

Development and validation of a preoperative nomogram for predicting positive surgical margins after laparoscopic radical prostatectomy

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Abstract

Background: Positive surgical margins are independent risk factor for biochemical recurrence, local recurrence, and distant metastasis after radical prostatectomy. However, limited predictive tools are available. This study aimed to develop and validate a preoperative nomogram for predicting positive surgical margins after laparoscopic radical prostatectomy (LRP).

Methods: From January 2010 to March 2016, a total of 418 patients who underwent LRP without receiving neoadjuvant therapy at Peking University Third Hospital were retrospectively involved in this study. Clinical and pathological results of each patient were collected for further analysis. Univariable and multivariable logistic regression (backward stepwise method) were used for the nomogram development. The concordance index (CI), calibration curve analysis and decision curve analysis were used to evaluate the performance of our model.

Results: Of 418 patients involved in this study, 142 patients (34.0%) had a positive surgical margin on final pathology. Based on the backward selection, four variables were included in the final multivariable regression model, including the percentage of positive cores in preoperative biopsy, clinical stage, free prostate specific antigen (fPSA)/total PSA (tPSA), and age. A nomogram was developed using these four variables. The concordance index (C-index) of the nomogram was 0.722 in the development cohort and 0.700 in the bootstrap validations. The bias-corrected calibration plot showed a limited departure from the ideal line with a mean absolute error of 2.0%. In decision curve analyses, the nomogram showed net benefits in the range from 0.2 to 0.7.

Conclusion: A nomogram to predict positive surgical margins after LRP was developed and validated, which could help urologists plan surgical procedures.

Keywords: Prostate cancer; Positive surgical margins; Laparoscopic radical prostatectomy; Nomogram

Introduction

Prostate cancer is the most common cause of non-epithelial male cancer, and it is the third leading cause of all non-epithelial male cancer deaths.^[1] Laparoscopic radical prostatectomy (LRP) is considered the most widely used treatment for patients with localized prostate cancer.^[2] However, after the surgery, approximately 20% of patients have a positive surgical margin (PSM), which is an independent risk factor for biochemical recurrence, local recurrence, and distant metastasis.^[3-8] In addition, a PSM is an important indication for adjuvant radiation therapy.^[9,10] Therefore, tools to predict PSM are needed so that optimal treatment strategies can be available.

In the past decade, several studies have correlated preoperative factors with the margin status after radical prostatectomy.^[11-13] However, many of these studies have been limited by a small sample size and various confounders; therefore, they have failed to give a validated nomogram for prediction. On top of that, most studies were based on a cohort of European or American people.

Among all predictors, preoperative predictors are of the utmost importance because they may be helpful in planning the surgery. As a result, this study aimed to develop and validate a nomogram for predicting the likelihood of a PSM by evaluating the preoperative

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000000161

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Chinese Medical Journal 2019;132(8)

Received: 06-01-2019 Edited by: Xin Chen

variables from 418 consecutive patients who underwent LRP.

Methods

Ethical approval

The present study was approved by the Ethics Committees of Peking University Third Hospital. Written informed consent forms were provided by all of the subjects prior to their enrollment of the study.

Patients

From January 2010 to March 2016, a total of 499 consecutive patients who underwent LRP without receiving neoadjuvant therapy at Peking University Third Hospital were retrospectively involved in this study. Of these patients, 81 were excluded because of incomplete outcome information. Data from the remaining 418 patients were used for further analysis. Previously defined preoperative risk factors, including the patient age, body mass index (BMI), total prostate specific antigen (tPSA) level, clinical stage, palpable nodules in digital rectal examination, number and percentage of positive cores in preoperative biopsy, surgeon experience (the experience of the surgeon was categorized into <20 cases, 20–49 cases, 50–100 cases and >100 cases) and primary and secondary biopsy Gleason Scores in preoperative biopsy, were assessed. Both biopsy and prostatectomy specimens were evaluated by the same uropathology group. The clinical stage was assessed by the experienced urologist based on the 2012 TNM system.^[14] For prostate biopsy, between six and 33 needle biopsy cores were obtained with a transrectal ultrasound-guided (TRUS) biopsy. All biopsy specimens were graded by experienced pathologists according to the Gleason system. The total number of cores obtained and number of cores containing cancer were also recorded. All prostatectomy specimens were processed according to the Stanford protocol and were graded according to the Gleason system. A positive surgical margin was defined as extension of tumor to the surface of the resected specimen on final pathology. The pathological stage of the cancer was evaluated according to the 2005 International Society of Urological Pathology Modified Gleason Grading System.^[15]

