

Development of a nomogram for predicting a positive repeat prostate biopsy

Ryo Iseki, Makoto Ohori, Alice Piccorelli, Changhong Yu, Annie Piccorelli, Yoshio Ohno, Masaaki Tachibana, Michael W Kattan

Ryo Iseki, Makoto Ohori, Yoshio Ohno, Masaaki Tachibana, Department of Urology, Tokyo Medical University, Shinjuku, Tokyo 160-0023, Japan

Alice Piccorelli, Changhong Yu, Annie Piccorelli, Michael W Kattan, Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland Clinic Foundation, Cleveland, OH 44195, United States

Author contributions: All the authors contributed to this work. Correspondence to: Ryo Iseki, MD, Department of Urology, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku, Tokyo 160-0023, Japan. iseki@tokyo-med.ac.jp

Telephone: +81-3-33426111 Fax: +81-3-33444813

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Abstract

AIM: To find risk factors of cancer in patients who had a repeat biopsy and to develop the nomogram using our cohort.

METHODS: Among 3500 patients who had a prostate biopsy over 11 years between 2000 and 2010 at our hospital, we studied a total of 807 repeat biopsy sessions in 459 patients who had at least 1 initial negative biopsy. At each biopsy session, we recorded patient age, number of previous biopsy sessions, number of biopsy cores, number of previously negative biopsy cores, months from the initial biopsy, months from the previous biopsy, serum PSA, PSA slope, digital rectal examination findings, hypoechoic lesions suspicious for a cancer on transrectal ultrasonography, total prostate volume, transitional zone (TZ) volume, PSA density, PSA TZ density and history of high grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP). Clinical and pathological variables were correlated with the outcome of repeat biopsies. A nomogram was developed based on logistic regression analyses and calibration was performed.

RESULTS: Overall, 17% of repeat biopsies had a cancer. With receiver operating characteristics analyses, the highest area under the curve (AUC) was obtained based on all available 13 variables, which were age, PSA, digital rectal examination, PSA density, prostate volume, TZ volume, PSA TZ density, cumulative number of biopsy cores, HGPIN, ASAP, months from previous negative biopsy, initial negative biopsy and number of biopsy cores. Based on multivariable logistic regression analysis, a nomogram was constructed with an AUC of 0.74, which was greater than that of any single risk factor. The calibration plot seemed to be good.

CONCLUSION: Our nomogram for predicting a positive repeat biopsy can provide probabilities for cancer and may help clinical judgment on whether to do a repeat prostate biopsy.

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Key words: Prostate; Repeat biopsy; Prostate cancer; Nomogram; Prostate-specific antigen

Core tip: Although prostate cancer is found in about 30% of patients at the initial biopsy session, there is a need to identify those with a negative result but who are at high risk. Although individual risk factors have been found to be associated with cancer, patient counseling requires the integration of multiple risk factors to obtain a prediction for the individual. We developed a nomogram that predicts a positive biopsy after a previous negative biopsy session. It provides a wide range of probabilities for cancer and may help clinical judgment of whether to do a repeat prostate biopsy.

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INTRODUCTION

With the advent of serum prostatic specific antigen (PSA) and transrectal ultrasonography in the late 1980s, prostate needle biopsy has markedly increased for a diagnosis of prostate cancer^[1,2]. About 70000 cases with prostate biopsies in a year in Japan^[3] have been estimated, so roughly 50000 cases should have no cancer in biopsy specimens if the detection rate of cancer is about 25%. It is obvious that no cancer in the first biopsy session does not give the perfect answer so a repeat biopsy will be done over and over^[4,5]. The procedure of prostate biopsy itself is not difficult but the complications, such as hematuria, dysuria and urinary tract infection, do exist and we should also not underestimate discomfort during the biopsy procedure.

