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Nomogram using transrectal ultrasound-derived information predicting the detection of high grade prostate cancer on initial biopsy

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Purpose: To develop a nomogram using transrectal ultrasound (TRUS)-derived information for predicting high grade (HG) prostate cancer (PCa) on initial biopsy.

Methods: Data were collected on 1,048 men with serum prostate-specific antigen (PSA) levels 4.0 to 9.9 ng/mL who underwent an initial prostate biopsy. Two logistic regression-based nomograms were constructed to predict the detection of PCa. Nomogram-1 incorporated age, digital rectal examination, PSA and percent free PSA data, whereas nomogram-2 incorporated those factors plus TRUS-derived information (i.e., prostate volume and the presence of hypoechoic lesions). The prediction of any PCa and HGPCa (Gleason score ≥ 7) were determined. Twenty percent of the data were randomly reserved for study validation, and the predictive accuracies of the two nomograms were directly compared.

Results: Of the 1,048 men who underwent biopsy, 216 (20.6%) were found to have any PCa, and 97 (9.3%) were found to have HGPCa. All six risk factors were found to be independent predictors for both any PCa and HGPCa. The area under curve (AUC) for nomogram-2 was 0.76 (95% confidence interval [CI], 0.72 to 0.81) for predicting any PCa, and 0.83 (95% CI, 0.79 to 0.88) for predicting HGPCa. These AUCs were greater than those for nomogram-1 (0.72 [95% CI, 0.68 to 0.76 for any PCa; $P < 0.001$], 0.78 [95% CI, 0.72 to 0.83 for HGPCa; $P < 0.001$]). Removing the TRUS-derived information from nomogram-2 resulted in an incremental AUC decrease of 0.052 for any PCa and 0.063 for HGPCa.

Conclusions: The nomogram using TRUS-derived information had a high predictive accuracy for HGPCa on initial prostate biopsy.

Keywords: Prostatic neoplasms, Biopsy, Nomograms, Ultrasonography

INTRODUCTION

Prostate cancer (PCa) is the most common nonskin cancer in men in the United States (US), with an estimated 186,320 new cases in 2008 [1]. The serum prostate-specific antigen (PSA) test is commonly used as a diagnostic screening tool for detecting PCa. A recent randomized European trial showed that while PCa screening decreased PCa mortality by 20%, it was associated with a high risk of overdiagnosis [2]. Approximately 1.5 million US men aged 40 to 69 years have a PSA level greater than 4.0 ng/mL, a value widely accepted as a positive test result [3].

In men with intermediate PSA range (4 to 10 ng/mL), the detection rate of prostate biopsy is approximately 25%. In this range, PSA alone does not differentiate men with the benign prostatic disease from those with PCa due to its lack of speci-

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ficity [4]. Therefore, several clinical and laboratory variables have been proposed in an attempt to improve the sensitivity and specificity of detecting PCa in men with intermediate PSA levels [5]. Models such as nomograms and artificial neural networks have been developed to integrate multiple prebiopsy risk factors, to predict initial biopsy outcomes on an individual basis [6-8]. Successful modeling will reduce the number of unnecessary prostate biopsies and assist in optimal disease management, and thus will have significant benefits in terms of costs and patient satisfaction.

Patients with high grade PCa (HGPCa) have a significantly worse prognosis compared with those with low grade PCa. Therefore, predicting the presence of HGPCa is important to treat these patients aggressively [9]. Transrectal ultrasound (TRUS) data (i.e., prostate volume and the presence of hypoechoic lesions) have been incorporated into conventional nomograms using serum PSA and digital rectal examination (DRE) to increase the predictive accuracy [10]. However, it remains unclear whether the inclusion of such TRUS-derived information improves the accuracy of HGPCa prediction in men with intermediate PSA levels.

In the present study, we developed a nomogram that incorporated TRUS-derived information for predicting HGPCa on initial biopsy in men with serum PSA levels of 4.0–9.9 ng/mL and tested whether the addition of TRUS-derived information would enhance nomogram accuracy for predicting HGPCa.

