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Abstract

Background
Nowadays a tool able to predict the risk of lymph-node invasion (LNI) in patients underwent target biopsy (TB) only before radical prostatectomy (RP) is still lacking. Our aim is to develop a model based on mp-MRI and target biopsy (TB) alone able to predict the risk of LNI.

Methods
We retrospectively extracted data of patients with preoperative positive mp-MRI and TB only who underwent RARP with ePLND from April 2014 to March 2020. A logistic regression model was performed to evaluate the impact of pre- and intra-operative factors on the risk of LNI. Model discrimination was assessed using an area under (AUC) the ROC curve. A nomogram, and its calibration plot, to predict the risk of LNI were generated based on the logistic model. A validation of the model was done using a similar cohort.

Results
461 patients were included, of which 52 (11.27) had LNI. After logistic regression analysis and multivariable model DRE, PI-RADS, seminal vesicle invasion, PSA and worst GS at I and II target lesions were significant predictors of LNI. The AUC was 0.74 [0.67–0.81] 95% CI. The calibration plot shows that our model is very close to the ideal one which is in the 95% CI. After the creation of a visual nomogram, the cut-off to discriminate between the risk or not of LNI was set with Youden index at 60 points that correspond to a risk of LNI of 7%. The model applied on a similar cohort shown a LH+ of 2.58 [2.17–2.98] 95% CI.

Conclusions
Our nomogram for patients undergoing MRI-TB only takes into account clinical stage, SVI at MRI, biopsy Gleason pattern and PSA and it is able to identify patients with risk of LNI when a score higher than 7% is achieved.

INTRODUCTION

The role of synchronous pelvic lymphadenectomy (PLND) in prostate cancer (PCa) patients undergoing radical prostatectomy remains a major dilemma [1, 2]. While extended PLND templates allow accurate staging in up to 94% of cases, a recent systematic review did not confirm an improvement in the oncological outcome [3,4,5].
Given the fact that PLND can significantly increase the surgical risk and the operative time [2, 6], patient selection should be done using a rigorous methodology. Different tools (nomograms or risk calculators) have been described with the aim of identifying those patients for whom PLND might be beneficial [7]. In more recent years these tools were updated to incorporate findings from multiparametric magnetic resonance imaging (mp-MRI) [8, 9].
MRI-Targeted Prostate Biopsy in addition to standard sampling (SB) currently represent the preferred diagnostic approach [10], especially in biopsy-naïve patients [5]. More recently, in tertiary care centers, with high experienced radiologists and urologists, TB alone is being implemented with similar results to the combined approach and growing evidence suggests that an increasing number of patients is likely undergo to TB alone in the near future [11,12,13,14,15,16,17]. Consequently, the decision about whether or not to perform a PLND will be based on the TB alone.
Aim of this study was to develop a novel model exclusively based on MRI-Targeted Prostate Biopsy findings to predict the risk of lymph node invasion (LNI) and identify the best candidates for an extended PLND.

MATERIALS AND METHOD

Study populations and surgical procedures

Our study cohort was extracted from our prospectively maintained robot-assisted radical prostatectomy (RARP) database, retrospectively including patients with preoperative positive MRI and TB who were submitted to RARP with ePLND from April 2014 to March 2020. Moreover, a validation cohort of patients was included from May 2020 to May 2021; the last cohort was not used for the creation of the model but only for the internal validation.
ePLND was performed in case of GS ≥ 3 + 4 and/or PSA ≥ 10 ng/dl and/or in case of ≥cT2 disease and/or presence of seminal vesicle invasion (SVI) or extracapsular involvement (ECE) at mpMRI. ePLND was defined as removal of obturator, internal iliac, external iliac and presacral lymph nodes. We excluded patients who received neoadjuvant hormonal therapy or with incomplete data collection. All the interventions were performed by a single, experienced, surgeon (FP) with more than 500 cases at the beginning of the study. The procedures were performed according to our previously published technique [18, 19].
The study was conducted in accordance with good clinical practice guidelines, and informed consent was obtained from patients. According to Italian law (Agenzia Italiana del Farmaco Guidelines for Observational Studies, March 20, 2008), no formal institutional review board or ethics committee approval was required.

