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Development and Validation of a Nomogram for Predicting Bladder Calculi Risk in Patients with Benign Prostatic Hyperplasia

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Abstract

Objective: To develop and validate a nomogram for predicting bladder calculi risk in patients with Benign Prostatic Hyperplasia (BPH).

Methods: A total of 368 patients who underwent Transurethral Resection of the Prostate (TURP) and had histologically proven BPH from January 2018 to January 2021 were retrospectively collected. Eligible patients were randomly assigned to the training and validation datasets. Least Absolute Shrinkage and Selection Operator (LASSO) regression was used to select the optimal risk factors. A prediction model was established based on the selected characteristics. The performance of the nomogram was assessed by calibration plots and the Area under the Receiver Operating Characteristic curve (AUROC). Furthermore, Decision Curve Analysis (DCA) was used to determine the net benefit rate of the nomogram.

Results: Among 368 patients who met the inclusion criteria, older age, a history of diabetes and hyperuricemia, longer intravesical Prostatic Protrusion (IPP) and larger Prostatic Urethral Angulation (PUA) were independent risk factors for bladder calculi in patients with BPH. These factors were used to develop a nomogram, which had a good identification ability in predicting the risk of bladder calculi in patients, with AUROCs of 0.911 (95% CI: 0.876–0.945) in the training set and 0.884 (95% CI: 0.820–0.948) in the validation set. The calibration plot showed that the model had good calibration. Moreover, DCA indicated that the model had a good clinical benefit.

Conclusion: We developed and internally validated the first nomogram to date to help physicians assess the risk of bladder calculi in patients with BPH, which may help physicians improve individual interventions and make better clinical decisions.

Keywords: Bladder calculi; Benign prostatic hyperplasia; Risk factors; Nomogram; Decision curve analysis

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Introduction

Benign Prostatic Hyperplasia (BPH) is the one of common benign diseases in urology, with a prevalence of 50% in men over 60 years of age, a figure that increases to 83% when men reach 80 years of age or older [1]. Bladder calculi is one of the common complications of BPH. Bladder calculi account for 5% of urinary calculi in developed countries, and they are responsible for 8% of urolithiasis-related mortalities in developed nations [2,3], with even worse incidence in developing countries [4]. With the increasing average life expectancy of the elderly population, the incidence of BPH due to bladder calculi is expected to increase. According to the European Association of Urology (EAU) recommendations [5], in general, the presence of bladder calculi in patients with BPH requires surgical intervention. Bladder calculi in patients with BPH not only increase patients' suffering and medical costs but can also increase perioperative risk due to a prolonged operative time. Although bladder calculi formation is believed to be associated with Bladder Outlet Obstruction (BOO) [6-8] and urinary stasis [9], in patients with urinary retention, bladder calculi develop in only 3% to 8% of patients with BOO due to BPH [10,11]. The role of the prostate in the pathogenesis of bladder stones remains unclear. Therefore, the condition is likely the result of complex interaction of multiple factors. Published studies [3,9,12] have identified some risk factors for bladder calculi in BPH patients, including older age, longer Intravesical Prostatic Protrusion (IPP), lower maximum uroflow rate (Qmax), lower urinary pH and magnesium, higher uric acid

super saturation and a history of gout. However, to date, there is no research to develop an ideal model for predicting bladder calculi risk in patients with BPH. Therefore, a quantifying and managing risk factor is extremely important for the prevention of bladder calculi to reduce both the rate of gravel surgery and the economic burden. In this study, we confirmed the independent risk factors that influence bladder calculi formation in patients with BPH. Based on the risk factors, we developed a nomogram for predicting the risk of bladder calculi in patients with BPH, which might help physicians provide further individualized clinical decisions.

