Original Article

Do prostate-specific antigen parameters have a similar role in predicting prostate cancer regardless of serum testosterone levels in men with gray-zone prostate-specific antigen levels?

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Background: To evaluate whether various prostate-specific antigen (PSA) parameters have a similar diagnostic value in predicting prostate cancer (PCa) in men with gray-zone PSA levels (4.0–10.0 ng/mL) depending on different serum testosterone levels.

Methods: We retrospectively reviewed the data of 635 men with gray-zone PSA levels who underwent prostate biopsy between January 2015 and December 2019. The study cohort was divided into two groups according to serum testosterone levels: normal (≥300 ng/dL) and low (<300 ng/dL) testosterone. Using the area under the receiver-operating characteristic curve (AUC), we analyzed the diagnostic accuracy of PSA parameters (total PSA, free PSA, free-to-total PSA ratio, testosterone-to-PSA ratio, and PSA density) in predicting PCa and compared the results between the two groups.

Results: The median age was 68 (range, 40–88) years, and 76.1% (483 of 635) of the men had low testosterone levels. The PCa incidence was higher in the low testosterone group than in the normal testosterone group (45.5% *vs.* 35.5%, P=0.030). The AUC of free-to-total PSA ratio for predicting PCa showed no difference between the normal and low testosterone groups (AUC 0.616 *vs.* 0.684, P=0.257). Moreover, total PSA, testosterone-to-PSA ratio, and PSA density showed similar performance in predicting PCa between the two groups.

Conclusions: The analyzed PSA parameters showed a similar diagnostic value in predicting PCa regardless of testosterone levels in men with gray-zone PSA levels.

Keywords: Prostate-specific antigen (PSA); prostatic neoplasms; testosterone

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Introduction

Prostate cancer (PCa) has become the second most common cancer in men worldwide, and its incidence has been rapidly increasing in the last 10 years in Asian populations (1,2). Although the serum prostate-specific antigen (PSA) level has been used as an index in screening for PCa, it has no established cutoff value for recommending biopsy and shows a lack of specificity, especially in patients whose PSA levels are within the "gray zone" (3). A serum PSA level of

between 4 and 10 ng/mL is considered to fall within the diagnostic gray zone, and PCa is detected in only 25% of patients whose PSA levels are within this interval (4). Thus, other diagnostic tools, such as the free-to-total PSA ratio, PSA density, PSA velocity, and other PSA parameters, have been proposed to improve the PCa screening performance and avoid unnecessary biopsies in men with gray-zone PSA levels (4-6).

The percentage of men with testosterone deficiency increases with age, and testosterone replacement therapy is widely used to improve hypogonadal symptoms in these men (7). Meanwhile, the association between serum testosterone levels and PCa has been inconsistently reported in the literature (8-14). Furthermore, few types of research have been conducted on PSA as a screening tool for PCa or on the best cutoff value of PSA in men with low testosterone levels (15,16). To our knowledge, only limited studies are available about the performance of various PSA parameters in predicting PCa according to serum testosterone levels in Asian men with gray-zone PSA levels. Among the PSA parameters, the free-to-total PSA ratio is known to be a simple and useful tool for predicting PCa. Its value could be obtained after a single blood sampling, without additional blood sampling (as required for determining PSA velocity) or ultrasonography (as required for determining PSA density). Therefore, in this study, we evaluated whether PSA parameters, especially the free-to-total PSA ratio, have similar diagnostic values in predicting PCa regardless of serum testosterone levels in Asian men with gray-zone PSA levels. We present our article in accordance with the STARD (Standards for Reporting of Diagnostic Accuracy Studies) reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-21-1051/rc).

Methods

Patient selection & clinicopathologic features

We retrospectively reviewed the electronic medical records of consecutive patients with high PSA levels (≥4 ng/mL) who underwent prostate biopsy followed by hospitalization at Chonnam National University Hwasun Hospital between January 2015 and December 2019. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and the Ethical Guidelines for Clinical Studies. The study protocol was reviewed and approved by the institutional review board of Chonnam National University Hwasun Hospital (approval No. CNUHH-2020-145), and informed patient consent was waived by the same ethical approval because this was a retrospective study.

