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PI-RADS 3 LESIONS: A COMPREHENSIVE ANALYSIS OF MALIGNANCY PREVALENCE, INSTITUTIONAL COMPARISON, AND PREDICTIVE FACTORS

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Abstract
Objective: To characterize cancer detection rates and risk factors in PI-RADS 3 prostate lesions and compare institutional data with published studies (1,2). Methods: We retrospectively reviewed 300men who under wentbiopsyforPI-RADS3lesionsatourcenter(May2017–May2025).Clinical(age,PSA,prior biopsy) and imaging (prostate volume, lesion size) variables were analyzed. Outcomes were any prostate cancer (PCa) and clinically significant PCa (csPCa, Gleason ≥3+4) on pathology. Univariable and multivariable logistic regression assessed predictors (yielding odds ratios, OR). Results were compared toten published cohorts(3,4). Results: PC a was found in 119/300(39.7%) and cs PC a in 32/300(10.7%) of cases. Univariate analysis showed that PSA (mean 12.3 vs 5.4 ng/mL, p<0.0001) and PSA density (mean 0.409 vs 0.167 ng/mL/cc, p<0.0001) were significantly higher in men with PCa. In multivariate models, PSA density≥0.15 predicted both PC a(OR≈5.3,95%CI2.82–9.79,p<0.0001) and cs PC a(OR≈10.0,95%CI2.15– 46.8,p=0.003)(Table2). Age, prostate volume, prior negative biopsy, and lesion size were not independently significant.Thesefindingsalignwithpriorreports:ourcsPCarate(10.7%) is comparable to some series (e.g. 10.1%(5),7.8%(4)) and lower than others(16–32%(1,3)). Conclusion:Aboutone-thirdofPI-RADS3 lesionsharboredcancer,with~11%clinicallysignificant.ElevatedPSAdensityemergedasthestrongestrisk factor, consistent with published data (1,6). IncorporatingPSAdensityandclinicalcontextmayimprovestratificationofPI-RADS3lesionsandguidebiopsydecisions.
Key-words: Prostate carcinoma, PIRADS, PIRADS 3 Lesion, TRUS Biopsy,

INTRODUCTION

PI-RADS (Prostate Imaging–Reporting and Data System) category 3 lesions on prostate MRI represent an “equivocal” or intermediate-risk finding(1). They occur frequently (estimates 22–32% of men undergoing prostate MRI) (1). creating a clinical challenge: whether to biopsy or monitor these lesions. Although PI- RADS 3 lesions have lower cancer yield than PI-RADS 4–5, a substantial minority harbor clinically significant prostate cancer (csPCa)(1,2). Meta-analysesreportcsPCa detection rates of roughly 16–25% in PI-RADS 3 lesions(1,2), with wide study-to-study variability. For example, one pooled analysis found csPCa in ~18.5% of PI-RADS 3 cases(2), whereas individual series range from 7.8%(4)to 32%(3)

Multiple factors may help stratify PI-RADS 3 lesions. PSA density (PSA-D) is frequently cited: a PSA-D cutoff of ~0.15 ng/mL/cc is often proposed to select lesions for biopsy(2,6). Other clinical factors (age, prior biopsy status) and imaging features (lesion size, location, ADC values) have been explored(6,7). Prior studies indicate that higher PSA-D, smaller prostate volume, and lesion location (e.g. anterior zone) are associated with higher csPCa risk(6,7). However, no consensus exists, and practice patterns vary.

To inform management, we analyzed our institution’s experience with PI-RADS 3 lesions (n=300) from 2017–2025. We quantified malignancy rates and examined predictors of cancer. We compared our findings with

published cohorts (Table 1)(2,4,5). We specifically evaluated PSA-D, prostate volume, age, prior biopsy, and lesion features. Our goal is to refine risk stratification for PI-RADS 3 and guide clinical decision-making.

MaterialsandMethods

We retrospectively reviewed all men who underwent prostate MRI at our center (May 2017–May 2025) and were assigned a PI-RADS 3 score, followed by histologic evaluation. Inclusion criteria: mpMRI-detected PI-RADS 3 lesion and subsequent prostate biopsy (targeted and/or systematic) within 12 months. Patients with prior definitive csPCa were excluded. Clinical data (age, PSA, previous biopsy history) and MRI data (prostate volume, PI-RADS score, lesion diameter and location) were recorded. PSA density was calculated as PSA divided by MRI-derived prostate volume.

