Original Article

Prostate-specific Antigen Density as a Proxy for Predicting Prostate Cancer Severity: Is There Any Difference between Systematic and Targeted Biopsy?

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Abstract

Background: Prostate cancer screening with prostate-specific antigen (PSA) can result in unnecessary biopsies and overdiagnosis. Alternately, PSA density (PSAD) calculation may help support biopsy decisions; however, evidence of its usefulness is not concrete.

Objective: To evaluate the predictive value of PSAD for clinically significant prostate cancer detection by systematic and MRI-targeted biopsies.

Methods: This prospective study was conducted at two tertiary hospitals in Riyadh, Saudi Arabia, between December 2018 and November 2021. Patients suspected of prostate cancer were subjected to multi-parametric MRI, and for those with positive findings, systematic and targeted biopsies were performed. Clinically non-significant and significant prostate cancer cases were classified based on histopathology-defined ISUP grade or Gleason score. The PSAD was measured using the prostate volume determined by the MRI and categorized into ≤0.15, 0.16–0.20, and >0.20 ng/ml^2 subgroups.

Results: Systematic and targeted biopsies were carried out for 284 patients. The discriminant ability of PSAD is higher in MRI-targeted biopsy compared with systematic biopsy (AUC: 0.77 vs. 0.73). The highest sensitivity (97%) and specificity (87%) were detected at 0.07 ng/ml^2 in targeted biopsy. More than half of the clinically significant cases were detected in the >0.2 ng/ml^2 PSAD category (systematic: 52.4%; targeted: 51.1%). The CHAID methodology found that the probability of having clinically significant cancer (CSC) in patients with PSAD >0.15 ng/ml^2 was more than threefold than that in patients with PSAD ≤0.15 ng/ml^2 (64% vs. 20.2%). When considered by age, in PSAD ≤0.15 ng/ml^2 subgroup, the percentage of CSC detection rate increased from 20.2% to 24.6% in patients aged ≥60 years.

Conclusion: PSAD has good discriminant power for predicting clinically significant prostate cancer. A cutoff of 0.07 ng/ml^2 should be adopted, but should be interpreted with caution and by considering other parameters such as age.

Keywords: Active surveillance, overdiagnosis, prostatic neoplasm, advanced prostate cancer, prostate-specific antigen, PSA density, screening, systematic biopsy, targeted biopsy

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INTRODUCTION

Prostate cancer (PC) is the second most commonly diagnosed cancer and the fifth principal cause of cancer deaths among males worldwide, with an estimated 1,414,000 new cases in 2020.[1] An upsurge in its burden is estimated due to an aging population and improvements in economic status.[2] However, the incidence of PC in the Middle East and Arab countries is low: a recent study from Saudi Arabia found that in a cohort of males aged >45 and <70 years, the incidence rate of PC was 0.24%.[3] In most cases, PC advances gradually, and treatment for early-stage illness is often more effective. However, in some cases, the aggressive form of PC results in worse prognosis, including metastases and mortality. Among other factors, a genome-wide association study has linked the aggressive form of PC with the rs11672691 SNP.[4]

Various definitions of clinically significant positive cancer cases have been utilized, primarily based on the number of positive cores, maximum cancer core length, grade at biopsy, Gleason score ≥7 or ≥30% of cores positive, prostate-specific antigen (PSA) ≥10 ng/ml, and/or PSA density (PSAD) >0.15 ng/ml^2. According to the Prostate Imaging-Reporting and Data System (PI-RADS) version 2, a clinically significant PC must have International Society of Urological Pathology (ISUP) histopathology grade ≥2 and/or a prostate volume ≥0.5 cc.[5]

Screening programs using PSA have been accepted in numerous developed countries, and this has resulted in decreasing mortality rates in countries such as the United States of America, Canada, the United Kingdom, and Japan.[6-9] However, a recent meta-analysis has found that PSA alone is highly sensitive but poorly specific in detecting PC.[10] Therefore, using PSA alone in the screening process can result in unnecessary biopsies and overdiagnosis. Alternately, Benson *et al*.[11] found that PSAD is a better predictor of PC than PSA alone; however, its use in clinical settings and studies on the same are limited. The current study was carried out to investigate the predictive accuracy of PSAD in detecting clinically significant PC using systematic and MRI-targeted biopsies. The findings of this study may result in providing active surveillance to a greater proportion of patients without undertreating them.

METHODS

Study design, setting, and patients

This is an observational prospective study that was conducted at King Khalid University Hospital and King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, between December 2018 to November 2021. Patients suspected of PC (i.e., high PSA >4 ng/ml and/or abnormal digital rectal examination findings) were randomly recruited for the study after examination by a consultant at the study centers. All patients were subjected to a multi-parametric MRI, and for those with positive findings in MRI, systematic and targeted biopsies were conducted.

