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A Nomogram for Predicting Pelvic Lymph Node Metastasis in Prostate Cancer

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Abstract: *Background*: Prostate cancer (PCa) is prone to lymph node metastasis. In this report, the authors described a model predictive of the probability of lymph node metastasis in prostate cancer patients. *Methods*: Two-hundred seventy-eight middle-high-risk PCa patients who received laparoscopic radical prostatectomy (LRP) combined with extended pelvic lymph node dissection (e-PLND) in our hospital were selected as the subjects and the authors performed a retrospective analysis. According to the postoperative pathological results, the patients were divided into a pelvic lymph node metastasis group (n=100) and a non-pelvic lymph node metastasis group (n=178). Univariable and multivariable logistic regression analyses were performed to identify independent risk factors for pelvic lymph node metastasis from PCa. Finally, a clinical prediction model nomogram was further established and verified, and a calibration plot was drawn to verify the accuracy of the model. *Results*: The TPSA level, FPSA level, PI-RADS score, biopsy ISUP classification and Gleason score of the two groups were statistically different (P<0.05), and there was no statistical difference between the age groups (P>0.05). Receiver operating characteristic curve (ROC) showed that the best diagnostic cut-off value of TPSA was 77.45 ng/ml (AUC=0.785, 95%CI: 0.729-0.842), and the best diagnostic cut-off value of FPSA was 0.085 ng/ml (AUC=0.282, 95%CI: 0.215-0.348). Univariable and multivariable logistic regression analyses showed that, TPSA level (OR=1.00, 95%Cl: 1.000-1.006, P<0.05), FPSA level (OR=0.00, 95%Cl: 0.000-0.089, P<0.01), PI-RADS score (OR=9.26, 95%CI: 5.278-16.248, P<0.01) and biopsy ISUP grade (OR=1.69, 95%CI: 1.163-2.450, P<0.01) were independent predictors of pelvic lymph node metastasis. *Conclusions*: The nomogram established in this study has a good predictive ability for pelvic lymph node metastasis in patients with PCa, and can provide a reference for the selection of clinical treatment options.

Keywords: Prostate Cancer, Pelvic Lymph Node Metastasis, Risk Factors, Nomogram

1. Introduction

At present, prostate-specific antigen screening has significantly improved the diagnosis rate of early PCa, but 15% of patients still have pelvic lymph node metastasis at the time of diagnosis [1]. Identification of Lymph node invasion (LNI) is important for the treatment of PCa because it not only determines whether there is a need to perform lymph node dissection and the scope of dissection during RP, but also affects whether the patient needs androgen deprivation therapy (ADT) and improves the prognosis of the patient. However, conventional imaging examinations, such as CT and MRI, have limited effect on the preoperative judgment of LNI [2-4]. In this study, the authors conducted a statistical analysis on the clinical factors that may affect LNI, established a nomogram scoring model, and explored the prediction of pelvic lymph node metastasis from PCa.

2. Materials and Methods

Patient Population

Clinical and pathological diagnosis dates were gathered from 278 middle-high-risk PCa patients treated with LRP combined with e-PLND between January 2018 and August

2020 at the Affiliated Hospital of Xuzhou Medical University. LNI was determined based on postoperative pathology. The clinical data collected from these patients included age, TPSA level, FPSA level, PI-RADS score, biopsy ISUP classification and Gleason score, and statistical analyses were performed.

The "RMS" data package and "ROCR" data package in R language version 4.0.0 software were used for statistical analysis and graphs were drawn. The rank sum test of a single sample was used to test whether the data were normally distributed. The normally distributed continuous variables were expressed by the mean ± standard deviation (Mean±SD), while the non-normally distributed variables were represented by median (range), and categorical data were described by percentage. For comparison between groups, T-test and ROC were used to analyze the AUC, sensitivity and specificity of each index, and calculate the optimal diagnostic threshold. Single factor and multivariate logistic regressions were performed to identify independent risk factors, followed by nomogram establishment and internal verification. The difference was considered statistically significant when P<0.05.

3. Results

In the LNI group, the TPSA level was (158.32±204.86) ng/ml, the FPSA level was (0.07±0.04) ng/ml, the median PI-RADS score was 5.00 (4-5), and the median biopsy ISUP classification was 4.00 (1- 5) and Gleason score was (GS≤7, n=4 (4%), GS>7, n=96 (96%)); in the non-LNI group, the TPSA level was (44.18±120.97) ng/ml, the FPSA level was (0.11± 0.59) ng/ml, the median PI-RADS score was 3.00 (2-5), the median biopsy ISUP classification was 3.00 (1-5) and the Gleason score was (GS≤7, n=28 (15.7%), GS>7, n=150 (84.3%)); the differences between the groups were statistically significant (P<0.05). The median age of the LNI group was (69.64±7.39) years, and the median age of the non-LNI group was (69.52±6.79) years; there was no significant difference between the groups (P>0.05).

