Original Article

Prostate-specific antigen density as the best predictor of low- to intermediate-risk prostate cancer: a cohort study

Dae Hyoung Park^, Ji Hyeong Yu^

Department of Urology, INJE University Sanggye Paik Hospital, Seoul, Republic of Korea

Contributions: (I) Conception and design: DH Park; (II) Administrative support: YH Yu; (III) Provision of study materials or patients: DH Park; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: DH Park; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Ji Hyeong Yu, MD, PhD. Department of Urology, INJE University Sanggye Paik Hospital, 1342, Dongil-ro, Nowon-gu, Seoul, Republic of Korea. Email: s5631@paik.ac.kr.

Background: Evaluation of prostate cancer (PCa) when serum prostate-specific antigen (PSA) level is vaguely elevated is complicated. This is because serum PSA levels only reflect the number of prostate epithelial cells. We aimed to compare PSA and various prostate volume-related factors to determine which one can best predict PCa in patients with a PSA level of 2.5–20 ng/mL.

Methods: Patients who underwent transrectal ultrasound (TRUS)-guided prostate biopsy at the Inje University Sanggye Paik Hospital between January 2018 and July 2021 and who had a PSA level of 2.5–20 ng/mL were retrospectively identified (n=275). Among them, based on biopsy results, patients were divided into cancer group and non-cancer groups, and age, PSA, total prostate volume (TPV), peripheral zone volume (PZV), peripheral zone PSA density (PZ-PSAD), transitional zone-PSAD (TZ-PSAD), and PSAD were compared and analyzed using receiver operating characteristic (ROC) and univariate analyses.

Results: The areas under ROC curves (AUCs) for age, total PSA, TPV, PZV, PZ-PSAD, TZ-PSAD, and PSAD for predicting PCa in patients with a PSA level of 2.5–20.0 ng/mL were 0.678, 0.680, 0.671, 0.639, 0.731, 0.736, and 0.764, respectively. In univariate and multivariate analysis, all categorical variables were divided based on the cut-off value and used to predict PCa. Those with a PSAD of ≥0.218 ng/mL^2 were found to be at an increased risk of PCa than those with a PSAD of <0.218 ng/mL^2 [odds ratio (OR) =3.51; 95% confidence interval (CI): 1.306–9.415], which was the best result, followed by TZ-PSAD with a cut-off value of 0.353. At a PSAD level of 0.218 ng/mL^2, 85.0% of the PCa group could avoid unnecessary biopsy and 61.4% of the non-PCa group could reduce missed diagnosis when the TRUS findings were inaccurate.

Conclusions: PSAD may inform biopsy decisions as the best predictor of PCa when TRUS findings are ambiguous in patients with a PSA level of 2.5–20.0 ng/mL.

Keywords: Prostate-specific antigen density; prostate cancer; lower urinary tract symptoms (LUTS); digital rectal examination (DRE)

Submitted Jul 06, 2022. Accepted for publication Feb 16, 2023. Published online Mar 17, 2023.
doi: 10.21037/tcr-22-1855
View this article at: https://dx.doi.org/10.21037/tcr-22-1855

^ ORCID: Dae Hyoung Park, 0000-0003-0380-5915; Ji Hyeong Yu, 0000-0001-8139-0036.

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men worldwide, and its global incidence in 2018 was 29.3 per 100,000 individuals (1). PCa is also the fourth leading cause of cancer death in men, with a mortality rate of 7.6 per 100,000 individuals.

Lower urinary tract symptoms (LUTS) are one of the main problems that adversely affect quality of life among elderly individuals. The prevalence of LUTS increases from 44% in men aged 40–59 years to 70% in men aged over 80 years (2). Benign prostatic hyperplasia (BPH) is the most common cause of LUTS, although neurological factors and infections may also cause LUTS (3). Because prostate-specific antigen (PSA) level increases in PCa as well as in BPH or other conditions including prostatitis, it is important that BPH and PCa are not misdiagnosed to guide appropriate treatment.

Currently, cancer evaluation is routinely performed when patients have a PSA level of >2.5 ng/mL or if any abnormality is noted on digital rectal examinations (DREs) (4). However, several men undergo unnecessary prostate biopsy when only PSA level is used for screening (5). Although many studies have attempted to utilize PSA as a means of PCa diagnosis, they have not been successful because of the lack of specificity of PSA for PCa or BPH (6). Transrectal ultrasound (TRUS) is used worldwide because it can be easily performed in consulting rooms, is cost-effective, and takes only 10 minutes. However, since PCa often appears hypoechoic in TRUS and it does not increase PCa detection compared to biopsy of isoechoic lesions, TRUS alone has limitations in diagnosing PCa (7). Therefore, identifying individuals who need to undergo biopsy, and thereby avoiding unnecessary procedures to minimize complications such as pain, infection, bleeding, and sepsis, is vital.

Besides PSA, many factors, including total prostate volume (TPV), PSA density (PSAD), ratio of free PSA to PSA, and transition zone index [TZI; ratio of the transition zone volume (TZV) to the TPV], have been studied as predictive factors for PCa. However, most studies have assessed these predictors in patients at low risk of PCa (8-12). Although the Prostate Imaging-Reporting and Data System (PI-RADS) score of multiparameter magnetic resonance imaging (mpMRI) can increase the diagnosis rate, it still has limitations, such as high cost and long waiting time. Therefore, this study aimed to examine best predictors of PCa among patients with PSA levels of 2.5–20.0 ng/mL who have a low-to-intermediate risk of PCa (4,13), and to investigate associations between PCa and age, total PSA, TPV, PZV, peripheral zone-PSAD (PZ-PSAD), transitional zone-PSAD (TZ-PSAD), and PSAD. We present the following article in accordance with the STARD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1855/rc).

Highlight box

Key findings

- PSAD is an important predictor of PCa when TRUS findings are ambiguous and may inform biopsy decisions in patients with a PSA level of 2.5–20.0 ng/mL.

What is known and what is new?

- When PSA is elevated above the normal range, cancer evaluation is routinely performed.
- As calculating PSAD, it could avoid unnecessary biopsy and reduce missed diagnosis of Pca, when the TRUS findings are inaccurate.

What is the implication, and what should change now?

- By applying PSAD, it is possible to increase the detection of Pca, which requires combination with other biomarker or radiologic development.

Methods

Study design

After obtaining approval from the Institutional Review Board (IRB) of the Inje University, we evaluated the records of 512 patients who underwent transrectal ultrasound prostate biopsy (TRUS-Bx) at our clinic between January 2018 and July 2021 and who had a high PSA level or abnormal findings in TRUS or DRE. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional board of Inje University of Sanggye Paik Hospital (No. 2021-10-001) and individual consent for this retrospective analysis was waived.