The study was approved by the Institutional Review Board of King Saud University, and written informed consent was obtained from the patients.

Procedure and characterization

After harvesting at least 2–3 cores or up to 6 cores from the target lesion, depending on the lesion size, a systematic 12-core technique was performed on each patient. Clinically nonsignificant and significant cancer cases were categorized according to histopathology-defined ISUP grade or Gleason score.[12] The PSAD was measured using the prostate volume determined by the MRI technique, and was categorized into three groups: ≤0.15, 0.16–0.20, and >0.20 ng/ml^2.

Statistical analysis

Descriptive statistics and Chi-square test were used to detect the association between nominal variables. Correlation *r* was measured to detect the significant association between PSAD and different variables. Receiver operating characteristic (ROC) curves were plotted for PSAD for each outcome (systematic and targeted biopsy). PSAD area under the curve (AUC) predicting clinically significant disease was calculated through comparison with non-clinically substantial cases. Youden's index (sensitivity + specificity −1) was used for the classification of the most appropriate cutoff point for PSAD. Chi-square automatic interaction detection (CHAID) strategies were used to divide the predictors into classes based on cancer detection and clinically significant cases. Statistical significance was defined as $P < 0.05$. Analyses were performed using SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY., USA).

RESULTS

The initial cohort with suspected PC was 353 patients. However, 69 patients were excluded because of artifacts in MRI, MRI findings being negative, and refusal of consent for biopsy; the remaining 284 patients were subjected to systematic and targeted biopsy. Systematic and targeted biopsies detected 42 and 90 clinically significant cancer (CSC) cases and 26 and 20 non-clinically substantial cases, respectively.

The correlation coefficient between PSAD and various parameters is presented in Table 1. PSAD was positively correlated with the outcomes of systematic ($r = 0.28$) and targeted ($r = 0.47$) biopsies, PI-RADs (version 2) ($r = 0.35$), and age ($r = 0.28$) (for all, $P = 0.001$). The correlation between PSAD and prostate size was not significant ($P = 0.07$). No significant correlation was detected with body mass index (BMI; $P = 0.87$).

Systematic versus MRI-targeted biopsy outcomes

Figure 1 illustrates the ROC for systematic and MRI-targeted biopsy outcomes. For systematic biopsy, the AUC to predict CSC was 0.73 (95% CI = 0.60–0.84; $P = 0.001$), and the highest sensitivity (95%) and specificity (90%) were detected at a PSAD of 0.06. For targeted biopsy, the AUC to predict CSC was 0.77 (95% CI = 0.68–0.85; $P = 0.001$), and the highest sensitivity (97%) and specificity (87%) were detected at 0.07 ng/ml^2.

The distribution of CSC cases across different categories of PSAD shows that while a higher percentage of cases were detected at PSAD >0.2 ng/ml^2 (systematic biopsy: 52.4%; targeted biopsy: 51.1%), a substantial proportion of cases were also detected at the lowest level of PSAD (i.e., ≤0.15 ng/ml^2) (systematic biopsy: 33.3%; targeted biopsy: 35.6%) [Table 2].

CHAID decision-tree analysis

In the CHAID decision-tree analysis, it was found that patients with PSAD >0.02 ng/ml^2 had a 32.4% chance of being diagnosed with CSC. In comparison, those with PSAD ≤0.15 ng/ml^2 had a significantly lower probability (20.2%) of having CSC ($P < 0.05$). The probability of having CSC cancer with PSAD between 0.16–0.2 ng/ml^2 was 31.6%. When considered by age, there was a difference in detection rates, and this was most pronounced in the PSAD ≤0.15 ng/ml^2 subcategory, where the detection rate increased to 24.6% in patients aged ≥60 years and dropped to 12.5% in those aged <60 years [Figure 2].

DISCUSSION

Screening for PC using PSA alone can lead to unnecessary biopsies and overdiagnosis, and thus there is a need to avoid complications related to a prostate biopsy and the prognosis of low-grade PC. Although PSAD is available, the early evidence supporting its use for biopsy decisions is conflicting and not universally supported by

Table 1: Correlation of prostate-specific antigen density with different parameters

Variables	*r*	*P*
Cancer detected by systematic biopsy	0.28	0.001
Cancer detected by targeted biopsy	0.47	0.000
PI-RADs	0.23	0.00
Age	0.28	0.000
Prostate size	−0.15	0.07
BMI	0.01	0.87

BMI – Body mass index; PI-RADs – Prostate imaging and reporting data system

Table 2: Distribution of cancer cases detected systematic and targeted biopsy across different categories of prostate-specific antigen density

