ARTICLE

Clinical Resaerch

Refining clinically relevant cut-offs of prostate specific antigen density for risk stratification in patients with PI-RADS 3 lesions

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BACKGROUND: Prostate Imaging Reporting and Data System (PI-RADS) 3 lesions, identified through multiparametric magnetic resonance imaging (mpMRI), present a clinical challenge due to their equivocal nature in predicting clinically significant prostate cancer (csPCa). Aim of the study is to improve risk stratification of patients with PI-RADS 3 lesions and candidates for prostate biopsy.
METHODS: A cohort of 4841 consecutive patients who underwent MRI and subsequent MRI-targeted and systematic biopsies between January 2016 and April 2023 were retrospectively identified from independent prospectively maintained database. Only patients who have PI-RADS 3 lesions were included in the final analysis. A multivariable logistic regression analysis was performed to identify covariables associated with csPCa defined as International Society of Urological Pathology (ISUP) grade group ≥2. Performance of the model was evaluated using the area under the receiver operating characteristic curve (AUC), calibration, and net benefit. Significant predictors were then selected for further exploration using a Chi-squared Automatic Interaction Detection (CHAID) analysis.
RESULTS: Overall, 790 patients had PI-RADS 3 lesions and 151 (19%) had csPCa. Significant associations were observed for age (OR: 1.1 [1.0–1.1]; $p = 0.01$) and PSA density (OR: 1643 [2717–41,997]; $p < 0.01$). The CHAID analysis identified PSAd as the sole significant factor influencing the decision tree. Cut-offs for PSAd were 0.13 ng/ml/cc (csPCa detection rate of 1% vs. 18%) for the two-nodes model and 0.09 ng/ml/cc and 0.16 ng/ml/cc for the three-nodes model (csPCa detection rate of 0.5% vs. 2% vs. 17%).
CONCLUSIONS: For individuals with PI-RADS 3 lesions on prostate mpMRI and a PSAd below 0.13, especially below 0.09, prostate biopsy can be omitted, in order to avoid unnecessary biopsy and overdiagnosis of non-csPCa.

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INTRODUCTION

In the last decade, multiparametric magnetic resonance imaging (mpMRI) has emerged as a crucial instrument, empowering urologists with optimized diagnostic capabilities and improved triage methods for patients with prostate cancer (PCa). Prostate mpMRI has solidified its position as the foremost modality in PCa diagnosis, demonstrating outstanding sensitivity in clinically significant prostate cancer (csPCa) detection and a robust negative predictive value. This advancement has notably contributed to minimizing unnecessary biopsies in the management of PCa [1–4].

The Prostate Imaging Reporting & Data System (PI-RADS) initially described in 2011 has been widely used by radiologists as an objective score to standardize reporting prostate lesions [5].

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Patients diagnosed with
prostate cancer by targeted
and systematic biopsies
(n=4841)
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Exclusion for patients with:
- PI-RADS 1-2 and 4-5 lesions
- Incomplete data
(n=4051)
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Patients with PI-RADS 3
lesions on MRI
(n=790)
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Patients with clinically
significant prostate cancer
(n=151)
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Patients without clinically
significant prostate cancer
(n=639)
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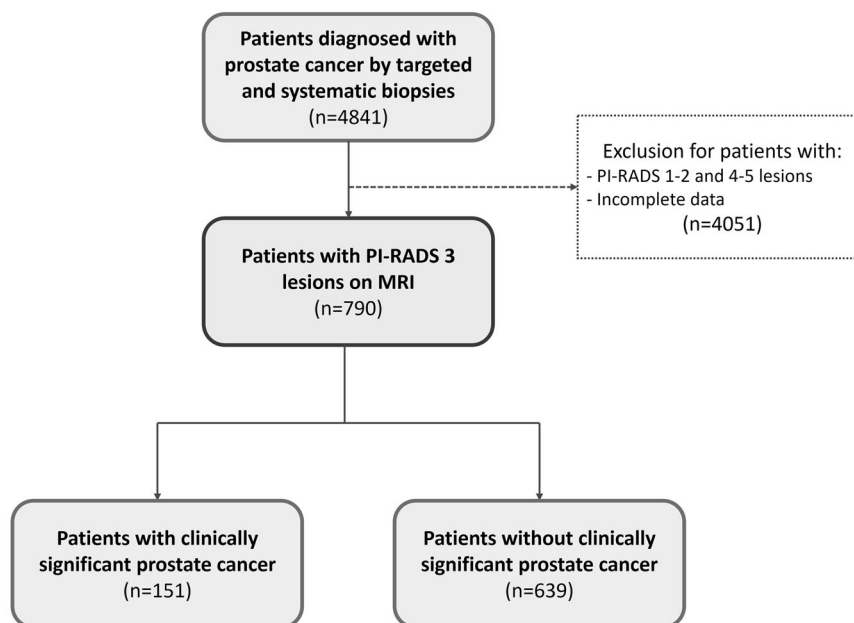
Fig. 1   Flowchart of the study. A total of 790 consecutive patients were enrolled in the study among which 19% were diagnosed with csPCa.