Patients were excluded if they had a PSA level below 2.5 ng/mL or above 20 ng/mL, received 5-alpha-reductase inhibitors over 3 months in the previous 2 years, or were diagnosed with atypical small acinar proliferation (ASAP) or high-grade prostate intraepithelial neoplasia. Other exclusion criteria were a history of other prostate surgeries including prostate biopsy, prostatitis, urinary retention within 1 year, or missed examination. After applying the exclusion criteria, a total of 275 patients were included in the study (*Figure 1*).

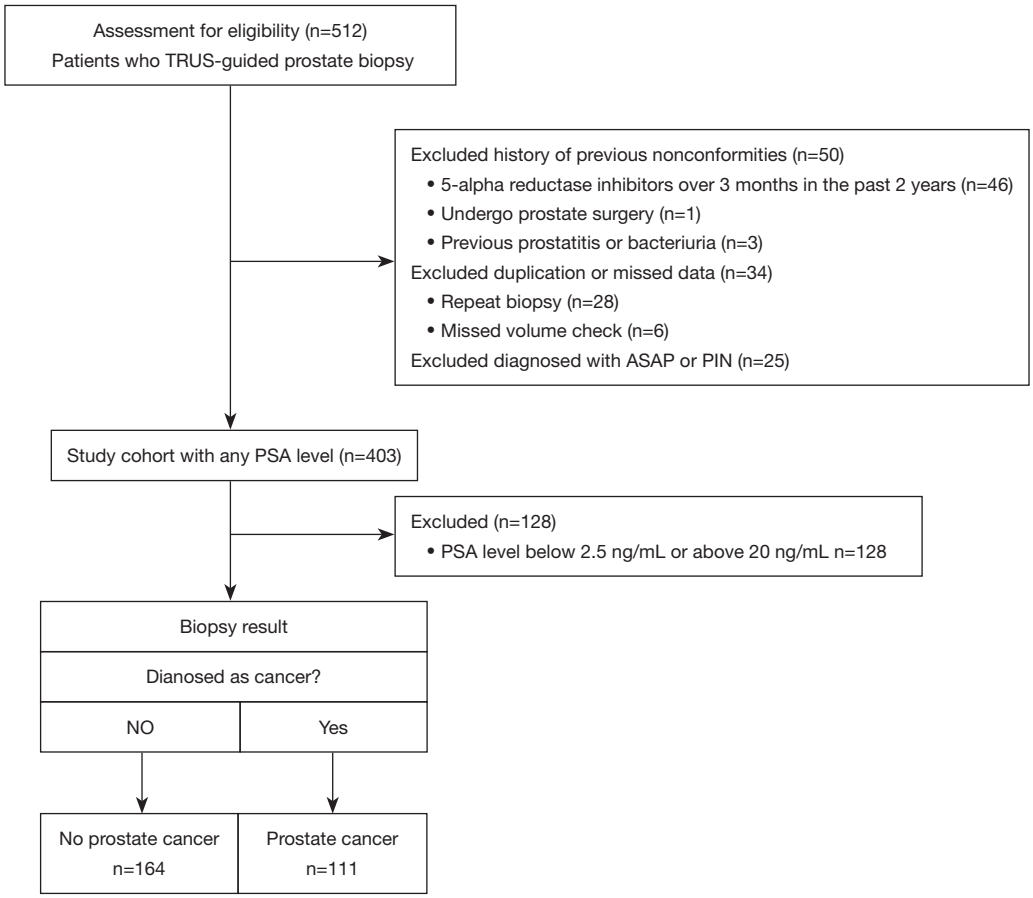

Figure 1 Flowchart of patient selection. TRUS, transrectal ultrasound; ASAP, Atypical Small Acinar Proliferation; PIN, Prostate Intraepithelial Neoplasia; PSA, prostate-specific antigen.

In patients with suspected PCa, PSA levels were measured in ng/mL by immunochemical analysis before biopsy, followed by DRE and TRUS. PSA levels were determined using a Cobas 8000 modular analyzer series (Roche Diagnostics International Ltd., Basel, Switzerland).

Study protocol

Five urologists (LH, JH, DY, JY, and HD) with more than 5 years of experience performed TRUS-Bx. Patients lay on the left side with both knees bent. Local anesthesia with 1% lidocaine was administered, and a urologist used a spring-loaded needle to collect tissue samples from different parts of the gland. Between 12–15 cores were obtained from each patient. Systematic 12 core biopsy were performed, including 6 sextant combined with 6 laterally directed cores at the apex, mid and base, bilaterally. Two or three biopsies of the transition zone at the mid gland were added to the routine biopsy scheme depending on the physician's preference. TRUS was performed to compute TPV and TZV by measuring the length, height, and width of the gland and multiplying the product by a coefficient of $\pi/6$ (ellipsoid formula). PZV was calculated as the difference between the TPV and TZV. PZ-PSAD and TZ-PSAD were measured by dividing the PSA level by PZV and TZV, respectively. PSAD was obtained by dividing the PSA level by TPV. Based on biopsy results, patients were divided into a cancer group and non-cancer group, and basic characteristics such as age, total PSA, TPV, PZV, PZ-PSAD, TZ-PSAD, PSAD, and Gleason score were collected for each group. Clinically significant PCa (csPCa) was defined as a Gleason score of ≥7 or Gleason score of 6 with ≥3 positive and/or maximum core participation of ≥50% (14).

Table 1 Comparison of characteristics between the cancer and non-cancer groups

Variables	Non-PCa group (n=164)	PCa group (n=111)	P value
Age (years), mean ± SD	66.9±7.98	72.1±7.3	<0.001[a]
Total PSA (ng/mL), mean ± SD	6.86±3.07	9.01±3.77	<0.001[a]
TPV (mL), mean ± SD	52.22±26.54	39.69±18.13	<0.001[a]
PZV (mL), mean ± SD	25.32±11.69	20.03±8.35	<0.001[a]
PZ-PSAD (ng/mL^2), mean ± SD	0.319±0.198	0.536±0.336	<0.001[a]
TZ-PSAD (ng/mL^2), mean ± SD	0.362±0.360	0.644±0.433	<0.001[a]
PSAD (ng/mL^2), mean ± SD	0.154±0.950	0.270±0.160	<0.001[a]
Abnormal finding in DRE, n (%)	6 (3.7)	11 (9.9)	0.035[b]
Abnormal finding in TRUS, n (%)	60 (36.6)	41 (36.9)	0.953[b]
Clinically significant cancer, n (%)	–	99 (89.2)	
Chronic inflammation, n (%)	124 (75.6)	52 (46.8)	<0.001[b]
ISUP grade group			
1	–	23 (20.7)	
2	–	31 (27.9)	
3	–	10 (9.0)	
4	–	36 (32.4)	
5	–	11 (9.9)	

[a], independent *t*-test; [b], Pearson's chi-squared test. PCa, prostate cancer; SD, standard deviation; PSA, prostate-specific antigen; TPV, total prostate volume; PZV, peripheral zone volume; PZ-PSAD, peripheral zone prostate-specific antigen density; TZ-PSAD, transition zone prostate-specific antigen density; DRE, digital rectal examination; TRUS, transrectal ultrasound; ISUP, International Society of Urological Pathology.

