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ORIGINAL ARTICLE

A nomogram based on age, prostate-specific antigen level, prostate volume and digital rectal examination for predicting risk of prostate cancer

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Nomograms for predicting the risk of prostate cancer developed using other populations may introduce sizable bias when applied to a Chinese cohort. In the present study, we sought to develop a nomogram for predicting the probability of a positive initial prostate biopsy in a Chinese population. A total of 535 Chinese men who underwent a prostatic biopsy for the detection of prostate cancer in the past decade with complete biopsy data were included. Stepwise logistic regression was used to determine the independent predictors of a positive initial biopsy. Age, prostate-specific antigen (PSA), prostate volume (PV), digital rectal examination (DRE) status, % free PSA and transrectal ultrasound (TRUS) findings were included in the analysis. A nomogram model was developed that was based on these independent predictors to calculate the probability of a positive initial prostate biopsy. A receiver-operating characteristic curve was used to assess the accuracy of using the nomogram and PSA levels alone for predicting positive prostate biopsy. The rate for positive initial prostate biopsy was 41.7% (223/535). The independent variables used to predict a positive initial prostate biopsy were age, PSA, PV and DRE status. The areas under the receiver-operating characteristic curve for a positive initial prostate biopsy for PSA alone and the nomogram were 79.7% and 84.8%, respectively. Our results indicate that the risk of a positive initial prostate biopsy can be predicted to a satisfactory level in a Chinese population using our nomogram. The nomogram can be used to identify and counsel patients who should consider a prostate biopsy, ultimately enhancing accuracy in diagnosing prostate cancer.
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INTRODUCTION

In 2011, prostate cancer was the most commonly diagnosed cancer and the second leading cause of cancer-related death in men in the United States.[1] The incidence of prostate cancer in Asian countries has been increasing in recent years, but it is still much lower than in Western countries.[2] Currently, measurement of prostate-specific antigen (PSA) remains the most commonly used method for diagnosing prostate cancer, although its usefulness as a factor associated with decreasing prostate cancer-specific mortality remains controversial.[3,4] Nevertheless, the specificity of PSA for predicting prostate cancer is not high.[5] Nomograms, which integrate multiple independent risk factors for prostate cancer, have been shown to improve prostate cancer detection rates and help reduce unnecessary prostate biopsies.[6] The Prostate Cancer Prevention Trial (PCPT) and the European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculators are the best known nomograms for incorporating known risk factors.[7] Additionally, the incidence of prostate cancer in men from industrialised countries has been shown to be substantially different from that in men from developing countries.[2] Therefore,

nomogram models used to predict the risk of prostate cancer that were generated from male populations in industrialised countries may not be directly applicable to Chinese men. Yoon *et al.*[8] used a Korean population to validate the performance of the Prostate Risk Calculator 3 (based on data from the Dutch cohort of the ERSPC). They found that use of the Prostate Risk Calculator 3 in a Korean population would miss 7% more cancers than in a Caucasian population. We recently reported that baseline PSA and PSA velocity in young Chinese men without prostate cancer differ from those of African American and Caucasian American men.[9] Furthermore, Zhu *et al.*[10] recently reported that the PCPT and ERSPC risk calculators overestimated the probability of predicting prostate cancer and high-grade disease when independently validated using a Chinese population. The existing evidence indicates that evaluation of prostate cancer risk should be tailored for different races.[8–10] As a result, the development and use of a nomogram for the population from which the nomogram was derived is particularly pertinent. To our knowledge, no nomogram to evaluate the risk of prostate cancer in a Chinese population has been published to date. In this study, we have

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developed a nomogram for predicting the probability of a positive initial prostate biopsy in a Chinese population.

MATERIALS AND METHODS

Study population

After institutional review board approval had been obtained, the records of 699 men who had undergone transrectal ultrasound (TRUS)-guided prostate biopsy for the detection of cancer between November 1999 and June 2011 were retrieved from our computer centre. Twelve men who were biopsied more than two times and 152 men without complete data were excluded. This left a total of 535 subjects who were included in the study. Within this cohort, 486 (90.8%) underwent a 13-core biopsy, 28 (5.2%) underwent a six-core biopsy and 21 (3.9%) underwent a 4–15 core biopsy (not a 6- or 13-core).

