Development of a Nomogram for Predicting High-grade Prostate Cancer on Biopsy: the Significance of Serum Testosterone Levels

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Abstract. *Background: A screening method that focuses on the early detection of high-grade prostate cancer is required. In this study, two sets of nomograms were developed, one to predict the presence of prostate cancer, and the other to predict the presence of high-grade prostate cancer (defined as Gleason Score ≥7). Patients and Methods: Prostate biopsies were obtained from 396 men with an abnormal serum level of prostate-specific antigen (PSA). Using factors including age, PSA, follicle stimulating hormone (FSH), serum teststerone level and prostate volume of the transitional zone (TZ), nomograms were created that incorporated these factors. External validations were performed involving 174 males, including 103 normal and 71 prostate cancer cases from our institution. Results: Out of the 396 patients referred for prostate biopsy, 146 were found to have prostate cancer. On logistic regression analysis, age, PSA, prostate volume of the TZ and FSH were significant predictors of prostate cancer, while serum PSA, and testosterone levels were significant predictors of high-grade prostate cancer. The pretreatment testosterone level was found to be a significant biomarker for predicting the pathological features. Conclusion: The testosterone level might be a useful biomarker to be included in conventional PSA screening programs to further improve the efficacy of detecting potentially lethal carcinomas.*

Prostate cancer is currently the second leading cause of cancer death among males and is the most commonly diagnosed cancer among males in the United States (1, 2). In Japan, the morbidity and mortality of prostate cancer is rapidly increasing (3). In many countries, including Japan, prostate-specific antigen (PSA) testing is part of routine medical check-ups. However, it is unclear whether PSA screening significantly reduces mortality from prostate cancer. Therefore, public health policy experts are uncertain whether to promote screening for the early detection of prostate cancer in asymptomatic males (4).

PSA is the leading marker for prostate cancer, though it has a low sensitivity and does not have a clear cut-off level to distinguish between those likely to have cancer and those who are not likely to have cancer. In the Prostate Cancer Prevention Trial (5), even within the 0-4.0 ng/ml range, the PSA level was a continuously increasing marker of prostate cancer risk, including high-grade tumors; there was no boundary level below which no prostate cancer was found. However, while lowering the PSA threshold is likely to increase the detection of aggressive carcinomas at an earlier stage, the unavoidable consequence is the increased detection of biologically insignificant carcinomas (5). To quantify the risk posed by a particular cancer, modern medical informatics can be used to create nomograms or algorithms that can account for the interactive effects of multiple independent prognostic factors. The two major objectives for developing a predictive model that could be used to detect prostate carcinoma are to reduce the number of males requiring prostate biopsy and to ensure potentially lethal high-grade tumors do not go undetected. Since the PSA level does not have a clear cut-off value that could be used to recommend biopsy, other indices or biomarkers are needed. To date, several nomograms have been proposed to increase the sensitivity of prostate biopsy. However, only one paper has reported a nomogram that predicts aggressive prostate cancer that is lethal when treatment is delayed (6).

Low testosterone levels have been shown to be associated with an advanced tumor stage at presentation, positive surgical margins, a high Gleason score and worse overall survival (7-11). Yano *et al.* (12) have reported that serum testosterone levels are an independent significant predictor of a positive prostate biopsy. This suggests that the efficiency of prostate cancer

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Key Words: Prostate cancer, nomogram, testosterone, prostate-specific antigen, prostate biopsy.

Table I. *Clinical characteristics of 396 patients with initial biopsy results.*

Variable	Total patients	Patients with positive biopsy	Patients with negative biopsy
Number	396	146	250
Age (Years)	69.28±8.1	71.46±7.42	67.98±8.24
(mean: range)	(70.0, 42-89)	(72.0; 42-89)	(68.0;43-89)
PSA (ng/ml)	15.34±37.33	24.02±50.22	10.34±26.02
Prostate volume (cm^3)	45.89±24.56	35.12±18.00	52.25±25.70
TZ volume (cm^3)	25.24±18.24	17.35±11.45	29.89±19.85
LH (mIU/ml)	9.34±7.65	10.83±9.32	8.49±6.35
FSH (mIU/ml)	16.01±15.40	19.44±20.23	14.01±11.31
Testosterone (ng/dl)	417.55±173.51	402.67±179.47	426.29±170.05

PSA: prostate-specific antigen; TZ: transitional zone; LH: luteinizing stimulating hormone; FSH: follicle stimulating hormone.