On the other hand, the indication for rebiopsy has remained unclear. Clinicians tend to recommend a repeat biopsy because of high PSA levels, an increasing PSA, abnormalities on digital rectal examination and/or imaging studies, and the presence of high grade prostatic intraepithelial neoplasia (HGPIN) and/or atypical small acinar proliferation (ASAP) in a previous biopsy. Age, race and family history are also sometimes considered. Realistically, however, it is extremely difficult to get the right answers to make a clinical decision at the time of whether to do a biopsy with these many factors and backgrounds. In the past, many investigators studied to find risk factors to predict a cancer in a repeat biopsy and to construct models to provide the accurate prediction of a cancer. Among them, a nomogram, the mathematical model based on a logistic analysis with multiple factors, seems to be the best model to provide an accurate prediction for an individual patient. Therefore, we tried to find risk factors of cancer in patients with a repeat biopsy and develop the nomogram using our cohort.

MATERIALS AND METHODS

We studied 459 patients who had at least 1 initial negative biopsy and underwent a total of 807 repeat biopsy sessions at our hospital for 11 years between 2000 and 2010. The indication of repeat biopsy and number of biopsy cores varied among a total of 10 attending physicians. However, the number of biopsy cores has changed; 8 cores in 2000 to 2005, 10 cores in 2005 to 2007, and 12 cores in 2008 to the present. The majority of patients had a transrectal biopsy under local anesthesia of 10 cc of 1% lidocaine under the guidance of transrectal ultrasonography (TRUS). Also, the additional cores were taken if there were hypoechoic lesions suspicious for a cancer on TRUS. On TRUS, the volume of

the prostate gland and transition zone were estimated with an ellipsoid formula, as previously described. PSA density^[6] was calculated as PSA divided by prostate volume and PSA transition zone density (PSATZD)^[7] was calculated as PSA divided by transition zone volume. PSA slope in ng/mL yearly was estimated by the difference between the most current serum PSA measured minus serum PSA at the previous biopsy, divided by elapsed time in years^[8].

Pathology

We obtained the pathology outcome from the official pathology reports. The majority of pathological reports indicated HGPIN as an indicator of cancer precursor and we neglected the reports of low grade PIN. We also recorded ASAP if the pathological reports indicated that there were a few atypical cells which were not enough to diagnose a cancer.

Statistical analysis

In analyses, the association of positive repeat biopsy with each clinical and biopsy feature was evaluated using multivariable logistic regression analysis. All the predictor variables included in the multiple logistic regression were based on a systematic literature review and clinical relevance with model selection. Restricted cubic splines were used for numeric or ordinal variables to accommodate the non-linear relationship. Generalized estimating equations (GEEs) implemented to adjust the clustering effect resulted from the repeat biopsies from the same patients. To evaluate the predictive accuracy of each factor in combination, we used the area under the receiver operating characteristic (ROC) curve (AUC) as the discrimination metric. Also, in the calibration plots, we compared the predictive values with the actual outcomes. Bootstrapping was used to correct for over-fitting bias. Based on the logistic analysis, we developed a nomogram to predict the probability of a positive repeat biopsy. Statistical significance was determined with a *P* value less than 0.05. All analyses were carried out using the commercially available software, STATA (Stata Corporation, College Station, TX, United States) and S-plus (Insightful Corporation, Seattle, WA, United States) or the open-source statistical software R-2.12.2 (R Development Core Team 2011) with Design and Zelig packages added.

RESULTS

Overall, 17% of patients had a prostate cancer on repeat biopsy. Table 1 lists the characteristics of the patients. A mean of 1.7 repeat biopsy sessions (or 2.7 all biopsy sessions including the initial biopsy) per patient were performed. Table 2 shows the rates of a positive repeat biopsy according to each variable. The cancer detection rates at biopsy 2 to 4 were consistent at 16%-18%. The number of patients was too small but the detection rates were high at 38%-50% if palpable nodules were identified. As prostate volume measured with ultrasonography increased, detection rates of cancer significantly de-