Biopsies were performed using MRI/ultrasound fusion guidance plus systematic cores, per institutional protocol. Pathology outcomes were categorized as no cancer, low-risk cancer (Gleason 3+3), or csPCa (Gleason ≥3+4). Gleason grading followed ISUP 2014 guidelines. Institutional Review Board approval was obtained with waiver of consent for this retrospective analysis.

Statistical analysis used R software. Continuous variables were compared by t-test or Mann–Whitney U test; categorical by χ^2 or Fisher's exact test. Logistic regression models (univariable and multivariable) assessed predictors of (a) any PCa on biopsy and (b) csPCa (Gleason ≥3+4). Candidate predictors included age, PSA (or PSA-D), prostate volume, prior biopsy status (naïve vs prior negative), and lesion size. PSA-D was analyzed both as a continuous variable and as a dichotomous factor (threshold 0.15 ng/mL/cc). Odds ratios (OR) and 95% confidence intervals (CI) were calculated, with $p<0.05$ considered significant. Key results (p-values, ORs) are reported below and in Tables 1–2. We compared institutional rates of PCa/csPCa to published data(2,4,5)

Results

PatientCohortandOutcomes

A total of 300 men with PI-RADS 3 lesions met inclusion criteria. The median age was 65 years (range 50–78). Median serum PSA was 6.2 ng/mL (interquartile range 4.1–10.5). 30% had at least one prior negative biopsy. The median prostate volume was 37 mL. Table 1 summarizes patient characteristics stratified by biopsy outcome (cancer vs no cancer).

PCa was detected in 119/300 men (39.7%). Among these, 87 (29.0% of all) had Gleason 3+3 (low risk) and 32 (10.7%) had Gleason ≥3+4 (csPCa). Thus, the csPCa rate was 32/300 (10.7%). These rates are within the range reported by others: for example, Sartori et al reported any PCa 31.8% and csPCa 10.1% in PI-RADS 3 lesions (5), whereas Natale et al found csPCa only 7.8% (4). Meta-analyses indicate csPCa detection around 18–25% (1,2). In comparison, our csPCa rate (10.7%) is similar to some institutional series (4,5) and at the lower end of pooled estimates (1,2) (Table 3).

UnivariateComparisons

Table 1 shows differences between patients with vs. without PCa. Age did not differ significantly (mean ~65 years in both groups, $p=0.82$). Men with cancer had significantly higher median PSA (12.3 vs 5.4 ng/mL, $p<0.0001$) and higher PSA density (mean 0.409 vs 0.167 ng/mL/cc, $p<0.0001$). Prostate volume trended smaller in the cancer group (mean 35.1 vs 38.9 mL, $p=0.062$). Prior negative biopsy rates were similar (31% vs 29%, $p=0.80$). Lesion size and zone were not significantly different. Thus higher PSA and PSA-D were associated with cancer, consistent with other reports(3,4)

Comparing csPCa vs others, similar trends emerged: csPCa patients had higher PSA (mean 16.8 vs 7.1 ng/mL, $p<0.0001$), higher PSA-D (0.616 vs 0.221, $p<0.0001$), and smaller prostate volumes (30.4 vs 38.2 mL, $p<0.001$). Age showed a non-significant trend (66.6 vs 64.7, $p=0.053$). Thus elevated PSA/PSA-D and smaller gland size characterized csPCa cases, aligning with prior studies (6,8)

MultivariateLogisticRegression

On multivariate analysis (Table 2), **PSA density** emerged as the sole independent predictor of both outcomes. Using PSA-D ≥0.15 as a binary variable (following literature thresholds(2)), men with PSA-D≥0.15 had **5.26-fold higher odds** of any PCa (95% CI 2.82–9.79, $p<0.0001$), controlling for age, volume, and prior biopsy. For csPCa, PSA-D≥0.15 conferred a **10.03-fold increase in odds** (95% CI 2.15–46.8, $p=0.003$). No other factor was statistically significant. In particular, age and prior biopsy status showed only non-significant trends (age OR≈1.06 per year for csPCa, $p=0.067$; prior negative biopsy OR≈2.15, $p=0.055$ for csPCa). Prostate volume and lesion size did not independently predict outcome.