Table II. *Clinical characteristics of 146 patients with high (7-10) and low (4-6) gleason score.*

Variable	Total patients	Gleason score	
		7-10	4-6
Number	146	80	66
Age	71.46±7.42	71.80±7.07	71.05±7.86
(mean: range)	(72; 42-89)	(73; 56-89)	(71; 42-87)
PSA	24.02±50.22	35.71±65.09	9.84±10.25
Prostate volume	35.12±18.00	33.17±16.01	37.48±20.01
TZ volume	17.35±11.45	17.23±10.85	17.49±12.22
LH	10.83±9.32	12.21±11.44	9.15±5.44
FSH	19.44±20.23	23.18±25.08	14.91±10.52
Testosterone	402.67±179.47	351.69±164.85	464.47±178.16

PSA: prostate-specific antigen; TZ: transitional zone.

screening can be improved by including serum testosterone level measurement. They also showed that serum testosterone levels were significantly lower in patients with a Gleason score ≥7 than in those with a Gleason score <7 (12). In the present study, age, PSA, transition zone (TZ) volume, testosterone and follicle stimulating hormone (FSH) levels were used to create two nomograms to predict the probability of prostate cancer of any grade and of high-grade on needle biopsy.

Patients and Methods

The medical records of 570 patients who had undergone transrectal ultrasound (TRUS)-guided prostate biopsy for an elevated serum PSA level and/or a digital rectal examination (DRE) suspicious for cancer from January 2002 through November 2004 at Teikyo University School of Medicine Hospital were reviewed. The serum PSA levels were measured by chemiluminescence enzyme immunoassay with a Lumipulse kit (Fujirebio, Tokyo, Japan). The serum testosterone levels were measured using an Architect testosterone kit (Abbott Japan, Tokyo, Japan). The luteinizing hormone (LH) and FSH levels were measured using an electrochemiluminescence immunoassay with an ECLusys kit (Roche Diagnostics, Basel, Switzerland). The patients eligible for this study were unselected and were accrued consecutively. All the patients gave their written informed consent, and approval was obtained from the hospital Research Ethics Board.

To build the nomograms, all the data obtained from the 396 patients who had had the earlier biopsies were collected. The data of the 174 patients who had had a biopsy at a later time were used for external validation. The total prostate volume and TZ volume were measured by TRUS and calculated by the formula: 0.00052 × width × length × height of each total prostate and the TZ area. Fourteen prostate biopsies were performed under TRUS guidance using an 18-gauge spring-loaded biopsy device. The biopsy specimens were examined for the presence of prostate cancer and were categorized based on the Gleason score.

The data were analyzed using SPSS 15.0 (SPSS, Inc., Chicago, IL, USA) and SAS statistics packages (SAS Institute Inc., Cary, NC, USA). The Mann-Whitney *U*-test was used to compare the means of the groups, as none of the variables was normally distributed. For each independent variable, the skewness was more than twice the standard error. Multivariate logistic regression analysis was performed in order to create the nomograms. Bootstrapping analysis was used for internal validation of the data.

All data are expressed as mean±SD. A *p*-value of <0.05 was considered to be statistically significant. For external validation, Somers' *D_{xy}* rank correlation, Nagelkerke-Cox-Snell-Maddala-Magee R-squared index x, and the discrimination index D were used.

Table III. *Multiple logistic regression analysis evaluating risk of positive biopsy.*

Variable	OR	95% CI	*P*-Value
Age	1.054	68.26-69.78	<0.001
PSA	1.01	11.22-19.38	0.043
TZ volume	0.963	22.71-27.06	<0.001
FSH	1.015	14.48-17.46	0.049
Testosterone	0.999	398.02-431.34	0.332

OR: odds ratio; 95% CI: 95% confidence interval; PSA: prostate-specific antigen; TZ: transitional zone.

Table IV. *Multiple logistic regression analysis evaluating risk of high gleason grade prostate cancer.*

Variable	OR	95% CI	*P*-Value
PSA	1.057	15.30-31.73	0.001
FSH	1.025	15.63-22.25	0.056
Testosterone	0.995	372.82-431.53	<0.001

OR: odds ratio; 95% CI: 95% confidence interval; PSA: prostate-specific antigen; TZ: transitional zone.