Table 1 Clinical and pathological characteristics *n* (%)

Predictor variables		No cancer <i>n</i> = 675	Cancer <i>n</i> = 132	<i>P</i> value
Digital rectal examination	Negative	642 (95.1)	122 (92.4)	0.209
	Positive	33 (4.9)	10 (7.6)	
TRUS	Negative	603 (89.3)	108 (81.8)	0.015
	Positive	72 (10.7)	24 (18.2)	
HGPIN in previous biopsy	Negative	648 (96)	121 (91.7)	0.032
	Positive	27 (4)	11 (8.3)	
ASAP in previous biopsy	Negative	627 (92.9)	116 (87.9)	0.051
	Positive	48 (7.1)	16 (12.1)	
Age, yr	Mean	67	68.8	0.008
	SD	7.3	6.3	
No. of previous biopsy sessions	Mean	1.7	1.7	0.894
	SD	1	1.1	
No. of biopsy cores	Mean	11.3	11.9	0.006
	SD	2.4	2.5	
Cumulative No. of cores	Mean	16.1	15.8	0.791
	SD	12.3	11.4	
Months from the initial biopsy	Mean	26.8	25.7	0.576
	SD	21.0	22.7	
Months from the previous biopsy	Mean	16.9	15.7	0.353
	SD	13.7	13.6	
PSA slope (ng/mL per year)	Mean	1.2	1.3	0.824
	SD	5.7	13.2	
PSA (ng/mL)	Mean	9.8	11.6	0.011
	SD	6.7	9.8	
Prostate volume (cc)	Mean	53.0	43.8	< 0.001
	SD	25.8	27.2	
TZ prostate volume (cc)	Mean	30.2	21.2	< 0.001
	SD	20.4	17.9	
PSA density (ng/mL per cc)	Mean	0.2	0.3	< 0.001
	SD	0.2	0.4	
PSA TZ density (ng/mL per cc)	Mean	0.4	0.8	< 0.001
	SD	0.4	0.9	

TRUS: Transrectal ultrasonography; HGPIN: High grade prostatic intraepithelial neoplasia; ASAP: Atypical small acinar proliferation; TZ: Transitional zone.

creased ($P < 0.001$). Of 38 repeat biopsies with HGPIN in previous biopsy specimens, 11 (32%) had cancer compared to 116 (15%) of 769 patients with no HGPIN ($P = 0.032$). Similarly, of 64 biopsies with ASAP, 16 (25%) had a cancer compared to 116 (16%) of 743 biopsies with no ASAP ($P = 0.05$).

Table 3 shows the results of the multivariable logistic regression analysis in predicting a positive biopsy after adjusting the clustering effect with GEEs. Of all variables, age, number of previous negative biopsy sessions, number of biopsy cores, cumulative number of biopsy cores, PSA slope, PSA density and history of ASAP were statistically significantly associated with repeat biopsy findings (all $P < 0.05$).

A nomogram was constructed incorporating all predictors (Figure 1). Although some variables were not statistically significant predictors of a positive repeat biopsy, they were retained in the nomogram because omitting them from the model tended to decrease accuracy. Also, other factors become falsely better if clinically important factors are omitted. The nomogram is used by first locating the patient position on each predictor variable scale. Each scale position has corresponding prog-

Table 2 Association between cancer detection rates and clinical variables according to the number of biopsy sessions

