Running head: Identify prostate biopsy candidates- Wagaskar et al

Development and External Validation of a Prediction Model to Identify Candidates for Prostate Biopsy

Authors:
Vinayak G Wagaskar MBBS, MCh[1*], Anna Lantz MD[1], Stanislaw Sobotka PhD DSc[1], Parita Ratnani MPH, BDS[1], Sneha Parekh MBBS[1], Ugo Giovanni Falagario MD[1], Li Li MD, PhD[3], Sara Lewis MD[2], Kenneth Haines III MD[3], Sanoj Punnen[4] , Peter Wiklund MD[1], Ash Tewari MBBS, MCh[1]

Affiliations:
[1] Department of Urology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA
[2] Department of Radiology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA
[3] Department of Pathology, Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA
[4] Department of Urology, University of Miami, Miller School of Medicine, Miami, USA.

ABSTRACT

Purpose: Prostate biopsies are associated with infectious complications and approximately 80% are either benign or clinically insignificant prostate cancer. Our aim is to develop and independently validate prediction model to avoid unnecessary prostate biopsies by predicting clinically significant prostate cancer (csPCa)

Materials and Methods: Retrospective analysis of single-center cohort (Mount Sinai Hospital, NY) of 1632 men who underwent systematic or combined systematic and Magnetic Resonance Imaging (MRI)/ultrasound fusion targeted prostate biopsy between 2014-2020. External cohort (University of Miami) included 622 men that underwent biopsy. Outcome for predicting csPCa was defined as International Society of Urologic Pathology (ISUP) Gleason grade ≥ 2 on biopsy. Multivariable logistic regression analysis was performed to build nomogram using coefficients of logit function. Nomogram validation was performed in external cohort by plotting receiver operating characteristics (ROC). We also plotted decision curve analysis (DCA) and compared nomogram-predicted probabilities with actual rates of csPCa probabilities in external cohort.

Results: Of 1632 men, 43% showed csPCa on biopsy. PSA density, prior negative biopsy, and Prostate Imaging and Reporting Data System (PI-RADS) scores 3, 4, and 5 were significant predictors for csPCa. ROC for prediction of csPCa was 0.88 in external cohort. There was agreement between predicted and actual rate of csPCa in external cohort. DCA demonstrated net benefit using the model. Using the prediction model at threshold of 30, 35% of biopsies and 46% of diagnosed indolent PCa could be avoided, while missing 5% of csPCa.

Conclusion: Using our prediction model can help reduce unnecessary prostate biopsies with minimal impact on csPCa detection rates.

Keywords: biopsy; logistic models; magnetic resonance imaging; nomograms; prostate cancer.

1. Introduction

Prostate cancer (PCa) is the second deadliest cancer in men in the United States. In 2019, there were 174,650 new diagnoses of PCa and 31, 620 prostate cancer deaths.[1] There is an ongoing debate around the degree of benefit from the screening for PCa given the poor diagnostic performance of prostate specific antigen (PSA) and the tumor agnostic nature of conventional Trans Rectal Ultrasound (TRUS)-guided biopsy, which has moderate ability to risk stratify patients using biopsy findings. Recent studies estimate that more than 80% of the million biopsies performed annually in the United States may be unnecessary,[1,2] resulting in patient morbidity and tremendous financial strain on the healthcare system that potentially could be avoided. Studies have shown that TRUS-guided biopsies are associated with infectious complications in 5-7% of cases, approximately 3% of which require hospitalization.[3,4]

Poor diagnostic accuracy with standard screening methods, PSA and digital rectal exam (DRE), has generated interest in multi-parametric magnetic resonance imaging (mpMRI), which has been investigated in a number of trials. The PRECISION study reported promising results with mpMRI for reducing unnecessary biopsies, yet men with negative MRI did not undergo biopsy.[5] Oishi et al reported detection of 38% PCa and 18% clinically significant prostate cancer (csPCa) rates in men with negative mpMRI.[6]

mpMRI has the potential to improve patient selection for biopsy.[7] To optimize mpMRI as a screening tool, given its limitations, it will be important to consider relevant clinical variables, including age and family history, as well as prior history of biopsy, and the results of standard screening tools, such as PSA density (PSAD), and DRE findings, in addition to mpMRI results for identifying csPCa. The objective of our study was to develop and externally validate a risk prediction tool for csPCa in order to identify men who might safely avoid prostate cancer biopsy and thus to reduce the burden of unnecessary biopsies and overtreatment using both clinical parameters and mpMRI results.

2. **Material and Methods**

2.1 **Study population**

With the approval of the Institutional Review Board (GCO 19-1711), we retrospectively reviewed our institution's prostate biopsy database to extract patient records. Between January 2014 and March 2020, 1678 men underwent biopsy by a single expert surgeon (A.K.T.) with 20 years' experience. These didn't include biopsies with a previous or current history of prostate cancer.