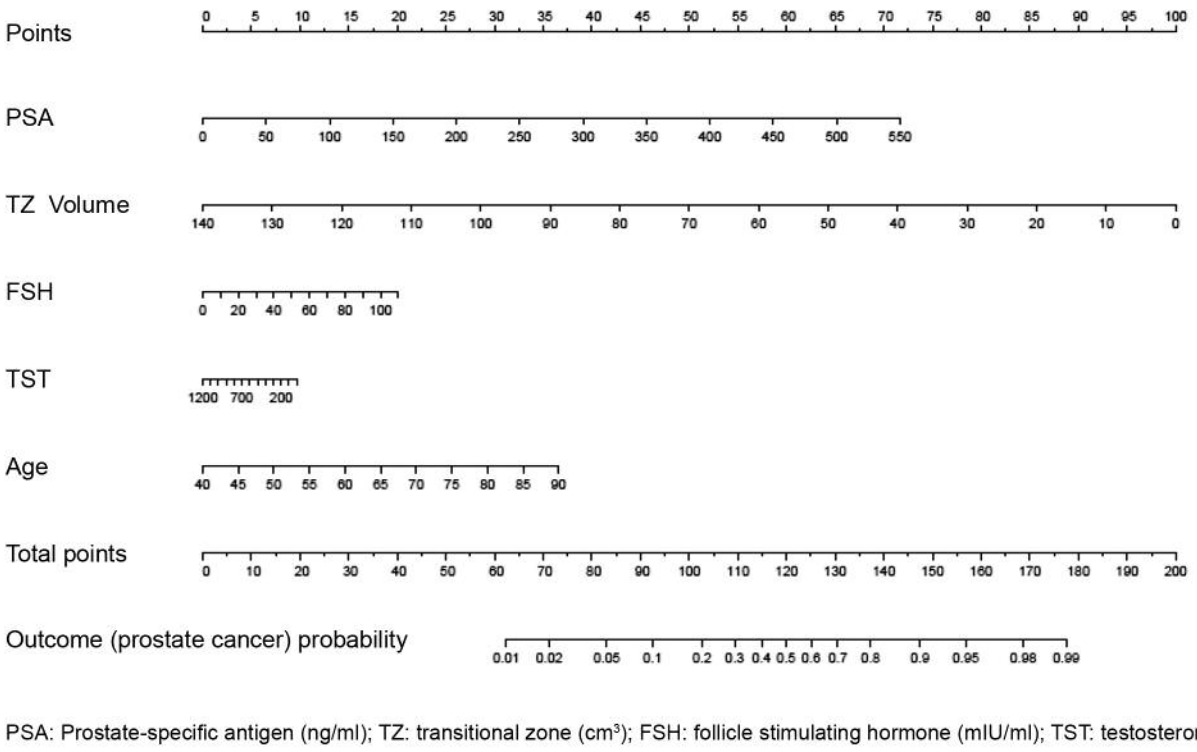

Figure 1. *The nomogram for predicting the presence of prostate cancer on the initial biopsy incorporated age, PSA, TZ volume, FSH and testosterone. A line is drawn upward to the number of points in each category. The points are then summed, and a line is drawn downward to find the risk of prostate cancer on biopsy.*

Results

The characteristics of the study population are shown in Table I. The characteristics according to cohorts of pathological Gleason score are shown in Table II. During the procedure, 14 cores were obtained from all the patients. The following potential factors associated with an increased prostate cancer risk were compared between control (prostate cancer not detected on biopsies) and prostate cancer patients: age, total prostate volume, TZ volume, and serum PSA, LH, FSH and testosterone levels. Adenocarcinoma of the prostate was detected on biopsy in 146 patients. On multivariate logistic regression analyses, there were statistically significant differences in age ($p<0.001$), PSA ($p=0.043$), TZ volume ($p<0.001$) and FSH ($p=0.049$) between patients with and without prostate cancer. The differences in testosterone levels did not achieve statistical significance (Table III). However, there were statistically significant differences in the testosterone levels between the high Gleason score group and the low Gleason score group ($p<0.001$). In these patients, the Gleason scores were classified as 4-6 in 80 (54.8%) and 7-10 in 66 (45.2%) positive biopsies. There were statistically significant differences in selected independent variables, such as the PSA ($p=0.001$), FSH ($p=0.056$) and testosterone ($p<0.001$) levels (Table IV). The high Gleason score group patients were significantly more likely to have lower serum testosterone levels.