Materials and Methods

Study population

In this retrospective observational study, patients aged 50 years or older who had IPSS ≥ 8, underwent TURP and had histologically proven BPH at the First Affiliated Hospital of Xi'an Jiaotong University between January 2018 and January 2021 were enrolled. The exclusion criteria included a history of upper urinary tract calculi, diagnosed with urological tumor, neurogenic bladder, and bladder foreign body, bladder diverticulum, bladder neck contracture, and urethral stricture, history of transurethral resection of the prostate or insufficient clinical data. Of the total patients, 1100 patients were selected, based on the inclusion and exclusion criteria, 368 patients were selected for the final data analysis in our study. The enrolled patients were randomly assigned to a development set (n=260) and a validation set (n=108) at a ratio of 7:3, and the flowchart of the study participants is shown in Figure 1. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Xi 'an Jiaotong University, Xi 'an, China.

Data collection

We collected patient variables, including age, Body Mass Index (BMI), BPH duration, Prostate Specific Antigen (PSA), IPSS, previous medical history of hypertension, diabetes, Coronary Heart Disease (CHD) and hyperuricemia/gout (uric acid ≥ 7 mg/dl), urodynamic examination, and transrectal ultrasonography. A single urologist performed Transrectal Ultrasonography (TRUS) using a single ultrasound machine (ProFocus, BK Medical, Herlev, Denmark) in the condition of proper filling of the bladder (150 mL to 200mL) to measure and record the Total Prostate Volume (TPV), Transitional Zone Volume (TZV), IPP, PUA. The TPV and TZV were measured using the prostate ellipsoid formula (height × width × length × π/6). IPP was defined by measuring the distance from the bladder circumference at the prostate base to the tip of the protruding prostate gland in the sagittal plane [13]. The PUA was defined as the angle formed by 2 rays of both the proximal and distal prostatic urethra on the mid sagittal plane image [14]. The peak flow rate and Post Void Residual (PVR) were determined according to International Continence Society Good Urodynamic Practices [15]. All the patients underwent TURP with or without endoscopic lithotripsy. Postoperative bladder stone composition data were also collected.

Statistical analysis

Statistical analyses were performed and graphs were generated using SPSS 22.0 software (IBM Corporation, Chicago, IL, USA), R version 3. 4.1 software (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism version 8 (GraphPad Software, La Jolla, CA, USA). Categorical variables are presented as frequencies and percentages and were compared using the Pearson chi-square test or Fisher's exact test, as appropriate. Continuous variables are presented as the means ± standard deviation or as medians and interquartile ranges according to their distribution and were compared using Student's t test or the Mann–Whitney U test. In the training set, a nomogram for screening and predicting bladder calculi risk in patients with BPH was developed using LASSO regression based on the selected factors. To validate the discriminatory performance of the nomogram, the AUROC of the nomogram was calculated for both the training and validation sets. The calibration of the nomogram was assessed using the Hosmer–Lemeshow test and calibration plots. Internal validation was performed via a bootstrap method with 1000 re-samples. Then, DCA was conducted to evaluate the nomogram's clinical benefit. All P<0.05 was considered statistically significant.

Results

Baseline characteristics between the training and validation sets

A total of 368 patients were randomly assigned to the training set (n=260) and the validation set (n=108). All data, baseline characteristics of patients in the training set and validation set, are provided in Table 1. There were no significant differences between the training set and the validation set (P>0.05).

Clinical parameters of patients in the bladder calculi group and non-bladder calculi group

Among 368 patients with BPH and 94 patients with BPH developed bladder calculi. Principal component analysis of the bladder stones revealed that pure stones comprised 52.1% of the total, with calcium oxalate stones accounting for 20.3%, uric acid/urate stones for 19.1%, and magnesium ammonium phosphate (struvite) stones for 12.7%. Age, IPSS, PUA and IPP were higher in the bladder

Table 1: Baseline characteristics of patients in the training and validation sets.

