value of Gleason score and TPSA in the training group were less than 0.01, but no statistically significant difference was found in the validation group.

Feature selection and model building

Potential risk factors were identified from overall univariate analysis, then multivariate logistic regression analysis was performed using 3 selection procedures (forward, backward, and stepwise) in the training group. We finally obtained a model from the forward selection process with $p<0.2$ after comparing each procedure. The model included 3 predictors – BPR, Hematuria, and Urine WBC – and Gleason score was excluded. The data are shown in Table 3. Evaluations of sample size and power analysis indicated the sample size was large enough, with a strong power of 0.907.

Performance of the model in the training group

For appraising and comparing the performance of the model in the training group, ROC and calibration curves were drawn in Figures 1 and 2. As shown in the figures and Table 3, the C-index of calibration from the model was 0.774 (95% CI=0.717 to 0.832). It is obvious in Figure 1 that the AUC of the complex model is larger than that of the individual factors, indicating that the complex model had the highest sensitivity. Moreover, the uniformity between the prediction and observation of the model was good, which was also proved by the Hosmer-Lemeshow test ($p=0.106$).

Validation of the model

We used the established model to validate 132 cases in the validation group, and the results are listed in Figures 1 and 2,

Table 1. Characteristics of all patients with fever after biopsy.

Characteristic	Fever*=0 (n= 368)		Fever=1 (n=72)		P**
Age, Me, years	70	(65, 76)	70	(67, 75)	0.62
BMI, No. (%)	24	(21.8, 26)	24.1	(22, 25.2)	0.32
<18.5	15	(4.1)	4	(5.6)	
18.5–24.9	221	(60.1)	48	(66.7)	
≥25	132	(35.9)	20	(27.8)	
Diabetes, No. (%)					0.62
No	343	(94.8)	65	(90.3)	
Yes	25	(5.2)	7	(9.7)	
Drinker, No. (%)					0.17
No	349	(94.8)	65	(90.3)	
Yes	19	(5.2)	7	(9.7)	
BPR***, Me	0.3	(0.0, 0.6)	0.7	(0.4, 0.8)	**<0.01**
Gleason score, No. (%)					**<0.01**
No prostate cancer	132	(35.9)	7	(9.7)	
<7	53	(14.4)	7	(9.7)	
7	67	(18.2)	18	(25)	
>7	116	(31.5)	40	(55.6)	
Hematuria, No. (%)					**<0.01**
No	345	(93.8)	54	(75)	
Yes	23	(6.2)	18	(25)	
Urine WBC, No. (%)					**<0.01**
No	341	(92.7)	53	(73.6)	
Yes	27	(7.3)	19	(26.4)	
Glu, No. (%)					0.17
<11.1	362	(98)	69	(95.8)	
≥11.1	6	(2)	2	(4.2)	
NLR****, Me	2.3	(1.7, 3.1)	2.4	(1.8, 3.3)	0.39
A/G, Me	1.6	(1.4, 1.8)	1.6	(1.4, 1.8)	0.33
TPSA, Me	17.5	(9.6, 40.4)	25.6	(13.7, 84.1)	**<0.01**

* Negative fever was defined as a temperature above 37°C after prostate biopsy, and it was recorded as fever=0. Positive fever was defined as a temperature below 37°C after prostate biopsy, and it was recorded as fever=1; ** Ordinal distributed and continuous variables were calculated using Mann-Whitney U test, and categorical variables were calculated using chi-squared test and Fisher's exact test. P value is derived from the univariable association analyses between each of the clinic variables and Fever. The value of <0.05 is considered to be significantly correlated; *** BPR – biopsy positive rate; **** NLR – neutrophil-to-lymphocyte ratio.

Table 2. Characteristics of patients of fever after biopsy in the training and validation groups.