The European Association of Urology (EAU) guidelines currently endorse MRI before prostate biopsies and recommend prostate biopsies in patients with PI-RADS ≥ 3 lesions, depending on the value of the Prostate Specific Antigen (PSA) density [6]. However, these values were developed in the pre-MRI-targeted biopsy era.

Approximately 45% of lesions with a PI-RADS ≥ 3 are found to have an International Society of Urological Pathology (ISUP) ≥ 2, but mostly in case of PI-RADS 4–5 tumors [7]. In case of equivocal MRI lesions defined as PI-RADS 3, only 20% of patients have csPCa highlighting the need for a better risk stratification to avoid unnecessary biopsy [8]. Moreover, the real occurrence of csPCa following an MRI-targeted biopsy in PI-RADS 3 lesions has been shown to differ among different patient subgroups depending on the lesion volume, ranging from 4% to 29% [9].

In the present study, we aimed to sub-stratify patients identified from a large European cohort of patients who underwent MRI-targeted and systematic biopsies for PI-RADS 3 lesions and to identify predictive factors of csPCa.

MATERIALS AND METHODS
Population
Data from 4841 consecutive patients who underwent MRI and subsequent MRI-targeted and systematic biopsies between January 2016 and April 2023 were retrospectively identified from an independent prospectively maintained and board-approved databases at fifteen European tertiary referral-centers.

MRI and biopsy procedures
All prebiopsy MRI were performed within 6 months before biopsy, following the European Society of Urogenital Radiology guidelines, and scored using the PI-RADS version 2.1 protocols by local dedicated genitourinary radiologists [10, 11]. MRIs done before 2019 were re-evaluated to ensure consistency. Prostate biopsies were carried out by dedicated urologists and exclusively with the KOELIS system (KOELIS®, La Tronche, France) allowing elastic MRI-tridimensional ultrasound images fusion. A minimum of three MRI-targeted cores per target were taken combined with concomitant bilateral systematic biopsy. A dedicated uropathologist evaluated the biopsy cores following the ISUP 2014 recommendation [12].

Selection criteria
Only patients who have PI-RADS 3 lesions on MRI were included in the final analysis. Patients with missing information on clinical, radiological, and biopsy data were excluded. Other missing data on demographic and secondary variables were managed by multiple imputations.

Data and outcomes
Covariables which were retrieved were: age, PSA, clinical stage at digital rectal exam (DRE), prostate volume calculated using ellipsoidal formula on prebiopsy MRI, PSA density (PSAd), maximum MRI lesion diameter, localization of the MRI lesion in the prostate, previous negative biopsy status, biopsy approach, and number of cores taken. The primary outcome was the identification of covariate significantly associated with a risk of csPCa defined as an ISUP grade group ≥2 on MRI-targeted and systematic biopsies.

Statistical analysis
Descriptive statistics were presented using frequency for categorical variables, and median with interquartile range (IQR) for continuous variables.

A multivariable logistic regression analysis was performed in order to identify covariables associated with csPCa within patients with PI-RADS 3 lesions on MRI. The minimum sample size for the multivariable logistic regression analysis was determined using two methods: (1) the first method, a classical approach, required a number of events equal to 10 subjects per included variable, and (2) the second method followed the criteria proposed by Riley et al. [13]. The more restrictive of the two methods was selected.