Type of biopsy	PSAD categories (%)			
	≤0.15	0.16–0.20	>0.20	Total
Systematic biopsy	14 (33.3)	6 (14.3)	22 (52.4)	42
Targeted biopsy	32 (35.6)	12 (13.3)	46 (51)	90

$\chi^2 = 26.1$ and $P = 0.001$. PSAD – Prostate-specific antigen density

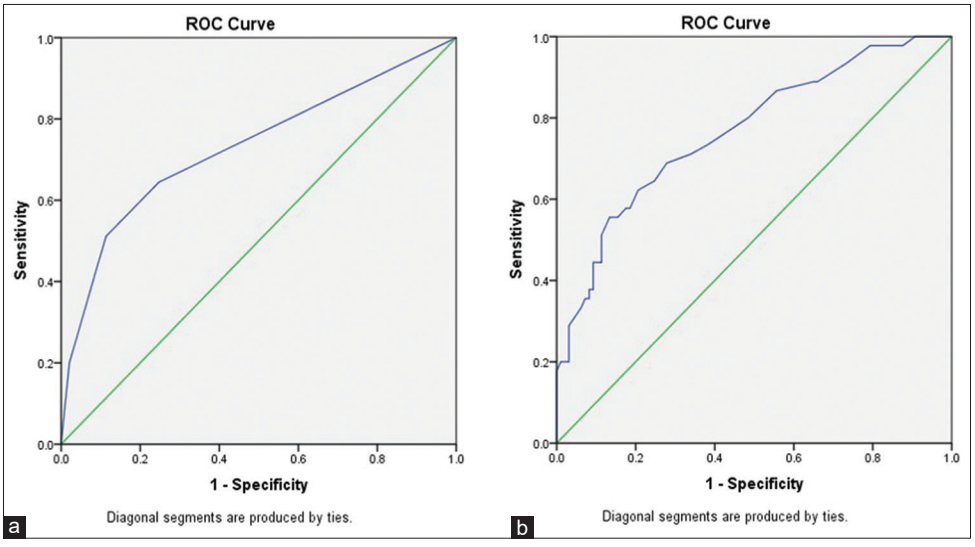

Figure 1: The receiver operating characteristic (ROC) for systematic and MRI-targeted biopsy outcome. (a) ROC for detecting CSC cases by systematic biopsy, (b) ROC for detecting CSC cases by MRI-targeted biopsy. CSC – Clinically significant cancer

guidelines.[13] Several previous studies have suggested that a PSAD >0.15 ng/ml/cm^3 increases the detection rates of patients at risk of cancer, and a PSAD >0.2 ng/ml/cm^3 is strongly associated with extracapsular cancer extension of the prostate.[14-16]

In the present study, PSAD was significantly correlated with many parameters, i.e., PI-RADs, age, and systematic and targeted biopsies, but not with prostate size and BMI. More than half of CSC cases were identified in patients with PSAD >0.20 ng/ml^2; however, the performance of PSAD was poor when comparing the value of 0.16–0.20 to that of ≤0.15 ng/ml^2, where the number of CSC cases detected was higher. Nordstrom *et al*.[17] showed that PSAD cutoffs of 0.10 ng/ml^2 and 0.15 ng/ml^2 resulted in the detection of 77% and 49% of CSC tumors. A significant correlation was detected between PSAD with primary tumor (r = 0.303, P < 0.01), metastatic lymph nodes (r = 0.331, P < 0.01), and organ-confined disease (r = 0.296, P < 0.05). In addition, there was a significant tendency to deteriorate the clinic-pathological predictive features associated with an upsurge in the PSAD, as indicated in the findings by Saidi *et al*.;[18] however, it is worth mentioning that only six cases had lymph node extension, and all of them had Gleason scores of ≥8.