Variable	Training set	Validation set	
	n=(260)	(n=108)	P value
Age (years)	68.3 ± 7.5	69.0 ± 7.8	0.421
Bladder calculi	63 (24.2)	31 (28.7)	0.37
IPSS	20.4 ± 4.4	20.3 ± 4.5	0.083
BMI (kg/m^2)	23.5 ± 3.2	23.6 ± 2.8	0.757
PSA (ng/ml)	6.5 ± 6.9	6.4 ± 7.5	0.932
BPH medication (months)	54.6 ± 51.5	61.6 ± 63.9	0.266
AUR	82 (31.5)	31 (28.5)	0.591
Comorbidities			
Hypertension	95 (36.5)	36 (33.3)	0.559
Diabetes	37 (14.2)	17 (14.2)	0.709
CHD	35 (13.5)	21 (21.3)	0.146
Hyperuricemia	26 (10.0)	13 (12.0)	0.563
Uroflow parameters			
Qmax (ml/s)	6.6 ± 3.3	6.3 ± 3.1	0.373
PVR (ml)	58.7 ± 70.0	63.6 ± 92.5	0.583
TRUS			
IPP (mm)	6.5 ± 4.5	7.0 ± 5.0	0.322
TPV (ml)	66.0 ± 36.0	65.0 ± 28.5	0.794
PUA (°)	32.7 ± 8.5	33.4 ± 8.4	0.432
TZV (ml)	34.0 ± 22.5	33.1 ± 18.5	0.704

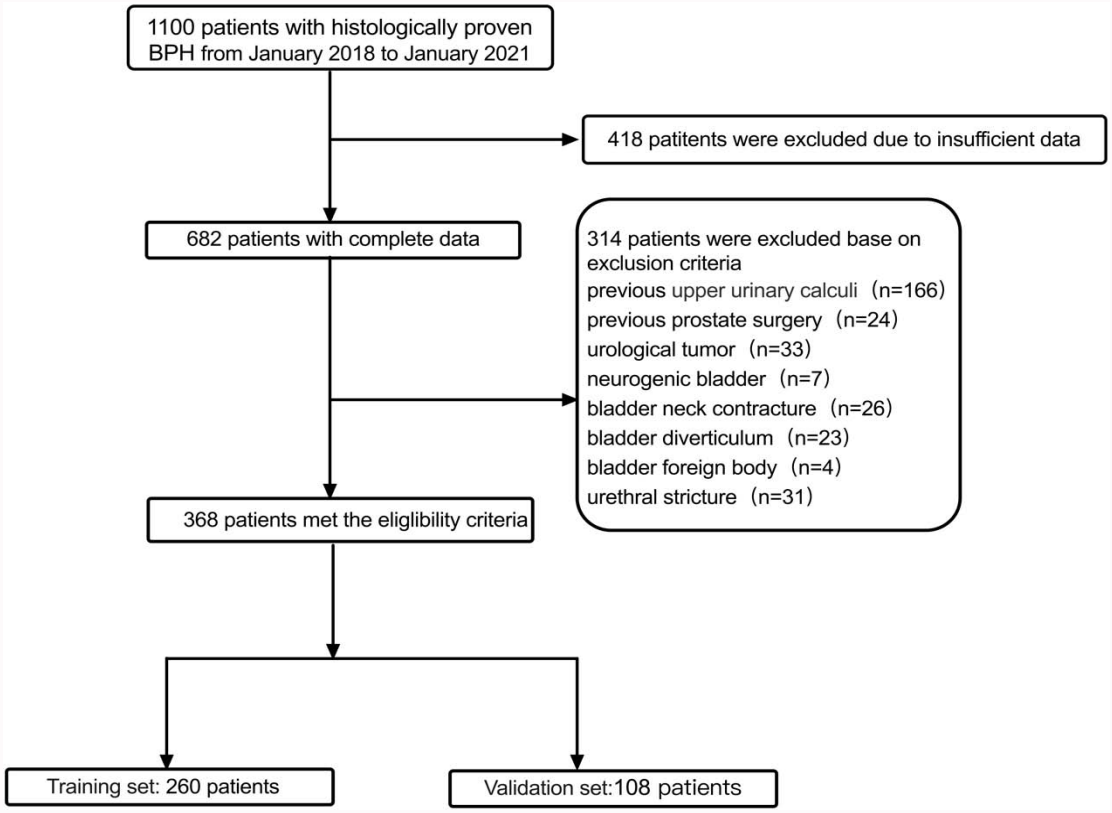

Figure 1: Admission flow chart of BPH patients.