Statistical analysis

Statistical comparisons of the cancer and non-cancer groups were performed using the independent *t*-test or Kolmogorov-Smirnov (K-S) test for parametric or nonparametric analysis, respectively. Receiver operating characteristic (ROC) curve analyses were performed to determine optimal cutoffs for age, total PSA, TPV, PZV, PZ-PSAD, TZ-PSAD, and PSAD for PCa diagnosis. Continuous data were compared using the *t*-test and K-S test, and categorical data were compared using the Pearson chi-square test, Fisher's exact test, and chi-square test. Univariate and multivariate logistic regression analyses were performed to compare age, total PSA, TPV, PZV, PZ-PSAD, TZ-PSAD, and PSAD in patients with a PSA level of 2.5–20.0 ng/mL to predict PCa. All analyses were performed using SPSS (version 22.0; IBM, New York, NY, USA). Comparisons were two sided, and differences were considered statistically significant at P values of <0.05.

Results

There were significant differences between the PCa and non-PCa groups with respect to age, total PSA, TPV, PZV, PZ-PSAD, TZ-PSAD, and PSAD (all P<0.001). Age, PSA, PZ-PSAD, TZ-PSAD, and PSAD were higher in the PCa group than in the non-PCa group. TPV and PZV were significantly lower in the PCa group than in the non-PCa group. The presence of an abnormal DRE finding was higher in the PCa group than in the non-PCa group (P<0.05). The presence of an abnormal finding in TRUS, however, showed no significant difference between the two groups. In the PCa group, the number of patients with clinically significant cancer was 99 (89.2%). The non-PCa group had more chronic inflammation than the PCa group (n=124, 75.6% *vs.* n=52, 46.8%) (*Table 1*).

Chronic inflammation was detected in 124 patients (75.6%) in the non-PCa group and in 52 patients in the PCa group (46.8%). Patients with PCa were older and had

Table 2 Patient clinical characteristics stratified by Gleason score

ISUP grade group	Age	PSA	TPV	PZV	PZ-PSAD	TZ-PSAD	PSAD
0	66.9±8.0	6.8±3.1	51.9±26.7	25.2±11.7	0.320±0.198	0.368±0.366	0.155±0.096
1	70.3±6.9	8.5±4.1	45.7±23.4	20.6±9.0	0.499±0.352	0.548±0.447	0.238±0.160
2	72.2±8.9	9.1±3.9	38.1±13.8	20.8±8.0	0.532±0.420	0.652±0.427	0.273±0.183
3	71.9±6.2	8.8±3.1	36.9±17.8	19.8±9.6	0.498±0.185	0.612±0.305	0.264±0.102
4	71.3±5.6	8.9±3.0	36.8±16.3	19.4±8.7	0.550±0.274	0.698±0.458	0.287±0.152
5	78.0±7.2	10.9±5.4	47.8±20.4	20.9±6.9	0.596±0.383	0.593±0.455	0.264±0.179

Data are shown as mean ± SD. ISUP, International Society of Urological Pathology; PSA, prostate-specific antigen; TPV, total prostate volume; PZV, peripheral zone volume; PZ-PSAD, peripheral zone prostate-specific antigen density; TZ-PSAD, transition zone prostate-specific antigen density.

Table 3 AUC, best cut-off, sensitivity, specificity, PPV, NPV, and accuracy at predicting overall PCa

Variables	AUC	Cut-off	Sensitivity (%), 95% CI	Specificity (%), 95% CI	PPV (%), 95% CI	NPV (%), 95% CI	Accuracy (%)
Age	0.678	≥68.5	69.4 (59.8–77.6)	58.5 (50.6–66.1)	53.1 (44.7–61.4)	73.8 (65.3–81.0)	62.9
PSA	0.680	≥6.425	73.0 (63.6–80.8)	55.5 (47.5–63.2)	52.6 (44.4–60.6)	75.2 (66.4–82.4)	62.5
TPV	0.671	<34.5	49.5 (40.0–59.1)	78.7 (71.4–84.5)	61.1 (50.2–71.0)	69.7 (62.5–76.1)	66.9
PZV	0.639	<19.9	55.9 (46.1–65.2)	64.6 (56.7–71.8)	51.7 (42.4–60.8)	68.4 (60.4–75.5)	61.2
PZ-PSAD	0.731	≥0.368	64.9 (55.2–73.5)	73.2 (65.6–79.6)	62.1 (52.6–70.8)	75.5 (67.9–81.8)	69.8
TZ-PSAD	0.736	≥0.353	71.2 (61.7–79.2)	68.9 (61.1–75.8)	60.8 (51.8–69.1)	77.9 (70.1–84.2)	69.8
PSAD	0.764	≥0.218	59.5 (49.7–68.5)	84.8 (78.1–89.7)	72.5 (62.0–81.1)	75.5 (68.6–81.4)	74.5

AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; CI, confidence interval; NPV, negative predictive value; PSA, prostate-specific antigen; TPV, total prostate volume; PZV, peripheral zone volume; PZ-PSAD, peripheral zone prostate-specific antigen density; TZ-PSAD, transition zone prostate-specific antigen density.

higher values of PZ-PSAD, PSA, PSAD, and TZ-PSAD and positive findings on DRE than patients with benign pathology (*Table 1*). The ISUP grades and other variables are shown in *Table 2*. The areas under the ROC curves (AUCs) for age, total PSA, TPV, PZV, PZ-PSAD, TZ-PSAD, and PSAD for predicting PCa in patients with a PSA level of 2.5–20.0 ng/mL were 0.678, 0.680, 0.671, 0.639, 0.731, 0.736, and 0.764, respectively (*Table 3*). PSAD was a significantly better predictor of PCa in this group than age, total PSA, TPV, PZV, PZ-PSAD, or TZ-PSAD (*Table 3* and *Figure 2*). The ROC curve analysis revealed the optimal cut-off value for PSAD to be 0.218 in patients with a PSA level of 2.5–20.0 ng/mL. At a cut-off value of 0.218, sensitivity and specificity were 59.5% and 84.8%, respectively.