MRI and biopsy technique

ESUR guidelines and PI-RADS score V.1 [20] and V.2 [21] were employed to classify the suspicious findings at multiparametric MRI.
The BioJet fusion system (D&K Technologies, Barum, Germany) was used to carry out all the TB as previously described [10], either by transrectal or transperineal approach, following EAU recommendation for antibiotics prophylaxis and local cleaning. On the basis of lesion extension, four or six samples were performed in case of areas <8 mm or ≥8 mm respectively, in a medio-lateral fashion according to our previously published experience [22].
Patients had been submitted to TB only for three different reasons: 1) they were in a re-biopsy setting; 2) they were included in our previously published RCT [10]; 3) they were enrolled in an unpublished ongoing trial with IRB approval (SRCTN registry number ISRCTN60263108).

Histopathological evaluation

The pathological examination of biopsy samples was carried out by an experienced uropathologist (EB), in accordance with the Standards of Reporting for MRI-targeted Biopsy Studies (START) criteria [23]. For the purpose of this study CsPCa was defined with the START criteria for target biopsy (biopsy GS ≥ 7 or maximum CCL ≥ 5 mm) [23].
Whole-mount histopathological sections of the prostate after RARP represented the reference standard. The organ was cut on the basis of a previously reported technique [24], lymph-nodes were sent separately, specifying their site of origin for each specimen. All samples were prepared to obtain 5 micro metre thick slices, subsequently stained with hematoxyline/eosin. For every lesion identified, Gleason Score and ISUP grade were assessed; the number and the presence/absence of lymph-nodes metastases were determined for each specimen.

Data collection

Patient's data included age, PSA, PSA density (based on prostate volume determined on MRI), digital rectal examination (DRE), prostate and lesion volume, lesion localization, PI-RADS score, biopsy Gleason score (GS), worst Gleason pattern (G-pattern) (defined as the worst pattern at biopsy cores) for the two largest lesions identified at mp-MRI, number of total positive cores, total and maximum

cancer core length (CCL), and maximum cancer core invasion rate (CCI; maximal amount of cancer tissue in each core expressed as percentage).
The detection rate (DR) was determined as a ratio between the number of PCa and csPCA identified with TB, and the number of patients biopsied.
Regarding the pathological examination, GS, ISUP grade and pathological stage were determined. Moreover, patients were stratified according to EAU risk group for biochemical recurrence [5]. Finally, number of removed lymph-nodes and the median number of positive lymph-nodes were assessed. LNI was defined as the presence of positive lymph nodes at final pathology.

Statistical analysis
Means and standard deviations were used to describe continuous variables, whilst median and interquartile ranges for discrete ones. Categorical variables were summarized by frequency tables. *T*-test and Chi-square test were used to compare the two groups for continuous and categorical variables, respectively.
A logistic regression model was used to evaluate the impact of preoperative factors on the risk of LNI. The results were shown in terms of Odds Ratio (OR) with 95% Confidence Interval (95% CI). For the selection of predictors, the "full model" principle was used: all the variables were tested, then significant ones were considered for the multivariate model. Moreover, we used the formula n=10kp, [25, 26] where k is the number of variables and p = 11% is the proportion of patients with the outcome, in order to calculate the needed sample size and assure the reliability of the model. Considering k = 5 variables, 455 patients are sufficient to have an adequate power. Model discrimination was assessed using an area under (AUC) the ROC curve and the calculation of net benefit [27] with Peirce formula [28]. We created a nomogram able to predict the risk of LNI on the basis of the logistic model. Moreover, the calibration plot for the nomogram was provided. The proposed cut-off of the model was chosen maximizing both sensitivity and Youden [29] score.
In addition, an internal validation was done using a new cohort of patients, which presented not statistically significant differences on age, PSA, DRE, PI-RADS score and GS in respect of the previous sample (Supplementary Table 2). Accuracy indicators were considered in order to test the reliability of the model. Moreover, Decision Curve Analysis (DCA) was implemented in order to show graphically the net benefit of the model. The free macro %DCA of Daniel Sjoberg was used.
SAS ® Statistics Software was used to perform all the statistical analyses.

RESULTS

Baseline characteristics
461 were included in our study to develop the nomogram, of which 52 (11.27) had LNI. The median number of lymph-nodes removed was 22 (IQR 17–27) and the median number of positive lymph-nodes was 2 (IQR 2–3). Preoperative PSA, PSA density, clinical stage on DRE, median volume of the index lesion on mpMRI, total CCL and maximum CCI significantly differed between patients with pN0 and pN1 disease (all $p < 0.05$) (Table 1).