Clinical variable evaluation

PSA was analysed with the Abbott AxSYM PSA (Bayer Corporation, Beijing, China) assay before 2006 and the Roche Elecsys 2010 PSA assay (Roche Diagnostics, Shanghai, China) after 2006. Prostate volume (PV) was determined during TRUS and was calculated using the formula, PV (ml)=0.52×anterior-posterior diameter (cm)×transverse diameter (cm)×superior–inferior diameter (cm). The criteria for a prostatic biopsy were a PSA $\geqslant 10$ ng ml^{-1} or a positive digital rectal examination (DRE; prostatic nodule or firm area). If a man had a PSA between 4 and 10 ng ml^{-1}, the indication for a prostate biopsy was based on clinician assessment or patient preference.

Statistical analysis

Age, PSA, PV, DRE status, % free PSA and TRUS findings (low echogenicity in the peripheral zone was defined as positive) were included in the stepwise regression analysis. Because PSA and PV had a non-normal distribution and a nonlinear effect of these variables was expected, these variables were transformed to the natural logarithm before analysis. Age, PSA, PV and % free PSA were treated as continuous variables, whereas DRE status and TRUS findings were categorical variables. Variables that did not reach statistical significance at a level of 0.05 were removed from the model in the backward stepwise process.

The independent variables from the final model were used to construct a nomogram to predict the probability of a positive initial biopsy. The nomogram was validated and predictive accuracy calculated using Harrell's Concordance Index C on 100 bootstrapped re-samples. Calibration plots were also generated to assess the discrimination capacity of the nomogram. A receiver-operating characteristic curve was used to evaluate the effectiveness of the nomogram and PSA alone in predicting a positive initial prostate biopsy. Statistical analyses were performed with R version 2.13.1 (http://www.r-project.org/).

RESULTS

The demographic characteristics of the study cohort are shown in **Table 1**. Of the 535 subjects included in the study, 223 (41.7%) had a positive initial prostate biopsy. The median and mean diagnostic PSA levels in our study cohort were 18.6 and 91.4 ng ml^{-1}, respectively. The median PSA level in men with a positive initial prostate biopsy was statistically higher than those with a negative biopsy (43.4 ng ml^{-1} vs. 13.1 ng ml^{-1}, $P<0.001$, Mann–Whitney U test). The results of univariate analysis of age, % free PSA, PV, rate of abnormal DRE and rate of TRUS abnormalities in men with a positive initial biopsy were all significantly different from those in men with a negative biopsy.

Table 1 Characteristics of the study cohort

Variables	Total	PCa	Non-PCa	P
No. of subjects (%)	535	223 (41.7)	312 (58.3)	
Diagnostic PSA (ng ml^{-1})				
Mean (s.d.)	91.4 (366.6)	176.5 (516.5)	28.5 (173.9)	
Median (IQR)	18.6 (9.2–47.6)	43.4 (18.9–141.9)	13.1 (6.8–20.7)	<0.001[b]
Range	0.0–6282.0	0.0–6282.0	0.0–2986.0	
Diagnostic % free PSA				
Mean (s.d.)	18 (47)	19 (73)	18 (11)	
Median (IQR)	14 (9–20)	11 (8–16)	16 (10–21)	<0.001[b]
Range	0–97	0–97	0–97	
Age at initial biopsy (year)				
Mean (s.d)	72 (9)	73 (9)	70 (9)	
Median (IQR)	72 (68–78)	74 (69–79)	72 (66–76)	<0.001[b]
Range	20–91	20–91	21–87	
Prostate volume (ml)				
Mean (s.d)	64 (37)	59 (38)	67 (37)	
Median (IQR)	54 (38–82)	47 (33–70)	60 (41–83)	<0.001[b]
Range	4–319	10–262	4–319	
TRUS finding[a]				
Positive	134	73	61	0.019[c]
Negative	401	173	228	
Digital rectal examination				
Positive	133	87	46	<0.001[c]
Negative	402	140	262	

Abbreviations: IQR, interquartile range; PCa, prostate cancer; PSA, prostate-specific antigen; TRUS, transrectal ultrasound.
[a] Low-echogenicity in the peripheral zone of the prostate was defined as 'positive'; other findings were defined as 'negative'.
[b] Mann–Whitney U test.
[c] Chi-square test.