Characteristic	Training group					Validation group				
	Fever*= 0 (n=255)		fever=1 (n=53)		P**	fever= 0 (n= 113)		fever= 1 (n= 19)		P
Age, Me, years	71	(64, 76)	70	(66, 75)	0.99	69	(65, 75)	71	(69, 74)	0.26
BMI, Me, kg/m²					0.48					0.33
<18.5	11	(4.3)	2	(3.8)		4	(3.5)	2	(10.5)	
18.5–24.9	155	(60.8)	37	(69.8)		66	(58.4)	11	(57.9)	
≥25	89	(34.9)	14	(26.4)		43	(38.1)	6	(31.6)	
Diabetes, No. (%)					0.56					1.00
No	238	(95.3)	48	(90.6)		105	(92.9)	18	(94.7)	
Yes	17	(6.7)	5	(9.4)		8	(7.1)	1	(5.3)	
Drinker, No. (%)					0.1					1.00
No	243	(95.3)	47	(88.7)		106	(93.8)	18	(94.7)	
Yes	12	(4.7)	6	(11.3)		7	(6.2)	1	(5.3)	
BPR***, Me	0.2	(0, 0.7)	0.8	(0.5, 0.8)	**<0.01**	0.3	(0, 0.5)	0.6	(0.4, 1)	**<0.01**
Gleason score, No. (%)					**<0.01**					0.35
No prostate cancer	97	(38)	3	(5.7)		35	(31)	4	(21.1)	
<7	34	(13.3)	6	(11.3)		19	(16.8)	1	(5.3)	
7	39	(15.3)	12	(22.6)		28	(24.8)	6	(31.6)	
>7	85	(33.3)	32	(60.4)		31	(27.4)	8	(42.1)	
Hematuria, No. (%)					**<0.01**					**<0.01**
No	234	(91.8)	39	(73.6)		111	(98.2)	15	(78.9)	
Yes	21	(8.2)	14	(26.4)		2	(1.8)	4	(21.1)	
Urine WBC, No. (%)					**<0.01**					**<0.01**
No	121	(91)	40	(75.5)		109	(96.5)	13	(68.4)	
Yes	23	(9)	13	(24.5)		4	(3.5)	6	(31.6)	
Glu, No. (%)					0.35					0.27
<11.1	250	(98)	51	(96.2)		112	(99.1)	18	(94.7)	
≥11.1	5	(2)	2	(3.8)		1	(0.9)	1	(5.3)	
NLR****, Me	2.3	(1.7, 3)	2.4	(1.9, 3.3)	0.28	2.3	(1.6, 3.1)	2.4	(1.4, 3)	0.70
A/G, Me	1.6	(1.4, 1.8)	1.6	(1.4, 1.8)	0.59	1.5	(1.4, 1.7)	1.6	(1.4, 1.8)	0.30
TPSA, Me	17.5	(10.1, 42)	26.1	(14.2, >89.2)	**<0.01**	17.3	(9.5, 38.6)	22.1	(10.1, 56.1)	0.38

* Negative fever was defined as a temperature above 37°C after prostate biopsy, and it was recorded as fever=0. Positive fever was defined as a temperature below 37°C after prostate biopsy, and it was recorded as fever=1; ** Ordinal distributed and continuous variables were calculated using Mann-Whitney U test, and categorical variables were calculated using chi-squared test and Fisher's exact test. P value is derived from the univariable association analyses between each of the clinic variables and Fever. The value of <0.05 is considered to be significantly correlated; *** BPR – biopsy positive rate; **** NLR – neutrophil-to-lymphocyte ratio.

Table 3. Predictors for postoperative fever following prostate biopsy.

		Model	
	β*	Odds ratio (95% CI)	P
Intercept and variable			
Intercept	−2.881	–	–
BPR**	2.186	8.896 (3.534 to 22.391)	<0.01
Hematuria	0.720	2.054 (0.856 to 4.928)	0.107
Urine WBC	0.800	2.226 (0.917 to 5.403)	0.077
C-index			
Training dataset		0.774 (0.717 to 0.832)	
Validation dataset		0.808 (0.706 to 0.909)	

* β is the regression coefficient; ** BPR – biopsy positive rate.
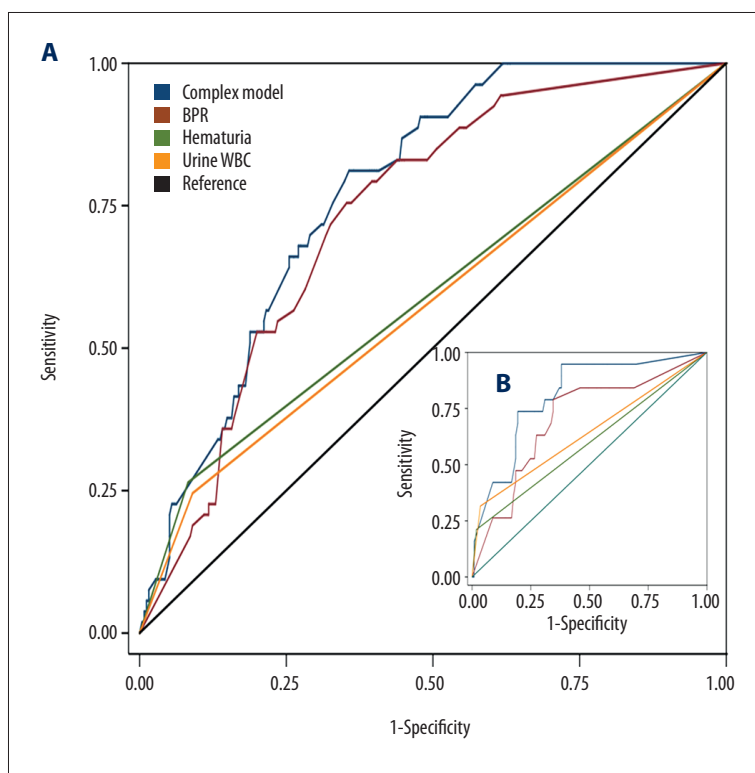
Figure 1. Receiver operating characteristic (ROC) curves of the established model and single feature in training group (**A**) and validation group (**B**).