Three models were created. The first model focused solely on clinical factors, incorporating age, PSAd, and DRE status (normal vs. abnormal). The second model integrated both clinical and radiological parameters, introducing index lesion diameter and index lesion localization. The third model expanded further by incorporating the previous biopsy status (positive vs. negative previous biopsy). Performance of the models was evaluated in terms of discrimination using the area under the receiver operating characteristic curve (AUC). To reduce overfit bias and for internal validation, 1000 bootstrap resamples were performed. The extent of over- or under-estimation of the confirmed vs. predicted csPCa was analyzed graphically using a calibration plot. The net clinical benefit was evaluated on decision-curve analysis (DCA). Dependent covariables found to be significant on the logistic regression analysis were then selected for further exploration using a Chi-squared Automatic Interaction Detection (CHAID) analysis. CHAID constructs a decision tree by iteratively partitioning the patient dataset into subgroups based on variables identified as influential in predicting the studied outcome. It determines the variables most pivotal in creating meaningful subgroups within the PI-RADS 3 cohort. It then generates nodes in the decision tree, with each node representing a patient subgroup defined by specific characteristics.

Table 1. Baseline characteristics of the included cohort of patients.

Variable		Whole population (n = 790)	Clinically significant cancer (n = 151)	No clinically significant cancer (n = 639)
Age, year (IQR)		65 (60–70)	68 (63–72)	65 (59–69)
PSA, ng/ml (IQR)		6.4 (4.8–9.4)	7.4 (5.6–10.5)	6.2 (4.7–9.2)
Positive digital rectal exam, n(%)		85 (11%)	24 (16%)	61 (10%)
Prostate volume, cc (IQR)		53 (40–74)	37 (29–48)	56 (44–77)
PSA density, ng/ml/cc (IQR)		0.13 (0.09–0.18)	0.19 (0.15–0.28)	0.11 (0.08–0.16)
Lesion diameter in mm (IQR)		10 (8–13)	10 (8–12)	10 (8–14)
Laterality of index lesion	Left	364 (47%)	69 (48%)	295 (47%)
	Mid	76 (10%)	6 (5%)	68 (11%)
	Right	328 (43%)	68 (47%)	260 (42%)
Antero-posterior location of index lesion	Anterior	203 (28%)	36 (26%)	167 (28%)
	Mid	92 (13%)	15 (11%)	77 (13%)
	Posterior	428 (59%)	85 (63%)	343 (59%)
Base-apex location of index lesion	Apex	206 (28%)	39 (29%)	167 (28%)
	Base	137 (19%)	28 (21%)	109 (18%)
	Mid	352 (48%)	57 (43%)	295 (50%)
	Mid-apex	16 (2%)	4 (3%)	12 (2%)
	Mid-base	17 (2%)	6 (4%)	11 (2%)
Previous negative biopsy, n(%)		184 (23%)	27 (18%)	157 (25%)
Biopsy technique, n(%)	Transrectal	325 (41%)	60 (40%)	265 (41%)
	Transperineal	465 (59%)	91 (60%)	374 (59%)
Number of biopsy cores	Targeted	3 (3–4)	3 (3–4)	3 (3–4)
	Systematic	9 (7–12)	12 (12–13)	9 (7–12)
Highest ISUP GG on systematic biopsy, n(%)	No PCa	568 (72%)	38 (25%)	530 (83%)
	1	117 (15%)	9 (6%)	109 (17%)
	2	58 (7%)	57 (38%)	0 (0%)
	3	27 (3%)	27 (18%)	0 (0%)
	4	13 (2%)	13 (9%)	0 (0%)
	5	6 (1%)	6 (4%)	0 (0%)
Highest ISUP GG on MRI-targeted biopsy, n(%)	No PCa	554 (72%)	38 (25%)	528 (85%)
	1	110 (14%)	9 (6%)	96 (15%)
	2	53 (7%)	57 (38%)	0 (0%)
	3	32 (4%)	27 (18%)	0 (0%)
	4	11 (1%)	13 (9%)	0 (0%)
	5	7 (1%)	6 (4%)	0 (0%)
Highest ISUP GG overall, n(%)	0	480 (61%)	0 (0%)	480 (75%)
	1	159 (20%)	0 (0%)	159 (25%)
	2	80 (10%)	80 (53%)	0 (0%)
	3	42 (5%)	42 (28%)	0 (0%)
	4	19 (2%)	4 (13%)	0 (0%)
	5	9 (1%)	5 (6%)	0 (0%)

IQR interquartile range, *PSA* prostate specific antigen, *TRUS* transrectal ultrasound, *ISUP GG* International Society of Urological Pathology Grade Group.