Variable	Total No./No. Ca (%)			
	Biopsy 2 459/75 (16.3)	Biopsy 3 208/34 (16.7)	Biopsy 4 82/15(18)	Biopsy 5 41/3(7)
Digital rectal examination				
Negative	437/73 (16.7)	195/29(14.9)	76/12 (15.8)	40/3 (7.5)
Positive	22/2 (9.1)	13/5(38.5)	6/3 (50)	1/0 (0)
Prostate volume on TRUS, (cc)				
Less than 20	15/7 (47.7)	6/4 (66.7)	0/0 (0)	0/0 (0)
20-40	181/39 (21.5)	69/12 (17.4)	24/6 (25.0)	14/1 (7.1)
40-60	145/19 (13.1)	75/12 (16.0)	35/5 (14.3)	16/2 (12.5)
60-80	71/7 (9.9)	32/6 (18.8)	13/2 (15.4)	5/0 (0)
80 or Greater	47/3 (6.3)	26/0 (0)	10/2 (20.0)	6/0 (0)
PSA density (ng/mL per cc)				
Less than 0.15	196/16 (8.2)	82/11 (13.4)	29/6 (20.7)	10/0 (0)
0.15-0.30	185/33 (17.8)	84/10 (11.9)	36/6 (16.7)	22/3 (13.6)
0.30-0.45	46/14 (30.4)	20/3 (15.0)	10/1 (10.0)	7/0 (0)
Greater than 0.45	32/12 (38.5)	22/10 (45.5)	7/2 (28.6)	2/0 (0)
PSA TZ density (ng/mL per cc)				
Less than 0.25	156/9 (5.8)	58/7 (12.1)	19/3 (18.8)	10/0 (0)
0.25-0.5	168/22 (13.1)	85/11 (12.9)	42/7 (16.7)	18/2 (22.2)
0.5-1.0	98/26 (26.5)	40/6 (15.0)	15/3 (20.0)	12/2 (18.3)
Greater than 1.0	37/18 (48.6)	25/10 (40.0)	6/2 (33.3)	1/0 (0)
PSA (ng/mL)				
Less than 4	18/1 (5.6)	1/1 (100)	0/0 (0)	0/0 (0)
4-10	313/48 (15.3)	136/19 (14.0)	49/8 (16.3)	20/2 (10.0)
10-20	108/21 (19.4)	54/11 (20.3)	25/5 (20.0)	17/1 (5.9)
Greater than 20	20/5 (25.0)	17/3 (17.6)	8/2 (25.0)	4/0 (0)
PSA slope (ng/mL per year)				
Less than 0.75	237/30 (12.7)	102/15 (14.7)	44/8 (18.2)	21/1 (4.8)
0.75 or greater	222/45 (20.3)	106/19 (17.9)	38/7 (18.4)	20/2 (10.0)
Previous HGPIN				
Negative	437/67 (15.3)	200/32 (16.0)	79/14 (17.7)	40/3 (7.5)
Positive	22/8 (36.4)	8/2 (25.0)	3/1 (33.3)	1/0 (0)
Previous ASAP				
Negative	427/68 (15.9)	190/30 (15.8)	75/13 (17.3)	38/2 (5.3)
Positive	32/7 (21.9)	18/4 (22.2)	7/2 (28.6)	3/1 (33.3)
Normal histology	406/61 (15.0)	184/29 (15.8)	72/12 (16.7)	37/2 (5.4)
Total	459/75 (16.3)	208/34 (16.4)	82/15 (18.3)	41/3 (7.3)

Results of cases with 6 or more biopsy sessions are not shown because of low numbers. HGPIN: High grade prostatic intraepithelial neoplasia; TZ: Transitional zone; ASAP: Atypical small acinar proliferation.

nostic points (top axis). Point values for all the predictor variables are determined consecutively and summed to arrive at a total point value. This value is located on the total point axis and directly below is the prediction for finding cancer. The nomogram was internally validated with 1000 bootstrap resamples and achieved an AUC of 0.74.

Figure 2 shows the calibration by plotting the nomogram predicted probability for positive repeat biopsy against the patient's observed probability. In general, the performance of the nomogram appears to be reasonably accurate while the predicted probability seems to overestimate a positive repeat biopsy in the higher range of predicted probability.

