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MRI-Derived PSA Density for Risk Stratification of PI-RADS 3 Peripheral Zone Lesions: Correlation with Radical Prostatectomy Pathology

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Abstract

Purpose

Although prostate-specific antigen density (PSAD) has been extensively investigated as an adjunctive biomarker for risk stratification of PI-RADS 3 lesions, most previous studies have relied on biopsy findings as the pathological reference standard. We aimed to evaluate the diagnostic performance of MRI-derived PSAD in patients with PI-RADS 3 peripheral zone lesions using anatomical concordance between MRI-reported lesion location and radical prostatectomy pathology

Materials and Methods

This retrospective study included consecutive patients with PI-RADS 3 lesions confined to the peripheral zone who subsequently underwent radical prostatectomy. MRI-reported lesion locations were compared with lesion locations described in radical prostatectomy pathology reports, and cases without anatomical concordance were excluded. MRI-derived prostate volume and serum prostate-specific antigen values were used to calculate PSAD. Clinically significant prostate cancer (csPCa) was defined as ISUP Grade Group ≥ 2. Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance of PSAD and determine the optimal threshold using the Youden index.

Results

A total of 59 patients met the inclusion criteria. Baseline demographic and clinical characteristics are summarized in **Table 1**. Clinically significant prostate cancer was identified in 42 patients (71.2%). Patients with csPCa demonstrated significantly higher PSAD values than those without csPCa (**Table 2**). MRI-derived PSAD demonstrated moderate discriminatory performance for identifying csPCa, with an area under the ROC curve (AUC) of **0.709** (95% CI, 0.537–0.864) (Fig. 1). The optimal PSAD threshold was **0.12 ng/mL/cc**, yielding a sensitivity of **83.3%**, specificity of **52.9%**, positive predictive value of **81.4%**, and negative predictive value of **56.3%**. Diagnostic performance across different PSAD thresholds is summarized in **Table 3**.

Conclusion

Using anatomical concordance between MRI-reported lesion location and radical prostatectomy pathology, MRI-derived PSAD demonstrated moderate ability to identify clinically significant prostate cancer in PI-RADS 3 peripheral zone lesions. A PSAD threshold of approximately **0.12 ng/mL/cc** may improve MRI-based risk stratification and support individualized biopsy decision-making in this diagnostically challenging subgroup.

INTRODUCTION

Multiparametric magnetic resonance imaging (mpMRI) has become an integral component of contemporary prostate cancer diagnosis, improving the detection of clinically significant prostate cancer (csPCa) while reducing unnecessary biopsies. To standardize prostate MRI interpretation and facilitate communication between radiologists and urologists, the Prostate Imaging Reporting and Data System (PI-RADS) was introduced and has become the internationally accepted reporting framework for prostate MRI interpretation [1]. Large prospective trials have demonstrated that MRI-based diagnostic pathways improve the detection of clinically significant disease while decreasing the diagnosis of clinically insignificant prostate cancer compared with systematic biopsy alone [2,3].

Despite these advances, management of PI-RADS 3 lesions remains one of the greatest unresolved challenges in prostate MRI. Unlike PI-RADS 1–2 and PI-RADS 4–5 lesions, which generally correspond to low-risk and high-risk categories, respectively, PI-RADS 3 lesions represent an equivocal group with substantial overlap between clinically significant and insignificant disease [10,11]. Consequently, biopsy decisions in patients with PI-RADS 3 lesions remain controversial, creating a need for reliable adjunctive biomarkers capable of improving individualized risk stratification.

PSAD has emerged as a useful adjunctive parameter for MRI-based prostate cancer risk assessment [4–7]. Several studies have demonstrated that incorporating PSAD into MRI-based diagnostic pathways may improve risk stratification and reduce unnecessary biopsies [4,7,8]. As a result, PSAD has become an increasingly important component of contemporary MRI-guided clinical decision-making.

However, an important methodological limitation exists within the current literature. Most studies evaluating PSAD have used prostate biopsy as the pathological reference standard[4,7–9]. Although biopsy remains the standard diagnostic procedure in clinical practice, it is inherently susceptible to sampling error, tumor undergrading, and lesion misclassification. Consequently, the true pathological performance of MRI-derived PSAD remains incompletely validated.