The inclusion criteria were men (I) with gray-zone PSA levels (4.0–10.0 ng/mL) and (II) who underwent transrectal ultrasound (TRUS)-guided prostate biopsy. The exclusion criteria were patients (I) with a history of PCa, high-grade intraepithelial neoplasia, or atypical small acinar proliferation; (II) with prior prostate surgery; (III) with any therapy that could influence the testosterone or PSA levels, such as finasteride or dutasteride or testosterone replacement therapy; and (IV) with missing laboratory data or indeterminate pathologic findings. A total of 635 men were finally included in our study (*Figure 1*). All biopsies were performed by one experienced radiologist at our institution, who obtained 12-core biopsy specimens using a standardized protocol. To diagnose PCa, the biopsy specimens were reviewed by one experienced pathologist who was blinded to the values of the PSA parameters. Clinically significant PCa (csPCa) was defined as a Gleason score of ≥7 (17). Clinicopathologic features (age, body mass index, hypertension, cardiovascular disease, diabetes mellitus, history of any cancer other than PCa, and medications for lower urinary tract symptoms) were investigated.

Various PSA parameters

The baseline total PSA, free PSA, and total testosterone levels were measured at the same time as the enrollment of patients. Blood samples were obtained in the morning (between 8 and 10 a.m.), when testosterone was relatively stable and at its highest level. The serum total testosterone-to-PSA ratio was calculated by dividing the serum total testosterone level by the serum total PSA level. The free-to-total PSA ratio was calculated by dividing free PSA by total PSA. PSA density was defined as the ratio of serum total PSA to the prostate volume measured during TRUS. These parameters were reviewed by the first author, who was blinded to the clinicopathologic information and the final histopathologic diagnosis.

Statistical analysis

Statistical analysis was performed using IBM SPSS software (version 24.0; IBM Co., Armonk, NY, USA), and receiver-operating characteristic curve (ROC) analysis