2.2 Inclusion and exclusion criteria

Indications for biopsy were PSA >4ng/ml and 4Kscore of >7%; PSAD $\geq$1.5; suspicious DRE; or Prostate Imaging and Reporting Data System (PI-RADS) scores of 3, 4, or 5 on mpMRI, or a combination of any of the above. Exclusion criteria were contra-indication for mpMRI (n=23); prior hormone therapy or radiation (n=10); or missing data on family history of prostate cancer, history of prior negative biopsy or DRE (n=13). In total, 1632 men were eligible for inclusion in the analysis. For external validation, a cohort of 622 men that underwent systematic or combined systematic and MRI/ultrasound fusion biopsy for PSA > 4

ng/ml or suspicious DRE, or PI-RADS 3, 4 or 5 score at University of Miami was used. All research was conducted with informed consent and IRB approval.

2.3 Procedures

All men underwent standardized mpMRI prior to prostate biopsy. Examinations were compliant with American College of Radiology recommendations for technical specifications and were performed using clinical 3-Tesla MRI systems equipped with an 18-element phased-array pelvic coil. mpMPI results were evaluated according the Prostate Imaging and Reporting Data System Version 2 (PI-RADS V2) by clinical radiologists with experience in prostate imaging.[8] All men underwent either systematic or systematic and MRI-TRUS-fusion targeted biopsy in the case of a positive MRI (PI-RADS $\geq$3), and 2-4 extra cores were taken from each lesion. All biopsies were performed by a single experienced urologist (A.K.T.) using an Artemis MRI/US fusion device (Innomedicus, Cham, Switerzland) using a spring-loaded biopsy gun and 18 gauge needles. Biopsies samples were reviewed by an experienced genitourinary pathologist (K.H.III).

2.4 Evaluation and statistical analysis

For our prediction model, the outcome for predicting csPCa was defined as a ISUP Gleason grade of $\geq$ 2 on biopsy; men with this outcome were considered cases. Men who showed no cancer on biopsy or with a ISUP Gleason grade 1 were considered controls. Descriptive statistics for the two groups were performed. Continuous variables were reported as median and interquartile range (IQR) and were compared using a Mann-Whitney test. Categorical variables were reported as rates and were tested with a chi-square test, as appropriate. The prediction model included age, family history of prostate cancer, history of negative prior biopsy, PSAD, DRE findings, or mpMRI findings of a PI-RADS score as variables. PI-

RADS scores of 1 and 2 were grouped for the purpose of analysis. PSAD was calculated from the prostate volume from MRI findings.

Nomogram validation was performed in external cohort of 622 men by grouping them into deciles based on their nomogram-predicted probabilities and then comparing the mean prediction of the group with the observed proportion of men with csPCa. Using nomogram-derived probability cut-offs, we calculated the number of biopsies that could be avoided without missing csPCa in the external cohort. Decision curve analysis (DCA) was performed to evaluate the performance of the prediction model. Statistical analyses were performed using STATA 12 (StataCorp LP, College Station, TX, USA) and SAS 9.4 (SAS Institute, Cary, NC, USA). All tests were two-tailed with a significance level of $P<0.05$.

3 Results

A total of 1632 men were included in the analysis. Of 1632 men, 701(43%) were diagnosed with csPCa. The median age was 64 years (IQR 58, 69), 65 years (IQR 59, 68); median PSA was 5.1 ng/mL (IQR 3,7, 7.6), 6.4 ng/mL (IQR 4.8, 9,5); and median PSA density was 0.09 ng/mL^2 (IQR 005, 0.14), 0.16 ng/mL^2 (IQR 0.11, 0.26) for controls and cases, respectively. While in an external cohort of 622 men, 173 (28%) were diagnosed with csPCa. The median age was 61 years (IQR 60,69), 60 years (IQR 60,70); median PSA was 5.6 ng/ml (IQR 4,8.1), 6.8 ng/ml (IQR 5,9.4) and median PSA density was 0.09 ng/mL^2 (IQR 0.06,0.14), 0.18 ng/mL^2 (IQR 0.12, 0.27) for controls and cases, respectively.(Table 1).

3.4 Univariable and multivariable analysis predicting csPCa

In univariate analysis, PSAD, family history of prostate cancer, prior negative biopsy, DRE findings, and PI-RADS 3, 4 and 5 emerged as significant predictors of csPCa. In multivariate

analysis, family of prostate cancer, history of prior negative biopsy, PSAD, and PI-RADS scores of 3, 4, and 5 were significantly associated with csPCa (all $P<.01$ (Table 2).

3.5 Construction and validation of a Nomogram to estimate risk of csPCa

A nomogram was created to predict the presence of csPCa (Fig. 1). AUC for predicting csPCa was 0.88 in an external cohort (Fig. 2). We evaluated the nomogram's calibration by comparing predicted and actual probabilities of csPCa in the external cohort (Fig. 3). There was an agreement between predicted and actual rate of probabilities for csPCa as seen by points at the diagonal line. In an external cohort, DCA plot for predicting csPCa showed superior clinical prediction of PI-RADS score vs our model or PSAD for 20-65% nomogram derived probabilities (Fig. 4).

Using our model in external cohort, 10% of biopsies could be avoided without missing csPCa, avoiding 21% of benign biopsies and 13% of indolent PCa (Fig. 5) Additionally, 15%, 20%, 25%, 30%, and 35% of biopsies could be avoided while missing 3%, 4%, 5%, 9%, and 12% of ISUP Gleason grade 2 PCa, respectively, avoiding 29%, 40%, 51%, 58%, and 66% of benign biopsies, respectively, and avoiding 21%, 26%, 31%, 39%, and 46% of clinically insignificant PCa, respectively. Figure 5 demonstrates the percentage of biopsies that could be avoided without significantly affecting detection of ISUP Gleason grade 3 and $\geq$ 4-5.