DISCUSSION

In 2003, Lopez-Corona *et al*^[9] first reported the nomo-

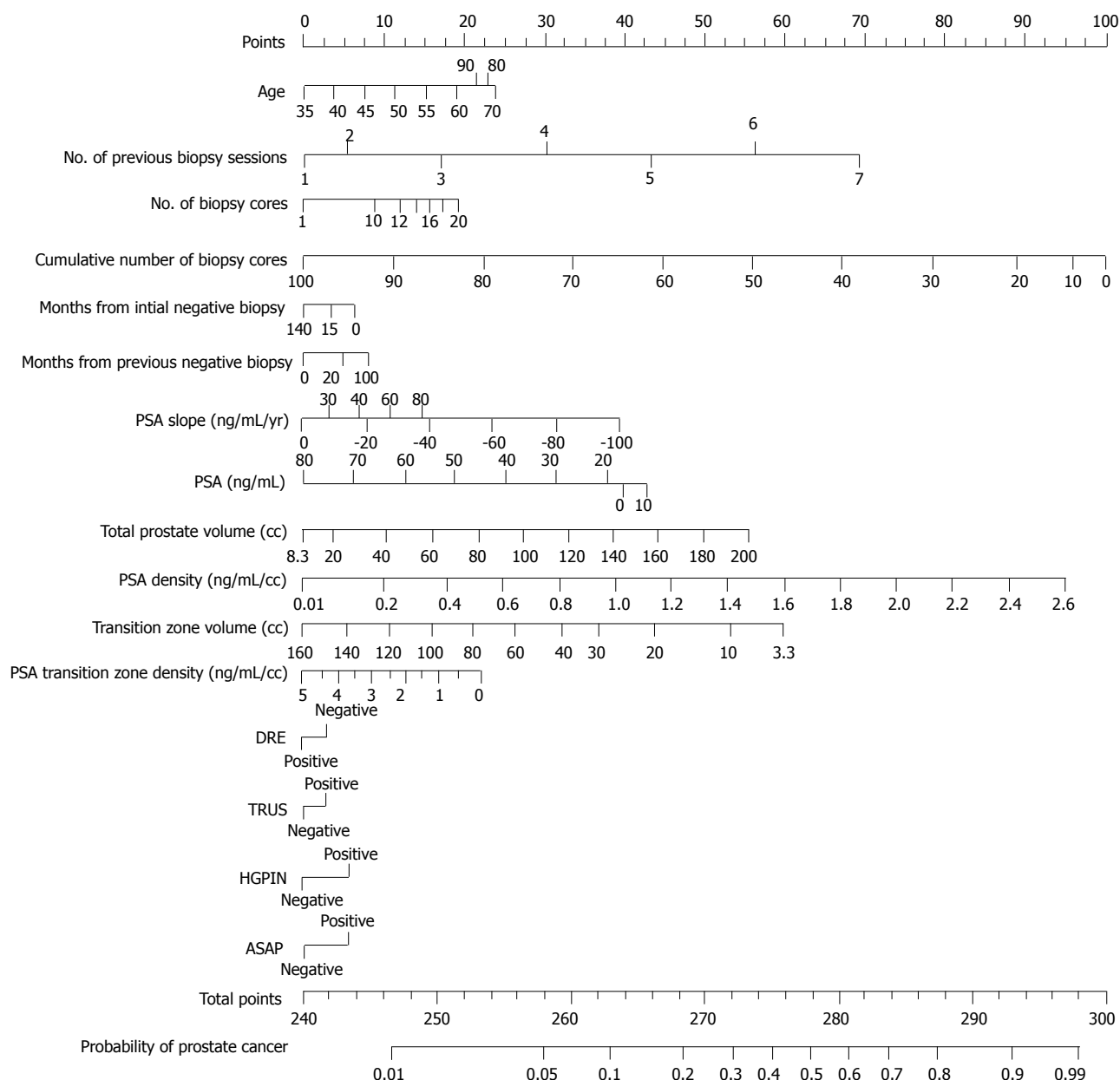


Figure 1 Nomogram (age, number of previous biopsy session, number of biopsy cores, number of previously negative biopsy cores, months from initial biopsy, months from previous biopsy, prostate specific antigen slope, prostate specific antigen, digital rectal exam, transrectal ultrasonography, prostate volume, transition zone volume, prostate specific antigen density, high grade prostatic intraepithelial neoplasia, atypical small acinar proliferation, prostate specific antigen transition zone density) for predicting the probability of a positive repeat biopsy. Nomogram is used by first locating the patient's position on each factor axis. Each factor has corresponding prognostic points (top axis). The points for each factor are added to achieve a total point that is subsequently plotted on the total point axis (the second scale from the bottom). The probability of prostate cancer is estimated by drawing a straight line downwards to the bottom line from the location of the total point. TRUS: Transrectal ultrasonography; HGPIN: High grade prostatic intraepithelial neoplasia; ASAP: Atypical small acinar proliferation; TZ: Transitional zone; PSA: Prostatic specific antigen; DRE: Digital rectal exam.

gram to predict a cancer in 661 patients with a previous negative biopsy using 8 factors, such as age, digital rectal examination, a total number of biopsy cores, HGPIN, ASAP, PSA, PSA slope and family history. Since then, to our knowledge there are a total of 8 published nomograms^[9-18], including 2 with an extended biopsy strategy^[10,18], to predict a positive biopsy in a setting of repeat biopsy. We have summarized these nomograms in Table 4. All nomograms, except 2, included age, PSA and DRE as standard predictive factors. Among variables in the previous nomograms, 4 nomograms included the results