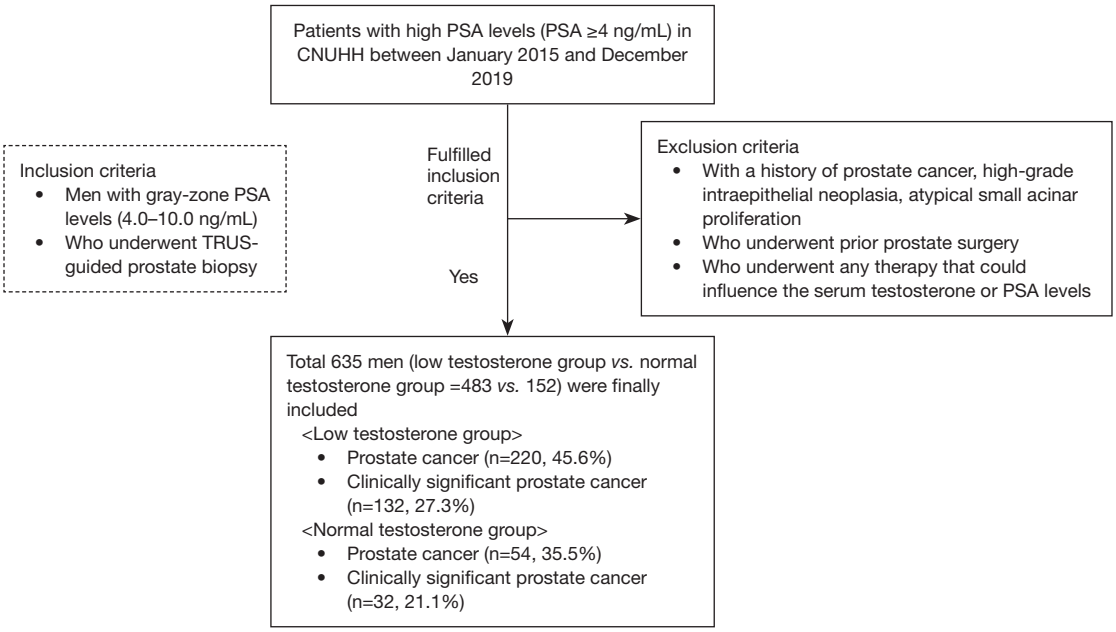

Figure 1 Flow diagram of the study. PSA, prostate-specific antigen; CNUHH, Chonnam National University Hwasun Hospital; TRUS, transrectal ultrasound.

was conducted using MedCalc Statistical Software version 17.6 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2017). We divided the patients into two groups according to the serum testosterone level: normal testosterone group (serum testosterone level ≥300 ng/dL) and low testosterone group (serum testosterone level <300 ng/dL) based on the European Association of Urology (EAU) and American Urological Association (AUA) guidelines (18,19). Categorical data were compared between the two groups using Fisher's exact test, and continuous data were compared using the Mann-Whitney U-test because continuous data reject normality. A P value of <0.05 was considered to indicate statistical significance. The diagnostic performance and cutoff values of serum total PSA, free-to-total PSA ratio, testosterone-to-PSA ratio, and PSA density in predicting PCa and csPCa were evaluated and compared between the groups using ROC analysis.

Results

Patient characteristics and PSA parameters

The patient characteristics and PSA parameters in the low testosterone and normal testosterone groups are summarized in *Table 1*. The median age was 68 (range, 40–88) years, and 76.1% (483 of 635) of the patients had low testosterone levels. PCa was diagnosed in 43.1% (274 of 635) and csPCa in 25.8% (164 of 635) of the men. In patients without PCa, the pathologic diagnoses were normal glandular tissue, benign prostatic hyperplasia, or benign prostatitis. The median time interval between the examination of PSA parameters and the diagnosis of PCa or csPCa was 1 day (range, 0–41 days). The patients in the low testosterone group showed significantly older age (P=0.001), higher rate of hypertension (P=0.005), larger prostate volume (P=0.004), higher PCa incidence (P=0.030), lower testosterone-to-PSA ratio (P=0.001), and lower PSA density (P=0.007) than those in the normal testosterone group. No adverse events occurred and no clinical intervention was needed during blood sampling or biopsy.

Diagnostic values of PSA parameters in predicting PCa and csPCa

We performed ROC curve analysis and evaluated the diagnostic performance of serum total PSA, free-to-total PSA ratio, testosterone-to-PSA ratio, and PSA density for diagnosing PCa and csPCa in patients with gray-zone PSA levels (Figures S1,S2). The AUC of total PSA, free-to-total PSA ratio, testosterone-to-total PSA ratio, and PSA density for diagnosing PCa was 0.577 [95% confidence interval (CI): 0.538–0.616], 0.650 (95% CI: 0.611–0.687), 0.577 (95% CI: 0.537–0.616), and 0.682 (95% CI: 0.644–0.718),

Table 1 Patient characteristics and PSA parameters in the low testosterone and normal testosterone groups of men with gray-zone prostate-specific antigen levels