For predicting csPCa in patients, the AUCs for age, total PSA, TPV, PZV, PZ-PSAD, TZ-PSAD, and PSAD were 0.687, 0.659, 0.662, 0.632, 0.714, 0.717, and 0.745, respectively (*Table 4*). PSAD was significantly the best predictor of csPCa in this group. ROC curve analysis revealed an optimal cut-off value of 0.218 (*Figure 2*). At this cut-off value, sensitivity and specificity were 59.6% and 81.8%, respectively. Therefore, PSAD did not improve the detection of csPCa compared with PCa in our clinic.

In univariate analysis, all categorical variables were divided based on the cut-off value and used to predict PCa. Among patients with a PSA level of 2.5–20.0 ng/mL, those with a PSAD of ≥0.218 ng/mL^2 were found to be at an increased risk of PCa than those with a PSAD of <0.218 ng/mL^2 [odds ratio (OR) =8.16; 95% confidence interval (CI): 4.612–14.419], which was the best result, followed by TZ-PSAD with a cut-off value of 0.353 (OR =5.47; 95% CI: 3.229–9.268), PZ-PSAD with 0.368 (OR =5.04; 95% CI: 2.991–8.475), TPV with 34.50 (OR =3.62; 95% CI: 2.137–6.133), PSA with 6.315 (OR =3.43; 95% CI: 2.026–5.814), age with 68.5 (OR =3.20; 95% CI: 1.921–5.321), and PZV with 19.85 (OR =2.31; 95% CI: 1.413–3.785). In the multivariate analysis,

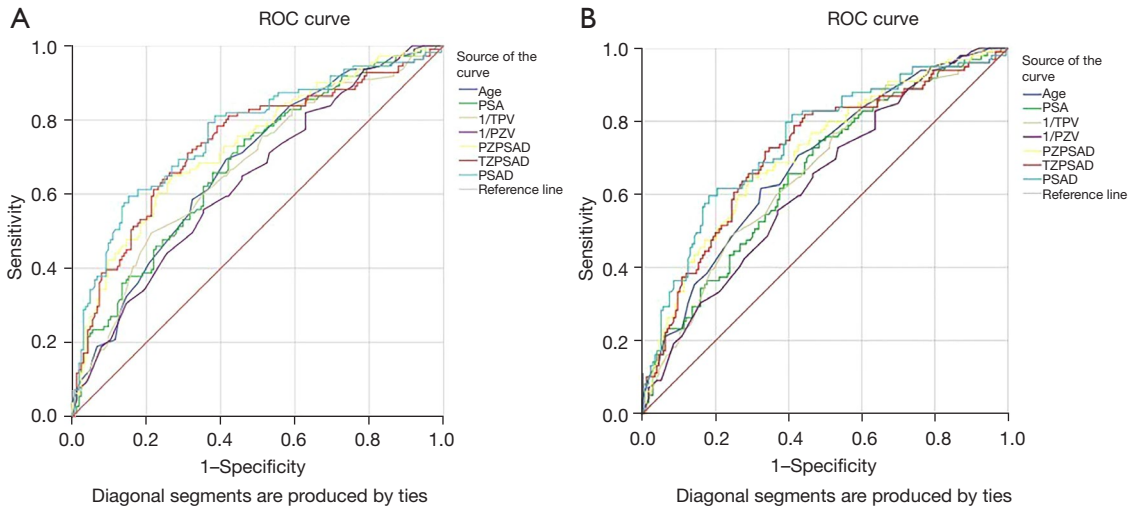

Figure 2 ROC curve analyses. ROC curve analyses of age, PSA, TPV, PZV, PZ-PSAD, TZ-PSAD, and PSAD in patients with PSA values of 2.5–20.0 ng/mL in detecting (A) prostate cancer and (B) clinically significant prostate cancer. ROC, receiver operating characteristic; PSA, prostate-specific antigen; TPV, total prostate volume; PZV, peripheral zone volume; PZ-PSAD, peripheral zone prostate-specific antigen density; TZ-PSAD, transition zone prostate-specific antigen density.

Table 4 AUC, best cut-off, sensitivity, specificity, PPV, NPV, and accuracy at predicting csPCa

Variables	AUC	Best cut-off	Sensitivity (%), 95% CI	Specificity (%), 95% CI	PPV (%), 95% CI	NPV (%), 95% CI	Accuracy (%)
Age	0.687	≥70.5	61.6 (51.3–71.1)	67.6 (60.1–74.3)	51.7 (42.4–60.9)	75.8 (68.2–82.1)	65.5
PSA	0.659	≥6.315	74.7 (64.8–82.7)	51.7 (44.1–59.2)	46.5 (38.7–54.6)	78.4 (69.7–85.3)	60
TPV	0.662	<52.6	84.8 (74.8–90.2)	40.3 (33.1–48.0)	44.1 (37.0–51.6)	81.6 (71.6–88.8)	56
PZV	0.632	<23.3	72.7 (62.7–81.0)	46.6 (39.1–54.2)	43.4 (35.8–51.3)	75.2 (65.9–82.8)	56
PZ-PSAD	0.714	≥0.368	64.6 (54.3–73.8)	70.5 (63.0–77.0)	55.2 (45.7–64.3)	80.0 (70.6–84.0)	68.4
TZ-PSAD	0.717	≥0.353	71.7 (61.6–80.1)	66.5 (58.9–73.3)	54.6 (45.7–63.3)	80.1 (73.1–86.6)	68.4
PSAD	0.745	≥0.218	59.6 (49.2–69.2)	81.8 (75.1–87.1)	64.8 (54.0–74.4)	78.3 (71.5–83.8)	73.8

AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; csPCa, clinically significant prostate cancer; CI, confidence interval; PSA, prostate-specific antigen; TPV, total prostate volume; PZV, peripheral zone volume; PZ-PSAD, peripheral zone prostate-specific antigen density; TZ-PSAD, transition zone prostate-specific antigen density.

patients with age ≥68.5 (OR =3.51; 95% CI: 1.920-6.417), TZ-PSAD ≥0.353 (OR =2.26; 95% CI: 1.019–4.993) and PSAD ≥0.218 ng/mL^2 (OR =3.51; 95% CI: 1.306–9.415) were found to be at the predictors of PCa, whereas PSA (P=0.656), PZ-PSAD (P=0.370) were not (*Table 5*).

We evaluated the efficacy of PSAD when TRUS findings were inaccurate (*Figure 3*).

Among 275 patients with PSA levels of 2.5–20.0 ng/mL, 60 patients in the non-PCa group had inaccurate TRUS findings, of whom 51 (85.0%) patients with PSAD of <0.218 ng/mL^2 could avoid unnecessary biopsies. Additionally, 70 patients in the PCa group had inaccurate TRUS findings; among them, 43 (61.4%) patients with a PSAD of ≥0.218 ng/mL^2 could avoid missed diagnosis.