MATERIALS AND METHODS

1. Study subjects

The study included a total of 1,048 eligible men who visited the Asan Medical Center (Seoul, Korea) between December 1997 and March 2008 for prostatic evaluation due to abnormal DRE and/or PSA results. Eligible patients were unselected and were accrued consecutively. All subjects had PSA levels ranging from 4.0 to 9.9 ng/mL. The enrolled subjects had visited hospitals for various reasons including PCa screening and voiding symptoms, and were included in the study regardless of whether those visits were primary or referred. Patients who had active acute prostatitis, were in active urinary retention, had recently undergone prostatic manipulation or were on medications that may affect total PSA levels were excluded. The Institutional Review Board of the Asan Medical Center approved all sampling and data collection procedures, and written, informed consent was obtained from all participants.

2. Baseline data information and primary end point

Demographic and laboratory data regarding age, serum total PSA level, percent free PSA, DRE findings and TRUS-derived information (prostate volume and presence of hypoechoic lesions) were obtained by reviewing medical records. The serum total and free PSA values were measured using a PSA-RIACT assay system (CIS Bio International, Gif-Sur-Yvette, France). All patients underwent TRUS-guided laterally directed sextant or systematic 10–12 core biopsies of the prostate. A C9-5ec probe was used with an IU-22 ultrasonography unit (Philips Medical Systems, Bothell, WA, USA). Prostate volume was calculated by TRUS using the following ellipsoid formula: volume = $(\pi/6) \times$ length $\times$ width $\times$ height. Six to 12 (median, 10) ultrasound-guided needle core biopsies were performed using an 18-gauge spring-loaded biopsy device. The primary end point was the histologic presence of adenocarcinoma of the prostate in the biopsy specimen. All grading was performed by genitourinary pathology specialists at our institute, and was based on the Gleason scoring system.

3. Statistical analysis

The primary endpoint was detection of any PCa or HGPCa (Gleason score > 7) in the biopsy material. Of 1,048 patients, 838 (80%) were randomly selected for model building, while the remaining 20% (n = 210) were reserved for model validation. Factors considered potentially associated with an increased risk of a positive biopsy result were compared between any cancer/HGPCa and controls, including age, total PSA level, percent free PSA, DRE findings and TRUS-derived information (prostate volume and TRUS findings). Age, total PSA, percent free PSA and prostate volume were analyzed as continuous variables, and DRE and TRUS findings were analyzed as categorical variables. Univariate and multivariate logistic regression analysis was used to examine whether factors alone or in combination affected the prediction of the presence of any or HGPCa. Ordinal logistic regression was used to model the probability of having any or HGPCa. The logistic regression model was the basis for constructing a nomogram. To construct nomograms predicting any or HGPCa, two outcome levels were defined: no cancer/any cancer; and no cancer + low grade cancer (Gleason score < 6)/HGPCa (Gleason score > 7). The predictive accuracy of a nomogram not using TRUS-derived information (nomogram-1) was directly compared to that of a nomogram using TRUS-derived information (nomogram-2). Nomogram validation comprised two activities. First, using the validation data set, discrimination was quantified using the area under the receiver operating characteristic curve (AUC). Second, calibration accuracy was

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determined. All statistical analyses were performed using STATA ver. 10.1 (StataCorp LP., College Station, TX, USA).

RESULTS

Of the 1,048 men, 216 (20.6%) were found to have adenocarcinoma of the prostate at biopsy, while the remaining 832 patients (79.4%) showed no evidence of cancer. Of the 216 patients with cancer, 97 (44.9%) had a Gleason score >7 (HGPCa). Table 1 shows the comparison of factors associated with PCa between any cancer/HGPCa and controls. Multivariate analysis showed that all risk factors examined were independently associated with PCa (Table 2).