Variable	Total (n=635)	Serum testosterone level		P value
		Normal (n=152)	Low (n=483)	
Age (years), median [range]	68 [40–88]	66 [41–87]	68 [40–88]	0.001
BMI (kg/m^2), median [range]	24.4 [13.3–74.4]	24.2 [18.5–32.6]	24.5 [13.3–74.4]	0.576
HTN	275 (43.3%)	51 (33.6%)	224 (46.4%)	0.005
Cardiovascular disease	50 (7.9%)	9 (5.9%)	41 (8.5%)	0.305
DM	129 (20.3%)	33 (21.7%)	96 (19.9%)	0.624
Previous other cancer	146 (23.0%)	29 (19.1%)	117 (24.2%)	0.189
LUTS medication	281 (44.3%)	69 (45.4%)	212 (43.9%)	0.745
Prostate volume (mL), median [range]	36.3 [8.0–122.0]	30.5 [8.0–110.0]	33.0 [9.0–122.0]	0.004
Serum testosterone level (ng/dL), median [range]	240.0 [51.0–619.0]	337.0 [301.0–619.0]	215.0 [51.0–300.0]	<0.001
Prostate cancer	274 (43.1%)	54 (35.5%)	220 (45.5%)	0.030
Clinically significant prostate cancer	164 (25.8%)	32 (21.1%)	132 (27.3%)	0.123
Serum total PSA (ng/mL), median [range]	6.0 [4.0–10.0]	6.1 [4.0–9.9]	6.0 (4.0–10.0)	0.658
Free PSA (ng/mL), median [range]	1.2 [0.1–4.4]	1.0 [0.1–3.3]	1.2 (0.2–4.4)	0.187
Free-to-total PSA ratio, median [range]	16.9 [2.3–63.1]	15.7 [2.3–61.6]	17.3 (2.9–63.1)	0.088
Testosterone-to-PSA ratio, median [range]	40.2 [9.4–121.4]	55.7 [31.2–121.4]	35.1 (9.4–71.1)	0.001
PSA density (ng/mL^2, mean ± SD)[‡]	0.22±0.12	0.24±0.13	0.21±0.11	0.007

[‡], PSA density (ng/mL^2) was defined as the ratio of serum total PSA to prostate volume measured during transrectal ultrasound. BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen; SD, standard deviation.

respectively. The cutoff value of free-to-total PSA ratio and PSA density with the best sensitivity and specificity for predicting PCa was 16.25 [sensitivity, 62.04%; specificity, 64.27%; accuracy, 63.3%; positive predictive value (PPV), 56.86%; and negative predictive value (NPV), 69.05%] and 0.197 ng/mL^2 (sensitivity, 63.14%; specificity, 68.98%; accuracy, 66.3%; PPV, 60.48%; and NPV, 71.06%), respectively. The AUC of total PSA, free-to-total PSA ratio, testosterone-to-total PSA ratio, and PSA density for diagnosing csPCa was 0.590 (95% CI: 0.551–0.629), 0.666 (95% CI: 0.627–0.702), 0.592 (95% CI: 0.553–0.631), and 0.673 (95% CI: 0.635–0.709), respectively. The cutoff value of free-to-total PSA ratio and PSA density with the best sensitivity and specificity for predicting csPca was 16.38 (sensitivity, 63.9%; specificity, 59.2%; and accuracy, 60.0%) and 0.195 ng/mL^2 (sensitivity, 66.5%; specificity, 61.4%; and accuracy, 56.3%), respectively. A contingency table evaluating the accuracy of free-to-total PSA ratio and PSA density in diagnosing PCa and csPCa is presented in Table S1.

Comparison of ROC curves of PSA parameters for predicting PCa between the low and normal testosterone groups of men with gray-zone PSA levels

A comparison of the ROC curves of serum total PSA, free-to-total PSA ratio, testosterone-to-PSA ratio, and PSA density for predicting PCa in patients with gray-zone PSA according to testosterone levels is shown in *Figure 2*. In men with normal testosterone levels, the AUC of total PSA, free-to-total PSA ratio, testosterone-to-total PSA ratio, and PSA density was 0.579 (95% CI: 0.496–0.658), 0.608 (95% CI: 0.538–0.675), 0.574 (95% CI: 0.491–0.653), and 0.629 (95% CI: 0.547–0.706), respectively. In men with low testosterone levels, the AUC of total PSA, free-to-total PSA ratio, testosterone-to-total PSA ratio, and PSA density