Discussion

Many studies related to PSAD in men with PSA levels in the gray zone (11,15,16) as well as in PSA <20 ng/mL (9,10,13,17,18) have been conducted, we investigate PSAD as a risk factor for PCa in patients with low-to-intermediate risk (PSA levels 2.5–20.0 ng/mL), and found that the risk of

Table 5 Univariate and multivariate analyses of PCa-associated factors in patients with PSA levels of 2.5–20.0 ng/mL

Variables	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)				
<68.5	–	–	–	–
≥68.5	3.20 (1.921–5.321)	<0.001	3.51 (1.920–6.417)	<0.001
PSA (ng/mL)				
<6.315	–	–	–	–
≥6.315	3.43 (2.026–5.814)	<0.001	–	0.656
TPV (mL)				
≥34.50	–	–	–	–
<34.50	3.62 (2.137–6.133)	<0.001	–	–
PZV (mL)				
≥19.85	–	–	–	–
<19.85	2.31 (1.413–3.785)	0.001	–	–
PZ-PSAD (ng/mL^2)				
<0.368	–	–	–	–
≥0.368	5.04 (2.991–8.475)	<0.001	–	0.370
TZ-PSAD (ng/mL^2)				
<0.353	–	–	–	–
≥0.353	5.47 (3.229–9.268)	<0.001	2.26 (1.019–4.993)	0.045
PSAD (ng/mL^2)				
<0.218	–	–	–	–
≥0.218	8.16 (4.612–14.419)	<0.001	3.51 (1.306–9.415)	0.013

PCa, prostate cancer; PSA, prostate-specific antigen; OR, odds ratio; CI, confidence interval; TPV, total prostate volume; PZV, peripheral zone volume; PZ-PSAD, peripheral zone prostate-specific antigen density; TZ-PSAD, transition zone prostate-specific antigen density.

PCa increased in this patient cohort when PSAD was 0.218 or higher.

In patients with high PSA levels, PCa should be excluded based on TRUS-Bx findings. For patients with enlarged prostates, assuming there is no acute inflammation or urinary retention, biopsy can be used to confirm the lack of cancer, which would indicate that the increase in PSA levels is because of enlarged prostate or chronic inflammation. However, TRUS-Bx may be unnecessary in such cases. In this study, 164 (59.6%) of 275 patients with a PSA level of 2.5–20.0 ng/mL were not diagnosed with PCa, indicating they had elevated PSA levels caused by BPH or chronic inflammation. Therefore, it is important to identify patients who would require biopsy to minimize complications such as bleeding, infection, and pain and avoid unnecessary procedures.

We conducted this retrospective study of patients with no evidence of acute inflammation and a PSA level of 2.5–20.0 ng/mL. It is not easy to identify which patients in this cohort have PCa. Porcaro *et al.* showed that a higher prostate volume (PV) index, defined as the ratio of TZV to PZV, and the presence of prostatic chronic inflammation predicted a decreased risk of PCa in patients with normal DRE findings and a PSA level of 2.0–10.0 ng/mL (8). Kalish *et al.* reported that serum PSA levels adjusted for TZV were more accurate in predicting cancer than PSA alone among patients with PSA levels of 4.0–10.0 ng/mL (19). Roobol *et al.* suggested that PCa screening could be improved by

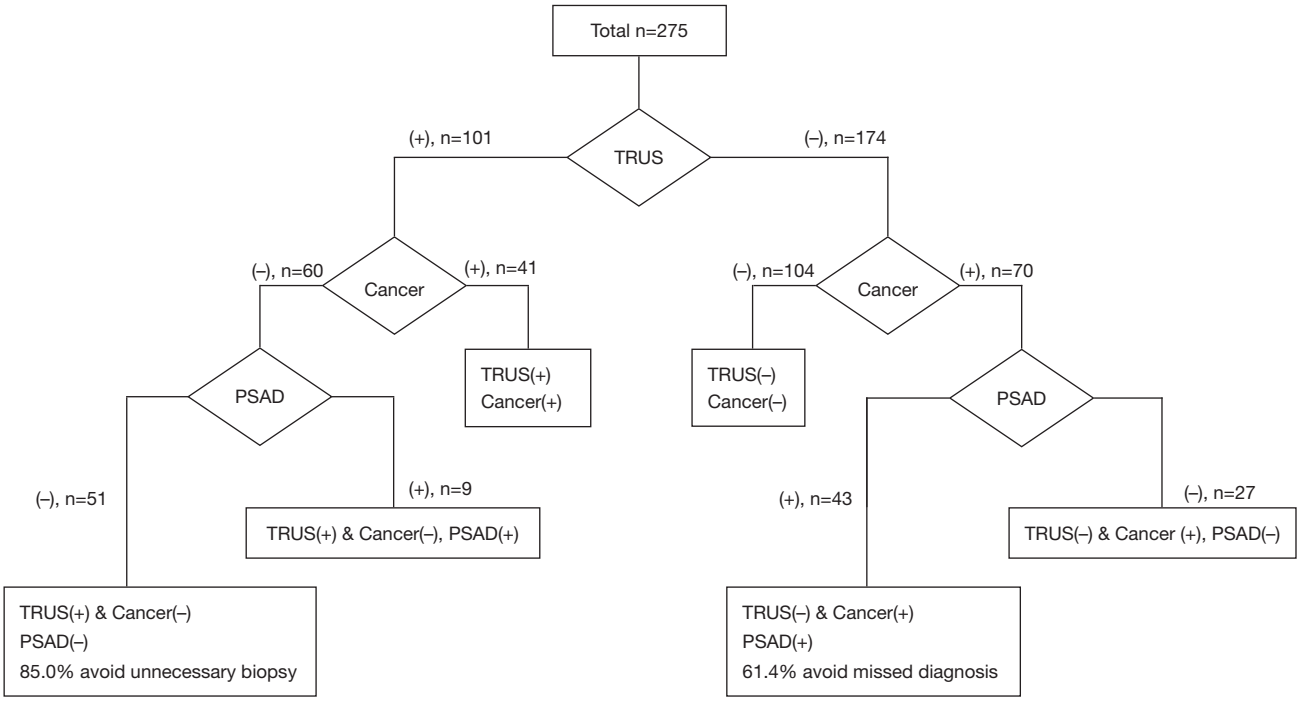

Figure 3 Cancer diagnosis using TRUS and PSAD in patients with PSA levels of 2.5–20.0 ng/mL. (–), negative; (+), positive; TRUS(+), abnormality findings in TRUS; TRUS(–), no abnormality findings in TRUS; PSAD(–), PSAD <0.218; PSAD(+), PSAD ≥0.218. TRUS, transrectal ultrasound; PSAD, prostate-specific antigen density; PSA, prostate-specific antigen.

a calculation method using PV data from TRUS at the European Randomized Study of Screening for Prostate Cancer (5). Additionally, Freedland *et al.* showed that a lower PV was associated with more advanced cancer and high-grade disease among patients with PCa (20). In all of these studies, the authors indicate that PSA levels should not be used alone, but rather we should refer to PV for a more accurate diagnosis of PCa.