Uni- and multivariable model predicting LNI
The logistic regression model showed that DRE, PI-RADS score, SVI, mpMRI findings (organ confined vs ECE+ vs SVI+), PSA and worst G-pattern at I and II lesion were significant predictors of LNI (Supplementary Table 1). These seven variables were then used in a multivariable logistic model in order to evaluate their weight on the outcome determination.
DRE (OR 0.56; C.I.: 0.30–1.05) and SVI (OR: 0.42; C.I.: 0.19–0.93) were the most significant variables, followed by PSA (OR: 0.30; C.I.: 0.21–0.73) and worst G-pattern at I (OR: 0.37; C.I.: 0.17–0.82) and II lesion (OR: 0.33; C.I.: 0.14–0.76). On the contrary, Pirads score were not significant in the multivariate model (Table 2). Therefore, the multivariate model is composed by five variables.

Performance of predictive model

The ROC curve and related AUC was 0.74 [0.67–0.81, 95%CI], proving the capability of the model to distinguish a case with LNI from a case without LNI (Fig. 1a). The net benefit of the model, calculated with Peirce formula, was 0.05 while 0.01 should be the net benefit without applying any nomogram. The model has a moderate calibration [28] in predicting the outcome. This is also confirmed by the calibration plot (Fig. 1b) which shows that our model (solid line) is very close to the ideal one (dotted line) which is in the 95% CI.

Development of the nomogram

The multivariable predictive model obtained was then transformed in a visual nomogram, as shown in Fig. 2. Aiming to maximize sensitivity (Se), specificity (Sp) and positive likelihood ratio (LH), the cut-off to discriminate between the risk or not of LNI was set with Youden index at 60 points, corresponding to a risk of LNI of 7% (Table 3).

Internal validation

126 patients with similar characteristics (Supplementary Table 2) were considered for an internal validation. These patients were not included in the 'model cohort' as mentioned in materials and methods section.

A good LH+ (2.58, 2.17–2.98 95% CI) were found, so patients which had a score >60 have more than two times the probability to be with LNI (LH+) than patients with a score <60. Also a good Negative Predictive Value (0.95, 0.88–0.98 95% C.I.) confirmed that patients which had a score <60 are more probably without LNI (NPV). However, a relatively high number of false positive (0.72) was found.

In Fig. 1c, the net benefit can be seen graphically in the DCA output. The model has a greater net benefit than 'treat all' or 'treat none'.

DISCUSSION

To the best of our knowledge, herein we present the first model based on mp-MRI and TB alone predicting the risk of LNI at PLND in PCa patients. Our model, based on clinical (such as DRE and PSA value), radiological (presence of SVI) and pathological (worst G-pattern) variables, is able to correctly predict the LNI with a Se and Sp of 77% and 60% respectively, with a foreordain cut-off of 7%.

To date, EAU Guidelines recommend the use of predictive tools based on disease characteristics in order to identify patients at higher risk of LNI who should be considered for PLND during the intervention [5]. Historical clinical based tools (Briganti, Partin and MSKCC nomograms) have shown similar capabilities in predicting LNI, with an AUC of 0.79, 0.78 and 0.78, respectively [31]. Nonetheless, all three nomograms tended to overestimate the risk of LNI, because their performances could be correlated with surgical experience.

Over the last years, the wider use of mpMRI in daily clinical practice, both with a diagnostic and staging purpose [5], has brought researchers to include imaging findings into the predictive models [16, 32]. In a previous study from our group, the presence of ECE, SVI or Gleason pattern 4 at mpMRI allowed to correctly identify 15% more of patients with pN1 and a risk of LNI < 5% at Briganti nomogram [9]. Following this path, in 2019 a novel nomogram combining mpMRI findings together with both standard and target biopsy cores was proposed by Gandaglia et al. [8]. However, today, a growing proportion of patients undergo TB only in different clinical setting such as re-biopsy [5], confirmation biopsy in active surveillance protocol [30] or in biopsy naïve setting [10, 11], as in case of in-bore biopsy.

A recently published multicenter Canadian RCT found that MRI TB is non-inferior to initial systematic biopsy in men at risk of PCa in detecting Gleason Group 2 or greater cancers [34]. This level 1A findings support our previously published data [10] revealing that in biopsy naïve patients the mpMRI pathway is superior to the standard one in terms of PCa detection rate. We can then

postulate that TB only might become the standard for prostate biopsy soon. In fact, the constant development of mpMRI techniques (such as the advent of 3T mpMRI) and the refinement of TB fusion imaging software will bring to a further improvement of TB performances, avoiding the necessity to perform standard biopsy without missing clinical significant PCa. Thus, "modern" predictive tools to identify patients at higher risk of LNI should combine clinical data, MRI parameters and findings from TB only.