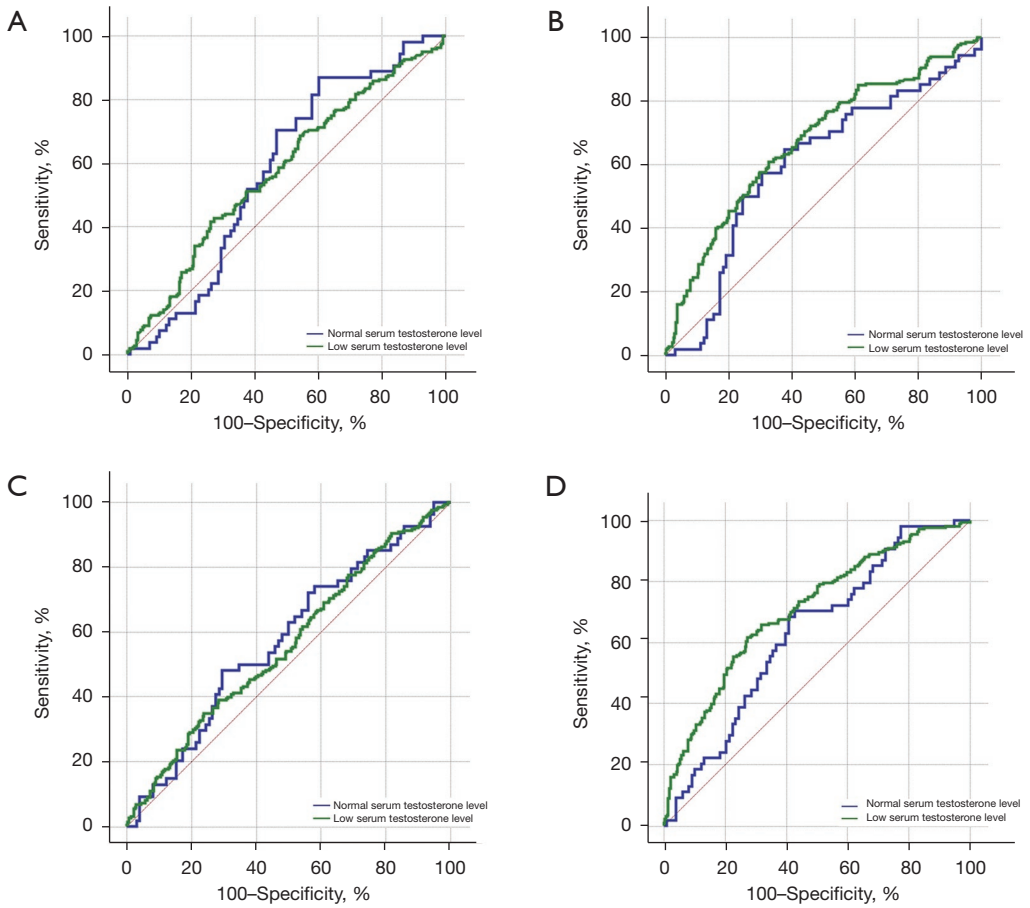

Figure 2 Receiver operating characteristic curves of each PSA parameter for predicting prostate cancer in both normal and low serum testosterone levels. (A) For total PSA, AUC was 0.579 (95% CI: 0.496–0.658) and 0.578 (95% CI: 0.533–0.623) in normal and low serum testosterone levels, respectively (P=0.991); (B) for free-to-total PSA ratio, AUC was 0.608 (95% CI: 0.538–0.675) and 0.619 (95% CI: 0.619–0.710) in normal and low serum testosterone levels, respectively (P=0.247); (C) for testosterone-to-total PSA ratio, AUC was 0.574 (95% CI: 0.491–0.653) and 0.559 (95% CI: 0.514–0.604) in normal and low serum testosterone levels, respectively (P=0.793); (D) for PSA density, AUC was 0.629 (95% CI: 0.547–0.706) and 0.707 (95% CI: 0.664–0.747) in normal and low serum testosterone levels, respectively (P=0.133). PSA, prostate-specific antigen; AUC, area under the receiver-operating characteristic curve; 95% CI, 95% confidence interval.

was 0.578 (95% CI: 0.533–0.623), 0.619 (95% CI: 0.619–0.710), 0.559 (95% CI: 0.514–0.604), and 0.707 (95% CI: 0.664–0.747), respectively. The comparison of the AUCs of all PSA parameters did not show significant differences between the groups (all, P>0.05).