4 Discussion:

We have developed and independently validated a prognostic tool for use in primary work-up to predict csPCa in men for whom biopsy is being considered. Our model confers two key benefits. 1) It reduces number of biopsies without compromising detection of csPCa (2) Our

model shows efficacy of PI-RADS scores, PSAD, and history of prior negative biopsy for prediction of csPCa.

The increasing number of prostate biopsies in recent years has focused the attention,, on the complications associated with these procedures. Common non-fatal complications after biopsy include pain, bleeding, and voiding dysfunction. Less common, but potentially fatal complications, include post-biopsy blood stream infections.(9) Additionally, we have seen a rising prevalence of antibiotic-resistant bacterial infections with biopsy-related infectious complications.(10) At the same time, standard systematic prostate biopsy is associated with increased detection of indolent or clinically insignificant PCa[11]. Our model shows that a significant number of biopsies could be avoided with only a modest impact on detection of csPCa, reducing unnecessary biopsies and the risk of associated complications. A number of prediction calculators for diagnosing csPCa have been developed. The Rotterdam European Randomized Study of Screening for Prostate Cancer risk calculators (ERSPC-RCs) help to avoid unnecessary transrectal ultrasound-guided systematic biopsies (TRUS-Bx).(12) Different from most prior studies, our model was both internally and externally validated to show the robustness of risk estimation. Lee et al., have built a prediction calculator for diagnosing csPCa based on age, PSAD, history of prior negative biopsy, and MRI PI-RADS score.(13) They showed that 10% of biopsies could be avoided using their model missing 17% of clinically insignificant PCa and 3% of csPCa. In our study, nonetheless, avoiding 10% of biopsies would have missed 13% of clinically insignificant prostate cancers and just 1% of csPCa. A prediction calculator developed by van Leeuwen et al., based on age, PSA, DRE, prostate volume, prior biopsy, and MRI PI-RADS lesion, showed 28% reduction of biopsies while missing 26% of clinically insignificant prostate cancers and 3.5% of csPCa. (14) Of note, in this study men were biopsied using transperineal mapping biopsies with a median of 30 cores.

Our model show that mpMRI PI-RADS scores of 3, 4, and 5 are significant for predicting csPCa. mpMRI has mediated visualization and localization of tumors owing to its capacity for soft-tissue contrast, better resolution, and ability to image functional parameters.(15) We, along with others, have found that PSAD is also a significant predictor of csPCa and can aid in reducing unnecessary biopsies.(16) Furthermore, studies have also shown prior negative biopsy as a predictor for avoiding repeat biopsies. (17) And Lee et al., found that mpMRI PI-RADS scores 3, 4, and 5, PSAD, and history of prior negative biopsy in combination are strong predictors for diagnosing csPCa.(16) Similar to our study, in the REDUCE trial, family history of prostate cancer was not associated with prostate cancer diagnosis in men in North America.(18) In the STHLM3 study, AUC for age or family history alone was 0.59 (0.57-061)

for predicting csPCa, suggesting minimal utility as compared to AUC of .63 for DRE alone, a finding similar to our own (AUC for DRE alone of 0.61).

We recognize that our study has a number of limitations. First, our cohort is based on stringent biopsy selection criteria which could affect generalizability. Consequently, our csPCa detection rate of 43% is higher than other studies. [13-14, 16] Inclusion of PSA and 4Kscores and/or inclusion of MRI for selection for biopsy may account for this higher detection rate as described in our previously published paper.[19] Additionally, all biopsies were performed by a single experienced, high-volume expert, which could affect generalizability. Finally, this study was conducted in a single center and our outcomes may not be reproducible.

5 Conclusion

We have developed an easily accessible tool to assist clinicians in biopsy decision making and patient counselling for men at risk for PCa. Using our novel prediction model could significantly reduce the large number of biopsies that detect benign or clinically insignificant PCa, while missing only a small proportion of csPCa. Our results demonstrate the importance of combining PSAD, prior negative biopsy, and mpMRI PI-RADS score for predicting csPCa.

Acknowledgment: We thank Ms Sima Rabinowitz for editorial revision.

Conflicts of interest: None

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7-34.
2. Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. Eur Urol. 2015;68:464-70.