Statistical analysis

The study objective was to determine the prognostic features associated with a PSM in a contemporary cohort of patients treated with radical prostatectomy. Accordingly, a nomogram for PSM prediction was developed. For model building, we conducted univariable regression for every covariate, and those with a two-sided $P < 0.05$ were included in the multivariable model. A backward stepwise method was used for variable selection in binary logistic regression. Furthermore, the nomogram was developed based on the logistic regression. The discrimination of the nomogram was measured by the concordance index. Calibration curves that assessed the agreement between the actual PSM risk and predicted risk were also conducted using 1000 bootstrap re-samples to decrease the overfitting bias. Decision curve analysis (DCA) was performed to

illustrate the accuracy of the three models by calculating the net benefit over a spectrum of probability thresholds. To minimize the information bias, missing values were substituted using the Expectation Maximization Algorithm in the case of continuous covariates or considered a separate class of categorical covariates.

This study used restricted cubic splines to fit the continuous variables to allow for nonlinearity in the relationship between these variables and the PSM. The SPSS version 20.0 (IBM Corporation, Armonk, NY, USA) and R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. A $P < 0.05$ was considered statistical significance.

Results

Descriptive analysis of the patient population

Patient characteristics are summarized in Table 1. Of 418 patients involved in this study, 142 patients (34.0%) had a positive surgical margin in the resected specimen on final pathology. Among patients with PSM, 26 (18.3%) had a solitary apical positive margin, 49 (34.5%) had a solitary non-apical positive margin, 67 (47.2%) had multiple positive margins.

Development and evaluation of the nomogram

Restricted cubic splines were used for all variables and Akaike information criterion (AIC) was calculated to choose the number of knots. As a result, age fit best with three knots, while for the tPSA, the fPSA/tPSA, BMI and percentage of positive cores were not restricted. The results of univariable and multivariable logistic regression analyses for predicting PSM are shown in Table 2. In the univariable analysis, the age, tPSA level, fPSA/tPSA, percentage of positive cores, biopsy primary and secondary Gleason Scores and clinical stage were all significant risk factors for a PSM ($P < 0.05$).

Four variables, including the percentage of positive cores, clinical stage, fPSA/tPSA and age, were included in the final multivariable model. A nomogram was then developed based on our logistic regression models [Figure 1]. The accuracy of this prediction model was relatively high, with a C-index of 0.722 in the development cohort and 0.700 in the bootstrap validations [Figure 2]. A calibration curve was developed using 1000 bootstrap re-samples [Figure 3]. The bias-corrected calibration plot showed a limited departure from the ideal line with a mean absolute error of 2.0%. In decision curve analyses, it was shown that the net benefit was high, in the range from 0.2 to 0.7, suggesting benefits in men within a wide probability range [Figure 4].

Discussion

A PSM after radical prostatectomy is a factor that contributes to adverse clinical outcomes, which can be affected by preoperative factors and surgical process.^[3-6] Therefore, practical tools are of utmost importance so that best candidates for surgeries can be selected and proper surgical process can be planned. Previous studies have identified several predictive factors for positive margins.

Table 1: Clinical characteristics of all patients in this study.