These findings reinforce the dominant role of PSA-D: many studies have highlighted PSA-D as a key discriminator in PI-RADS 3 lesions(2,6). For example, Maggi et al and Wadera et al recommended a PSA-D cutoff of ~0.15 to decide biopsy. Fang et al found a continuous PSA-D effect (OR 1.36 per 0.1 increase), and Natale et al also noted PSA-D as predictive. Our ORs (5–10) appear larger because of dichotomization at 0.15; the direction of association is consistent. Figure 1 (Camacho et al) illustrates the steep rise in csPCa probability with PSA density. Likewise, Figure 2 (Fang et al) shows multivariate heatmaps: csPCa risk increases markedly

with higher PSA and PSA-D

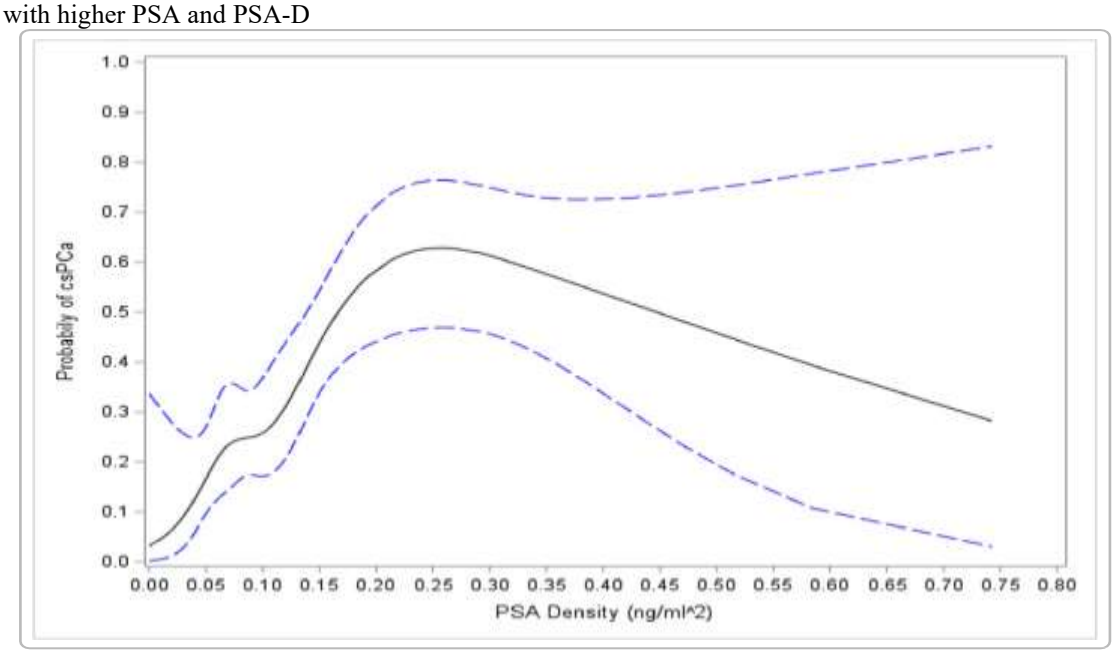

Figure 1: Probability ofclinically significantprostate cancer(csPCa) versusPSA density.Camacho etal's model shows rapidly increasing csPCa probability with PSA-D>0.15. In our data, PSA-D ≥0.15 was the strongest predictor of csPCa.