3. Halpern JA, Shoag JE, Artis AS, et al. National Trends in Prostate Biopsy and Radical
Prostatectomy Volumes Following the US Preventive Services Task Force Guidelines Against Prostate-Specific Antigen Screening. JAMA Surg. 2017;152:192-98.
4. Loeb S, Carter HB, Berndt SI, Ricker W, Schaeffer EM. Complications after prostate biopsy: data from SEER-Medicare. J Urol. 2011;186:1830-34.
5. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. NEMJ. 2018;378:1767-77.
6. Oishi M, Shin T, Ohe C, et al. Which Patients with Negative Magnetic Resonance Imaging Can Safely Avoid Biopsy for Prostate Cancer? J Urol. 2019;201:268-76.
7. Delongchamps NB, Portalez D, Bruguière E, et al. Are Magnetic Resonance Imaging-Transrectal Ultrasound Guided Targeted Biopsies Noninferior to Transrectal Ultrasound Guided Systematic Biopsies for the Detection of Prostate Cancer? J Urol. 2016;196:1069-75.
8. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging – Reporting and Data System: 2015, Version 2. Eur Urol. 2016;69:16-40.
9. Borghesi M, Ahmed H, Nam R, et al. Complications After Systematic, Random, and Image-guided Prostate Biopsy. Eur Urol. 2017;71:353-65.
10. Aly M, Dyrdak R, Nordström T, et al. Rapid increase in multidrug-resistant enteric bacilli blood stream infection after prostate biopsy—A 10-year population-based cohort study. The Prostate. 2015;75:947-56.
11. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014;384:2027-35.
12. Roobol MJ et al. A Risk-Based Strategy Improves Prostate-Specific Antigen–Driven Detection of Prostate Cancer, Eur Urol 2010. 57:79-85.
13. Lee SM, Liyanage SH, Wulaningsih W, et al. Toward an MRI-based nomogram for the prediction of transperineal prostate biopsy outcome: A physician and patient decision tool. Urol Oncol. 2017;35:611-18.
14. van Leeuwen PJ, Hayen A, Thompson JE, et al. A multiparametric magnetic resonance imaging-based risk model to determine the risk of significant prostate cancer prior to biopsy. BJU Int. 2017;120:774-81.
15. Fütterer JJ, Briganti A, De Visschere P, et al. Can Clinically Significant Prostate Cancer Be Detected with Multiparametric Magnetic Resonance Imaging? A Systematic Review of the Literature. Eur Urol. 2015;68:1045-53.
16. Nordström T, Akre O, Aly M, Grönberg H, Eklund M. Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. Prostate Cancer Prostatic Dis. 2018;21:57-63.
17. J.G. Rivas, M. Alvarez-
Maestro, M. Czarniecki, S. Czarniecki, M.R. Socarras, S. Loeb. Negative biopsies with rising prostate-specific antigen. What to do? EMJ Urol.2017:76-82
18. Thomas JA, 2nd, Gerber L, Moreira DM, et al. Prostate cancer risk in men with prostate and breast cancer family history: results from the REDUCE study (R1). J Intern Med. 2012;272:85-92.
19. Wagaskar VG, Sobotka S, Ratnani P, Young J, Lantz A, Parekh S, et al. A 4K score/MRI-based nomogram for predicting prostate cancer, clinically significant prostate cancer, and unfavorable prostate cancer. Cancer Rep (Hoboken). 2021;4:1357.

Corresponding Author:
Vinayak G Wagaskar MBBS, MCh
Department of Urology, Icahn School of Medicine at Mount Sinai Hospital, 1425 Madison Avenue, New York, NY 10029, USA
E-mail address: vinayakwagaskar99@gmail.com
vinayak.wagaskar@mountsinai.org
Phone number: +1-2122414812
Fax number: +1-6465378508
ORCID ID: 0000-0001-8027-6661

Table 1. Comparison of factors between cases and controls for csPCa

	MSSM*(N=1632)			UM**(N=622)		
Factors	Cases N=701	Controls N=931	*P*-value	Cases N=173	Controls N=449	*P*-value
Age years (Median, IQR)	65 (59, 69)	64 (58, 69)	.449	60 (60, 70)	61 (60, 69)	.6283
PSA, ng/mL (Median, IQR)	6.4 (4.8, 9.5)	5.1 (3.7, 7.6)	<.0001	6.8 (5, 9.4)	5.6 (4, 8.1)	<.0001
PSAD (Median, IQR)	0.16 (0.11,0.26)	0.09 (0.05,0.14)	<.0001	0.18 (0.12,0.27)	0.09 (0.06, 0.14)	<.0001
Family History PC			<.0001			.8834
Negative	467 (66.6 %)	740 (79.5 %)		135(82.3%)	337(81.8%)	
Positive	234 (33.4 %)	191 (20.5%)		29 (17.7%)	75 (18.2%)	
PNB			<.0001			.0001
No	685 (97.7%)	624 (67.0%)		135(78.0%)	277(61.7%)	
Yes	16 (2.3%)	307 (33.0%)		38 (22.0%)	172(38.3%)	
DRE			<.0001			.0016
Normal	382 (54.5%)	703 (75.5%)		110(63.6%)	342(76.2%)	

Suspicious	319 (45.5%)	228(24.5 %)		63 (36.4%)	107(23.8%)
MRI lesion PI-RADS			<.0001		<.0001
0-2	68 (9.7%)	414 (44.5%)		11 (6.4%)	171(38.0%)
3	62 (8.8%)	201 (21.6%)		17 (9.8%)	136(30.3%)
4	342(48.8%)	255 (27.4%)		90 (52.0%)	118(26.2%)
5	229 (32.7%)	42 (4.5%)		55 (31.8%)	24 (5.5%)
ISUP Gleason grade					
0	0	546 (58.6%)		0	328(73.0%)
1	0	385(41.4%)		0	121(27.0%)
2	341 (48.6%)	0		77 (44.6%)	
3	165 (23.5%)	0		29 (16.7%)	0
4	120 (17.1%)	0		29 (16.7%)	0
5	75 (10.7%)	0		38 (22.0%)	0

*MSSM: Mount Sinai school of Medicine,

**UM-University of Miami (External validation cohort),

Abbreviations: csPCa- clinically significant prostate cancer; IQ Range- interquartile range; PSA- prostate specific antigen; PSAD-prostate specific antigen density; PC-prostate cancer; PNB- prior negative biopsy; DRE- digital rectal examination; MRI- Magnetic Resonance Imaging; PI-RADS- Prostate Imaging Reporting and Data System version 2; ISUP- International Society of Urologic Pathology.