An additional limitation of previous studies is the heterogeneity of study populations. Many previous studies evaluating PI-RADS 3 lesions included lesions from both the peripheral and transition zones [10,11]. Relatively few investigations have focused specifically on PI-RADS 3 lesions confined to the peripheral zone. By restricting our cohort to peripheral zone lesions, we aimed to reduce zonal heterogeneity and provide a more focused assessment of MRI-derived PSAD in this equivocal lesion category.

To address these limitations, we evaluated MRI-derived PSAD in a homogeneous cohort of patients with PI-RADS 3 lesions confined exclusively to the peripheral zone using anatomical concordance between MRI-reported lesion location and radical prostatectomy pathology as the pathological reference framework. By excluding cases without anatomical concordance, we sought to reduce lesion misclassification and improve the internal validity of the pathological correlation. Therefore, the aim of

this study was to determine the diagnostic performance and optimal threshold of MRI-derived PSAD for predicting clinically significant prostate cancer in this clinically challenging patient population.

MATERIALS AND METHODS

Study Design and Patient Population

This retrospective observational study was approved by the Institutional Review Board and the requirement for informed consent was waived because of its retrospective design.

The institutional radical prostatectomy database was retrospectively reviewed to identify consecutive patients who underwent multiparametric prostate MRI followed by radical prostatectomy between January 2018 and December 2021. The study was designed to evaluate MRI-derived prostate-specific antigen density (PSAD) using anatomical concordance between MRI-reported lesion location and radical prostatectomy pathology.

Patients were eligible if they met all of the following criteria:

1. A single PI-RADS 3 lesion confined to the peripheral zone on preoperative multiparametric MRI.
2. Serum PSA measurement obtained before MRI.
3. MRI-derived prostate volume available for PSAD calculation.
4. Complete radical prostatectomy pathology available for lesion-level comparison.

Patients with incomplete clinical data, unavailable MRI examinations, or inconclusive pathological localization were excluded.

MRI–Pathology Anatomical Concordance

A key methodological feature of this study was the assessment of anatomical concordance between MRI-reported and pathology-reported lesion locations.

MRI reports and radical prostatectomy pathology reports were reviewed independently. Lesion localization described in each report was compared according to anatomical location (base, mid-gland, apex), laterality (right/left), and anterior-posterior distribution.

Only patients demonstrating anatomical concordance between MRI-reported and radical prostatectomy pathology-reported lesion locations were included in the final analysis. Patients with discordant lesion localization were excluded before statistical analysis to minimize lesion misclassification and reduce potential lesion misclassification.

MRI Acquisition and Interpretation

All examinations were performed according to the institutional multiparametric prostate MRI protocol.

MRI examinations were interpreted by experienced genitourinary radiologists at the time of clinical reporting.

Lesions were assigned PI-RADS scores according to Prostate Imaging Reporting and Data System Version 2 (PI-RADS v2) recommendations [1].

PSA Density Calculation

Serum PSA values obtained before MRI were retrieved from institutional medical records.

Prostate volume was calculated from MRI using the ellipsoid formula:

Volume = transverse × anteroposterior × craniocaudal diameter × 0.52

MRI-derived PSAD was calculated as:

PSAD = PSA / prostate volume

and expressed as ng/mL/cc.

Reference Standard

Whole-mount radical prostatectomy pathology served as the reference standard.

Clinically significant prostate cancer (csPCa) was defined as ISUP Grade Group ≥ 2.

Statistical Analysis

Continuous variables are presented as median and interquartile range (IQR), whereas categorical variables are expressed as frequencies and percentages.

Comparisons between csPCa-positive and csPCa-negative groups were performed using the Mann–Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, where appropriate.

Receiver operating characteristic (ROC) analysis was performed to evaluate the discriminative performance of MRI-derived PSAD.

The optimal PSAD threshold was determined using the Youden index.

Diagnostic performance was summarized by calculating the area under the ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

A two-sided p value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of **59 patients** fulfilled all eligibility criteria and demonstrated **anatomical concordance between MRI-reported lesion location and radical prostatectomy pathology**. Baseline demographic and clinical characteristics are summarized in **Table 1**.

Clinically significant prostate cancer (ISUP Grade Group ≥ 2) was identified in **42 patients (71.2%)**, whereas **17 patients (28.8%)** had ISUP Grade Group 1 disease.

Patients with csPCa demonstrated significantly higher serum PSA levels (median, 7.50 vs. 5.27 ng/mL; *p* = 0.002) and MRI-derived PSAD values (median, 0.185 vs. 0.107 ng/mL/cc; *p* = 0.013) than patients without csPCa (**Table 2**). No statistically significant differences were observed regarding patient age or MRI-derived prostate volume.