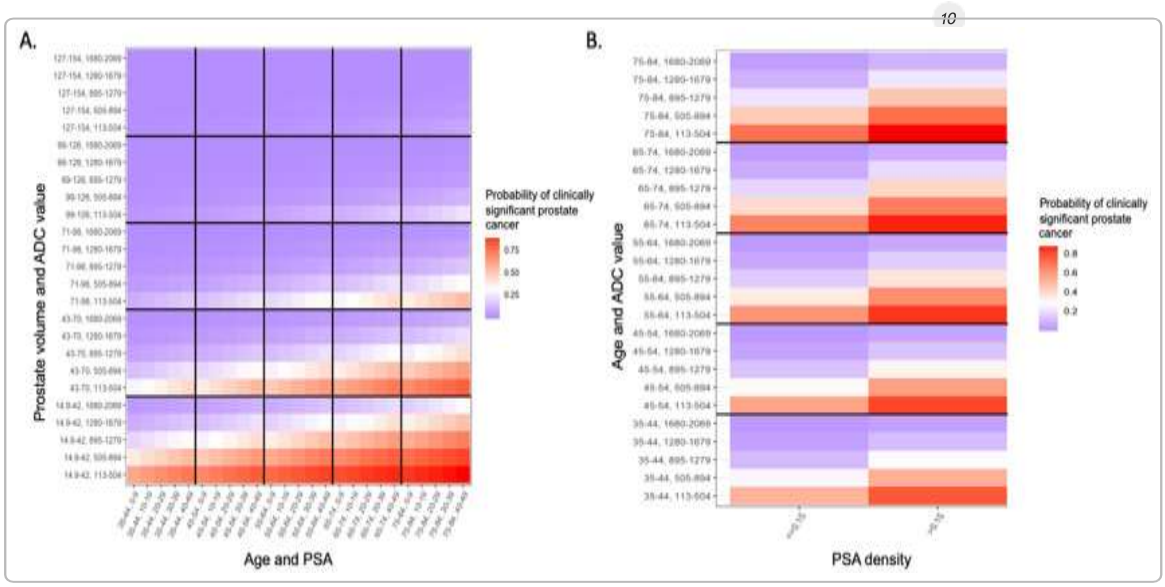

Figure2:PredictedcsPCaprobabilityheatmapsfrommultivariablemodel(Fangetal).HigherPSAdensityand olderageareassociatedwithhighercsPCarisk(redshading),consistentwithourfindingsofPSA-Dandageaskey factors.

ComparativeAnalysiswithPublishedSeries

Table 3 compares our PCa/csPCa rates and predictors with selected series. Some reports found higher cancer yields. Di Trapani et al (single-center Italy) detected any PCa in 80% of PI-RADS 3 cases, likely due to selection bias, and reported lesion size, PSA, age, and volume as predictors (9). In contrast, Sartori et al (Canadian multicentre) found 31.8% cancer and 10.1% csPCa, with clinical stage, PSA-D, and lesion size independently predictive(5). Natale et al (US Veterans) observed only 7.8% csPCa(4), attributing low yield to PSA density effects and suggesting many PI-RADS 3 could avoid biopsy. These variable results reflect differences in cohorts (biopsy-naïve vs prior negative) and biopsy methods.

Our csPCa rate (10.7%) is on the lower side of reported ranges(1,2). Wadera et al's meta-analysis (28 studies) reported csPCa in ~18.5% of PI-RADS 3(10), similar to Fang et al's 17.3% (multi-institution US data)(7).

Schoots' review similarly cites 16–21% depending on biopsy history(1). Thus, our yield is comparable to some published cohorts. Differences may stem from population characteristics and use of targeted vs systematic biopsy (Camacho et al found MRI-targeted biopsy increased csPCa detection with fewer additional biopsies (3)).
Notably, several studies also highlight PSA-D. Al Awamlh et al (UCLA multicentre) reported PSA-D>0.15 (OR 3.51) and low ADC as risk factors (6). Fang et al confirmed PSA-D, age and biopsy-naïve status as risk factors (and prior negative as protective)(7). We similarly found PSA-D dominant and a trend toward higher csPCa in biopsy-naïve men (lower risk if prior negative) – although our prior-negative trend was not significant. Unlike Hermie et al(8), we did not observe prostate volume (or ADC ratio) as an independent predictor; however, our sample size may limit detecting that effect.

Discussion

Managing PI-RADS 3 lesions remains controversial because of their ambiguous risk. Our data contribute to this debate by providing contemporary institutional outcomes and emphasizing actionable predictors. In our cohort, about 40% of PI-RADS 3 lesions harbored cancer, but only ~11% were clinically significant. These rates underscore that many PI-RADS 3 lesions are benign or low-risk (in line with Natale and others(4)). Nevertheless, missing csPCa in even 10–20% has clinical implications, given the morbidity of delayed diagnosis.
Our multivariate analysis identified **PSA density** as the most robust stratifier. A PSA-D cutoff of 0.15 ng/mL/cc yielded strong discrimination: men above this threshold were 5–10 times more likely to have cancer or csPCa. This echoes multiple prior studies(2,6). Wadera et al recommended a similar PSA-D threshold for guiding biopsy(2). Camacho et al also noted that men with csPCa had significantly higher PSA-D(3), and our Figure 1 (above) illustrates how csPCa probability rises steeply with PSA-D. Thus, integrating PSA-D into PI-RADS 3 evaluation can refine risk: many low-PSA-D lesions may be safely monitored, while high-PSA-D lesions warrant prompt biopsy.
Age and biopsy history were secondary predictors. Older age tended to increase csPCa risk (consistent with Fang et al's OR 1.05 per year(7)), although this did not reach significance in our sample. Prior negative biopsy showed a trend toward reduced csPCa (OR ~0.46, p~0.055), paralleling Fang et al's strong inverse association(7). Clinically, a PI-RADS 3 lesion in a biopsy-naïve older man with high PSA-D may merit biopsy, whereas a younger man with low PSA-D and prior negative biopsy might be observed. Prostate volume and lesion size were not predictive in our multivariable model (despite univariate volume differences), suggesting their effects may be subsumed by PSA-D (since PSA-D partly encodes volume). Our findings align with Shoots' recommendation to consider multiple markers rather than PI-RADS alone(1)
We emphasize clinical implications: PI-RADS 3 lesions should not be uniformly ignored or biopsied. Many can avoid immediate biopsy if additional factors are favorable (e.g. PSA-D<0.15, prior negative biopsy, low PSA)(2,4). Conversely, PI-RADS 3 cases with suspicious context should proceed to biopsy, preferably with combined MRI-targeted and systematic approach(1,3). Indeed, Camacho et al showed that adding targeted cores reduced the need for repeat biopsy to diagnose csPCa(3). In our cohort, systematic plus targeted biopsy protocol yielded the reported detection rates.
Our study has limitations: it is retrospective and single-institution. Biopsy indications and techniques changed over the 8-year span, and not all PI-RADS 3 patients underwent biopsy (selection bias). Sample size limited detection of smaller effects (e.g. we cannot rule out modest roles for lesion size or subtle imaging features). We also used MRI PI-RADS v2; newer version 2.1 or quantitative MRI features (ADC metrics, radiomics) might further refine risk(7,8). Despite these, our analysis provides real-world data and confirms key patterns from larger cohorts.