We constructed two nomograms to predict the presence of both any PCa and HGPCa according to biopsy results. Nomogram-1 incorporated age, total PSA, percent free PSA and DRE findings, while nomogram-2 incorporated the same factors plus TRUS-derived information (prostate volume and presence of hypoechoic lesions) (Fig. 1). For nomogram-1, the total AUC for predicting any PCa was 0.72 (95% CI, 0.68 to 0.76), and for predicting HGPCa was 0.78 (95% CI, 0.72 to 0.83). For nomogram-2, the total AUC for predicting any PCa was 0.76 (95% CI, 0.72 to 0.81), and for predicting HGPCa was 0.83 (95% CI, 0.79 to 0.88). Statistical analysis showed that nomogram-2 was better than nomogram-1 at predicting the presence of both any PCa ($P=0.001$) and HGPCa ($P<0.001$). The calibration of nomogram-2 using the validation data set is shown in Fig. 2.

We investigated which nomogram-2 risk factors were important for predicting PCa by removing one factor at a time and observing the effect on the AUC. We found that age was the most important predictor, with its removal resulting in an incremental decrease of 0.077 for any and 0.067 for HGPCa. The removal of percent free PSA resulted in an incremental AUC decrease of 0.003 and 0.025 for any and HGPCa, respectively. The removal of all TRUS-derived information (prostate volume and presence of hypoechoic lesions) resulted in incremental AUC decreases of 0.052 for predicting any PCa and 0.063 for predicting HGPCa (Table 3).

Table 1. Comparison of factors associated with any and high grade prostate cancer

Factor	Any cancer (n=216)	Control (n=832)	*P*-value	High grade cancer (n=97)	Control (n=951)	*P*-value
Median age (yr)	67	62	<0.001[a]	69	63	<0.001[a]
Mean (range)	66.8 (41–88)	61 (25–87)		67.6 (45–88)	61.7 (25–87)	
Median PSA (ng/mL)	6.9	6.2	<0.001[a]	7.6	6.2	<0.001[a]
Mean (range)	7.0 (4.0–9.9)	6.5 (4.0–9.9)		7.3 (4.0–9.0)	6.5 (4.0–9.9)	
Median percent free PSA	15.4	17.4	0.03[a]	13.9	18.1	<0.001[a]
Mean (range)	16.9 (4.6–43.2)	18.2 (1.2–51.1)	<0.001[b]	15.5 (6.0–43.2)	18.1 (1.2–21.1)	<0.001[b]
Digital rectal examination, n (%)						
No nodule	154 (71.3)	793 (88.1)		64 (66.0)	823 (86.5)	
Nodule	62 (28.7)	99 (11.9)		33 (34.0)	128 (13.5)	
Median prostate volume	28.0	35.0	<0.001[a]	26.6	34.2	<0.001[a]
Mean (range)	31.6 (11.0–92.0)	39.1 (10.0–169.3)		29.7 (13.0–78.3)	38.4 (11.0–169.9)	
TRUS findings, n (%)			<0.001[b]			<0.001[b]
Hypoechoic lesion (-)	155 (71.8)	687 (82.6)		54 (55.7)	788 (82.9)	
Hypoechoic lesion (+)	61 (28.2)	145 (17.4)		43 (44.3)	163 (17.1)	

PSA, prostate-specific antigen; TRUS, transrectal ultrasound.
[a]Wilcoxon rank-sum test. [b]Fisher's exact test.

Table 2. Multivariate analysis of factors associated with any and high grade prostate cancer

Factor	Any cancer			High grade cancer		
	RR	95% CI	*P*-value	RR	95% CI	*P*-value
Age	1.09	1.07–1.12	<0.001	1.10	1.07–1.13	<0.001
PSA	1.15	1.06–1.25	0.001	1.22	1.09–1.36	0.001
Percent free PSA	0.97	0.95–0.99	0.028	0.94	0.90–0.97	0.001
Abnormal DRE findings	2.00	1.31–3.05	0.001	1.89	1.09–3.30	0.024
Prostate volume	0.95	0.94–0.97	<0.001	0.95	0.93–0.97	<0.001
Abnormal TRUS findings	1.51	1.01–2.24	0.043	3.45	2.09–5.71	<0.001

RR, relative risk; CI, confidence interval; PSA, prostate-specific antigen; DRE, digital rectal examination; TRUS, transrectal ultrasound.