A risk assessment based solely on PSA is not optimal. PSAD has been proposed to predict biochemical recurrence after prostatectomy better than PSA (21). Therefore, when PSA is elevated (PSA levels 2.5–20.0 ng/mL), it can be further refined by assessing PSAD. Our study showed that PSAD was most associated with PCa risk in patients with a PSA level of 2.5–20.0 ng/mL. We suggest that patients with a PSA level of 2.5–20.0 ng/mL should be carefully examined for malignancy and that PSAD should be considered before performing mpMRI or biopsy.

Although there is no clear molecular or genetic relationship between BPH and PCa, suggesting two distinct etiological pathways, epidemiologic studies have shown that both conditions are hormone dependent and associated with prostate inflammation, which can represent a common denominator, elevated PSA levels (22). In this study, 176 of 275 patients with a PSA level of 2.5–20.0 ng/mL had chronic inflammation. Microarray studies revealed overlap in gene clusters associated with inflammation between BPH and PCa (23). Obesity, diabetes, dyslipidemia, and high blood pressure have all been identified as risk factors for the development of BPH and PCa (24-26). The studies argue that these two diseases should be regarded as metabolic syndromes, which are related to chronic inflammation, because they do not have separate pathologies and are associated with complex factors such as geriatric disease.

Abnormal DRE and TRUS are individual findings and are biased, and not all physicians performing DRE or TRUS to the one patient give the same results. According to a recent study, Chang *et al.* reported positive or ambiguous DRE findings lead to only 42.1% sensitivity for detection of csPCa (27). And about 30–40% of PCa are not hypoechoic (28,29), TRUS has disadvantage of low specificity (30) for PCa. In our study, one physician reported abnormal DRE or TRUS findings in 76 of 141 patients (53.9%), and another submitted only 5 of 52 patients (10%), which we expected to be somewhat less reliable. Also, there was no significant difference between the PCa group and

non-PCa group for abnormal TRUS findings (P=0.953). In case of DRE, 6 patients (3.7%) in the non-PCa group and 11 patients (9.9%) in the PCa group were abnormal, showing a little difference (P=0.035). However, only one physician reported 14 patients (82.4%) out of all abnormal DRE findings, with confirmation bias, and as a result of analyzing these findings separately, there was no difference between the two groups (P=0.261). Therefore, in this study, both subjective visual and tactile information were judged to be less accurate, and both were included in the study at PSA 2.5–20.0 ng/mL.

In *Tables 3*,*4*, the best cut-off of PSA was lower in the predicting csPCa than in the predicting PCa (P=0.680, 0.659 respectively). Yusim *et al.* reported that 167 of 338 overall PCa had csPCa (49.4%) (13), while our study suggested 88 of 111 overall PCa had csPCa (79.3%), showing larger proportion in our study. This seems to be because the total number of study participants was small and there was not much difference between the number of csPCa and non-csPCa. Also PCa. is the result of diagnosis by TRUS-Bx. and is not the final Bx. after radical prostatectomy, so the possibility of downgrade cannot be ruled out (31). However, this study included real world data and proves that PSA alone cannot predict csPCa in patients with a PSA level of 2.5–20.0 ng/mL.

In this study, patients underwent TRUS-Bx. without the aid of mpMRI. However, mpMRI for the evaluation of PCa have been covered by the National Health Insurance in Republic of Korea since 2019. Currently, MRI of the prostate +/– fusion biopsy has become mainstream. According to recent study by Zhen *et al.*, a meta-analysis of 29 studies with 8,503 patients reported the sensitivity and specificity of pre-boipsy mpMRI were 0.87 (95% CI: 0.81–0.91) and 0.68 (95% CI: 0.56–0.79) respectively (32). Our view on use of PSAD in the diagnostic workup in the ideal scenario is apply PSAD prior to performing mpMRI to aid in PCa diagnosis.

Although many diagnostic techniques such as mpMRI are being developed, TRUS is the world's most popular, inexpensive, and has few complications. It can also provide exact size and anatomy of each zone in detail (33). Because it provides efficient information for cancer diagnosis, TRUS which is described as a urologist's finger, was selected as a characteristic for investigation. Also, TRUS is always necessary for prostate biopsy.

Many studies have shown that PSAD is more effective than PSA in predicting PCa (15,34,35). Although they only mentioned the gray zone (PSA level upper normal limit 10 ng/mL), our results suggest that a PSA level up to 20 ng/mL could also help predict cancer based on PSAD. Verma *et al.* showed that the PSADs of 141 patients with PSA 10 or higher had higher AUC values than those of PSA within the gray zone (0.72 *vs.* 0.61), showing better results in predicting PCa (36). Therefore, extending the PSA range, as reflected in our study, does not appear to significantly change the prediction of PCa.

Kalish *et al.*, assuming that BPH is mainly induced in TZ and that PSA change due to BPH is caused by an enlarged gland in TZ, showed that TZ-PSAD calculated by adjusting PSA with TZV is the most important predictor in predicting PCa (19). However, on the contrary, Wang *et al.* reported that PZ-PSAD was the most important in predicting PCa by increasing the positivity rate of biopsy from 21.7% to 54.7% when TRUS and mpMRI were ambiguous (17). There are also several studies that state that TZ-PSAD is not superior to PSAD in PCa prediction (16,35).

Our study showed that PSAD performed better than PZ-PSAD, TZ-PSAD, and PSA in univariate and multivariate analyses of PCa-associated factors. Patients with a PSAD of 0.218 ng/mL^2 or greater had an 3.5-fold increased risk of PCa compared with patients with a PSAD of <0.218 ng/mL^2.

Although not listed in the table, the patient with PSAD of ≥0.218 ng/mL^2 with a PSA level of 10–20.0 ng/mL also showed increased risk of PCa than those with a PSAD of <0.218 ng/mL^2 (P=0.001) However, at PSA with 10–20 ng/mL, the possibility of chronic inflammation should always be borne in mind. Indeed, in this study, the number of chronic inflammation was significantly higher in PSA with 10–20 ng/mL than PSA with 0–10 ng/mL (P=0.024).