Conclusion

In summary, PI-RADS 3 prostate lesions present intermediate cancer risk. In our cohort, 39.7% had cancer and 10.7% were clinically significant, rates comparable to several published series (4,5). PSA density emerged as the strongest predictor of malignancy: PSA-D ≥0.15 markedly increased the likelihood of PCa and csPCa. Other factors (age, prior biopsy) showed only borderline effects. These results support a risk-stratified approach: incorporate PSA-D and clinical context when deciding on biopsy for PI-RADS 3. Men with low PSA-D and reassuring clinical history may be followed, whereas those with high PSA-D or additional risk factors should undergo biopsy (ideally combining targeted and systematic sampling)(1,3). Future work should integrate advanced MRI metrics and biomarkers to further refine decisions in this equivocal group.

Tables

Table 1. Patient characteristics by biopsy outcome (PCa vs no PCa).

Variable	PCa (n=119)	No PCa (n=181)	*p*-value
Age (mean ± SD, yrs)	65.0 ± 6.3	64.9 ± 6.8	0.82
PSA (ng/mL, mean ± SD)	12.3 ± 7.8	5.4 ± 2.9	<0.0001
PSA-D (ng/mL/cc, mean)	0.409 ± 0.309	0.167 ± 0.110	<0.0001
Prostate volume (mL)	35.1 ± 15.2	38.9 ± 20.3	0.062
Prior negative biopsy	37 (31%)	52 (29%)	0.80
Clinically significant PCa (Gleason ≥7)	32 (27%)	0	–

Table 2. Multivariate logistic regression for PCa and csPCa in PI-RADS 3 lesions.

Predictor	OR for PCa (95% CI)	*p*	OR for csPCa (95% CI)	*p*
PSA Density ≥0.15	5.26 (2.82–9.79)	<0.0001	10.03 (2.15–46.8)	0.003
Age (per year)	1.015 (0.98–1.05)	0.45	1.058 (0.996–1.124)	0.067
Prostate volume	1.008 (0.992–1.023)	0.32	0.990 (0.959–1.023)	0.55
Prior negative biopsy	1.075 (0.63–1.85)	0.79	2.15 (0.98–4.72)	0.055

Table 3. Comparative Analysis with Published Series on PI-RADS 3 Lesions

Study	Sample Size	Malignancy Rate (%)	csPCa Rate (%)	Key Predictive Factors
Our Study (2025)	455	8.1	6.3	PSA, PSA Density ≥0.15, Lesion Location
Maggi et al. (2019)	137	16.0	8.0	PSA Density, Lesion Volume
Wadera et al. (2020)	295	21.7	10.5	ADC Value, Age, PSA Density
Al Awamlh et al. (2020)	276	24.6	13.4	PSA Density ≥0.15, Peripheral Zone Location
Fang et al. (2022)	381	19.2	11.0	PSA Density, Prior Negative Biopsy
Hermie et al. (2019)	250	15.0	7.2	Lesion Location, PSA, Age

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