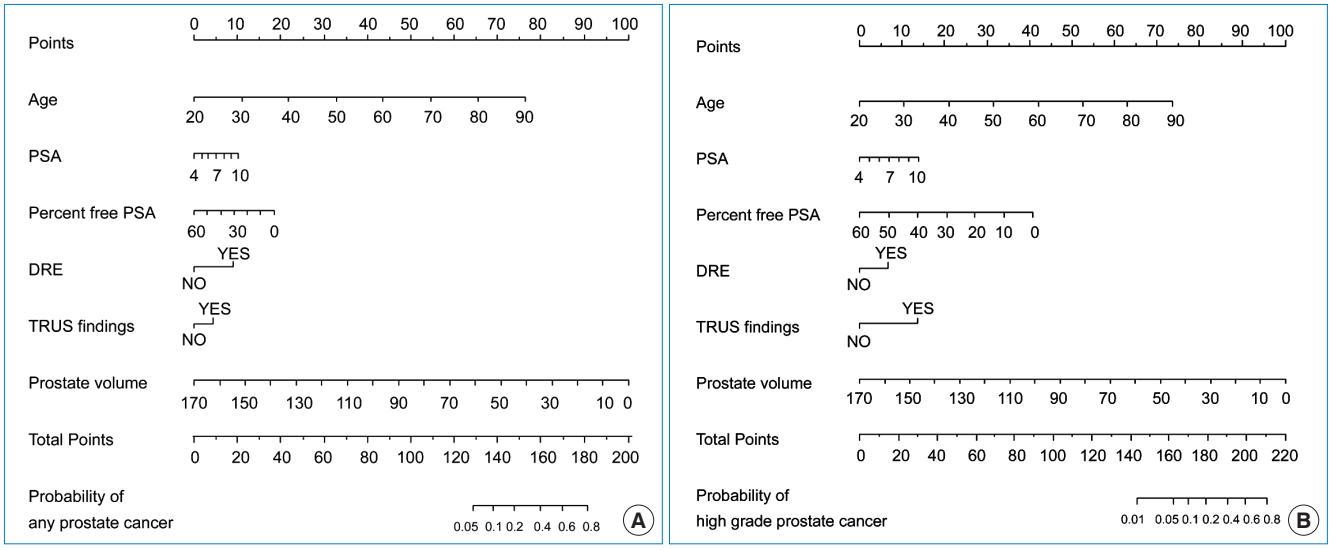

Fig. 1. Logistic-based nomogram-2 prediction model for predicting (A) any and (B) high grade prostate cancer on initial biopsy. To obtain the predicted probability of cancer, locate the patient position for each variable on the horizontal axis and determine the assigned point value. The probability value for having cancer corresponds to the summed all points scale for all variables. PSA, prostate-specific antigen; DRE, digital rectal examination; TRUS, transrectal ultrasound.