Table 2: Multivariable analysis predicting presence of csPCa

Variable	Estimate	Standard Error	Odds Ratio	95% CI (UL, LL)	*P*-Value
Age	0.007	0.011	1.007	0.91,1.01	.496
FH	0.464	0.176	1.590	1.1,1.9	.008
PNB	-2.958	0.366	0.052	0.04,0.06	.000
PSAD	4.576	0.737	97.138	86, 103	.000
DRE	0.400	0.171	1.492	1.1,1.9	.020
PI-RADS					.000
PI-RADS 3	0.938	0.257	2.555	1.4,3.2	.000

PI-RADS 4	2.151	0.203	8.595	4.4,13.1	.000
PI-RADS 5	2.612	0.273	13.621	9.2,21.1	.000

Abbreviations: csPCa- clinically significant prostate cancer; CI- Confidence Interval ; UL-Upper limit; LL-Lower limit; PNB- prior negative biopsy; PSAD- prostate specific antigen density; FH-family history; DRE- digital rectal examination finding; PI-RADS- Prostate Imaging Reporting and Data System.

Supplementary Table: Number of biopsies performed and missed in an external cohort for clinically significant prostate cancer as per nomogram-derived cut-offs

Probability csPCa cut-off (%)	Biopsy performed, n (%)	Biopsy not performed, n (%)	csPCa missed, n	For clinically significant prostate cancer			
				Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
10	510/539	29 (5.4)	0	99.6	9.86	49.8	96.5
15	451/539	88 (16.3)	9	96.5	27.8	54.6	89.8
20	410/539	129 (23.9)	11	95.7	41.6	59.5	91.5
25	376/539	163 (30.2)	19	92.6	50.7	62.8	88.3
30	354/539	185 (34.3)	24	90.6	56.7	65.3	87.0

Abbreviations: csPCa- clinically significant prostate cancer; PPV- Positive predictive value; NPV- Negative predictive value.

Figure legends

Figure 1. Nomogram for predicting presence of csPCa at the time of biopsy.

The reading of cancer probability from nomogram can be described in following steps: 1. Locate the patient's variable Age on corresponding axis. 2. Then draw a line straight download to the score axis to determine how many points towards the probability of cancer the patient receives for his Age. 3. Repeat the process for each additional variable [Family history, prior negative biopsy, DRE, PI-RADS score]. 4. Sum the points for each of the predictors. 5. Locate the final sum on the total score axis. 6. Draw a line straight up to find

patient's probability [Prob] of having cancer. Total scores correspond to a probability value for csPCa. DRE- digital rectal examination. PIRADS –PI-RADS Score on MRI

Abbreviations: PC- prostate cancer, csPCa- clinically significant prostate cancer; PSA density- prostate specific antigen density; DRE- digital rectal examination finding; PI-RADS- Prostate Imaging Reporting and Data System.

Figure 2. Area under curve predicting csPCa in external cohort using variables used to build model.

Abbreviations: csPCa- clinically significant prostate cancer; CI- Confidence interval; PSA density- prostate specific antigen density; DRE- digital rectal examination finding; MRI- Magnetic resonance imaging; PI-RADS- Prostate Imaging Reporting and Data System.

Figure 3: Calibration curve in the external cohort.

Predictive probabilities of cancer for each case in the external cohort are sorted by probability of clinically significant prostate cancer calculated from the training model respectively. Each point (average of 60 subsequent cases) illustrates the comparison between predictive probability (calculated from the training model) and actual cancer rate for this group of cases. Points at the diagonal line (0, 0 and 1, 1), show the agreement between predicted and actual rate of cancer and validate training model.

Figure 4. Decision curve analyses showing the net benefit associated with the use of nomogram-derived probability for prediction of clinically significant prostate cancer (Figure 3B) in an external cohort vs relying on PSA density or PI-RADS score alone.

Abbreviations: PSA density- prostate specific antigen density; PI-RADS – Prostate Imaging Reporting and Data System.

Figure 5. Graph showing number of biopsies that can be avoided in an external cohort using the prediction tool predicting clinically significant prostate cancer.