As the algorithm progresses, the tree branches into different paths, discerning key factors influencing the prediction of csPCa. The process continues until further splitting ceases to significantly enhance the prediction of csPCa within patients with PI-RADS 3 lesions. The terminal nodes, situated at the endpoints of the branches, represent the final, distinct subgroups with varying risks. The model was tested using a different number of nodes (two vs. three). The model with the highest discerning capability was retained. Missing data were considered missing at random, and a complete-case analysis was performed. All statistics were performed using STATA (StataCorp®, Texas, USA) software using packages *pmsampsize*, *logit*, and *chaid*. A *p*-value < 0.05 was considered as statistically significant.
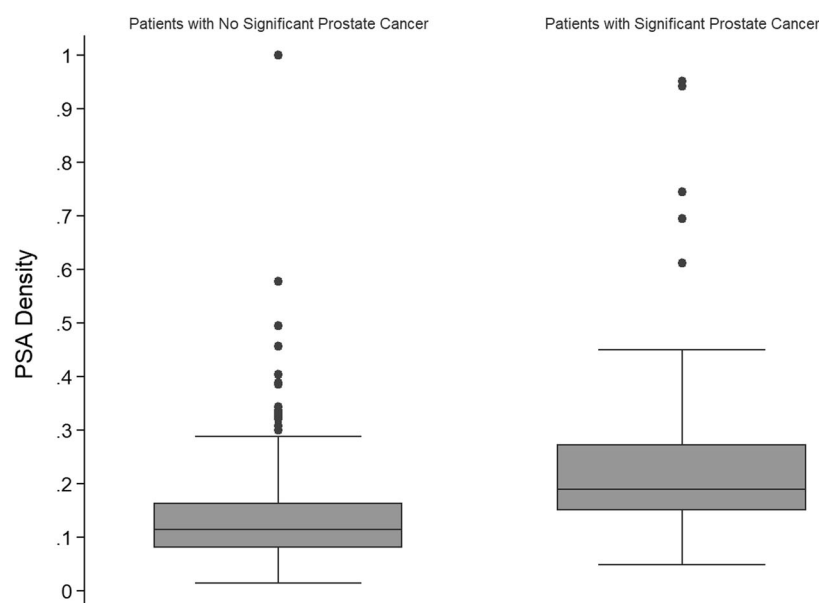
Fig. 2 PSA density. Values of PSA density in patients with/without clinically significant prostate cancer with PI-RADS 3 lesions on MRI.

Table 2. Results of the multivariable logistic regression.

			Model 1		Model 2		Model 3	
			OR [95%CI]	p-value	OR [95%CI]	p-value	OR [95%CI]	p-value
Clinical parameters	PSA density		**83 [10–699]**	**<0.001**	**1434 [60–34,049]**	**<0.001**	**1643 [2717–41,997]**	**<0.001**
	Age		1.0 [0.9–1.1]	0.05	**1.1 [1.0–1.1]**	**0.02**	**1.1 [1.0–1.1]**	**0.01**
	Digital rectal exam status		2.2 [0.8–6.2]	0.07	2.2 [0.8–6.3]	0.13	2.1 [0.7–5.9]	0.17
MRI parameters	Index lesion diameter		–	–	0.9 [0.8–1.0]	0.212	0.9 [0.9–1.0]	0.19
	Index lesion localization	Anterior	–	–	ref	ref	ref	ref
		Mid	–	–	2.0 [0.7–5.7]	0.18	2.3 [0.8-6.6]	0.12
		Posterior	–	–	1.8 [0.7–4.4]	0.2	1.8 [0.7–4.5]	0.19
	Previous biopsy status		–	–	–	–	0.6 [0.3–1.4]	0.21
Area under the curve (AUC) [95% CI]			0.77 [0.74–0.79]		0.78 [0.75–0.79]		0.79 [0.76–0.81]	

Statistically significant p-values are in bold.