Our findings perfectly fit in this scenario providing the clinician with a new nomogram assisting his decision-making process. The ROC curve revealed an AUC of 0.74 [0.67–0.81] 95% CI, in line with the performance of systematic biopsy based predictive models [31].

Furthermore, the performance of our model still remains good also in internal validation cohort showing a LH+ (2.58, 2.17–2.98 95% CI), proving that patients which had a score >60 have more than two times the probability to be with LNI (LH+) than patients with a score <60.

A direct comparison with the previously published nomograms (such as Briganti, Gandaglia and Partin) is not possible because our cohort of patients was submitted to TB only, therefore some of the variables included in these nomograms, that are based on systematic samples, were not available in our cohort.

Nevertheless, some indirect comparisons can still be made. Looking at the net benefit (0.05) of our model, it is slightly inferior to the one proposed by Gandaglia et al. [8] (0.08), the Briganti 2012 [35] (0.07), Briganti 2017 [36] (0.07) and MSKCC [37] (0.07). However, the 'harm of the test' [27] should also be considered. In fact, our patients underwent a less invasive biopsy approach involving a potential reduction of the procedure invasiveness compared to the patients enrolled in the other previously mentioned studies. Taking into account a bettering of the harm of 1–2%, the net benefit of the presented model is absolutely comparable to the other ones.

Moreover, our proposed model allows to avoid PLND in patients with a risk of LNI below 7%, in order to spare approximately 59.1% of PLNDs at the cost of missing only 4.7% positive LNs. Similarly, the adoption of Gandaglia model [8] could avoid up to 60% of PLND at the cost of missing only 1.6% patients with LNI, but with the addition of SB samples. On the other hand, not grossly worsening of the nomogram's performance was recorded (our AUC 0.74 vs Gandaglia AUC 0.86).

Even if our model appears less performant, it is important to point out that our findings are based on mpMRI and TB only, and this may be related with a subsequent lower risk of post-biopsy complications [33] and non-inferior satisfaction rate by the patients [34].

These findings can be contextualized in the current precision surgery era [1]; in fact, a tailored biopsy approach leads to a next tailored surgical approach [38, 39] with a significant reduction of the procedural invasiveness and the oncological outcomes were comparable with the standard approach. In other words, we can obtain very similar results in terms of models performance reducing the invasiveness of the diagnostic pathway.

Despite several strengths, our study is not devoid of limitations. First, the good performance characteristics of our nomogram lack of formal external validation before its implementation in daily clinical practice and this represents a challenge for the future. Second, our study is limited by its retrospective nature and might be influenced by patient selection biases typical of all retrospective series. Third, despite the standardization of mpMRI included in our study, the different degree of expertise of the radiologists might have introduced heterogeneity biases. However, all the mpMRI were reviewed by expert urologists and radiologists at our centre before the execution of TB. Finally, all the extended LNDs were performed by an experienced surgeon and the surgical experience can affect the templates and number of LN removed, limiting the reproducibility of our findings. Even considering these limits we think that our results may be helpful for the urological community as this nomogram specifically built for patients undergoing MRI based target biopsy only may drive the clinicians in the decision-making process when managing these patients.

In conclusion, our predictive model specifically built for patients undergoing MRI-TB only and taking into account clinical stage, SVI at MRI, biopsy Gleason pattern and PSA is able to identify patients at higher risk of LNI. ePLND may be reasonably omitted in patients with a nomogram-derived LNI risk

lower than 7%. Further studies to externally validate this novel tool with a multicentre prospective study are need.

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Table 1. Preoperative variables.