Characteristics	Overall (N=418)	Patients with PSM (n=142)	Patients without PSM (n=276)
Age (years)	70.0 (65.0, 75.0)	70.0 (62.8, 75.0)	71.0 (66.0, 75.0)
BMI (kg/m ²)	24.4 (22.5, 26.6)	24.7 (22.8, 26.6)	24.5 (22.4, 26.6)
tPSA (ng/ml)	11.4 (7.3, 19.8)	13.7 (9.3, 25.0)	10.2 (6.7, 17.7)
fPSA (ng/ml)	1.6 (0.9, 2.6)	1.6 (0.9, 2.8)	1.5 (0.8, 2.4)
Digital rectal examination			
Nodule negative	250 (59.8)	83 (58.5)	167 (60.5)
Nodule positive	111 (26.6)	39 (27.5)	72 (26.1)
Missing	57 (13.6)	20 (14.1)	37 (13.4)
Biopsy Primary Gleason score			
3	189 (45.2)	47 (33.1)	142 (51.4)
4	136 (32.5)	57 (40.1)	79 (28.6)
5	26 (6.2)	14 (9.9)	12 (4.3)
Missing	67 (16.0)	24 (16.8)	43 (15.6)
Biopsy Secondary Gleason score			
3	160 (38.3)	46 (32.4)	114 (41.3)
4	161 (38.5)	58 (40.8)	103 (37.3)
5	29 (6.9)	14 (9.9)	15 (5.5)
Missing	68 (16.3)	24 (16.9)	44 (15.9)
Clinical stage			
1	32 (7.7)	3 (2.1)	29 (10.5)
2	315 (75.3)	105 (73.9)	210 (76.1)
3	34 (8.1)	15 (10.6)	19 (6.9)
4	12 (2.9)	9 (6.3)	3 (1.1)
Missing	25 (6.0)	10 (7.0)	15 (5.4)
Pathological stage			
2	287 (68.7)	75 (52.8)	212 (76.8)
3	109 (26.1)	54 (38.0)	55 (19.9)
4	22 (5.3)	13 (9.2)	9 (3.3)
Surgeon volume			
<20 cases	104 (24.9)	39 (27.5)	65 (23.6)
20–49 cases	56 (13.4)	16 (11.3)	40 (14.5)
50–100 cases	47 (11.2)	17 (12.0)	30 (10.9)
>100 cases	211 (50.5)	70 (49.3)	141 (51.1)

The data are shown as *n* (%) or median (Q1, Q3). BMI: Body mass index; PSM: Positive surgical margin; tPSA: Total prostate specific antigen; fPSA: Free prostate specific antigen.

The most widely recognized one was the pathologic stage. In a meta-analysis of oncologic outcomes after robot-assisted radical prostatectomy, the mean PSM rate was 9% in pT2 cancers, 37% in pT3 cancers, and 50% in pT4 cancers,^[16] suggesting that a more extensive tumor has a higher risk of PSM. Other factors have also been identified as risk factors, including a higher BMI,^[17] serum PSA level,^[13] PSA density,^[18] percentage of cancer in the biopsy specimens,^[19,20] Gleason Scores, and a lower prostate weight^[21] and volume.^[22] These observations indicated that a larger tumor and smaller prostate, which lead to a higher tumor-to-prostate ratio, have a positive association with a PSM. In addition, the surgical technique and surgical experience are also important. In the meta-analysis, several surgeon-related characteristics (e.g., prior surgical experience) or procedure-related issues (e.g., type of nerve-sparing approach) may play a major role in the PSM rates. Unfortunately, these studies failed to give a predictive model for the PSM,^[11] which may confuse surgeons making clinical decisions. A nomogram is a user-friendly tool with a graphic interface, which is widely used for clinical decisions.^[23] Herein, we developed one from

a logistic regression model based on the preoperative information, which can be helpful in clinical settings.

In our research, the PSM rate was 34.0%, which was higher than those reported in Western countries. In the meta-analysis conducted by Novara *et al*,^[16] the mean PSM rate was 15%. However, Xu *et al*^[24] and Yang *et al*^[25] reported PSM rates of 44.2% and 29.1% in the Chinese population, which were comparable to our study. There are several possible reasons. First, all patients in our study were treated by LRP without robot assistance, while other study only included robot-assisted laparoscopic LP, and it had been proved that robot assisted prostatectomy may reduce the incidence of a PSM.^[3,26,27] In a study carried out by Porcaro *et al*,^[28] which included many open surgery patients, the PSM rate was comparable with ours; these may also demonstrate this hypothesis. Second, in China, patients usually get diagnosed at a later stage and as a result, patients in Chinese cohorts always tend to have a higher PSA as well.^[24,29] Differences in the genetic and racial make-up between the Chinese cohort and Western population may also lead to different pathologic outcomes.^[30]

Table 2: Univariable and multivariable logistic regression analyses of risk factors for PSM.