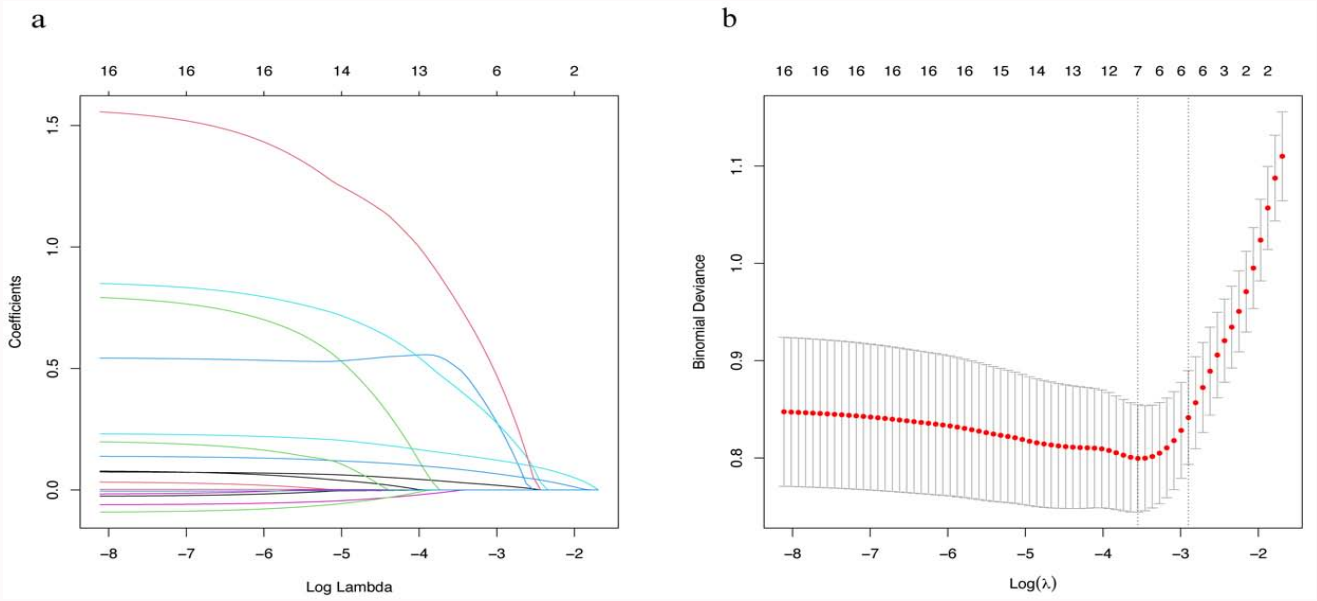

Figure 2: Risk predictor selection using the LASSO regression model. (a) LASSO coefficient profiles of 16 variables. (b) Identification of the optimal penalization coefficient (λ) in the LASSO model was achieved by 10-fold cross-validation and the minimum criterion. A vertical line was drawn at the value selected with tenfold cross-validation, where optimal lambda resulted in 6 predictors with nonzero coefficients (lambda =0.060).

calculi group. Moreover, BPH patients with bladder calculi had higher prevalence rates of AUR, diabetes, hypertension and hyperuricemia than those without bladder calculi, and the Qmax was significantly lower in the bladder calculi group. The differences were statistically significant ($p<0.05$). Conversely, the difference in other indicators was not statistically significant. The clinical parameters of the bladder calculi and non-bladder calculi groups were summarized in Table 2.

Independent predictors for bladder calculi in BPH patients

Because LASSO regression could effectively avoid redundancy or over fitting in the selection of the most informative factors, we performed LASSO regression to confirm risk predictors for

Table 2: Clinical parameters of patients in the bladder calculi group and non-bladder calculi group.