Based on these results, a nomogram was developed using the independent risk factors to diagnose prostate carcinoma. In each of the categories, an individual accumulated a certain number of points that were then totaled to calculate the overall likelihood of a positive biopsy. A nomogram was created to predict the probability of prostate cancer on needle biopsy using age, PSA, TZ volume, FSH and testosterone (prostate cancer model, Figure 1). Evaluation of the internal validation resulted in a concordance-index of 0.77. Figure 2 shows the ROC curve for the prostate cancer model to compare the nomogram results and PSA. The ROC curve obtained using the nomogram was better than that using PSA alone (0.77 *vs*. 0.56). The predictive ability of our newly established nomogram has been generally accepted. For example, Eastham *et al*. have shown that the combination of age, race and PSA yields an area under the curve (AUC) of 75% for predicting the presence of prostate cancer on needle biopsy (13). Previous nomograms for the prediction of prostate cancer on needle biopsy have shown a predictive

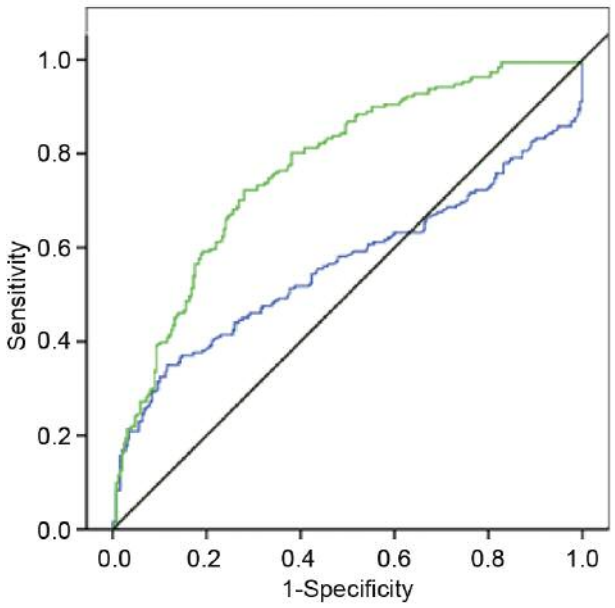

Figure 2. *Comparison of the nomogram results and the PSA alone using receiver operating characteristic (ROC) analysis. The ROC curve evaluated the accuracy of the predicted probability as 77.2% for the nomogram model compared to 56.2% for PSA alone. Green line: PSA alone; blue line: nomogram model.*

accuracy between 0.69 and 0.81 (6, 13-16). Figure 3 shows a nomogram for predicting the presence of high-grade prostate cancer using the PSA, FSH and TST levels (cancer severity model). Figure 4 shows the ROC curve for high-grade prostate cancer. The evaluation of internal validation resulted in c-index of 0.78.

The external validation set consisted of 174 patients (71 with prostate cancer, 103 without prostate cancer). The c-index was 0.70, which is generally considered moderate and indicates a good fit with a chance of little over-fitting. In addition, the external validation set included 40 patients with a high Gleason score and 31 patients with a low Gleason score; a c-index of 0.70, which is moderate, was obtained.

Discussion

Since the late 1990s, extended biopsy has been the standard procedure for detecting prostate cancer (17, 18). A few reports have proposed nomograms to predict the presence of prostate cancer on prostate biopsy (19). In the Japanese population, Suzuki *et al*. demonstrated that an 8-core biopsy nomogram could be used to predict the probability of prostate cancer on initial prostate biopsy (16). They analyzed age, total PSA level, free/total PSA ratio, prostate volume