Table 2 The predictors of a positive initial biopsy in multivariate analysis

Variables	Odds ratio	95% CI		P
		Lower	Upper	
Age at biopsy	1.0	1.0	1.1	0.026
Log (PSA)	9.9	6.1	16.0	<0.001
Log (prostate volume)	0.06	0.02	0.16	<0.001
Diagnostic % free PSA	7.1	0.1	366.6	0.331
DRE				
Negative	Reference			
Positive	2.8	1.7	4.7	<0.001
TRUS finding[a]				
Negative	Reference			
Positive	1.5	0.7	3.4	0.302

Abbreviations: CI, confidence interval; PCa, prostate cancer; PSA, prostate-specific antigen; TRUS, transrectal ultrasound; DRE, digital rectal examination.
[a] Low-echogenicity in the peripheral zone of the prostate was defined as 'positive'; other findings were defined as 'negative'.

In a multivariate analysis, only age, PSA, LogPSA, and LogPV were found to be independent predictors of a positive initial prostate biopsy (**Table 2**). The logistic regression model yielded the equation below:

Positive initial prostate biopsy probability equation for Chinese population =

$$\frac{e^{-1.163+0.033\text{Age}+1.032\text{DRE}-2.821\text{LogPV}+2.292\text{LogPSA}}}{1+e^{-1.163+0.033\text{Age}+1.032\text{DRE}-2.821\text{LogPV}+2.292\text{LogPSA}}}$$

Using the information from multivariate regression analysis, a nomogram model was developed that allows the calculation of an individual patient's risk for a positive initial prostate biopsy (**Figure 1**). **Figure 2** shows validation of the nomogram. A concordance index of 0.848, representing predictive accuracy, was found upon internal validation of the nomogram. Our nomogram was superior in predictive accuracy to that with diagnostic PSA data, increasing the area under the curve (AUC) from 79.7% to 84.8% (**Figure 3**).

DISCUSSION

To our knowledge, this study is the first to examine the accuracy of a nomogram for the prediction of the prostate cancer risk in Chinese men, using a Chinese cohort for validation. We found that age, DRE, PSA and PV were independent predictors of prostate cancer risk. These findings are consistent with those in previous reports.[6,7] However, after multivariate analysis, % free PSA and TRUS findings were not independent predictors of a positive initial prostate biopsy. Previous studies have found % free PSA to be an independent predictor of prostate cancer;[11,12] however, a report from Korea demonstrated that % free PSA provided no added diagnostic benefit in Korean men from 50 to 65 years old with a PSA of 4.0–10.0 ng ml^{-1}.[13] Likewise, in our study cohort, % free PSA did not improve the accuracy of the nomogram for predicting a positive initial prostate biopsy. This discrepancy suggests that urologists in Asian and Western countries likely face different situations with regard to prostate cancer. Additionally, our findings were in agreement with those of Cavadas et al.,[7] who demonstrated that TRUS findings are not an independent predictor of prostate cancer. Conversely, Kawakami et al.[14] reported that TRUS findings is an independent predictor of prostate cancer. In their study, they found that the accuracy of their nomogram for predicting prostate cancer was improved if TRUS findings were added.