Comparison of ROC curves of PSA parameters for predicting csPCa between the low and normal testosterone groups of men with gray-zone PSA levels

The comparison of the AUCs of total PSA (P=0.559), free-to-total PSA ratio (P=0.257), and testosterone-to-total PSA ratio (P=0.793) did not show significant differences between the low and normal testosterone groups (Figure S3). However, the AUC of PSA density was significantly higher in the low testosterone group than in the normal testosterone group (AUC 0.580, 95% CI: 0.498–0.660 *vs.* AUC 0.701, 95% CI: 0.658–0.741; P=0.039).

Discussion

The free-to-total PSA ratio showed a similar diagnostic value in predicting PCa regardless of testosterone levels in men with gray-zone PSA levels. In addition, other PSA parameters including total PSA, testosterone-to-total PSA ratio, and PSA density also showed no difference

in diagnostic value between the two groups categorized according to serum testosterone levels. However, for csPCa prediction in men with gray-zone PSA levels, PSA density showed a different diagnostic performance in that it had a higher AUC in the low testosterone group than in the normal testosterone group.

In usual clinical practice, serum total PSA at a cutoff value of 3.0–4.0 ng/mL has been used as a criterion for performing TRUS-guided biopsy to screen for PCa; however, no standardized measurement of PSA levels is available and the specificity of PSA for PCa detection is insufficient (20). The serum PSA level can also be elevated in benign conditions (10), and it is difficult to differentiate between benign prostatic hyperplasia and PCa when the PSA level is <10 ng/mL. Therefore, using the PSA level alone for PCa screening is limited, especially in men with PSA levels in the 4.0–10.0 ng/mL range (diagnostic gray zone). Many studies have attempted to identify the diagnostic value of other PSA parameters, such as free-to-total PSA ratio, PSA density, PSA density of the transition zone, and PSA velocity (4-6,15,21-24). Partin *et al.* investigated whether percent free PSA could increase the specificity for PCa detection in men with gray-zone PSA levels and concluded that percent free PSA may be a useful tool in distinguishing PCa from benign disease in this population (23). They suggested that using percent free PSA <20% as a criterion could detect PCa in 95% and eliminate unnecessary biopsy in 29% of patients. Among the PSA parameters, the free-to-total PSA ratio is known to be simple and useful for diagnosing PCa, as its value could be obtained after a single blood sampling without additional blood sampling (as required for determining PSA velocity) or ultrasonography (as required for determining PSA density). In addition, Chen *et al.* reported that PSA density may be superior to the free-to-total PSA ratio as a predictor of PCa in a repeated prostate biopsy setting (5). Similar to their results, we observed in the present study that the PSA density and free-to-total PSA ratio had higher AUCs (PSA density: AUC 0.682, 95% CI: 0.644–0.718; free-to-total PSA ratio: AUC 0.650, 95% CI: 0.611–0.687) than the other PSA parameters.

Meanwhile, the circulating androgens, particularly testosterone, are known to play fundamental roles in prostate growth (25). Their underlying mechanism of action remains unclear because androgens mediate complex interactions with many prostate growth factors, hormones, and cell lines (26). The association of testosterone levels and PCa is also complex and has been the topic of numerous studies, with conflicting results (8,27,28). Huggins and Hodges reported that elevated serum testosterone levels due to testosterone replacement therapy may be associated with the potential development or progression of PCa (8). However, other studies reported that low serum testosterone levels are associated with an aggressive biology of PCa and worse survival of patients (27). Previously, Shin *et al.* reported that patients with lower serum testosterone levels had a higher risk of PCa than those with higher serum testosterone levels, although low testosterone level was not associated with a higher grade of PCa (28). In the present study, the low testosterone group showed a higher incidence of PCa than the normal testosterone group (45.5% *vs.* 35.5%, P=0.030), although the incidence of csPCa did not differ between the groups.