Total (461)	**LNI (52)**	**Without LNI (409)**	***p* value**		
Age, years; mean (SD)	66.5 (7.1)	65.5 (7.0)	66.9 (6.5)	0.16	
PSA, ng\dL; mean (SD)	9.0 (7.0)	11.1 (6.0)	8.7 (7.0)	0.02	
PSA density, ng/ml^2; mean (SD)	0.26 (0.2)	0.28 (0.17)	0.22 (0.19)	0.02	
Suspicious DRE, number (%)	202 (43.8)	32 (61.5)	170 (41.6)	0.007	
Prostate volume, CC; mean (SD)	42.1 (15.0)	41.9 (17.0)	43.8 (21.0)	0.53	
Lesion volume, CC; mean (SD)	1.46 (3.13)	1.9 (1.7)	1.2 (2.0)	0.04	
PiRads score, number (%)					
● 3	61 (13.2)	7 (13.4)	54 (13.2)	0.18	0.19
● 4	251 (54.4)	18 (34.6)	233 (56.9)	0.10	
● 5	149 (32.3)	27 (51.9)	122 (29.8)	0.35	
Clinical stage					
cT1	205 (44.4)	15 (28.8)	190 (46.4)	0.79	0.77
cT2	217 (47.0)	30 (57.7)	187 (45.7)	0.88	
cT3	39 (8.4)	7 (13.5)	32 (7.8)	0.47	
Clinical stage on mpMRI, n (%)					
Organ-confined	303 (65.7)	34 (65.4)	269 (65.8)	0.95	0.38
Extracapsular extension	110 (23.8)	10 (19.2)	100 (24.4)	0.40	
Seminal vesicle invasion	48 (10.4)	8 (15.4)	40 (9.8)	0.21	
Biopsy GS, number (%)					
● 6	20 (4.3)	3 (5.8)	17 (4.2)	0.10	0.12
● 7	334 (72.4)	22 (42.3)	312 (76.3)	0.28	
● 8	69 (14.9)	14 (26.9)	55 (13.4)	0.24	
● >8	38 (8.2)	13 (25.0)	25 (6.1)	0.32	
Biopsy ISUP grade, number (%)					
● 1	20 (4.3)	3 (5.8)	17 (4.2)	0.10	0.29
● 2	165 (35.7)	6 (11.5)	159 (38.9)	0.46	

Total (461)	**LNI (52)**	**Without LNI (409)**	***p* value**		
● 3	169 (36.6)	16 (30.8)	153 (37.4)	0.77	
● 4	69 (14.9)	14 (26.9)	55 (13.4)	0.24	
● 5	38 (8.2)	13 (25.0)	25 (6.1)	0.32	
Overall detection rate of csPCa, number (%)	441 (95.6)	49 (94.2)	392 (95.8)	0.78	
Total CCL, mm; mean (SD)	22.3 (17.9)	29.6 (21.4)	21.5 (17.2)	0.01	
Maximum CCL, mm; mean (SD)	8.0 (4.6)	9.0 (4.0)	7.9 (4.6)	0.19	
Maximum CCI rate, mean (SD)	58.0 (26.4)	67.9 (23.4)	57.0 (26.4)	0.02	
Median cores taken overall, *n* (IQR)	5 (4–6)	5 (4–6)	5 (4–6)	0.24	
Median positive cores overall, *n* (IQR)	3 (2–5)	4 (3–5)	3 (2–4)	0.016	
Median percentage positive cores overall, %	81	83.3	80	0.14	
RP GS, number (%)					
● 6	0 (0)	0 (0)	0 (0)	–	
● 7	329 (71.3)	18 (35.2)	311 (76.0)	<0.001	0.28
● 8	62 (13.4)	8 (15.3)	54 (13.2)	0.66	
● >8	70 (15.1)	26 (50.9)	44 (10.7)	<0.001	
RP ISUP grade, number (%)					
● 1	0 (0)	0 (0)	0 (0)	–	
● 2	145 (31.4)	2 (3.9)	143 (34.9)	<0.001	0.31
● 3	184 (39.9)	16 (31.3)	168 (41.0)	0.15	
● 4	62 (13.4)	8 (15.3)	54 (13.2)	0.66	
● 5	68 (14.7)	26 (50.9)	44 (10.7)	<0.001	
Pathological stage					
T1	0 (0)	0 (0)	0 (0)		
pT2	154 (33.4)	15 (28.8)	139 (33.9)	0.50	0.016
pT3a	241 (52.2)	22 (42.3)	219 (62.8)	0.11	
pT3b	66 (14.3)	15 (28.8)	51 (12.6)	0.02	
pT4	0 (0)	0 (0)	0 (0)		
Any upgrading, *n* (%)	117 (25.3)	20 (39.2)	97 (23.7)	0.021	