Variables	Univariable logistic regression		Multivariable logistic regression (Backward Stepwise)	
	OR (95% CI)	P	OR (95% CI)	P
Age (years)				
Age	0.92 (0.87–0.98)	0.008	0.92 (0.86–0.98)	0.010
Age [*]	1.09 (1.01–1.17)	0.020	1.11 (1.02–1.20)	0.008
BMI (kg/m ²)	1.02 (0.95–1.09)	0.600	–	–
tPSA (ng/ml)	1.02 (1.01–1.03)	<0.001	–	–
fPSA/tPSA (%)	0.95 (0.92–0.98)	<0.001	0.96 (0.93–0.99)	0.010
Percentage of positive cores (%)	1.03 (1.02–1.04)	<0.001	1.02 (1.01–1.03)	<0.001
Digital rectal examination				
Nodule positive	1.00 (reference)	–	–	–
Nodule negative	0.92 (0.57–1.47)	0.720	–	–
Missing	1.00 (0.51–1.95)	0.990	–	–
Biopsy Primary Gleason score				
3	1.00 (reference)	–	–	–
4	2.18 (1.36–3.50)	0.001	–	–
5	3.53 (1.52–8.15)	0.003	–	–
Missing	1.67 (0.93–3.07)	0.090	–	–
Biopsy Secondary Gleason score				
3	1.00 (reference)	–	–	–
4	1.40 (0.87–2.23)	0.160	–	–
5	2.31 (1.03–5.17)	0.040	–	–
Missing	1.35 (0.74–2.47)	0.330	–	–
Clinical stage				
1	1.00 (reference)	–	1.00 (reference)	–
2	4.83 (1.44–16.23)	0.010	3.91 (1.13–13.55)	0.030
3	7.63 (1.94–29.97)	<0.003	5.49 (1.31–22.84)	0.010
4	29.00 (4.96–169.63)	<0.001	15.08 (2.37–95.99)	0.004
Missing	6.44 (1.54–27.00)	0.010	4.78 (1.09–20.98)	0.040
Surgeon volume				
<20 cases	1.00 (reference)	–	–	–
20–49 cases	0.67 (0.33–1.35)	0.260	–	–
50–100 cases	0.94 (0.46–1.93)	0.880	–	–
>100 cases	0.83 (0.51–1.35)	0.450	–	–

* The third part of age group divided by restricted cubic splines. –: not applicable; BMI: Body mass index; CI: Confidence interval; fPSA: Free prostate specific antigen; OR: Odds ratio; PSM: Positive surgical margin; tPSA: Total prostate specific antigen.

After selection with the backward method, the percentage of positive cores, clinical stage, fPSA/tPSA, and age were included in the final regression model, which approximately conformed to the contemporary practice.

As mentioned before, the pathologic stage is a well-recognized predictor of a PSM. However, it is not a preoperative factor. A factor similar to it is the clinical stage. Coelho *et al*^[11] evaluated preoperative factors associated with PSM and concluded that clinical stage was the only independent predictive factor for PSM. In our study, clinical stage was also a powerful predictor because it had the highest AUC in all variables. We also noticed that portion of clinical stage T1 was much less than the Western studies. The first reason might be that we used both magnetic resonance imaging (MRI) and digital rectal examination to determine the clinical stage, while many studies only used digital rectal examination.^[31,32] In our study, a patient would be considered to have T1 cancer with neither palpable abnormalities nor abnormal MRI findings. As mentioned above, late diagnose and racial difference may also contribute to this situation, as a result,

studies conducted in China shared a similar portion of clinical stages.^[29]

Because percentage of positive cores is directly associated with the tumor proportion, it is not surprising to find it is a strong predictor in both our univariate and multivariate regression models. There are a few studies supporting this point. Tulião *et al*'s study^[20] suggested that the number of preoperative positive biopsy cores was a predictor of PSM. Yang *et al*^[25] reported that PSM was more common in patients with a more positive core number and bilateral positive cores.

In addition, we found that fPSA/tPSA was a strong predictor for a PSM and it was included in the final model. Although evidence to prove this relationship was insufficient, the work of Sfoungaristos *et al*^[33] showed that those with a lower fPSA/tPSA tended to yield a PSM ($P=0.138$). One possible explanation was that the fPSA/tPSA indirectly reflected the proportion of the tumor tissue and, therefore, had a negative influence on surgical margins.^[34]