Figure 1

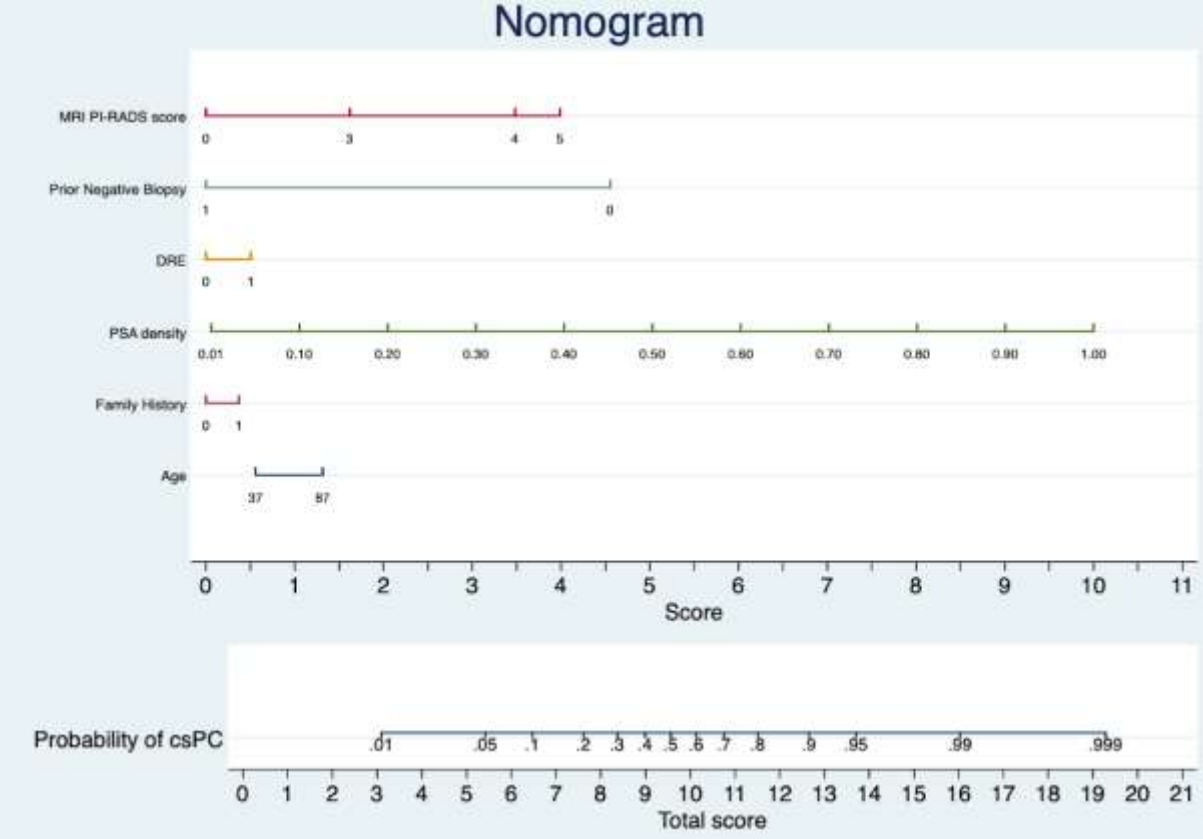
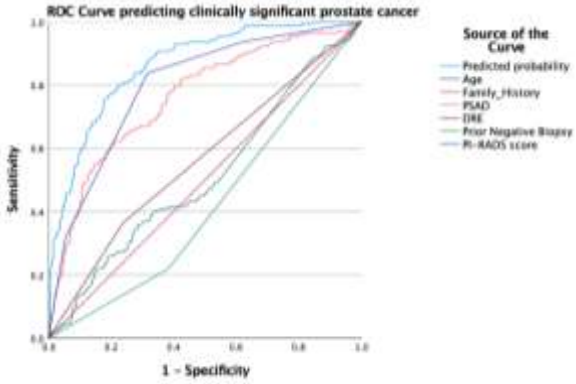

Nomogram
MRI PI-RADS score
0
3
4
5
Prior Negative Biopsy
1
0
DRE
0
1
PSA density
0.01
0.10
0.20
0.30
0.40
0.50
0.60
0.70
0.80
0.90
1.00
Family History
0
1
Age
37
87
0 1 2 3 4 5 6 7 8 9 10 11
Score
Probability of csPC
.01
.05
.1
.2
.3
.4
.5
.6
.7
.8
.9
.95
.99
.999
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Total score

Figure 2.



Variable	AUC	95% CI (upper limit, lower limit)
Model	0.88	(0.87,0.89)
Age	0.51	(0.49,0.54)
Family history of PCa	0.50	(0.47,0.52)
PSA density	0.77	(0.73, 0.80)
DRE	0.57	(0.50, 0.60)
Prior negative biopsy	0.41	(0.36,0.46)
MRI PI-RADS score	0.81	(0.76,0.85)

Figure 3.