of %free PSA which seemed to be most valuable predictor since it had a large scale of points in the nomograms with a relatively higher AUC of 0.76 to 0.856^[10,11,14,18]. Following %free PSA, prostate volume seemed to be important since 6 out of 9 nomograms included it as a significant predictor. Only Sakura *et al*^[18] reported that age was the largest scale in the nomogram, while another 7 nomograms showed a short scale for age. There were many other factors and none of 9 nomograms used identical factors, which may represent the complexity of the situation of a repeat biopsy.

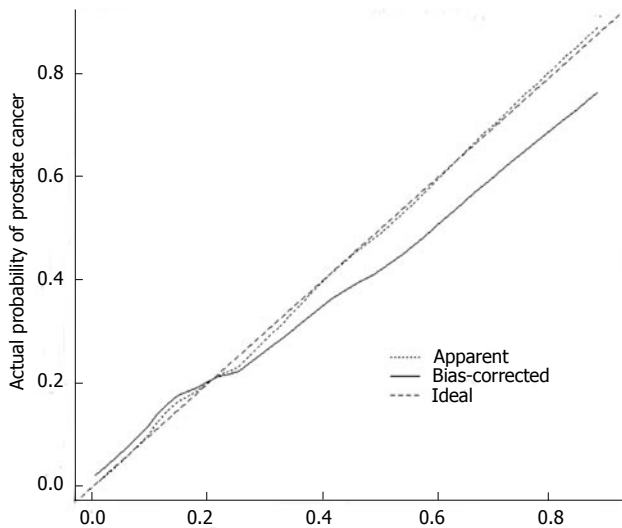


Figure 2 A calibration plot of the nomogram predicting the probability of a positive repeat biopsy.

Early studies reported relatively high rates of cancer detection on repeat biopsy after an initial biopsy finding of HGPIN, but recent studies have reported substantially lower rates^[19,20]. Park *et al.*^[21] analyzed 45 patients with ASAP and 43 with HGPIN on initial biopsy and found cancer in 51% of repeat biopsies in each group. Abouassaly *et al.*^[22] reported that the findings of ASAP were associated with a high likelihood of cancer on repeat biopsy regardless of the number of cores taken on initial biopsy. In our study, in 32 patients with ASAP and 22 patients with HGPIN in the previous biopsy session, cancer was found in 21.9% of repeat biopsies in the ASAP group and in 36.4% in the HGPIN group. Since the proportion of ASAP and/or HGPIN of the entire group is small, the impact on the detection rates of cancer may not be huge but we still think that they should be included in the nomogram since they are a different entity from the other markers and it would be important to include the findings by pathologists.