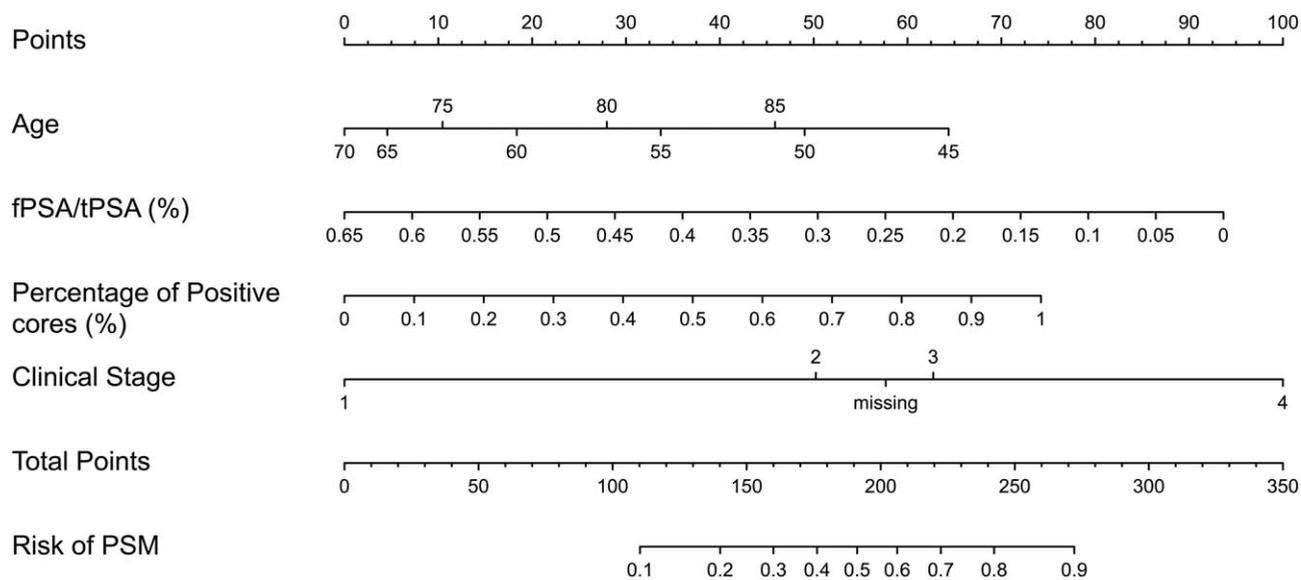


Figure 1: Preoperative nomogram for predicting PSM after radical prostatectomy. The preoperative variables are presented in rows two to four. The first step is to compute points by drawing a vertical line from each variable axis upward to the point's axis. Then sum up the four points and draw a vertical line from the total points line downward to the last row to work out the risk of PSM. fPSA: Free prostate specific antigen; PSM: Positive surgical margin; tPSA: Total prostate specific antigen.

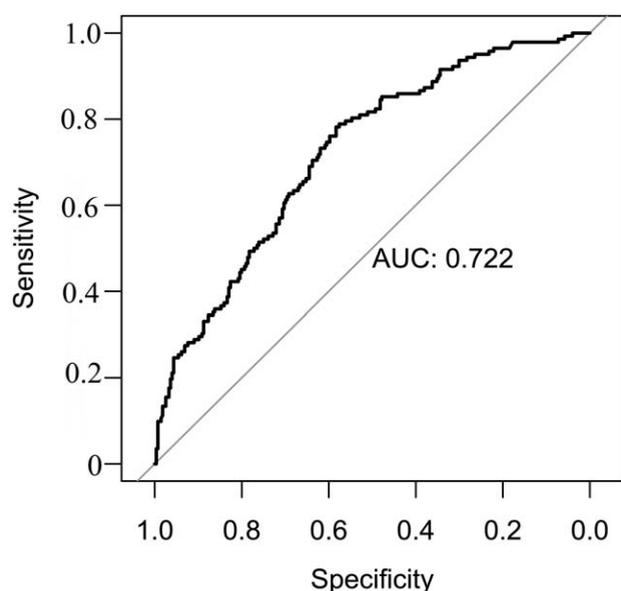


Figure 2: Receiver operating characteristic curves of the nomogram.