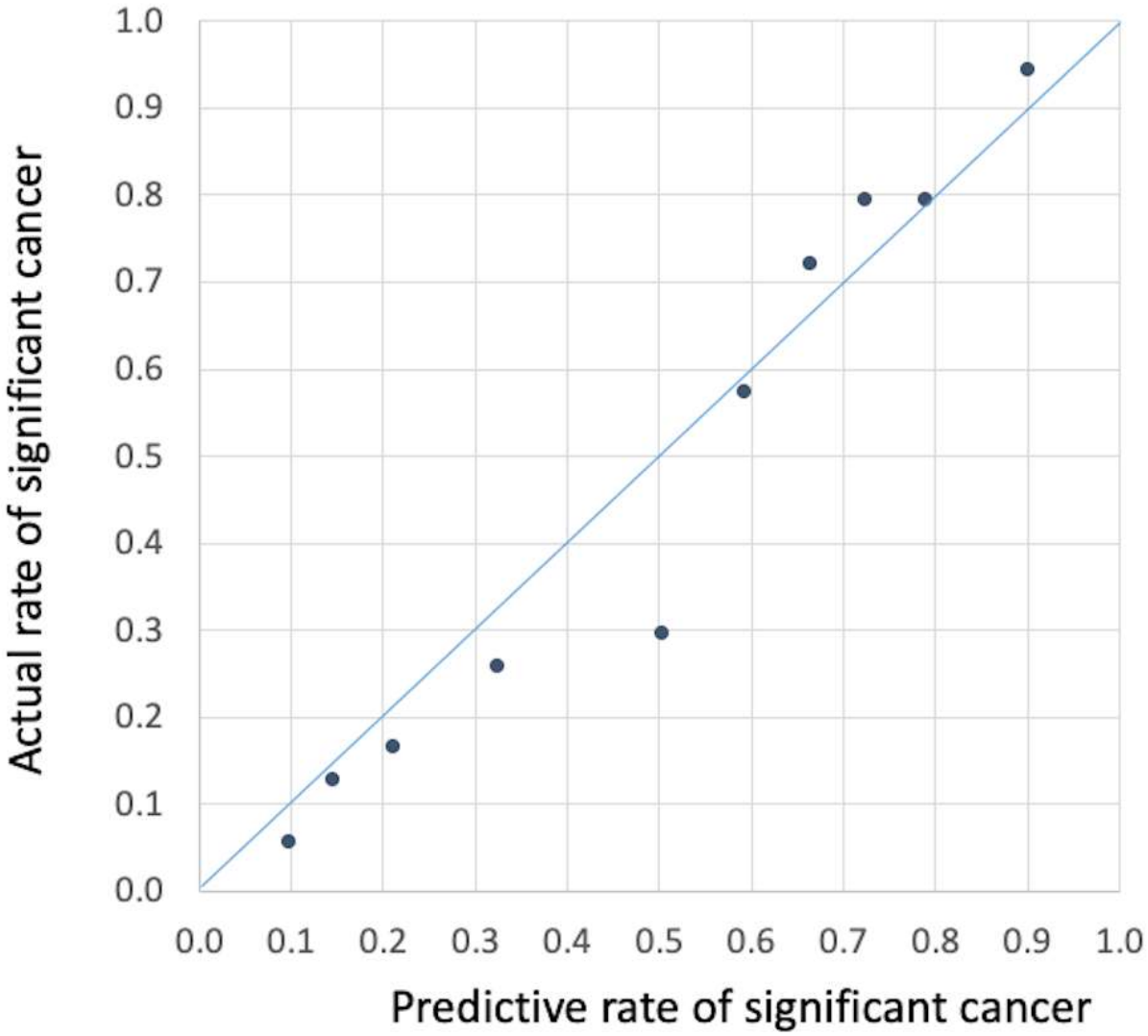

Actual rate of significant cancer
Predictive rate of significant cancer
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

Figure 4.