RESULTS

Patient characteristics

A total of 790 consecutive patients presented PI-RADS 3 lesions on MRI and were enrolled in the study (Fig. 1). Among them, 151 patients (19%) were diagnosed with csPCa. Comprehensive clinical, imaging, and biopsy parameters for the entire cohort and subgroups based on csPCa status are detailed in Table 1. Median PSAd was 0.19 ng/ml/cc (0.15–0.28) in patients with csPCa, compared to 0.11 ng/ml/cc (0.08–0.16) in patients with non-csPCa (Fig. 2).

Multivariable logistic regression

Table 2 displays the outcomes of the multivariable logistic regression analysis. In the first model, which focused solely on clinical factors, only PSAd emerged as a significant predictor of csPCa status (OR: 82.7 [9.7–699]; $p < 0.001$), yielding an AUC of 0.77 in the ROC curve. The second model, incorporating both clinical and radiological parameters, identified age (OR: 1.1 [1.0–1.1]; $p = 0.01$) and PSAd (OR: 1414 [63–31,957]; $p < 0.001$) as the sole significant predictors of csPCa, maintaining the AUC at 0.78 in the ROC curve. The third model, which included clinical, radiological, and previous biopsy status, affirmed that age (OR: 1.1 [1.0–1.1]; $p = 0.009$) and PSAd (OR: 1619 [66–39,535]; $p < 0.001$) remained the only significant predictors of csPCa, with an AUC of 0.79 in the ROC curve. Supplementary Fig. 1 shows the calibration plots, and Supplementary Fig. 2 illustrates the net benefit on DCA, demonstrating enhanced detection of csPCa within the 0–30% probability range.

The statistical analyses were repeated, excluding patients with a history of previous biopsies and focusing solely on biopsy-naïve individuals. The results remained consistent in the multivariate analysis, with only PSAd demonstrating statistical significance (OR: 466 [18–12,257]; $p < 0.001$), while age, DRE status, and index lesion localization were found to be non-statistically significant.
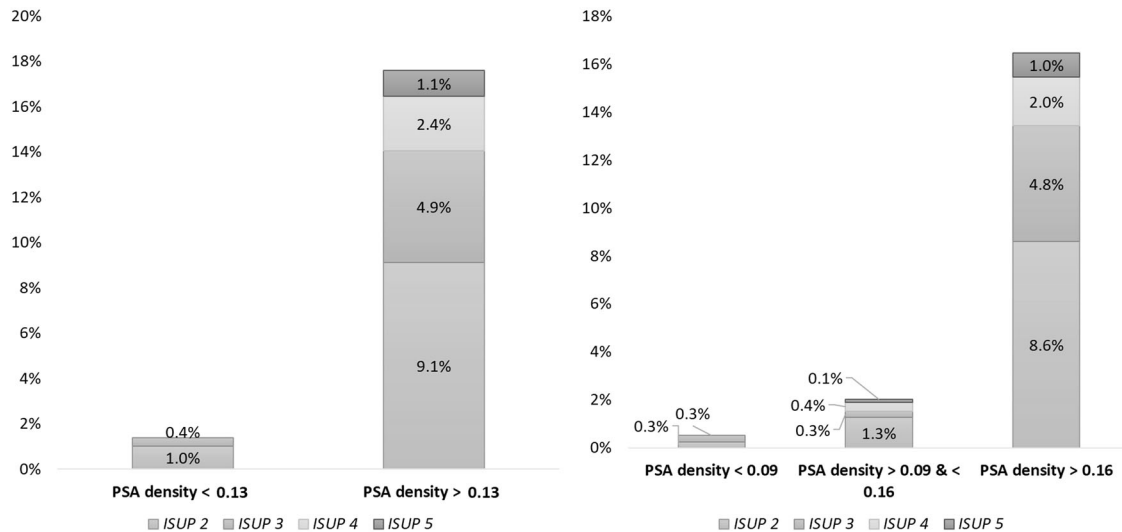
Fig. 3 CHAID analysis results. Percentage of csPCa in the different subgroups depicted according to the different cut-off points.