which show that the C-index of the complex model in the validation group was 0.808 (95% CI=0.706 to 0.909), indicating a surprising improvement compared with the C-index of single features. Good predictive discrimination was shown by the calibration curve, and this was verified by the Hosmer-Lemeshow test. The *p* value of the H-L test was 0.157, which was not statistically significant, indicating no difference between observed and predicted values.

Development of the fever-prediction nomogram

Comparison of the complex model and single features showed that BPR, Hematuria, and Urine WBC were predictors (Table 3). We eventually presented the nomogram using the above features and show it in Figure 3.

Clinical use

Decision curve analysis was used to test the nomogram's clinical value [12]. As shown in Figure 4, the threshold probability ranged from about 4% to 45%. This indicated the nomogram
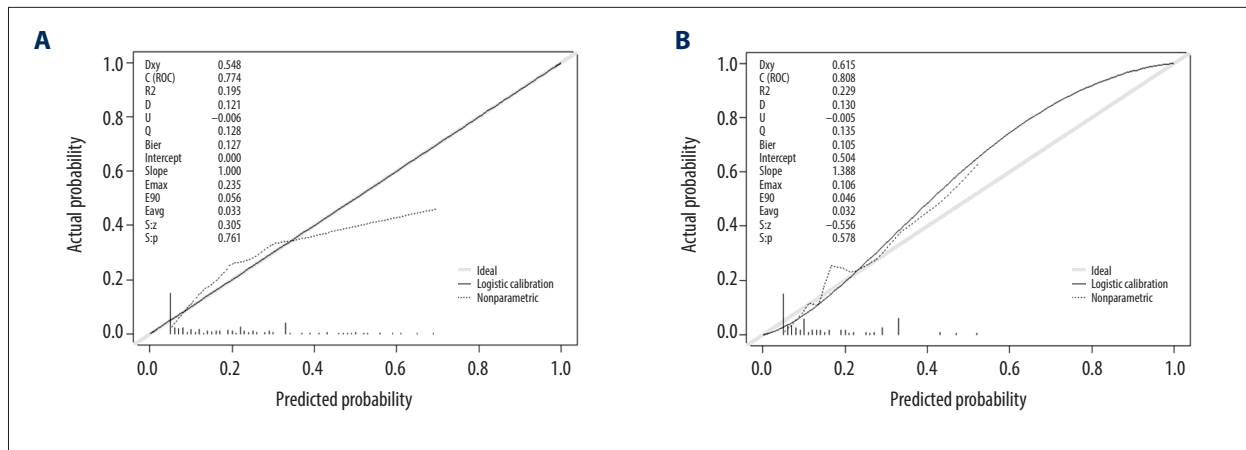
Figure 2. Calibration curves of the model in training group (**A**) and validation group (**B**). Calibration curves depict the calibration of the established model in terms of agreement between the predicted risks of fever and observed outcomes of fever after prostate biopsy. The y-axis represents the actual fever rate. The x-axis represents the predicted risk.
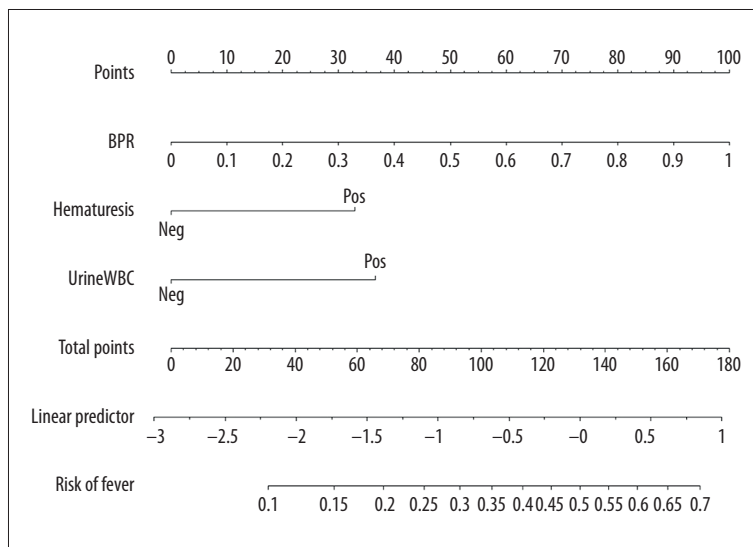