Table 1. *Descriptive characteristics of patients between LNI group and non-LNI group.*

Variable	LNI group	Non-LNI group	P value
Age	69.64±7.39	69.52±6.79	0.09
TPSA (ng/ml)	158.32±204.86	44.18±120.97	<0.001
FPSA (ng/ml)	0.07±0.04	0.11±0.59	<0.001
PI-RADS	5.00 (4-5)	3.00 (2-5)	<0.001
ISUP	4.00 (1-5)	3.00 (1-5)	<0.001
Gleason score			
≤7	4 (4)	N=28 (15.7)	0.006
>7	96 (96)	N=150 (84.3)	

*Measurement data were described by (Mean ± SD) or median (range). The categorical data were described by examples (percentage).

The establishment of Lymph node metastasis from PCa nomogram:

(1) The establishment of logistic regression model and the identification of independent risk factors: LNI status was used as the dependent variable, and age, TPSA, FPSA, PI-RADS score, biopsy ISUP grade and Gleason score were used as independent variables. Because the dependent variable was a binary variable, we chose binary logistic regression modeling, and the logit function was used as the link function. First, a single independent variable was included for analysis, with a P value of<0.05 as a meaningful independent variable, and a multivariate analysis was performed based on the results of the single-factor analysis to identification independent risk factors for lymph node metastasis from PCa.

Table 2. *Univariable and multivariable logistic regression analyses predicting the presence of lymph node invasion.*

Variable	Univariate analysis		Multivariable analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Age	1.01 (0.569-1.789)	0.977	—	—
TPSA	1.01 (1.004-1.011)	<0.001	1.00 (1.111-1.006)	0.032
FPSA	0.00 (0.000)	<0.001	0.00 (0.000-0.089)	<0.001
PI-RADS	11.12 (6.569-18.833)	<0.001	9.26 (5.278-16.248)	<0.001
ISUP	1.82 (1.475-2.256)	<0.001	1.69 (1.163-2.450)	0.006
Gleason score	4.48 (1.524-13.173)	0.006	1.05 (0.170-6.453)	0.960

(2) ROC analysis and variable assignment: use the "ROCR" data package in the R language 4.0.0 software to evaluate the diagnostic performance of TPSA and FPSA, and select the point with the largest Youden index to determine the best diagnostic boundary value of each index, and the results are displayed: The best diagnostic threshold of TPSA is 77.45 ng/ml (AUC=0.785, 95%CI: 0.729-0.842), and the best diagnostic threshold of FPSA is 0.085 (AUC=0.282, 95%CI: 0.215-0.348), Further transform the continuous variable into a binary variable, assign TPSA>77.45 ng/ml to 1, TPSA≤77.45 ng/ml to 0, FPSA≤0.085 ng/ml to 1, and FPSA>0.085 ng/ml Assign a value of 0, and according to the professional meaning, assign a value of 1 to age>65 years, and assign a value of 0 to age ≤ 65 years.

(3) The establishment and internal verification of the nomogram of Lymph node metastasis from PCa: Use the "RMS" data package in the R4.0.0 software to establish and internally verify the nomogram. First, use the lrm function to establish a prediction model, and then draw a nomogram (Figure 1) through the nomogram function and the plot function to realize the visualization of the model. The C-index of the model is 0.936 (95%CI: 95%CI: 0.910-0.963) (Figure 2), which indicates that the model has a good discrimination ability. The Calibration function performs internal verification of the model. The verification

method uses Bootstrap re-sampling 1000 times. The model calibration plot (Figure 3) shows that the actual value is basically consistent with the prediction probability of the model, indicating that the model has a good accuracy.