Diagnostic Performance of MRI-Derived PSAD

Receiver operating characteristic analysis demonstrated **moderate diagnostic performance** of MRI-derived PSAD for identifying clinically significant prostate cancer (Fig. 1).

The area under the ROC curve was **0.709** (95% CI, 0.537–0.864).

Using the Youden index, the optimal PSAD threshold was **0.12 ng/mL/cc**, corresponding to a sensitivity of **83.3%**, specificity of **52.9%**, positive predictive value of **81.4%**, and negative predictive value of **56.3%**.

The diagnostic performance of alternative PSAD thresholds is summarized in **Table 3**.

DISCUSSION

The present study evaluated MRI-derived PSAD in a homogeneous cohort of patients with PI-RADS 3 peripheral zone lesions **using** anatomical concordance between MRI-reported lesion location and radical prostatectomy pathology. MRI-derived PSAD demonstrated moderate ability to identify clinically significant prostate cancer, yielding an AUC of **0.709**, with an optimal threshold of **0.12 ng/mL/cc**.

Management of PI-RADS 3 lesions remains one of the most challenging issues in prostate MRI because these lesions represent an equivocal diagnostic category[10–11]. Consequently, several investigators have proposed incorporating PSAD into MRI-based biopsy decision algorithms [4,7,8,12].

An important methodological consideration in studies evaluating MRI-visible lesions is the pathological reference standard. Most previous investigations have used prostate biopsy, which remains susceptible to sampling error, tumour undergrading, and imperfect lesion localization. Furthermore, prostate cancer is frequently multifocal, and clinically significant disease may be present outside the MRI-visible index lesion [13,14]. Consequently, pathological cancer identified elsewhere in the prostate should not automatically be attributed to the PI-RADS 3 lesion under investigation.

To reduce this potential source of misclassification, we compared the anatomical localization described in MRI reports with that reported in radical prostatectomy pathology and included only patients demonstrating lesion-level anatomical concordance. Importantly, this approach was not intended to alter the diagnostic performance of PSAD, which is a patient-level biomarker, but rather to improve the internal validity of lesion-specific pathological correlation by minimizing erroneous attribution of clinically significant disease to unrelated tumour foci [13,14].

Another strength of the present study is the inclusion of an exclusively peripheral zone PI-RADS 3 cohort. Previous studies evaluating PI-RADS 3 lesions have frequently included lesions from both the peripheral and transition zones [10,11]. Restricting our analysis to peripheral zone lesions reduced zonal heterogeneity and allowed a more focused evaluation of MRI-derived PSAD.

Recent studies continue to demonstrate the potential value of PSA density–based approaches for risk stratification of PI-RADS 3 lesions [12,16]. The optimal PSAD threshold identified in our cohort (0.12 ng/mL/cc) closely approximates the 0.13 ng/mL/cc threshold reported by Mjaess et al. [12]. Importantly, however, most contemporary studies remain biopsy-based, whereas our cohort was restricted to patients with anatomically concordant radical prostatectomy pathology.

Nevertheless, MRI-derived PSAD demonstrated only moderate discriminatory performance and should not be considered an isolated determinant of biopsy decisions. Rather, PSAD should be interpreted together with MRI findings, clinical characteristics, and patient preferences within a multidisciplinary decision-making process.

Several limitations should be acknowledged. First, this was a retrospective single-center study with a relatively small sample size. Second, inclusion was limited to patients who underwent radical prostatectomy, introducing selection bias and limiting generalizability. Third, excluding patients without anatomical MRI–pathology concordance further reduced the sample size and may have introduced additional selection bias. Finally, lesion localization was based on comparison of MRI and pathology reports rather than formal image-to-specimen co-registration[15]. Therefore some degree of localization error cannot be excluded

CONCLUSION

MRI-derived PSAD demonstrated moderate diagnostic performance for identifying clinically significant prostate cancer in patients with PI-RADS 3 peripheral zone lesions.

By restricting the analysis to patients demonstrating anatomical concordance between MRI-reported lesion location and radical prostatectomy pathology, we sought to improve the internal validity of lesion-specific pathological correlation while minimizing potential misclassification related to multifocal prostate cancer.

MRI-derived PSAD may therefore represent a useful adjunctive biomarker for individualized biopsy decision-making when interpreted together with multiparametric MRI findings and other established clinical risk factors.