Figure 3. Nomogram to predict fever after prostate biopsy. The nomogram was developed in the training group. Each clinical factor corresponds to a specific point by drawing a line straight upward to the Points axis. After the sum of the points is located on the Total Points axis, the sum represents the probability of risk of fever after prostate biopsy axis.

has clinical value, and when the prediction probability was in this range, there was a net benefit. For example, if the personal threshold probability of a patient is 11% (the Youden index, sensitivity+specificity–1) – in other words, the patient would opt for treatment if the probability of fever was 11% – then the net benefit is 0.086, when using the radionics nomogram to make the decision of whether to undergo treatment, with more benefit than with the treat-all scheme or the treat-none scheme, and 8.6 out of 100 patients benefited at no expense to anyone else. Figure 4B shows that the net reduction in interventions per 100 patients was about 38.5.

Discussion

Biopsy of suspected prostate cancer by transrectal prostate biopsy (TRPB) for pathological diagnosis has a low incidence of complications, has good patient tolerance, and is generally considered safe, but infectious complications can also occur. In particular, the incidences of severe urinary tract infection (UTI) and sepsis are about 6% and 1%, respectively [14,15], which negatively affect patient health and emotional well-being, as well as incurring economic costs [16].

Nomograms are widely used in many aspects of clinical medicine, such as for detecting diseases and complications, or predicting prognosis. In fact, as early as 2010, the NCCN clinical guidelines recommended use of nomograms to screen for prostate cancer [17]. In the present study, we established a predictive nomogram based on patient clinical characteristics to assess the probability of fever after a prostate biopsy. We tried to provide a convenient and effective method for individualized prediction, which we hope will improve treatment and prevent infection.
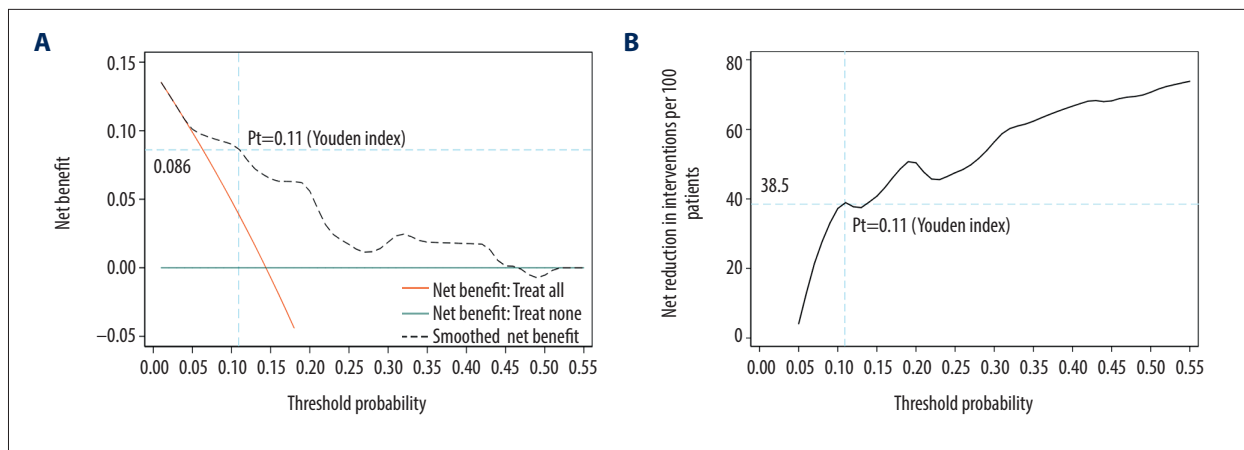
Figure 4. Decision curve analysis for the model. The y-axis measures the net benefit (**A**) and net reduction in interventions per 100 patients (**B**). The x-axis shows the threshold probability. The black line represents the nomogram, the orange line represents the assumption that all patients have fever, the green line represents the assumption that no patients have fever, and the light blue line represents the Youden Index (sensitivity+specificity–1).