Variable	Bladder calculi	Non-bladder calculi	
	(n=94)	(n=274)	P valve
Age (years)	71.6 ± 6.9	67.5 ± 7.5	<0.001*
IPSS	21.1 ± 3.0	20.1 ± 4.8	0.026*
BMI (kg/m^2)	23.8 ± 3.5	23.4 ± 2.9	0.329
PSA (ng/ml)	6.1 ± 7.8	6.6 ± 6.8	0.607
BPH duration (months)	65.5 ± 51.0	53.6 ± 56.6	0.073
AUR	38 (40.4)	75 (27.4)	0.018*
Comorbidities			
Hypertension	47(50.0)	84 (30.7)	0.001*
Diabetes	22 (23.4)	32 (11.7)	0.006*
CHD	19 (19.4)	37 (13.5)	0.118
Hyperuricemia	18 (19.1)	21 (7.7)	0.002*
Uroflow parameters			
Qmax (ml/s)	5.3 ± 2.5	6.9 ± 3.4	<0.001*
PVR (ml)	62.3 ± 80.0	59.4 ± 76.4	0.375
TRUS			
IPP (mm)	9.9 ± 4.6	5.5 ± 4.1	<0.001*
TPV (ml)	63.1 ± 33.6	66.5 ± 34.1	0.396
PUA (°)	38.8 ± 6.5	30.9 ± 8.1	<0.001*
TZV (ml)	34.3 ± 23.7	33.5 ± 20.6	0.745

Values are presented as n (%) or as the mean ± SD

Table 3: LASSO regression analysis of independent risk factors for bladder calculi in patients with BPH.

Variable	β	OR (95% CI)	P value
Hyperuricemia	1.377	3.963 (1.404, 11.503)	0.010*
Age (years)	0.058	1.059 (1.005, 1.119)	0.035*
Diabetes	0.985	2.679 (1.029, 7.129)	0.045*
IPP (mm)	0.198	1.219 (1.131, 1.326)	<0.001*
PUA (°)	0.132	1.141 (1.084, 1.209)	<0.001*

β: Regression Coefficient; OR: Odds Ratio; CI: Confidence Interval

bladder calculi in BPH patients (Figure 2). Sixteen risk predictors were reduced to six potential risk factors based on the training set. Subsequently, multivariate analysis of the six potential factors was performed. Five factors were found to be associated with bladder calculi risk in patients with BPH (P<0.05). The five independent risk factors were age, diabetes, hyperuricemia, IPP and PUA, which is summarized in Table 3.

Construction and evaluation of the nomogram

For convenient clinical use, based on the independent risk factors, we drew a readily visualized nomogram of this predictive model (Figure 3a). The nomogram consisted of five variables: Age, diabetes, hyperuricemia, IPP and PUA. The total score value of each individual patient was obtained by adding the corresponding scores of different categories of each independent risk factor, and then the corresponding total points scale represented the probability of bladder calculi of BPH patients. The training and validation sets had AUROCs of 0.911 (95% CI: 0.876–0.945) and 0.884 (95% CI: 0.820–0.948), respectively (Figure 3b, 3c). In addition, the Hosmer–Lemeshow test AUROCs for the nomogram to predict bladder calculi were 0.564 and 0.544 in the training and validation sets, respectively, which demonstrated reasonable calibration performance, and the favorable calibration curves of our nomogram are shown in Figure 3d, 3e. Finally, the DCA showed a high net benefit across the entire spectrum of probability thresholds (Figure 3f), indicating that the model could provide additional clinical benefit when predicting the threshold of bladder stone probability in BPH patients from 4% to 78%.