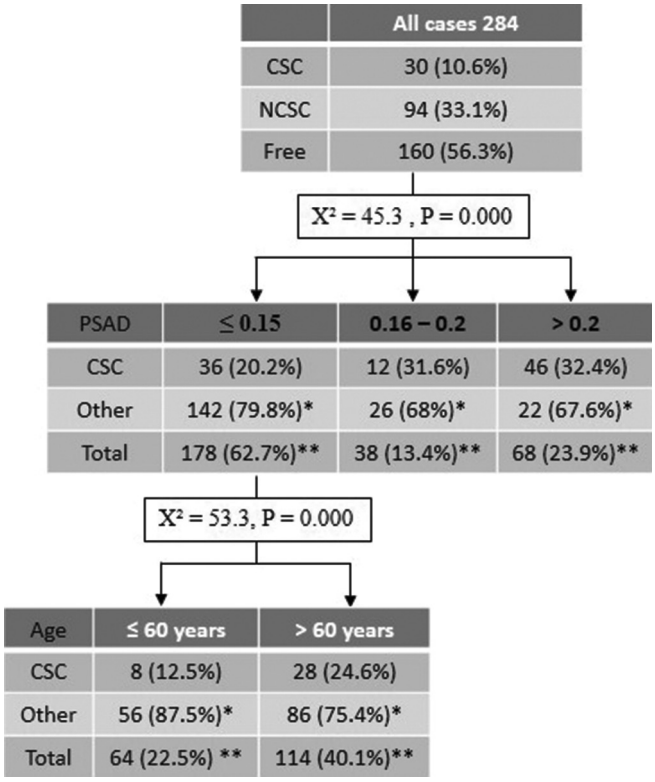

Figure 2: Chi-square automatic interaction detection decision tree for the detection of clinically significant cancer of cancer prostate. *Other cases included free cases and clinically nonsignificant cases, **Percent relates to the total number of patients (N = 284). CSC – Clinically significant cancer; NCSC – Nonsignificant CSC; PSAD – Prostate-specific antigen density

The propensity of PSAD to distinguish clinically significant PC has been revealed in several clinical scenarios. The discriminant power of PSAD is notably high in the present study, where the AUC to predict CSC was 0.73 and 0.77 for systematic and MRI-targeted biopsies, respectively. The highest sensitivity and specificity were detected at the 0.07 ng/ml^2 cutoff in targeted biopsy. Arafa *et al*.[19] indicated that the detection of CSC cases is meaningfully higher with the targeted modality than the systematic modality. Further, in two different studies, the AUC to predict the CSC cases was similar to our result (0.75 and 0.78).[17,20] In various studies, the ROC curve analysis has been used to determine the cutoffs with highest sensitivity and specificity for detecting CSC cases of PC. Ha *et al*. recommended 0.085 ng/ml^2 as the optimal PSAD cutoff value for predicting advanced stage disease, resulting in decreasing the risk of advanced disease to 17.5–21.7%.[21] Nordström *et al*.[17] and Aminsharifi *et al*.[22] concluded that using a cutoff for PSAD at 0.08 ng/ml^2 could have avoided 13%–20% of biopsies and missing only 2%–7% of CSC cases. On the other hand, the highest Youden's index reported by Yusim *et al*. was a PSAD of 0.20 ng/ml^2 (sensitivity: 70%; specificity: 79%).[20]

Using the CHAID methodology, it found that the probability of having CSC in patients with PSAD >0.15 ng/ml^2 was more than threefold in comparison to patients with PSAD ≤0.15 (64% vs. 20.2%). In the PSAD ≤0.15 ng/ml^2 subgroup, the influence of patient's age on the detection rate of CSC was noticeable. Age at the time of cancer diagnosis is a recognized prognostic factor in patients with an advanced disease stage. However, the association between the patient's age and the severity of PC has not been well studied in the Arab region.

The results of two earlier studies mentioned that increasing age has a significant impact on CSC detection, and men aged <55 years, were more likely to have a less aggressive clinical and pathological PC, which in turn has potential inferences for therapeutic decision-making.[23,24] Similarly, Godtman *et al*. concluded that for each 1-year increase in age, the possibility of detecting cancer prostate with a Gleason score ≥3 + 4 PC (vs. <7) augmented by 11%, while the possibility of being identified with a Gleason score ≥4 + 3 cancer (vs. <7) augmented by 8.5%.[25]

Limitations

The study has a few limitations, such as the relatively small sample size included. This is mainly due to the lower

incidence rate of prostate cancer in our region, and the study period coinciding with the COVID-19 pandemic, which resulted in fewer patients being admitted. In addition, no information was collected about those who were MRI-positive and refused to do the biopsy. Finally, individuals with the first biopsy were not separated from those with repeated biopsies.

CONCLUSION

PSAD is a good predictor of the aggressive form of PC; however, in the view of lower incidence of PC and lower PSA reference values in our region, the discriminant power of PSAD should be interpreted with caution and by considering other parameters such as age. As a PSAD cutoff of ≤0.15 ng/ml^2 encompasses a considerable percentage of CSC cases, it could result in misinformation. On the other hand, a 0.07 ng/ml^2 cutoff has a good discrimination ability because of its high sensitivity and specificity.

Ethical considerations

The study was approved by the Institutional Review Board of King Saud University, Riyadh, Saudi Arabia (Ref. no.: E-18-3451; date: March 06, 2019). All study participants provided written consent before inclusion in the study. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by four independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: M.A.A., K.H.F., D.M.R.; Methodology: M.A.A., K.H.F.; Data analysis: M.A.A., A.M., W.A.; Writing–original draft preparation: M.A.A., K.H.F.; Writing – review and editing: D.M.R.

All authors have read and agreed to the published version of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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