All patients in the present research were prepared for biopsy following standard procedures, and they took cefdinir and metronidazole orally for 3 days prior to biopsy. Transrectal prostate biopsies were performed by the same group of professionally trained physicians who followed standard, internationally recognized methods of disinfection such as rectal-cleaning enema and intrarectal iodine perfusion [6]. Patients underwent biopsies from 12 cores, and there were no repeat biopsies or indurations of catheters 1 week before biopsy. This eliminated the effect of different biopsy methods and procedures, allowing us to better explore the role of individual factors in post-biopsy fever.

For the construction of the host-related signature, 12 clinical features were reduced to 3 risk factors via crude univariate analysis and selection procedures in multivariate analysis, which included forward, backward, and stepwise regression analysis [11]. We selected $p<0.1$ as the statistical significance level for choosing variables to include in the model, and the prediction-outcome association of the 3 signatures was also verified by best subset regression. Eventually, the nomogram, composed of 3 features, showed adequate discrimination in the training group and validation group, with C-indexes of 0.774 and 0.808, respectively. Hosmer-Lemeshow test results also proved good consistency between the calibration curve and the 45-degree ideal line.

It is interesting that the coefficient of biopsy-positive rate (BPR) is the highest one in the nomogram, which suggests a close relationship between high BPR and postoperative fever. From this we conclude that a biopsy of cancerous tissue is more likely to cause fever than is a biopsy of normal prostate tissue. This conclusion has not been reported in previous studies, suggesting BRP may be a new predictor of fever and infection after biopsy. Although BPR can only be known after biopsy, we can still estimate it by evaluating the range of suspected cancer nodules through prostate MRI and other relevant tests before biopsy, so as to provide individualized treatment for patients with high risk of fever and infection.

Hematuria and Urine WBC indicated possible UTI and prostatitis. Previous reports have confirmed that urogenital tract infection is a risk factor for antibiotic resistance [18], as well as risk for infection after prostate biopsy [19,20]. These 2 characteristics were also important components of our nomogram, which showed that our research had good agreement with previous results. It was reported that diabetes increases the risk of drug-resistant bacteria and infectious complications [19,21]; however, in our study, unifactorial analysis in the training group showed no significant correlation between diabetes ($p=0.56$), fasting blood glucose before biopsy ($p=0.35$), or fever after biopsy.

Our study has certain limitations. Firstly, there are some other clinical factors that can also affect fever and infection after biopsy, such as recent travel [22,23], exposure to unclean water sources, and staying in a healthcare facility [16,24]. It is unfortunate that we could not find and assess accurate information about these conditions from case records, which is why our nomogram did not include these factors. Secondly, for patients with fever after biopsy, reactive fever and infectious fever could not be effectively distinguished. In addition, the effective threshold in DCA ranged from approximately 4% to 45%. These limitations require that our results be verified by studies with larger sample sizes and more accurate patient records. We plan to conduct a prospective study in the future to make up for these weaknesses.

Although it has certain shortcomings, our study shows the close relationship between high BPR and fever after a prostate biopsy, and the nomogram allows individualized prediction of fever after biopsy. In conclusion, we successfully established a new nomogram to assist in development of individualized treatment plans for patients and to prevent infectious complications after prostate biopsy.

Conclusions

We constructed a nomogram that predicts postoperative fever in patients with prostate biopsy, and 3 features – biopsy-positive rate (BPR), Hematuria, and Urine WBC – were considered as risk factors. We hope that use of our nomogram will help prevent fever and infection and improve individualized medical treatment after prostate biopsy.
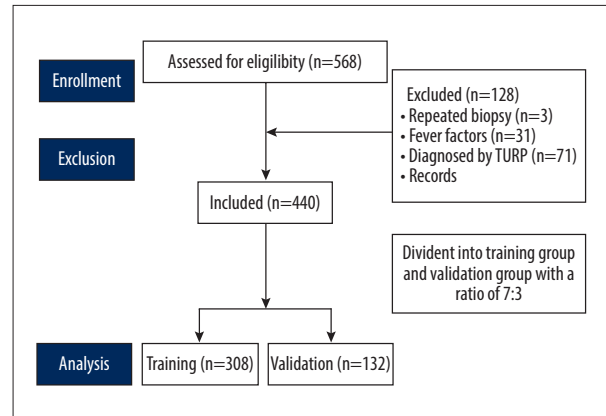
Conflict of interest

None.

Supplementary Data

Supplementary Figure 1. Flowchart of selection and grouping procedures.

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