There are a number of reasons why our findings differ from those of previous studies. First, the different study populations used in developing the models may result in substantially different findings because the characteristics of patients with prostate cancer in Western countries and Asian countries are different.[6] To further evaluate the characteristics of our nomogram, we need to validate other nomograms using a Chinese population and compare the accuracy of our nomogram with others in subsequent studies. Additionally, the variables, especially the PSA range that was included in the prediction models, were very different from those found in other cohorts. In our model, we included age, PSA, PV, DRE status, % free PSA and TRUS findings. Furthermore, all men, regardless of the PSA level, were included. Finally, different prostatic biopsy strategies at different
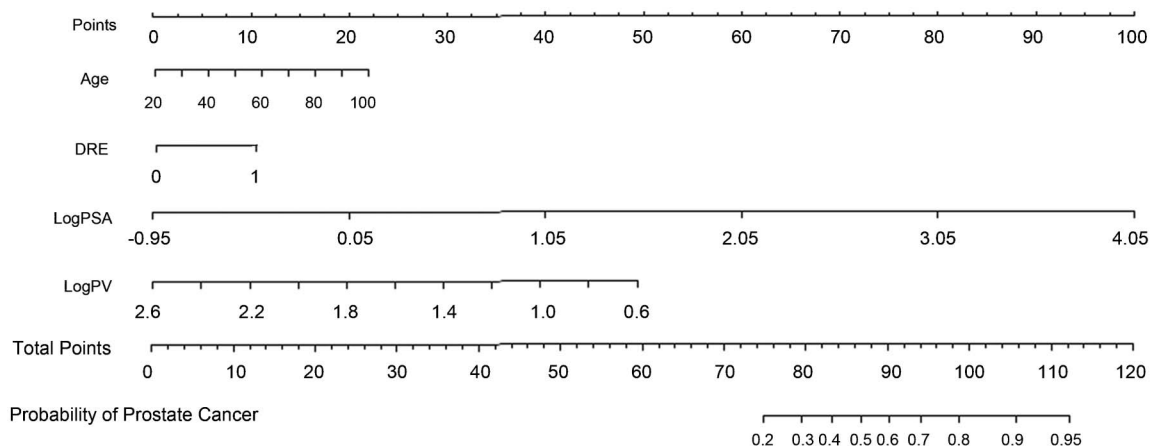
Figure 1 Nomogram for predicting a positive initial prostate biopsy. To determine the predicted probability of prostate cancer on initial biopsy, locate patient values on each axis. Draw a vertical line to the 'Point' axis to determine how many points are attributed to each variable. After summation of the points for all variables, locate the sum on the 'Total Points' line to determine the individual probability of prostate cancer on initial prostate biopsy on the 'Probability of Prostate Cancer' line. DRE, digital rectal examination (1=positive, 0=negative); PSA, prostate-specific antigen; PV, prostate volume.
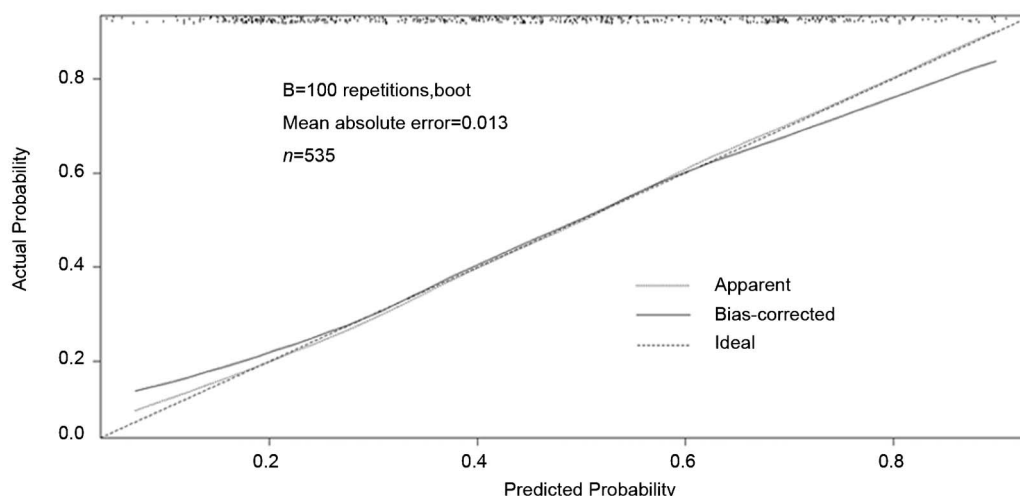
Figure 2 Result validation and predictive accuracy (84.8%).

centres may lead to different prostate cancer detection rates, which could impact the results of the study.[11]

In the present study, we found that the accuracy of our nomogram for predicting a positive initial prostate biopsy was better than using PSA levels alone (AUCs were 84.8% and 79.7%, respectively). While these results are similar with those reported from previous studies (**Table 3**),[15–19] this is the first report to do so in a Chinese population, using a Chinese cohort. Recently, a systematic review comparing different models for predicting the risk of a positive prostate biopsy using PSA levels alone was reported.[6] Twenty-three studies examining 36 models were included in this review. They found, with the exception of two studies, that all models had AUC values of 0.70 or greater, with eight reporting an AUC of $\geqslant 0.80$ and four reporting an AUC $\geqslant 0.85$. Fourteen studies compared the AUC with that with PSA levels alone, and all showed an added benefit from the added data, ranging from