CHAID analysis

The CHAID analysis, considering only age and PSAd, identified PSAd as the sole significant factor influencing the decision tree (Supplementary Fig. 3). Cut-offs for PSAd were 0.13 ng/ml/cc for the two-nodes model and 0.09 ng/ml/cc and 0.16 ng/ml/cc for the three-nodes model. For the two-nodes model, the low-risk subgroup (PSAd < 0.13 ng/ml/cc) comprised 11 patients (1%) with csPCa, while the high-risk subgroup (PSAd ≥ 0.13 ng/ml/cc) included 140 patients (18%) with csPCa (Fig. 3). In the three-nodes model, the low-risk subgroup (PSAd < 0.09 ng/ml/cc) had 4 patients (0.5%) with csPCa, the intermediate-risk subgroup (PSAd between 0.09 ng/ml/cc and 0.16 ng/ml/cc) included 16 patients (2%), and the high-risk subgroup (PSAd ≥ 0.16 ng/ml/cc) encompassed 131 patients (17%) (Fig. 3).

For PSAd <0.09 ng/mL/cc, 13.6% of biopsies could be avoided. For PSAd <0.13 ng/mL/cc, 26% of biopsies could be avoided.

DISCUSSION

Despite the efforts put in scoring suspicious prostate lesions, PI-RADS 3 lesions continue to present a challenge in the daily clinical practice due to their equivocal nature [11, 14]. The importance of MRI quality, as indicated by the PIQUAL classification, is underscored by the critical role played by the expertise of the uro-radiologist in interpretation [15]. PIRADS 3 lesions are particularly susceptible to variations in radiologists' experience, given their indeterminate or equivocal nature for csPCa; expert uroradiologists are more inclined to confidently reclassify PIRADS 3 lesions as either PIRADS 1–2 or 4–5, leading to caution regarding immediate biopsy in cases classified as PIRADS 3 [15].

Previous studies have been conducted in the literature with the objective of refining biopsy indications specifically for these PI-RADS 3 lesions. To the best of our knowledge, this is the largest multi-institutional European study aimed at defining the association between clinical parameters of patients with PI-RADS 3 lesions and the presence of csPCa. Significant associations were observed for age and PSAd. In the CHAID analysis, PSAd emerged as the only statistically significant factor influencing the construction of the decision tree, with a cut-off of 0.13 in the two-nodes model and 0.09–0.16 in the three-nodes model. This study gives therefore an update of the PSA density cut-off to consider in the era of MRI-targeted biopsies when tackling PI-RADS 3 lesions.

According to the EAU-EANM-ESTRO-ESUR-ISUP-SIOG Guidelines on Prostate Cancer (2024), the decision to proceed with a biopsy based on MRI findings incorporates various thresholds for PSAd in PI-RADS 3 lesions [16]:

- If PSAd <0.10 ng/mL/cc, a biopsy is generally not recommended.
- If PSAd is between 0.10 and 0.15 ng/mL/cc, a biopsy should be considered.
- If PSAd is between 0.15 and 0.20 ng/mL/cc, a biopsy should be highly considered.
- If PSAd >0.20 ng/mL/cc, a biopsy should definitely be performed.

Our study proposes new PSAd cut-offs for patients with PI-RADS 3 lesions, suggesting that biopsies could be omitted for those with PSAd below 0.13 ng/mL/cc, especially below 0.09 ng/mL/cc. By establishing these cut-offs, our findings aim to reduce unnecessary biopsies and overdiagnosis of non-clinically significant prostate cancer.

Although opting for an MRI-targeted biopsy may appear to be the primary strategy for handling PI-RADS 3 lesions, it is worth considering a practical and acceptable alternative. This alternative entails monitoring the features of these lesions through subsequent MRI examinations, which can effectively decrease the workload and potential risks linked with additional biopsies. This approach gains significance, especially when other signs like consistent findings in DRE and PSAd are evident. Based on Boschheidgen et al.'s study, individuals who were initially diagnosed with PI-RADS 3 lesions and later confirmed to have PCa consistently experience an elevation in their PI-RADS assessment during the follow-up period when undergoing a subsequent mpMRI within 12 to 24 months. In contrast, individuals with PI-RADS 3 lesions who were negative for PCa tend to experience a downgrade in their PI-RADS assessment after 25 to 36 months [17]. Zhang et al., in their cohort of PI-RADS ≤ 3, individuals who were confirmed to have csPCa exhibited elevated levels of PSA, reduced prostate volume, and higher PSAd. Similarly, in a study involving 1057 men conducted by Venderink et al., it was demonstrated that for PI-RADS 3 lesions, when the PSAd is less than 0.15 ng/ml/cc, the rate of false negatives was only 6%, resulting in a high negative predictive value of 94% for csPCa, which stands in line with our results [18]. Szemplinski et al. retrospectively analyzed 740 men (including 17% of PI-RADS 3) who underwent MRI-targeted biopsy and found a 10% csPCa detection in PI-RADS 3 lesions [19]. A significant association for the detection of csPCa in PI-RADS 3 lesions was demonstrated only for

smaller prostate volume. This is in contrast to other studies that demonstrated older age, peripheral zone location, higher PSAd, and positive DRE to be associated with detection of csPCa in PI-RADS 3 lesions [20–23].