Some biomarkers have been developed to predict the diagnosis of PCa (*Table 6*). Among them, Prostate Health Index (PHI) is a novel screening tool presented in a prospective multi-center studies that can improve the prediction of PCa along with the 4K score and is suggested in the current guidelines (18,40,46). It is calculated using the following formula: (p2PSA/free PSA) × √total PSA. Chiu *et al.* reported that PHI density obtained by dividing PHI by PV value was an excellent predictor of csPCa, and at 90% sensitivity, reduced unnecessary biopsies (43.7%) and missed the fewest csPCa (8.5%) (18). Although our clinic has not been able to perform the PHI test in the absence of p2PSA to date, there seems to be no disagreement on the premise that cancer detection should be improved by referring to the PV. In addition, since the half-life of free

Table 6 List biomarkers for predicting PCa

Biomarker	PSA (ng/mL)	References	Overall PCa			Clinically significant PCa		
			Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC
Serum								
PHI	>4	Russo *et al.* (37)	0.89	0.34	0.76	0.93	0.34	0.82
PHI	2–10	Catalona *et al.* (38)	0.80–0.95	–	0.70	–	–	0.72*
PHI	2–10	Nordström *et al.* (39)	–	–	0.70	–	–	0.70
PHI	2–10	Loeb *et al.* (40)	0.80–0.95	–	0.70	–	–	–
4K panel	Median 6.3 (4.4–10.7)	Braun *et al.* (41)	–	–	0.78	–	–	0.69
4K panel	2–10	Nordström *et al.* (39)	–	–	0.69	–	–	0.71
Urine								
PCA3	4–10	Wang *et al.* (42)	–	–	0.75	–	–	–
PCA3	>3	Hessels *et al.* (43)	–	–	0.72	–	–	–
Interleukin 18 binding protein	–	Fujita *et al.* (44)	0.69	0.56	0.65	–	–	–
2,6-dimethyl-7-octen-2-ol, pentanal, 3-octa none and 2-octanone	–	Fernández-Peralbo *et al.* (45)	0.80	0.57	0.76	–	–	–

* for detection of Gleason ≥7 (4+3) prostate cancer. PCa, prostate cancer; PSA, prostate-specific antigen; AUC, area under the receiver operating characteristic curve; PHI, Prostate Health Index; PCA3, Prostate Cancer gene 3.

PSA is approximately 2 h (47), it is necessary to refer to it in consideration of laboratory conditions.

As shown in *Figure 3*, our study showed that at PSAD of 0.218, 85.0% of the PCa group could avoid unnecessary biopsy and 61.4% of the non-PCa group could reduce avoid diagnosis when the TRUS findings were inaccurate.

Our study has some limitations. First, it was retrospective and conducted at a single institution. Second, we measured TPV using TRUS rather than prostatectomy specimens, and using the ellipsoid formula underestimates PV by 18% (48). However, it would have been impossible to confirm tumor volume through prostatectomy in all patients with PCa because watchful waiting, active surveillance, hormone therapy, and radiation therapy were performed in addition to surgery. Third, variability among different operators was not considered. And, no fusion prostate biopsy was performed, so some cancers may have been undiagnosed. Lastly, this study could not accurately describe for patients simultaneously having BPH and small csPCa, where PSAD would probably be lower than cutoff value.

However, our findings are expected to be helpful in screening patients for PCa. Alongside PSA, the cancer detection rate could be increased when PSAD was 0.218 or higher in patients with PSA levels of 2.5–20.0 ng/mL.

Conclusions

Various models have been proposed to predict the diagnosis of PCa, but none have yet been definitive, and our study suggests that PSAD is the best model for PSA levels of 2.5–20 ng/mL.

PSAD may inform biopsy decisions as the best predictor of PCa when TRUS findings were ambiguous in patients with a PSA level of 2.5–20.0 ng/mL.

Acknowledgments

We thank Editage Korea (www.editage.co.kr) for its linguistic assistance during the preparation of this manuscript.

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tcr.amegroups.com/

article/view/10.21037/tcr-22-1855/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1855/dss

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1855/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1855/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional board of Inje University of Sanggye Paik Hospital (No. 2021-10-001) and individual consent for this retrospective analysis was waived.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol 2006;50:1306-14; discussion 1314-5.
3. Lee CL, Kuo HC. Videourodynamic analysis in men with lower urinary tract symptoms: Correlation between age and prostate size with lower urinary tract dysfunction. Urological Science 2016;27:21-5.
4. Gilbert SM, Cavallo CB, Kahane H, et al. Evidence suggesting PSA cutpoint of 2.5 ng/Ml for prompting prostate biopsy: review of 36,316 biopsies. Urology 2005;65:549-53.
5. Roobol MJ, van Vugt HA, Loeb S, et al. Prediction of prostate cancer risk: the role of prostate volume and digital rectal examination in the ERSPC risk calculators. Eur Urol 2012;61:577-83.
6. Benson MC, Whang IS, Pantuck A, et al. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. J Urol 1992;147:815-6.
7. Smeenge M, Barentsz J, Cosgrove D, et al. Role of transrectal ultrasonography (TRUS) in focal therapy of prostate cancer: report from a Consensus Panel. BJU Int 2012;110:942-8.
8. Porcaro AB, Tafuri A, Sebben M, et al. Prostate volume index and prostatic chronic inflammation have an effect on tumor load at baseline random biopsies in patients with normal DRE and PSA values less than 10 ng/ml: results of 564 consecutive cases. Ther Adv Urol 2019;11:1756287219868604.
9. Nordström T, Akre O, Aly M, et al. Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. Prostate Cancer Prostatic Dis 2018;21:57-63.
10. Erdogan A, Polat S, Keskin E, et al. Is prostate volume better than PSA density and free/total PSA ratio in predicting prostate cancer in patients with PSA 2.5-10 ng/Ml and 10.1-30 ng/Ml? Aging Male 2020;23:59-65.
11. Zlotta AR, Djavan B, Marberger M, et al. Prostate specific antigen density of the transition zone: a new effective parameter for prostate cancer prediction. J Urol 1997;157:1315-21.
12. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969-74.
13. Yusim I, Krenawi M, Mazor E, et al. The use of prostate specific antigen density to predict clinically significant prostate cancer. Sci Rep 2020;10:20015.
14. Epstein JI, Walsh PC, Carmichael M, et al. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994;271:368-74.
15. Lee J, Yang SW, Jin L, et al. Is PSA density of the peripheral zone as a useful predictor for prostate cancer in patients with gray zone PSA levels? BMC Cancer 2021;21:472.