PCa can occur in older men and in men with low testosterone levels, regardless of the association of serum testosterone levels with aging (29). Although several studies have investigated the diagnostic value of various PSA parameters in predicting PCa, there is still limited evidence on whether the same cutoff value of each PSA parameter can be sufficiently sensitive and specific for detecting PCa in men with low testosterone levels compared with men with normal testosterone levels or all men. Karamanolakis *et al.* reported the usefulness of the serum testosterone-to-PSA ratio as a predictor of PCa in men with low testosterone levels (30), and Rhoden *et al.* also reported that the testosterone-to-PSA ratio was significantly associated with PCa in men with low testosterone levels (15). Therefore, we designed our study to evaluate whether the four PSA parameters have similar diagnostic values in predicting PCa (and csPCa) in men with low testosterone levels compared with men having normal testosterone levels.

Morote *et al.* reported the relationship between PSA parameters and the risk of PCa and analyzed the potential usefulness of PSA parameters as predictors of PCa in a consecutive cohort of men with normal digital rectal examination findings and a serum PSA level of 4.1–20 ng/mL (31). However, they failed to prove whether the testosterone-to-PSA ratio can be a predictor of PCa in clinical practice. In our study, the AUCs of serum total PSA, free-to-total PSA ratio, testosterone-to-total PSA ratio, and PSA density showed similar diagnostic values in predicting PCa regardless of testosterone levels in men with gray-zone PSA levels. The free-to-total PSA ratio and PSA density showed higher AUCs than the other PSA parameters for the prediction of PCa in men with low testosterone levels. Recently, Schwarzman *et al.* reported that serum total PSA,

free-to-total PSA ratio, and PSA density have comparable diagnostic values in screening for PCa in both men with low testosterone levels and men with normal testosterone levels and serum PSA levels of 2.5–10 ng/mL (16). The AUCs of total PSA, free-to-total PSA ratio, and PSA density for predicting overall PCa and csPCa in the low testosterone group were similar to those in the normal testosterone group. Our study showed similar results in that the diagnostic performance of PSA parameters showed no difference in predicting PCa and csPCa between the low and normal testosterone groups; however, PSA density showed a statistical difference in predicting csPCa in our study. Our study would be a useful reference for physicians considering prostate biopsy and testosterone replacement therapy in men with gray-zone PSA levels.

Our study had several limitations. This was a retrospective study conducted at a single tertiary-care center in a specific region in Asia. Owing to the difference in laboratory and prostate biopsy protocols and the relatively small sample size of this study, the diagnostic value of PSA parameters and the PCa detection rate in men with gray-zone PSA levels could be different from those in previous studies. In addition, as no standardized criterion for low testosterone has been established, the cutoff value for low testosterone levels may differ across different studies and institutions. We set <300 ng/dL as the criterion for low testosterone levels, with reference to the EAU and AUA guidelines (18,19). Despite the limitations, our study is important as it is the first study in Asia to evaluate the diagnostic values of variable PSA parameters according to testosterone levels men with gray-zone PSA levels. A randomized, prospective study with a larger sample size is warranted to verify the diagnostic value of PSA parameters depending on the serum testosterone levels.

Conclusions

The diagnostic performance of various PSA parameters in predicting PCa was not significantly different between the low testosterone and normal testosterone groups of men with gray-zone PSA levels.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-21-1051/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-21-1051/dss

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-21-1051/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-21-1051/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. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and the Ethical Guidelines for Clinical Studies. The study protocol was reviewed and approved by the institutional review board of Chonnam National University Hwasun Hospital (approval No. CNUHH-2020-145), and informed patient consent was waived by the same ethical approval because this was a retrospective study.

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