Discussion

Bladder calculi secondary to BPH have the characteristics of high rates of urinary tract infection and surgery; they not only bring great pain to patients but also increase their economic burden. Unfortunately, management of bladder calculi in conjunction with BPH is a laborious, time-consuming and arduous procedure, particularly in patients with comorbidities who might not tolerate lengthy and extended procedures. Moreover, Chu et al. [16] found that that people with a previous diagnosis of bladder calculi were more likely to develop bladder cancer. Therefore, we used LASSO regression to identify independent risk factors for cystolithiasis and developed a visual nomogram to predict bladder calculi risk in patients with BPH to reduce the burden on the health of older men and on medical costs. In the present study, we found five independent risk factors associated with bladder calculi in patients with BPH, including age, history of diabetes and hyperuricemia/gout, IPP and PUA. More importantly, we developed and validated a nomogram for predicting bladder calculi in patients with BPH. Our nomogram combines the reported clinical risk factors (i.e., age, history of gout, and IPP) [3,9,12] and incorporates several novel risk factors that are relevant in this patient population: PUA and history of diabetes. PUA correlates with BPH clinical progress and poor uroflow rate. PUA is an ultrasound parameter for predicting BOO, which is a bent tube, and the clinical significance of the PUA was recently reported [17-20]. An increased PUA may be the result of a higher bladder neck in men, which can better reflect the fluid dynamics of the urine passing through the prostatic urethra. Cho et al. [21] suggested that energy loss in the bending tube in the prostatic urethra could occur during micturition, which could reflect the degree of obstruction in the process of urination. Our study found that the urine flow rate is inversely associated with PUA. Excessive PUA affects the smooth discharge of urine and is more likely to lead to the formation of urinary salt deposits in the bladder. Some studies [22,23] have confirmed that diabetes is significantly associated with an increased risk of upper urinary calculus. Interestingly, in our study, we also found that diabetes was an independent risk factor for the development of bladder stones in patients with BPH, suggesting a role of metabolic abnormalities in the formation of bladder stones. Stone formers with diabetes may have more acidic urine than stone formers without diabetes [24], and a low urinary pH plays a major role in the formation of uric acid stones. In addition, the compensatory hyperinsulinemia of insulin resistance may increase the urinary excretion of calcium [25]. At the same time, previous studies suggested that IPP could be a predictor for bladder calculi, and in our study, we found that longer IPP was an independent risk factor for bladder calculi. The corrected OR was 1.219, indicating that each 1 mm increase in IPP was associated with an 21.9% increased risk of bladder calculi in patients with BPH. Thus, the application of the five risk predictors in our nomogram is well founded. In this study, we considered the variables needed in our nomogram to be prevalent in clinical practice and convenient to acquire. Regarding the prediction of bladder calculi in patients with BPH, the AUROCs, calibration