16. Aksoy Y, Oral A, Aksoy H, et al. PSA density and PSA transition zone density in the diagnosis of prostate cancer in PSA gray zone cases. Ann Clin Lab Sci 2003;33:320-3.
17. Wang C, Wang YY, Wang SY, et al. Peripheral zone PSA density: a predominant variable to improve prostate cancer detection efficiency in men with PSA higher than 4 ng ml(-1). Asian J Androl 2021;23:415-20.
18. Chiu ST, Cheng YT, Pu YS, et al. Prostate Health Index Density Outperforms Prostate Health Index in Clinically Significant Prostate Cancer Detection. Front Oncol 2021;11:772182.
19. Kalish J, Cooner WH, Graham SD Jr. Serum PSA adjusted for volume of transition zone (PSAT) is more accurate than PSA adjusted for total gland volume (PSAD) in detecting adenocarcinoma of the prostate. Urology 1994;43:601-6.
20. Freedland SJ, Isaacs WB, Platz EA, et al. Prostate size and risk of high-grade, advanced prostate cancer and biochemical progression after radical prostatectomy: a search database study. J Clin Oncol 2005;23:7546-54.
21. Freedland SJ, Wieder JA, Jack GS, et al. Improved risk stratification for biochemical recurrence after radical prostatectomy using a novel risk group system based on prostate specific antigen density and biopsy Gleason score. J Urol 2002;168:110-5.
22. Alcaraz A, Hammerer P, Tubaro A, et al. Is there evidence of a relationship between benign prostatic hyperplasia and prostate cancer? Findings of a literature review. Eur Urol 2009;55:864-73.
23. Prakash K, Pirozzi G, Elashoff M, et al. Symptomatic and asymptomatic benign prostatic hyperplasia: molecular differentiation by using microarrays. Proc Natl Acad Sci U S A 2002;99:7598-603.
24. Hammarsten J, Högstedt B. Hyperinsulinaemia: a prospective risk factor for lethal clinical prostate cancer. Eur J Cancer 2005;41:2887-95.
25. Irani J, Lefebvre O, Murat F, et al. Obesity in relation to prostate cancer risk: comparison with a population having benign prostatic hyperplasia. BJU Int 2003;91:482-4.
26. Nandeesha H, Koner BC, Dorairajan LN, et al. Hyperinsulinemia and dyslipidemia in non-diabetic benign prostatic hyperplasia. Clin Chim Acta 2006;370:89-93.
27. Chang CM, McIntosh AG, Shapiro DD, et al. Does a screening digital rectal exam provide actionable clinical utility in patients with an elevated PSA and positive MRI? BJUI Compass 2021;2:188-93.
28. Onur R, Littrup PJ, Pontes JE, et al. Contemporary impact of transrectal ultrasound lesions for prostate cancer detection. J Urol 2004;172:512-4.
29. Kuligowska E, Barish MA, Fenlon HM, et al. Predictors of prostate carcinoma: accuracy of gray-scale and color Doppler US and serum markers. Radiology 2001;220:757-64.
30. Pallwein L, Mitterberger M, Pelzer A, et al. Ultrasound of prostate cancer: recent advances. Eur Radiol 2008;18:707-15.
31. Fernandes ET, Sundaram CP, Long R, et al. Biopsy Gleason score: how does it correlate with the final pathological diagnosis in prostate cancer? Br J Urol 1997;79:615-7.
32. Zhen L, Liu X, Yegang C, et al. Accuracy of multiparametric magnetic resonance imaging for diagnosing prostate Cancer: a systematic review and meta-analysis. BMC Cancer 2019;19:1244.
33. Weiss BE, Wein AJ, Malkowicz SB, et al. Comparison of prostate volume measured by transrectal ultrasound and magnetic resonance imaging: is transrectal ultrasound suitable to determine which patients should undergo active surveillance? Urol Oncol 2013;31:1436-40.
34. Wolff JM, Scholz A, Boeckmann W, et al. Differentiation of benign prostatic hyperplasia and prostate cancer employing prostatic-specific antigen density. Eur Urol 1994;25:295-8; discussion 304.
35. Elliott CS, Shinghal R, Presti JC Jr. The performance of prostate specific antigen, prostate specific antigen density and transition zone density in the era of extended biopsy schemes. J Urol 2008;179:1756-61; discussion 1761.
36. Verma A, St Onge J, Dhillon K, et al. PSA density improves prediction of prostate cancer. Can J Urol 2014;21:7312-21.
37. Russo GI, Regis F, Castelli T, et al. A Systematic Review and Meta-analysis of the Diagnostic Accuracy of Prostate Health Index and 4-Kallikrein Panel Score in Predicting Overall and High-grade Prostate Cancer. Clin Genitourin Cancer 2017;15:429-39.e1.
38. Catalona WJ, Partin AW, Sanda MG, et al. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. J Urol 2011;185:1650-5. Erratum in: J Urol 2011;186:354.
39. Nordström T, Vickers A, Assel M, et al. Comparison Between the Four-kallikrein Panel and Prostate Health Index for Predicting Prostate Cancer. Eur Urol 2015;68:139-46.
40. Loeb S, Catalona WJ. The Prostate Health Index: a new test for the detection of prostate cancer. Ther Adv Urol 2014;6:74-7.
41. Braun K, Sjoberg DD, Vickers AJ, et al. A Four-

kallikrein Panel Predicts High-grade Cancer on Biopsy: Independent Validation in a Community Cohort. Eur Urol 2016;69:505-11.
42. Wang FB, Chen R, Ren SC, et al. Prostate cancer antigen 3 moderately improves diagnostic accuracy in Chinese patients undergoing first prostate biopsy. Asian J Androl 2017;19:238-43.
43. Hessels D, Klein Gunnewiek JM, van Oort I, et al. DD3(PCA3)-based molecular urine analysis for the diagnosis of prostate cancer. Eur Urol 2003;44:8-15; discussion 15-6.
44. Fujita K, Ewing CM, Isaacs WB, et al. Immunomodulatory IL-18 binding protein is produced by prostate cancer cells and its levels in urine and serum correlate with tumor status. Int J Cancer 2011;129:424-32.
45. Fernández-Peralbo MA, Gómez-Gómez E, Calderón-Santiago M, et al. Prostate Cancer Patients-Negative Biopsy Controls Discrimination by Untargeted Metabolomics Analysis of Urine by LC-QTOF: Upstream Information on Other Omics. Sci Rep 2016;6:38243.
46. Carroll PH, Mohler JL. NCCN Guidelines Updates: Prostate Cancer and Prostate Cancer Early Detection. J Natl Compr Canc Netw 2018;16:620-3.
47. Richardson TD, Wojno KJ, Liang LW, et al. Half-life determination of serum free prostate-specific antigen following radical retropubic prostatectomy. Urology 1996;48:40-4.
48. Aprikian S, Luz M, Brimo F, et al. Improving ultrasound-based prostate volume estimation. BMC Urol 2019;19:68.

Cite this article as: Park DH, Yu JH. Prostate-specific antigen density as the best predictor of low- to intermediate-risk prostate cancer: a cohort study. Transl Cancer Res 2023;12(3): 502-514. doi: 10.21037/tcr-22-1855