Total (461)	LNI (52)	Without LNI (409)	*p* value	
Upgrading with risk group change, *n* (%)	62 (13.4)	10 (19.6)	52 (12.7)	0.19
Upgrading without risk group change, *n* (%)	55 (11.9)	10 (19.6)	45 (11.0)	0.085
Any downgrading, *n* (%)	43 (9.3)	1 (1.9)	42 (10.2)	0.051
Downgrading with risk group change, *n* (%)	19 (4.1)	1 (1.9)	18 (4.4)	0.39
Downgrading without risk group change, *n* (%)	24 (5.2)	0 (0)	24 (5.8)	0.073
Positive surgical margins, *n* (%)	111 (23.8)	11 (21.1)	100 (24.4)	0.39
Median lymph nodes removed, *n* (IQR)	22 (17–27)	23 (17–34)	21 (16–27)	0.95
Median positive lymph nodes, *n* (IQR)	2 (2–3)	2 (2–3)	–	

PSA prostate specific antigen, *DRE* digital rectal exploration, *SD* standard deviation, *GS* Gleason Score, *mpMRI* multiparametic magnetic resonance imaging, *CC* cubic centimeters, *IQR* interquartile range, *RP* radical prostatectomy, *ISUP* Interational Society of Urological Pathology.

Table 2. Estimation of odds ratio and Wald's 95% confidence interval (CI).

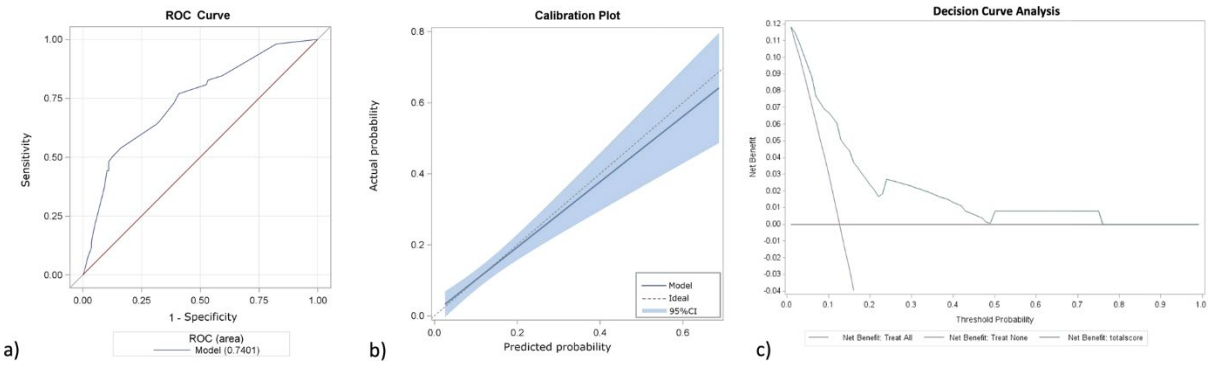
	Estimate	95% CI
Worst lesion Gp-I class (3 vs 4)	0.376	0.172–0.822
Worst lesion Gp-II class (≤4 vs 5)	0.336	0.147–0.768
SVI class (negative vs positive)	0.425	0.194–0.931
PSA level (≤10 vs >10 ng/ml)	0.396	0.212–0.739
DRE (negative vs positive)	0.563	0.301–1.054

The identified variables with logistic regression models were then used in a multivariable logistic model in order to evaluate their weight on the outcome determination.
Gp Gleason pattern, *SVI* seminal vesicle invasion, *PSA* prostate specific antigen, *DRE* digital rectal examination.

Table 3. Sensitivity, Specificity, Positive Likelihood and Youden index in relation of nomogram score.

% risk of LNI	Score	Sensibility	Specificity	LH	Youden index
4%	21	98.1	17.6	1.2	115.7
6%	44	80.8	47.4	1.5	128.2
7%	60	76.9	59.2	1.9	136.1
10%	72	73.1	61.1	1.9	134.2
11%	83	63.5	69.4	2.1	132.9

Fig. 1. Evaluation of model's performance.



a ROC curve of our predictive model showing an area under the curve (AUC) of 0.74; **b** Predictive model calibration plot. Solid line shows the performance of our predictive model; Dotted line performance of ideal model; **c** Decision Curve Analysis showing the net benefit of the model.

Fig. 2. Novel nomogram to predict the risk of limph-node invasion (LNI) in patients diagnosed with target biopsy only who underwent radical prostatectomy and extended limph-node dissection. (DRE digital rectal examination, SVI seminal vesicles invasion, Worst G- pattern worst Gleason pattern at biopsy specimen, PSA prostate specific antigen).