Declarations

Author Contribution

E.Y. contributed to the conceptualization and design of the study, data collection, data analysis, statistical analysis, interpretation of the results, and preparation of the original manuscript. R.T. supervised the study, provided scientific and methodological guidance, and critically reviewed and revised the manuscript. Both authors reviewed and approved the final manuscript.

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Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures

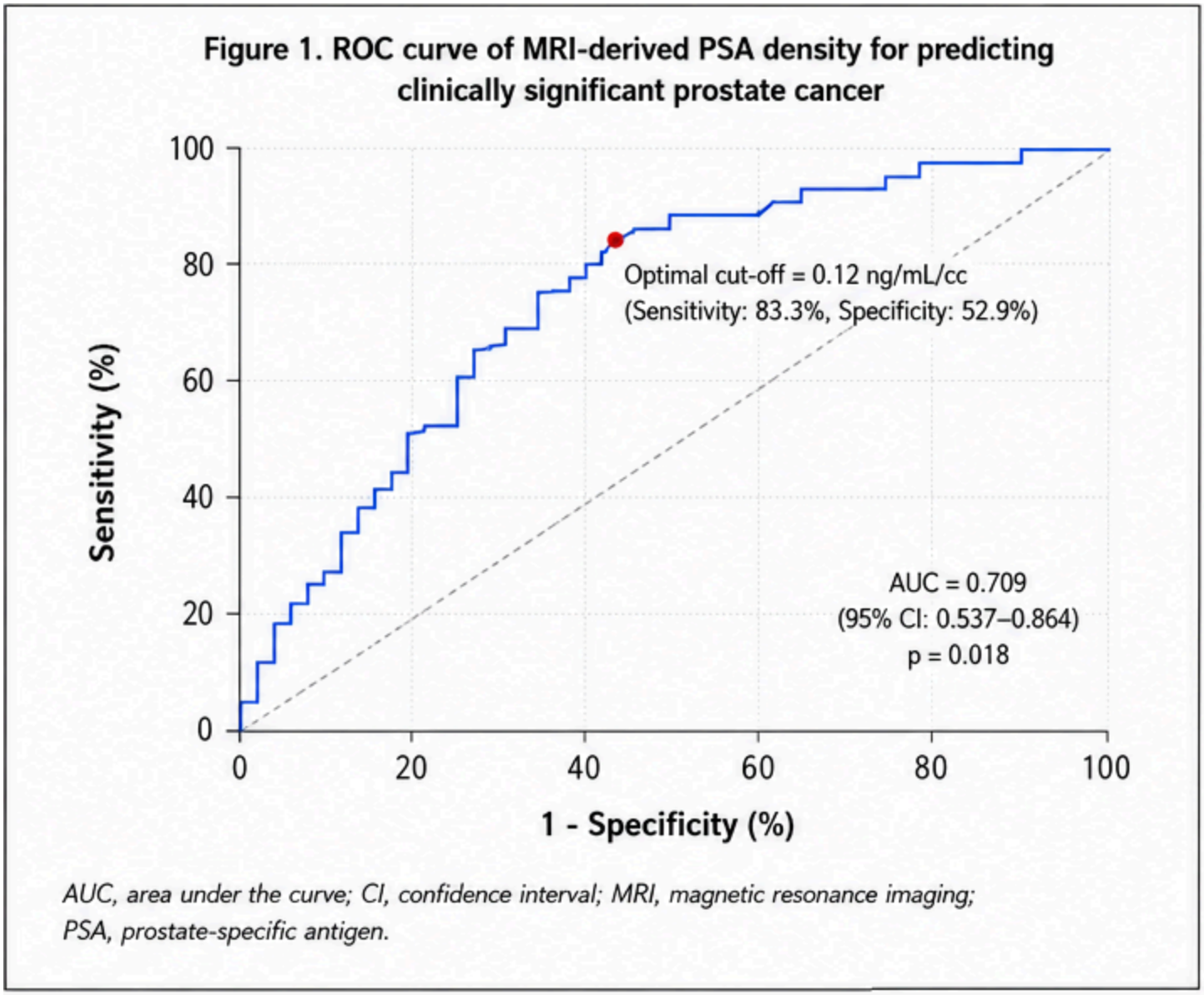


Figure 1

See image above for figure legend.

Supplementary Files

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- table11.png
- table21.png
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