In studies by Walz *et al.*^[10] and ourselves, PSA density was the best factor to predict a cancer in a repeat biopsy. Benecchi *et al.*^[13] also included PSA density, which was the second predictor after %free PSA, while Walz *et al.*^[10] indicated that PSA density was a stronger predictor than %free PSA. Previously, Keetch *et al.*^[23] noted that PSA density and PSA slope were the best predictors of cancer on a repeat biopsy. In men with a PSA density of ≥ 0.15 ng/mL per milliliter and a PSA slope of 0.75 ng/mL per year, the rate of cancer detection was 46% compared to 13% in men with a PSA density of < 0.15 ng/mL per milliliter and a PSA slope of < 0.75 ng/mL per year ($P < 0.001$)^[23]. In contrast, Fowler *et al.*^[24] found that percent free PSA was the best predictor of cancer compared with the other PSA derivatives. Eventually, the inclusion of these important factors enhances the detection rate of cancer in a repeat biopsy and a nomogram would be the best method to combine these factors to provide an accurate prediction for the individual patient.

Table 3 Multivariable logistic regression analysis in predicting positive repeat biopsy with generalized estimating equations adjustment for clustering repeat biopsies from the same patients

Predictor variables	Q1	Q3	Odds ratio	Lower 0.95	Upper 0.95	P
Age, yr	62	73	1.6	1.1	2.5	0.002
No. of previous biopsy sessions	1	2	2.3	0.8	6.2	0.002
No. of biopsy cores	10	12	1.6	1.3	2.1	0.001
Cumulative No. of cores	8	20	0.3	0.1	0.8	0.001
Months from the initial biopsy	10.3	36	0.6	0.2	2.0	0.727
Months from the previous biopsy	7.1	22.7	1.5	0.6	3.8	0.651
PSA slope (ng/mL per year)	-0.3	2.4	0.9	0.9	1.0	0.007
PSA (ng/mL)	6	11.4	1.0	0.3	4.0	0.098
Prostate volume (cc)	33.5	60.5	3.3	0.5	20.8	0.081
TZ prostate volume (cc)	15	36.1	0.1	0.0	1.0	0.116
PSA density (ng/mL per cc)	0.1	0.3	2.5	0.3	24.7	0.045
PSA TZ density (ng/mL per cc)	0.2	0.6	0.8	0.1	6.9	0.328
DRE-positive: negative	NA	NA	0.7	0.3	1.7	0.393
TRUS-positive: negative	NA	NA	1.4	0.8	2.6	0.218
HGPIN-positive: negative	NA	NA	2.2	0.9	5.2	0.080
ASAP-positive: negative	NA	NA	2.2	1.1	4.7	0.035

TRUS: Transrectal ultrasonography; HGPIN: High grade prostatic intraepithelial neoplasia; ASAP: Atypical small acinar proliferation; TZ: Transitional zone; PSA: Prostatic specific antigen; DRE: Digital rectal exam.

There are several limitations in the present study. Firstly, we could not include the results of %free PSA since it was frequently not measured at our clinic. However, all variables in our nomogram are readily available so it is not necessary for patients to come to the clinic frequently to get the result of %free PSA. Also, in the present study, we showed a similar accuracy to predict a positive repeat biopsy without %free PSA. Thus, our nomogram can help many patients and their physicians after appropriate validations. Secondly, there are 16 variables in our nomogram to achieve the highest AUC. The accuracy, AUC 0.74, seems to be reasonable but some may feel that there are too many variables to calculate the probability at a busy clinic. We agreed that the calculation on paper may not be realistic so we have put our nomogram on the web. Thirdly, because the nature of a nomogram is based on multivariable analysis, the values of some variables were reversed. For example, the points on the nomogram increase with a decrease of the PSA transition zone density. This happened because we included similar variables, such as transition zone volume, PSA density and prostate volume. Therefore, it may slightly confuse clinicians when they put each value of variables into our nomogram. However, the inclusion of such variables is valuable to get accurate estimations. Fourthly, in the present study, we did not do model selection that would be accomplished on the modeling data alone. Instead, we built the model by including all predictors that were clinically relevant to the disease based on the literature whether they were statistically significant or not on the current data. With enough number of events in the modeling data, theory driven models normally have better generalizability than data driven models when applied to other patient populations and