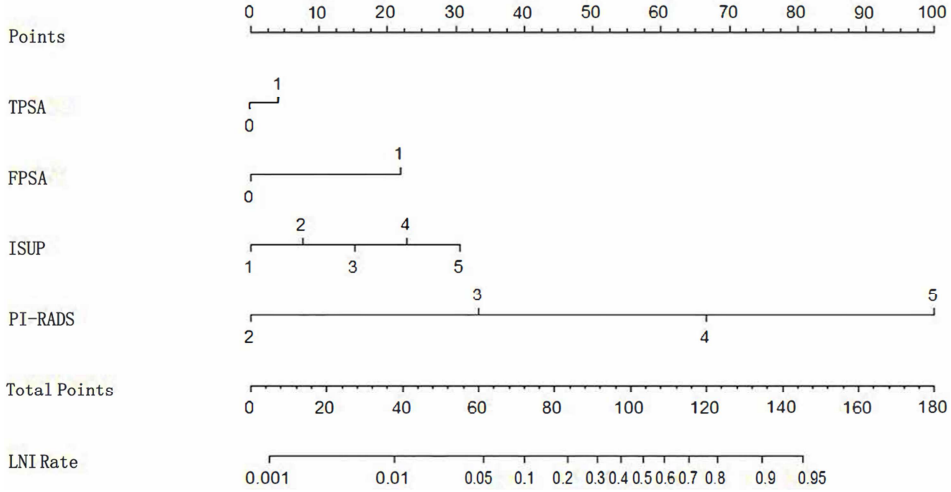

Figure 1. *Nomogram predicting the probability of lymph nodes invasion (LNI) in patients undergoing extended pelvic lymphadenectomy based on TPSA, FPSA, biopsy ISUP classification, PI-RADS score.*