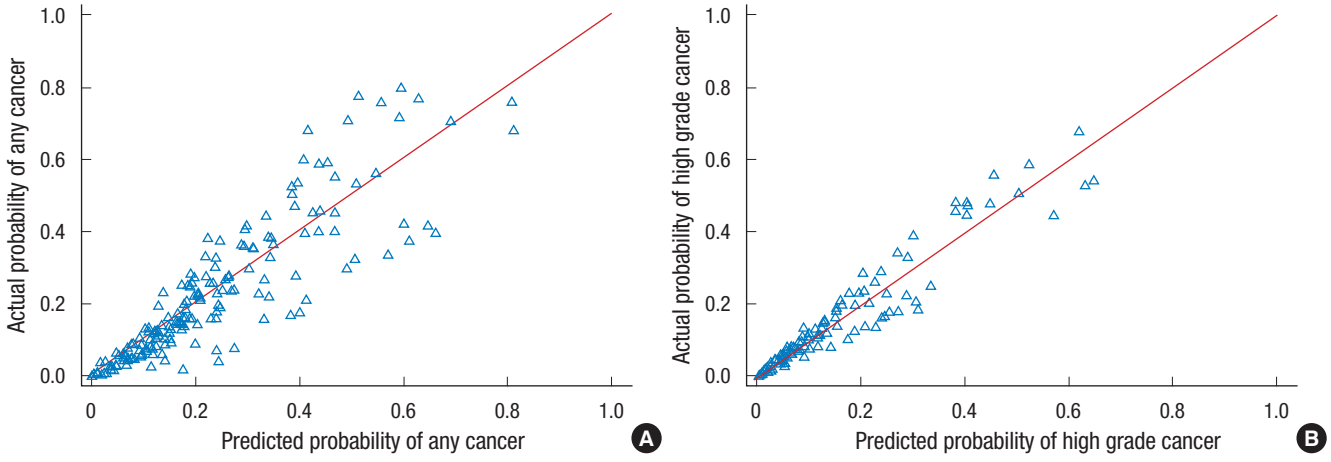

Fig. 2. Calibration of the nomogram-2 prediction model when predicting (A) any and (B) high grade cancer. Perfect predictions correspond to the line with a slope of 1 (if the predictive model were perfect, triangles would lie on the 45° dotted line).

Table 3. Incremental drops in the AUC for each predictor variables when removed from the nomogram-2

Variable	Incremental drop in AUC	
	Any cancer	High grade cancer
AUC for nomogram-2 (95% CI)	0.76 (0.72–0.81)	0.83 (0.79–0.88)
Age	0.077	0.067
PSA	0.003	0.003
Digital Rectal Examination	0.004	0
Percent free PSA	0.003	0.025
Prostate volume	0.049	0.038
Abnormal TRUS findings	0.003	0.025

AUC, area under the receiver operating characteristic curve; CI, confidence interval; PSA, prostate-specific antigen; TRUS: transrectal ultrasound.

DISCUSSION

The present report describes a nomogram for predicting HGPCa using TRUS-derived information in men with intermediate PSA levels. This is the first such nomogram reported to our knowledge. This nomogram incorporating TRUS-derived information outperformed a model not incorporating TRUS-derived information in predicting any PCa as well as HGPCa.

In the present nomogram, although TRUS-derived information was found to be a strong factor in predicting any PCa, it was particularly influential for predicting HGPCa. The incremental drop in AUC when TRUS-derived information was removed from the model was 0.052 for any cancer and 0.063

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for HGPCa. Conversely, when TRUS data was incorporated into the nomogram, the increase in accuracy of predicting HGPCa was greater than the increase for predicting any PCa. In addition, the AUC was very high (0.83), even though urinary voiding symptoms score and family history were not considered.

The present nomogram developed in an Asian population is important given that the epidemiology and biology of PCa may differ between Western and Asian men. Therefore, it may be incorrect to directly apply nomograms developed in Western countries to Asian populations. For example, although percent free PSA is the most important prebiopsy factor in improving the specificity of PSA testing in men with intermediate PSA ranges in Western countries, it is not the most important factor in Korean men [4,11].

Although several studies have described nomograms that included prostate volume as a predictive variable, to our knowledge only two studies have also included hypoechoic lesion data [7,12]. Garzotto et al. [7] incorporated TRUS data (presence of hypoechoic lesions and PSA density) into a nomogram predicting PCa in men with PSA levels of < 10 ng/mL. The AUC for that model was 0.73, in contrast to 0.62 for the prediction based on PSA alone. Kawakami et al. [12] also reported that predictive accuracy for detection of PCa was improved when TRUS-derived information was incorporated into a conventional nomogram using age, PSA and DRE (AUC = 0.79 ver. 0.73, $P < 0.05$). In our study, the AUC was 0.76 when using a nomogram incorporating all factors, including TRUS-derived information, indicating a similar predictive power for any prostate cancer as that of the nomogram reported by Kawakami et al. [12]. However, they did not examine HGPCa prediction, which most urologists are desirable to detect.

Needle biopsy Gleason grade is routinely used to plan PCa patient counseling and management [13]. Many studies reveal an association between an increased biopsy Gleason score and decreased disease-free survival after radical prostatectomy or radiation therapy [14-17]. In this context, predicting HGPCa is very important on initial biopsy in men with increased serum PSA levels to help identify patients at high risk for aggressive PCa.