0.02 to 0.26.[6] Compared to reports in the literature, our model had a higher AUC and improved the predictive ability of PSA alone, increasing the AUC by 5.1% (from 79.7% to 84.8%). In our study cohort, the majority of subjects (90.8%) underwent 13-core biopsies. This may have led to higher positive biopsy rates and improved the predictive accuracy of the nomogram.[11] Furthermore, our nomogram was derived from a population based out of a Chinese tertiary hospital. The mean and median PSA values in our study cohort were extremely high because PSA testing is still not routinely used for early detection of prostate cancer in China; thus, the majority of prostate cancers are diagnosed at a later disease stage. PV, which was included in our predictive model, may also be a key factor in improving the accuracy of the nomogram.[20]
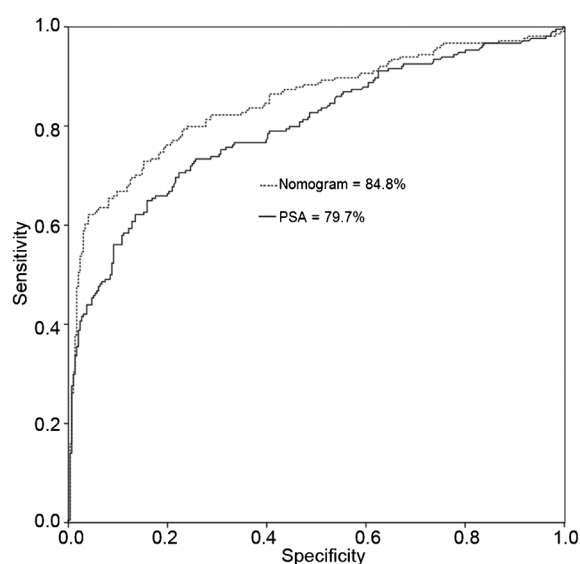
The present study is limited by the fact that nomograms for predicting a positive initial prostate biopsy are not new. However, many nomograms generated in Western countries may not be directly applicable to a Chinese population. Here we present the first nomogram for predicting a positive initial prostate biopsy developed using a completely Chinese population. The second limitation of our study is that it is retrospective. To confirm our findings, larger, prospective and randomized studies are warranted. Third, all the data in our study were obtained from a single, tertiary hospital, which may lead to biased results. The strategies used to diagnose prostate cancer may differ between centres, even those in a close geographical area. Our nomogram was derived from an unscreened cohort, and most men were diagnosed with late stage prostate cancer, which currently represents the majority of prostate cancer diagnoses in China.[21,22] Finally, our nomogram has not been validated externally. Whether it can be universally applied to Chinese populations must be confirmed, and further studies are warranted.

AUTHOR CONTRIBUTIONS

PT, MU and KJX conceived and designed the study. HC, XRD, YRL and BW collected the data. PT and WJY performed statistical analyses. PT and MU wrote the manuscript with input from all co-authors. All authors revised the manuscript and approved the final version.

Figure 3 The area under the receiver-operating characteristic curve (AUC) for the nomogram and PSA alone for predicting a positive initial prostate biopsy. PSA, prostate-specific antigen.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

Table 3 Predictive accuracy of various prostate cancer nomograms

Study	n	Patients	Cancer rate (%)	Validation	Mean age (year)	Median PSA (ng ml^{-1})	AUC for model (%)	AUC for PSA (%)	Increase in AUC vs. PSA alone (%)
PCPT[15]	5519	CA (95.6%)	21.9	Internal	⩾55	1.5	70.2	67.8	2.4
Hernandez *et al.*[16]	1108	CA (85.0%)	35.6	NA	63	5.4	66.7	61.9	4.8
Suzuki *et al.*[17]	834	Japanese	28.9	NA	70	13.1 (mean)	81.8	69.8	12.0
Park *et al.*[18]	602	Korean	28.6	NA	66	6.77	72	66	6
Garzotto *et al.*[19]	1239	CA (93.5%)	24.3	Internal	66	5.10	73	62	11
Our model	535	Chinese	44.8	Internal	72	17.8	84.8	79.7	5.1

Abbreviations: AUC, area under the curve; CA, Caucasian American; NA, not available; PCPT, Prostate Cancer Prevention Trial; PSA, prostate-specific antigen.

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