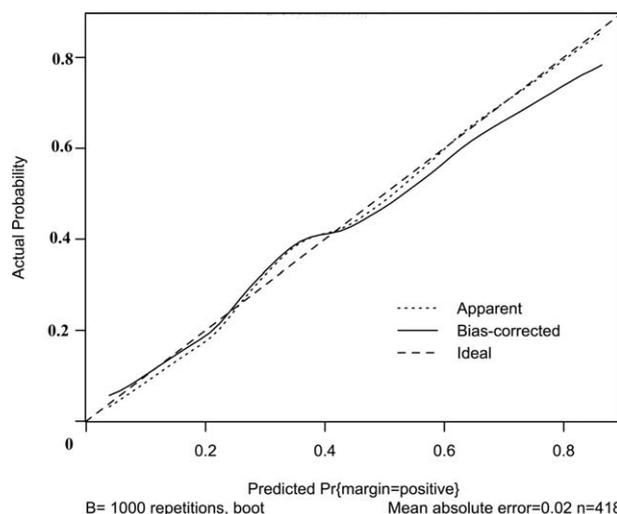


Figure 3: Calibration curve of the nomogram using 1000 bootstrap re-samples. The ideal reference line represents that the predicted likelihood perfectly matches the actual incidence.

Some studies related age to the occurrence of PSM. For instance, Magheli *et al*^[35] showed that elderly people had a higher risk of a PSM. However, it was intriguing that in our study, the risk of PSM showed a U-shaped curve with increased age, which was similar to the study of Yang *et al*^[25] Theoretically, individuals who develop cancer at a young age tend to suffer from non-organ confined tumor, and the reduced tolerance to extensive surgeries in elderly patients may result in a less desirable pathological outcome.^[36]

The preoperative PSA level^[13] and biopsy Gleason score^[22,24] were related to a PSM. The univariable analyses

in our data also agreed with this viewpoint. However, they were not included in our final model following stepwise selection. Some research also related PSM to the surgeon's experience,^[18,37] but our study demonstrated absence of this correlation.

The proposed nomogram with four variables showed good discrimination; it had a C-index of 0.722 in the development cohort and 0.700 in the bootstrap validations. In addition to the C-index, the calibration and decision curves also performed well in our model. Therefore, we conclude that our study might facilitate

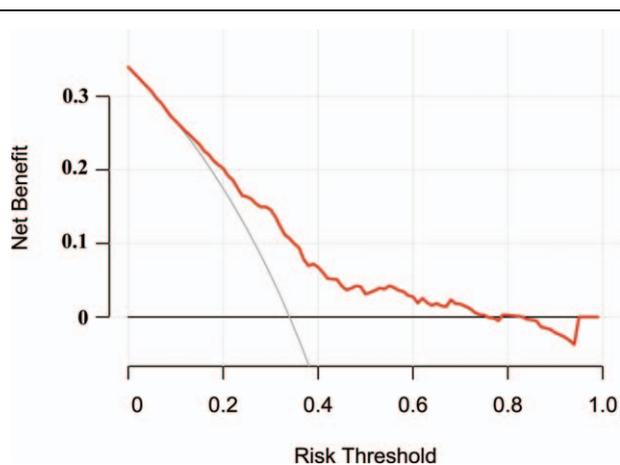


Figure 4: Decision curve of the nomogram. The nomogram showed net benefits in the range from 0.2 to 0.7.

clinical situations, such as those including surgery decisions, by providing a user-friendly tool.

Unfortunately, there were also several limitations to our study. First, because of incomplete radiology, it was difficult to record the prostate volume and the clinical staging was mainly based on the existing report. Second, the nomogram was calibrated with 1000 bootstrap resamples, which might result in overfitting. As a result, further studies to validate our model with external data are needed. Third, because our study was a retrospective one, selection bias was inevitable.

In conclusion, this study developed a nomogram for predicting PSM after radical prostatectomy based on the percentage of positive cores, clinical stage, fPSA/tPSA and age in Chinese patients. Our nomogram could provide an accurate prediction of PSM after radical prostatectomy and benefit patients in a broad range of threshold probabilities. Therefore, this model might help urologists plan surgical procedures.

Conflicts of interest

None.

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How to cite this article: Tian XJ, Wang ZL, Li G, Cao SJ, Cui HR, Li ZH, Liu Z, Li BL, Ma LL, Zhuang SR, Xiao QY. Development and validation of a preoperative nomogram for predicting positive surgical margins after laparoscopic radical prostatectomy. *Chin Med J* 2019;132:928–934. doi: 10.1097/CM9.0000000000000161