Few studies have directly investigated predicting HGPCa in men undergoing prostate biopsy for elevated PSA. Thompson et al. [18] developed a predictive model of PCa from the placebo group of the Prostate Cancer Prevention Trial who underwent prostate biopsies to assess HGPCa risk. They found that higher serum PSA levels, abnormal DRE results, advanced age at biopsy and African American race were predictive of high grade disease (Gleason score > 7). Nam et al. [19] also constructed a nomogram to predict both the probability of any PCa as well as the probability of high grade cancer using age, ethnicity, family history, urinary voiding symptom score, percent free PSA and DRE findings. However, neither of these two studies incorporated TRUS-derived information into the nomogram for predicting the HGPCa.

The association between TRUS-derived information and PCa aggressiveness remains unclear. Because small prostate volume has been reported to be associated with HGPCa after radical prostatectomy for PCa, we hypothesized that incorporation of prostate volume into the nomogram would increase the accuracy of the nomogram predicting HGPCa on initial prostate biopsy [20,21]. In addition, because we found that men with HGPCa were found to have more hypoechoic lesions compared with those with any PCa (44.3% ver. 28.2%), we also tested whether incorporating data regarding the presence of hypoechoic lesions improved the predictive accuracy of the nomogram predicting HGPCa. We found that removal of TRUS findings resulted in a small decrease in the AUC for predicting any cancer, but a larger decrease when predicting HGPCa (0.004 ver. 0.025). Further study is required to understand the apparent link between the presence of hypoechoic lesions and HGPCa.

We found that percent free PSA, which is accepted as a standard adjunct PSA test, had minimal predictive value in our study [4]. This finding is consistent with previous study showing that percent free PSA did not have better specificity than total PSA in Korean men aged < 65 years with a palpably benign prostate gland and a PSA level of 4.0–10.0 ng/mL [11]. We found that age was the strongest factor in predicting both any cancer and HGPCa. The incremental drop in AUC when age was removed from the model was 0.077 for any cancer and 0.067 for HGPCa. Interestingly, these findings are similar to those of a study examining subjects with normal PSA levels (< 4.0 ng/mL) [19]. In that study, age was a more powerful predictor than percent free PSA in the subset of men with healthy serum PSA levels, which differs from the findings in men with increased PSA (> 4 ng/mL). In addition, the detection rate of PCa observed in our study (20.6%) is similar to that reported in men with a healthy PSA level (24.3%), and is much lower than that observed in men with elevated PSA (44.6%) [19]. It is not clear why the present findings are similar to those in Western men with normal PSA levels. Further prospective comparative studies on the detection rate and detailed clinico-pathologic characteristics of detected PCa between Korean men with intermediate PSA ranges and Western populations with normal PSA levels are needed.

The present findings indicate that TRUS-derived informa-

tion should be incorporated into nomograms predicting HGPCa in men with a PSA range of 4.0–9.9 ng/mL. Some clinicians are reluctant to perform TRUS in men with increased PSA levels as they feel it is an invasive procedure. However, considering that curative therapy results in significantly improved life expectancy even in older men with moderately or poorly differentiated localized PCa, physicians should be assessing the advantages and disadvantages of TRUS in men with intermediate PSA levels to assess the individualized risk for HGPCa [22].

Previous study showed that extended biopsy-based nomograms have greater accuracy than 6 –10 core biopsy-based nomograms in predicting PCa [23]. However, we did not include the method of prostate biopsy into our nomogram because a previous study showed that biopsy cores made no difference in the detection rate of PCa in Korean men with PSA levels of 4.0–9.9 ng/mL [24].

A limitation of the present study was that model validation was internal. Ideally, the predictive accuracy of a model should be tested using an external cohort. Therefore, greater understanding of the power of the present nomogram using TRUS-derived information awaits external validation in another cohort.

In conclusion, we developed a new nomogram using TRUS-derived information for predicting any cancer and HGPCa on initial biopsy in men with PSA levels 4.0–9.9 ng/mL. The nomogram using TRUS information had a high predictive accuracy for HGPCa. Our results indicate that TRUS-derived information should be included in predictive nomograms for HGPCa which most physicians are desirable to detect on initial biopsy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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