Given the relevant research question and the advancement of artificial intelligence, Aussavavirojekul et al. aimed to address the challenge of the low cancer detection rate in patients with PI-RADS 3 lesions by developing machine learning models to assist in decision-making regarding the need for prostate biopsies or monitoring based on clinical data without biopsy result. The study incorporated clinical factors such as age, PSA, prostate volume, PSAd, and prior biopsy status. Radiological data included the number of lesions, maximum lesion size, lesion location, and zone within the prostate. They showed that machine learning models streamline the process of selecting PI-RADS 3 patients for MRI-targeted biopsy, potentially unlocking the full potential of established clinical risk factors [24].

In addition to PSAd, other biomarkers such as PSA isoforms and the Prostate Health Index (Phi) density have shown promise in enhancing the stratification of patients with PI-RADS 3 lesions. Studies have indicated that incorporating these biomarkers could improve the prediction of csPCa and assist in decision-making regarding prostate biopsies [25, 26]. For instance, the Phi, which combines total PSA, free PSA, and [-2]proPSA, has been demonstrated to provide a higher specificity for csPCa detection. Moreover, the combined use of PHI and mpMRI has shown superior performance in predicting positive biopsy outcomes and identifying high-grade cancers, which helps in minimizing over-diagnosis and overtreatment [25, 26].

The rise of biparametric MRI (bpMRI) has also an impact on the assessment of PI-RADS 3 lesions. The recently published VISION-ING study investigates the use of bpMRI as a primary screening tool for PCa without relying on PSA levels [27]. The findings indicate that bpMRI has higher sensitivity for detecting csPCa compared to traditional methods. The protocol adjustment led to a 54.6% reduction in biopsies for PI-RADS 3 lesions, demonstrating that bpMRI can reduce unnecessary procedures while maintaining high detection rates of csPCa [27].

We acknowledge the retrospective nature of the present analysis which confers a potential selection bias. The presented figures likely reflect a pre-existing selection bias towards patients at a higher risk of cancer with a PI-RADS 3 classification. Therefore, despite the excellent results, this must be analyzed in consideration of this potential selection bias. It is probable that there is a limited representation of patients with low PSAd and possibly other risk parameters for prostate cancer, which could have influenced the biopsy outcomes. Moreover, the study was conducted in tertiary referral centers with dedicated physicians for each step of the procedure, which may limit the generalizability of the findings. While all participating centers adhered to prevailing guidelines and terminology, the absence of centralized review resulted in notable heterogeneity in both MRI reporting and biopsy analysis. The variability in mpMRI interpretation and PI-RADS scoring can be attributed to differences in radiologists' training and experience, since the level of expertise significantly influences the consistency and accuracy of PI-RADS assessments, with expert radiologists more likely to reclassify equivocal lesions accurately. Despite employing the KOELIS system to minimize subjectivity and variability in biopsy core analysis compared to a cognitive approach, we acknowledge variations in prostate biopsy protocols across institutions, potentially introducing sources of variability in csPCa detection and impacting study outcomes. It is worth noting that prostate volume was determined using the ellipsoidal formula based on MRI, and alternative calculations could introduce uncertainty, especially in PSAd estimation. Finally, external validation of the prediction model could not be done due to sample size restriction (i.e., minimum required sample size was 2660 and the number of required events was 426 events using Ryley et al. method).

CONCLUSION

For individuals with PI-RADS 3 lesions on prostate mpMRI and a PSAd below 0.13, especially below 0.09, prostate biopsy could be omitted, in order to avoid overdiagnosis of non-csPCa. This nuanced strategy may lead to more precise and informed decision-making, potentially sparing certain patients from unnecessary invasive procedures. Prospective and randomized studies are needed to confirm our findings.

DATA AVAILABILITY
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

COMPETING INTERESTS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

ADDITIONAL INFORMATION