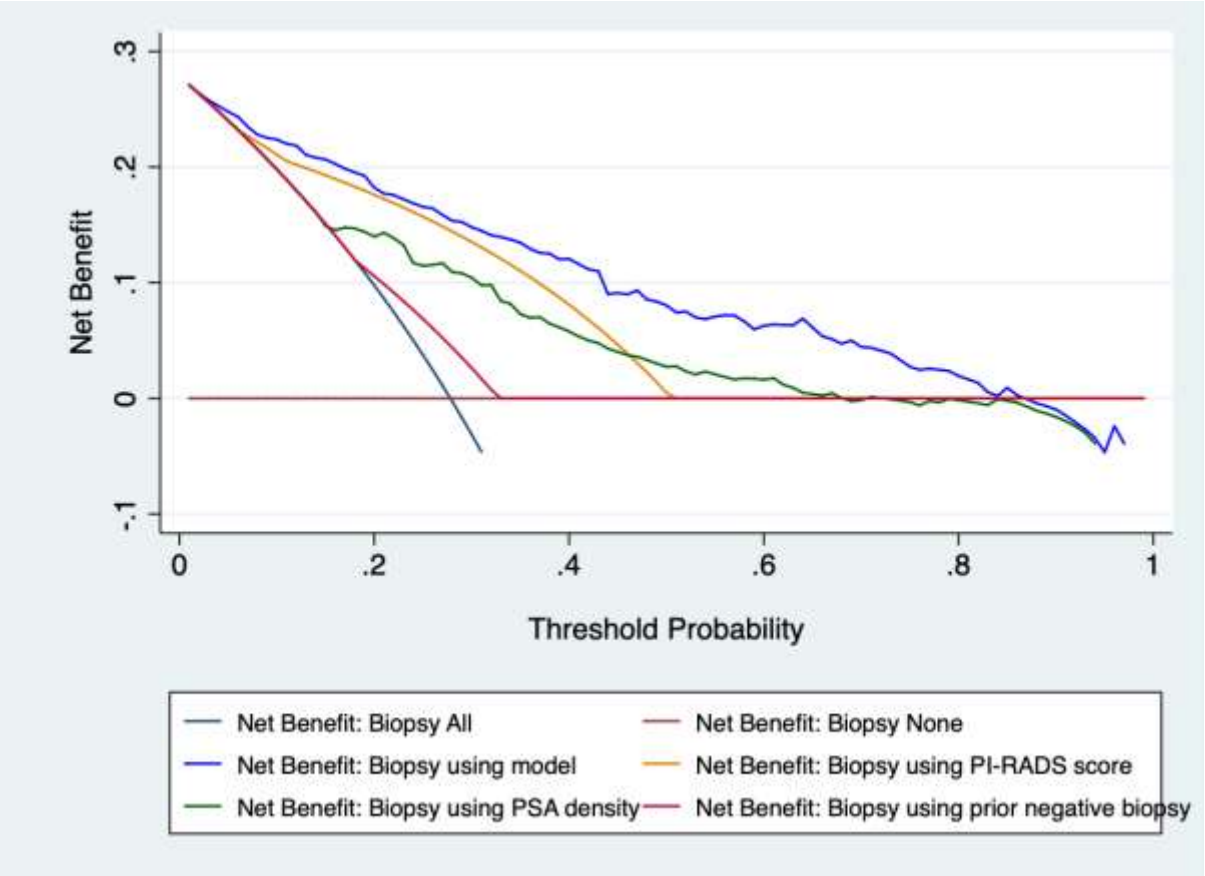
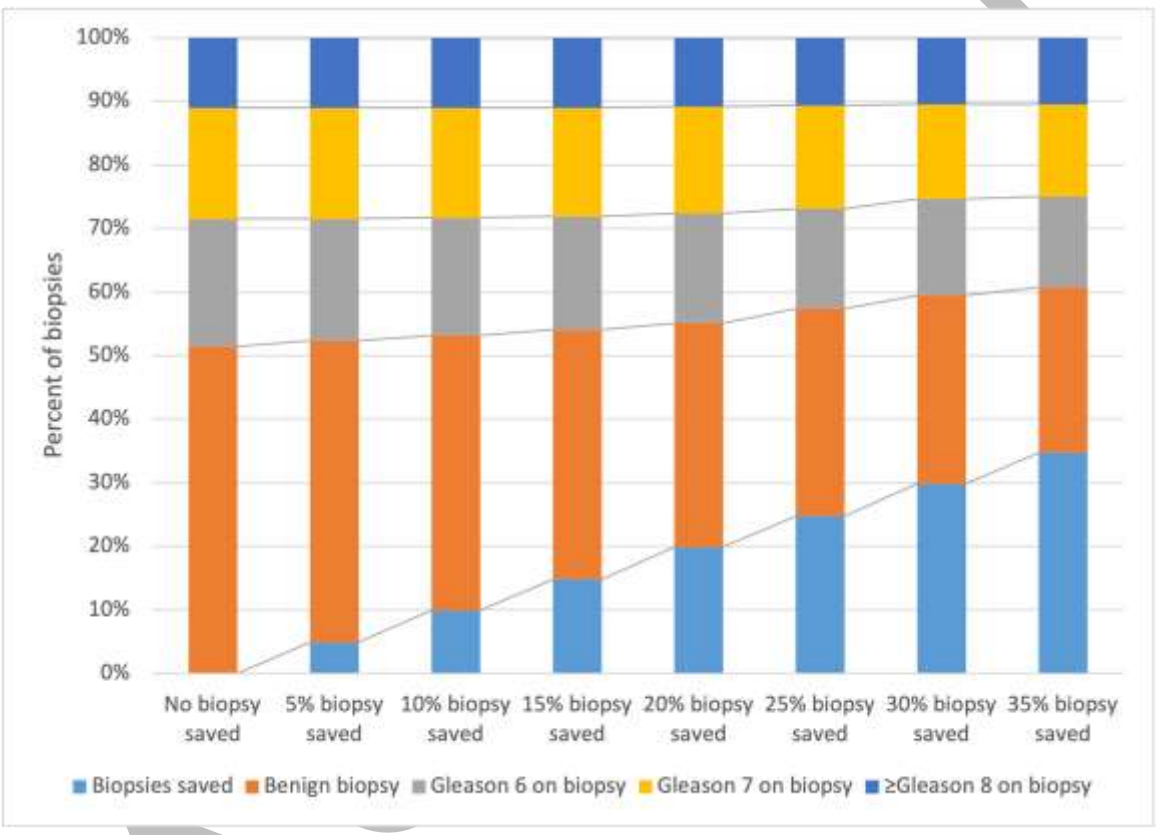

Net Benefit
-.1
0
.1
.2
.3
0
.2
.4
.6
.8
1
Threshold Probability
Net Benefit: Biopsy All
Net Benefit: Biopsy None
Net Benefit: Biopsy using model
Net Benefit: Biopsy using PI-RADS score
Net Benefit: Biopsy using PSA density
Net Benefit: Biopsy using prior negative biopsy

Figure 5.


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Percent of biopsies
No biopsy saved
5% biopsy saved
10% biopsy saved
15% biopsy saved
20% biopsy saved
25% biopsy saved
30% biopsy saved
35% biopsy saved
Biopsies saved
Benign biopsy
Gleason 6 on biopsy
Gleason 7 on biopsy
≥Gleason 8 on biopsy