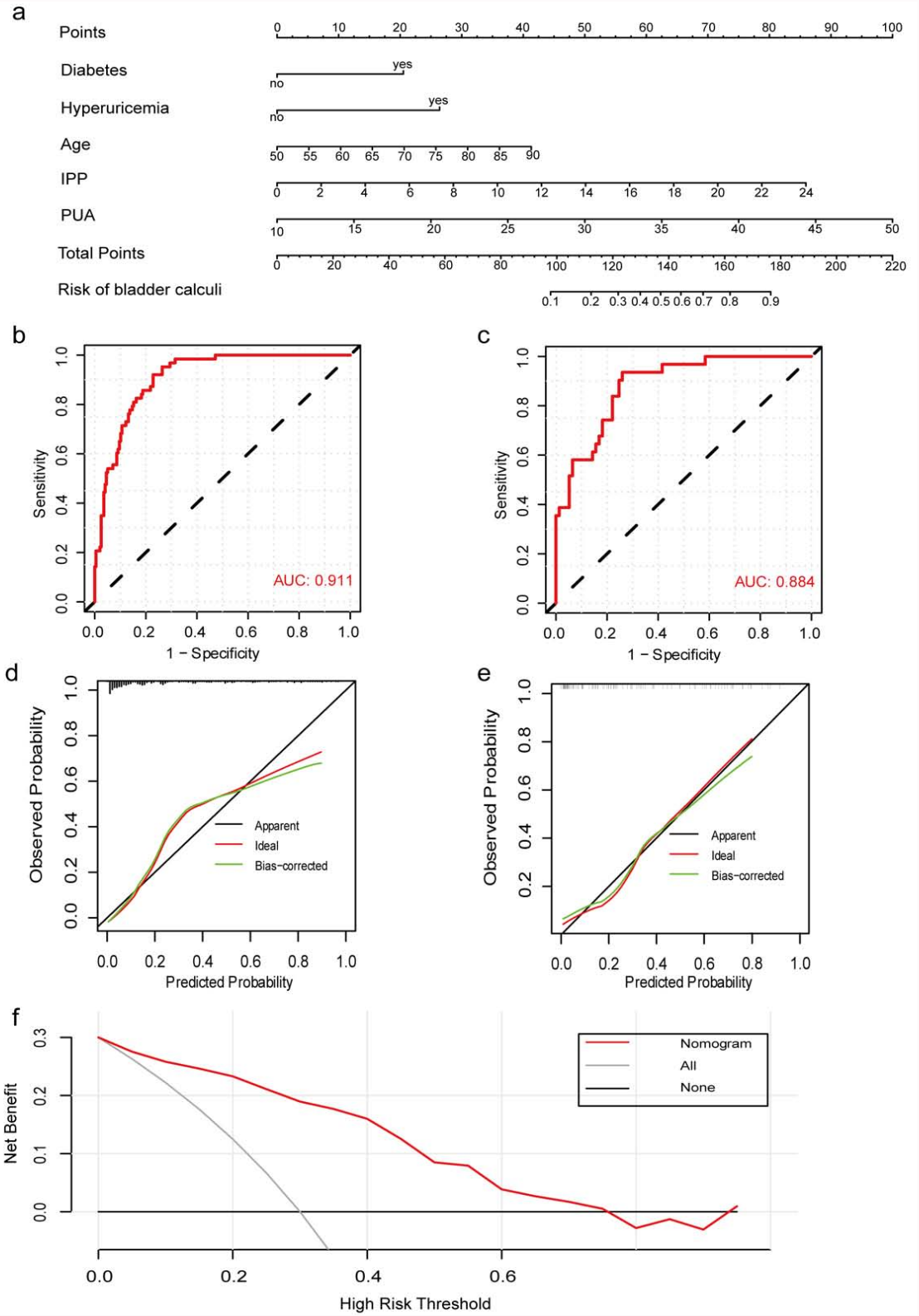

Figure 3: (a) A nomogram based on the selected independent risk factors from the LASSO regression model for predicting bladder calculi in BPH patients. The nomogram consisted of five variables: Age, diabetes, hyperuricemia, IPP and PUA. Based on the sum of corresponding points of each variable, total points could be calculated and therefore evaluated for the risk of bladder calculi. **(b)** ROC curve of the nomogram. The area under the receiver operating characteristic curve of the nomogram was 0.911 (95% CI: 0.876–0.945). **(c)** ROC curve of the nomogram. The area under the receiver operating characteristic curve of the nomogram was 0.884 (95% CI: 0.820–0.948). Calibration plots for the nomogram in the training set **(d)** and in the validation set **(e)**. The X-axis represents the nomogram-predicted probability of bladder calculi, and the Y-axis represents the actual probability of bladder calculi. Plots along the 45-degree line indicate a perfect calibration model in which the predicted probabilities are identical to the actual outcomes. **(f)**. DCA revealed that the nomogram shows a positive net benefit, indicating that it has good clinical utility in predicting the risk of bladder calculi in patients with BPH. The x-axis represents the threshold probability, and the y-axis measures the net benefit. The threshold probability is where the expected benefit of treatment balances the expected benefit of avoiding treatment.

plots and the decision curve showed a good correspondence and a high net benefit. Therefore, this nomogram can serve as an excellent tool for predicting bladder calculi in patients with BPH. To our knowledge, this is the first study to establish a nomogram that can objectively and accurately predict the individualized risk of bladder calculi for patients with BPH. This nomogram will help to screen the risk of bladder calculi in BPH patients and provide individualized interventions, which may effectively reduce the rate of gravel surgery in BPH patients. Although our nomogram demonstrated impressive performance in bladder calculi prediction, there are some limitations associated with our study. First, factors such as pH, magnesium, and uric acid in 24-h urine were not included in this study because the relevant data could not be obtained from our institution. However, we did our best to include systemic metabolic factors. Second, this is a retrospective study with inevitable bias. Third, the validation set was derived from the same institution as the training set. Even with perfect internal validation, the presented nomogram is not yet suitable for general use prior to validation in external cohorts. Thus, external and multicenter prospective clinical trials with large sample sizes are still needed to validate the clinical application of our model.

Conclusion

In conclusion, the nomogram based on the results of LASSO regression can individually predict the risk of bladder calculi in patients with BPH. Therefore, it may help physicians improve individual interventions and make better clinical decisions.

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