Table 4 Published nomograms to predict positive prostate biopsy in repeat biopsy

Ref.	No. of patients	AUC	AUC of external validation	No of factors	Nomogram factors	Mean of no of biopsy cores	Ca detection rate, %
Lopez-Corona <i>et al</i> ^[9,12]	343	0.700	0.710	8	Standard factors + PSAV, HGPIN, ASAP, No. of total cores, biopsy history, family history	9.15	20
Walz <i>et al</i> ^[10]	161	0.720	-	9	Age, PSA, %free PSA, PSA density, TZ density, prostate volume, TZ volume, no of previous biopsy, no of cores.	24	41
Chun <i>et al</i> ^[11]	1082	0.760	0.68-0.78	6	Standard factors, prostate volume, biopsy history, %free PSA, sampling density	11.1	30.2
Benecchi <i>et al</i> ^[13]	419	-	0.856	7	DRE + PSA slope, HGPIN, %free PSA, PSA density	-	31
Rochester <i>et al</i> ^[14]	110	0.818	0.696	7	Standard factors + PSA velocity, HGPIN, biopsy history, %free PSA	-	30-31
Chun <i>et al</i> ^[15,16]	809	0.700	0.73-0.75 ¹	6	Standard factors + prostate volume, biopsy history, PCA3	15	39.1
Moussa <i>et al</i> ^[17]	408	0.720	0.620	12	Standard factors + prostate volume, PSA velocity, HGPIN, ASAP, No. of total cores, family history, time from initial/previous biopsy, BMI	19.1	31.6
Sakura <i>et al</i> ^[18]	515	0.791	-	5	Age, %free PSA, prostate volume, previous extended biopsy, PSA doubling time	26	31.6
Present series	459	0.740	-	16	Age, No. of biopsy core, PSA, PSA density, prostate volume, TZ volume, PSA TZ density, TRUS, DRE, HGPIN, ASAP, months from initial biopsy and previous biopsy, No. of previous negative biopsy, PSA slope	11.4	17

¹Standard factors include age, PSA and digital rectal examination; ²Extended biopsy. AUC: Area under the curves; TZ: Transitional zone; TRUS: Transrectal ultrasonography; HGPIN: High grade prostatic intraepithelial neoplasia; ASAP: Atypical small acinar proliferation; PSA: Prostatic specific antigen, DRE: Digital rectal exam; BMI: Body-mass index.

preserve the predictive performance that was evaluated based on the modeling data^[25,26].

In conclusion, we developed a nomogram to predict a cancer in a repeat biopsy using 16 readily available clinical factors with reasonable calibration. This helps both patients and clinicians to decide whether to do a repeat prostate biopsy.

COMMENTS

Background

Prostate cancer is found in about 30% of patients at the initial biopsy session but there is a need to identify those with a negative result who are at high risk. Although individual risk factors have been found to be associated with cancer, patient counseling requires the integration of multiple risk factors to obtain a prediction for the individual.

Innovations and breakthroughs

The authors developed a nomogram that predicts a positive biopsy after a previous negative biopsy session.

Applications

It provides a wide range of probabilities for cancer and may help clinical judgment of whether to do a repeat prostate biopsy.

Peer review

This paper is well-written and the topic is timely and appropriate.

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