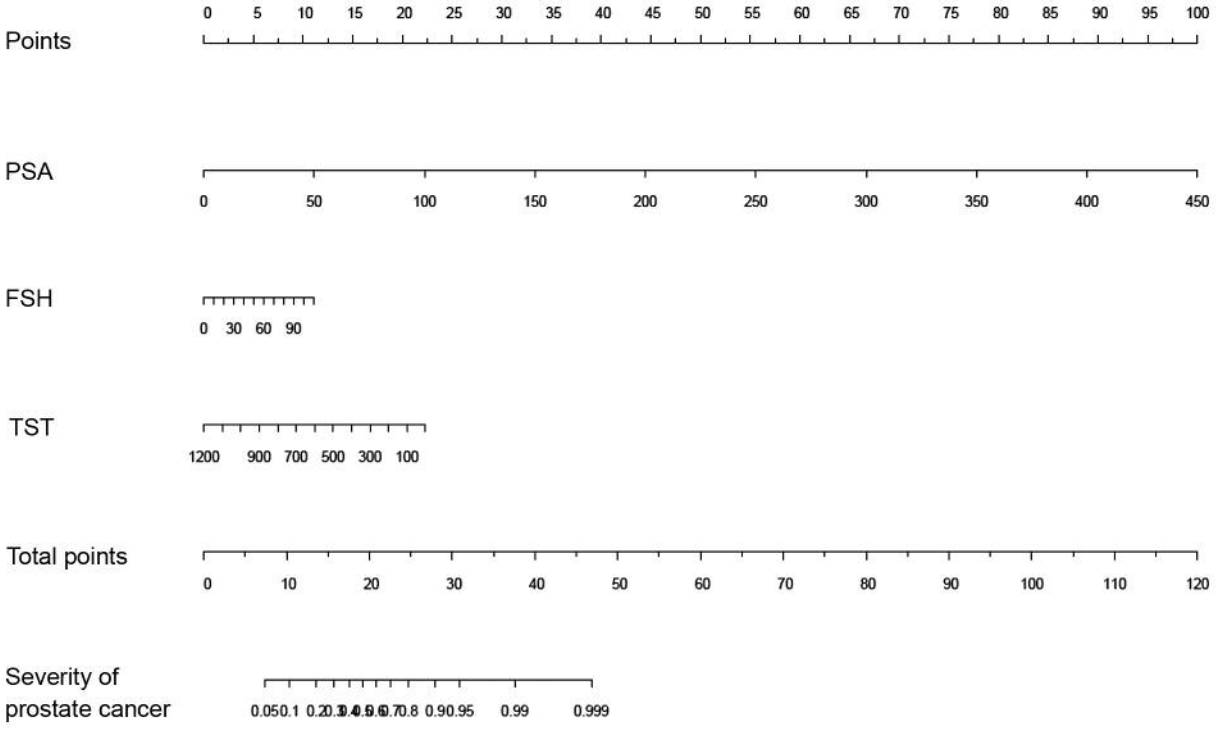

Figure 3. *Nomogram for predicting aggressive prostate cancer defined as patients with a Gleason score ≥7.*

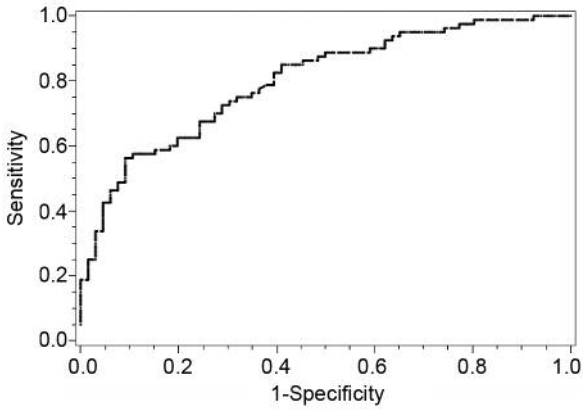

Figure 4. *ROC curve for predicting high-Gleason score prostate cancer, which incorporated three independent risk factors (PSA, FSH and testosterone levels).*

and DRE findings. Although ethnic-specific biopsy nomograms developed in Japan may not be applicable worldwide, their predictive model could provide important information for clinicians and Asian patients. As an increased number of biopsy cores is now more prevalent in Japan, our nomograms based on 14-core biopsies are more acceptable for many clinicians. In addition, our nomogram for risk of high-grade prostate cancer provides more information to help identify patients at high risk for aggressive prostate cancer. Other PSA-related measures have shown good operating characteristics that outperform PSA (20), although PSA velocity provides no independent predictive value for cancer risk (21). In a cohort of patients under active surveillance, the baseline PSA value and the PSA velocity were actually poor predictors of lethal prostate cancer (22).

Androgen drives both the proliferation and differentiation of developing prostate epithelial cells (23). The maintenance of prostate epithelium requires continuous physiological levels of androgens to avoid apoptosis. The notion that low testosterone levels confer an increased risk of a high Gleason score and poor outcomes in males already diagnosed with prostate cancer is gaining momentum. Nishiyama *et al*. have reported that intraprostatic dihydrotestosterone (DHT) levels were significantly reduced in males with Gleason 7-10 carcinomas compared with males with Gleason scores ≤6 (24). Further studies are needed to determine whether the androgen level can function as a biomarker that specifically detects high-grade cancer.

In the present study, the nomogram to predict high-Gleason score prostate cancer incorporated three independent risk factors (PSA, FSH and testosterone levels), it did not include DRE findings. DRE is not standardized and varies widely among physicians (25). Furthermore, DRE is not routinely performed by primary care physicians (26).

One limitation of the present study was that the patients were biopsied due to a suspiciously elevated PSA level. Since the analyzed population included advanced prostate cancer patients, the prostate cancer risk may have been higher than that in a population being screened to detect early prostate cancer. Garzotto *et al*. have proposed predictive nomograms for the presence of prostate cancer in patients with a PSA level ≤10 ng/ml (27).

In conclusion, nomograms that incorporate the serum testosterone level to estimate patient risk for high-grade prostate cancer are better than those using PSA alone. The serum testosterone level may be a useful biomarker that could be included with conventional PSA screening to further improve the efficacy of detecting potentially lethal carcinomas.

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