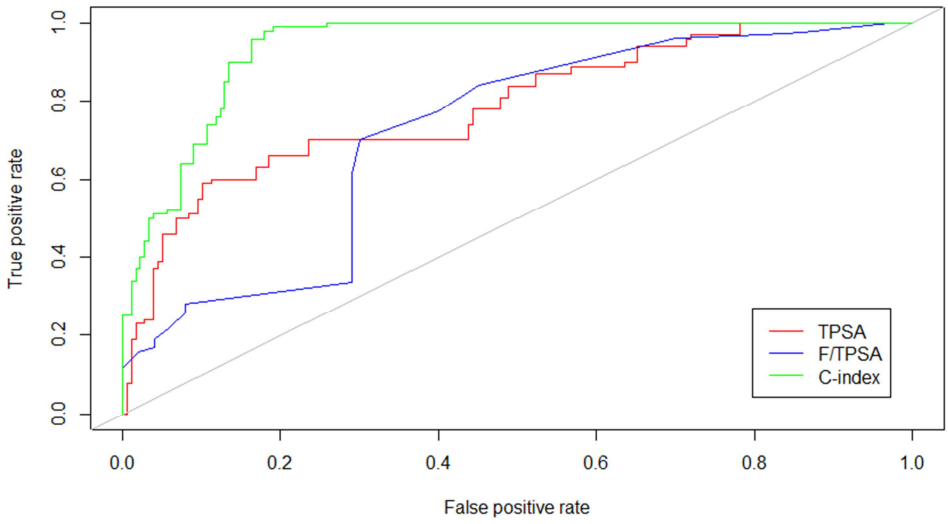

Figure 2. *C-index diagram of the model.*

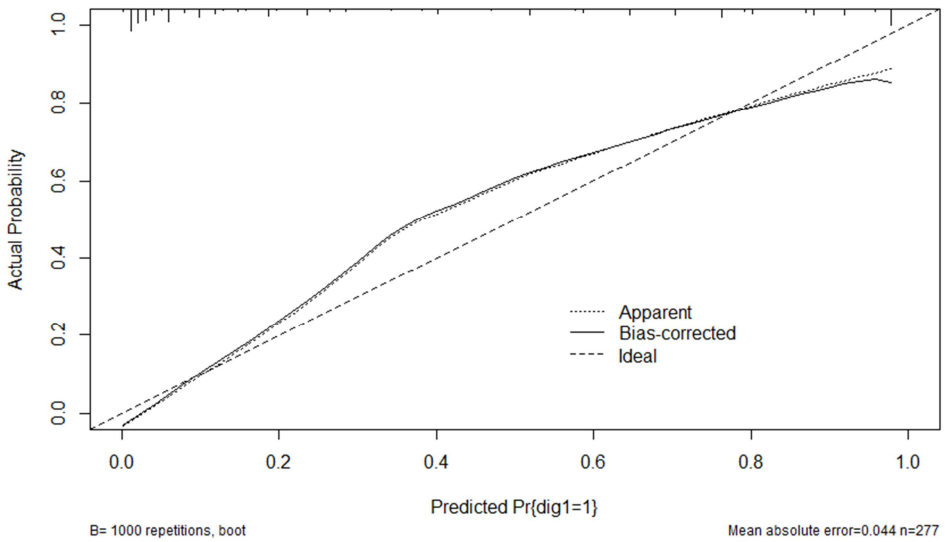

Figure 3. *Nomogram calibration plot.*

4. Discussion

A total of 278 patients with middle-high-risk PCa were included in this study. The results showed that TPSA level, FPSA level, PI-RADS score, biopsy ISUP grade and other indicators were independent risk factors affecting pelvic lymph node metastasis from PCa. There was no significant correlation between biopsy Gleason score and LNI. This was attributable to the purpose of treatment. After different scores were pooled, the subjects were considered to have similar prognosis. For example, in the group of Gleason=7, including subjects with a score of 3+4 and 4+3, the retrospective analysis performed on them showed that he latter had a worse prognosis [5, 6]. In addition, although a number of examination indicators might be correlated with PCa staging and grading, the ROC analysis curve showed that the optimal diagnostic cut-off value of TPSA for predicting LNI was 77.45 ng/ml (AUC=0.785, 95%CI: 0.729- 0.842), and the optimal diagnostic cut-off value of FPSA was 0.085 ng/ml (AUC=0.282, 95%CI: 0.215-0.348). Therefore, we pooled TPSA, FPSA, PI-RADS score, biopsy ISUP and other indicators to establish a nomogram to predict LNI in PCa patients. The nomogram model, often used in studies on imaging omics, can evaluate the probability of clinical events through the individual characterization of patients, and it is a good predictive classification model [7-9]. Compared with other predictive statistical models, its visualized iconic results can more intuitively reflect the patient's disease probability and provide individualized prognostic risk assessment. The principle of this nomogram was to give a score to the value level of each independent variable, during which each score was added to calculate the sum, and then calculate the occurrence of LNI in each patient through the conversion function between the score and the probability of the outcome probability. An analysis showed that the nomogram AUC of 0.936 (95%CI: 0.910-0.963) had a good ability to predict LNI. As urologists may face the challenge of making a choice of whether or not to perform lymph node dissection during surgery, the present study provided a method for predicting LNI in order to provide surgeons a certain clinical basis for the decisions of PCa treatment.

In recent years, the incidence and fatality rate of PCa have increased significantly, which seriously threatens the life and health of elderly men [10]. In the past few decades, the treatment regimens for PCa have changed, but RP is still the gold standard for the treatment of PCa, and the presence or absence of pelvic lymph node metastasis is considered to be one of the most important factors that affect the surgical method and subsequent auxiliary ADT as well as the survival of the patient [11]. The 2020 guidelines of the European Association of Urology (EAU) recommend that when the estimated risk of positive lymph nodes exceeds 5%, e-PLND should be implemented for middle-high-risk patients [12], However, it does not present a specific calculation method, and the therapeutic effect of e-PLND in RP still remains controversial. Guillaume Ploussard [13] et al. have found that the combination of PLND during RP may increase the operation duration, blood loss, hospital stay, and postoperative complications. FOSSATIN [14] et al. also believed that intraoperative dissection of pelvic lymph nodes could not improve the prognosis and survival of patients. Therefore, for PCa patients who are planning to undergo RP, it is very important to determine whether there is pelvic lymph node metastasis before surgery for the treatment of PCa. However, commonly used imaging methods such as CT and MRI, as well as the main diagnostic criteria can be used to detect the presence or absence of enlarged lymph node diameter and morphological changes. The results of a Meta analysis involving 24 studies suggest that, CT had a sensitivity of 42%, and a specificity of 82%; MRI had a sensitivity of 39%, and a specificity of 82% [15]. In addition, it can be seen that the sensitivity of the two methods is low, and when there is fibrosis or lipoma in the lymph node, it is difficult to distinguish benign tissues from cancer. Previously, the Partin table was used to predict the LNI of PCa patients, but the incidence of pelvic lymph node metastasis in the Partin table was based on the standard pelvic lymph node dissection, so only the obturator fossa and the lymph nodes around the external iliac arteries and veins were cleaned. This is inconsistent with the actual incidence of pelvic lymph node metastasis from PCa [16]; moreover, Elisa Zanelli [17] et al. also found that the nomogram and CAPPA score of MSKCC were of low diagnostic value (AUC values were 0.62 and 0.64, respectively). Compared with the above studies, the nomogram established in the present study has better predictive power (AUC: 0.936) for pelvic lymph node metastasis from PCa, and has noticeable advantages. The present study also has certain clinical significance to auxiliary ADT for PCa. Randomized controlled trials have shown that only when auxiliary ADT was used for LNI patients, the overall survival (OS) benefits were achieved, and when auxiliary ADT was used for patients with high-risk PCa undergoing surgery, they did not show OS benefit [18]. Therefore, for older patients with physical conditions that temporarily do not allow for surgery, once PCa is diagnosed with a confirmed or suspicious LNI, the neoadjuvant treatment model of systemic treatment followed by surgery can reduce the risk of clinical recurrence and death.

5. Conclusions

The results of this study showed that the prediction of LNI in PCa patients by nomogram was more accurate and effective than traditional imaging examinations and some scoring scales, with a good prospect for clinical application. In clinical practice, the application of this nomogram has certain reference value for urologists to balance the benefits and risks of lymphatic dissection to make case-based decisions. However, the sample size of this study was small

and multi-center data were lacking. From the perspective of oncology, the long-term safety is not yet known. In the future, prospective, large-sample, multi-center controlled studies are still needed for verification.

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Compliance with Ethical Standards

Conflict of interest: The authors report no conflicts of interest.

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