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Clinical and prostate multiparametric magnetic resonance imaging findings as predictors of general and clinically significant prostate cancer risk: A retrospective single-center study

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Abstract

Background: To evaluate the predictive values of Prostate Imaging Reporting and Data System version 2 (PI-RADS v2), prostate-specific antigen (PSA) level, PSA density (PSAD), digital rectal examination findings, and prostate volume, individually and in combination, for the detection of prostate cancer (PCa) in biopsy-naive patients.

Methods: We retrospectively analyzed 630 patients who underwent transrectal systematic prostate biopsy following prostate multiparametric magnetic resonance imaging. A standard 12-core biopsy procedure was performed. Univariate and multivariate analyses were performed to determine the significant predictors of clinically significant cancer but not PCa.

Results: The median age, PSA level, and PSAD were 70 years, 8.6 ng/mL, and 0.18 ng/mL/mL, respectively. A total of 374 (59.4%) of 630 patients were biopsy-positive for PCa, and 241 (64.4%) of 374 were diagnosed with clinically significant PCa (csPCa). The PI-RADS v2 score and PSAD were independent predictors of PCa and csPCa. The PI-RADS v2 score of 5 regardless of the PSAD value, or PI-RADS v2 score of 4 plus a PSAD of <0.3 ng/mL/mL, was associated with the highest csPCa detection rate (36.1%–82.1%). Instead, the PI-RADS v2 score of <3 and PSAD of <0.3 ng/mL/mL yielded the lowest risk of csPCa.

Conclusion: The combination of the PI-RADS v2 score and PSAD could prove to be a helpful and reliable diagnostic tool before performing prostate biopsies. Patients with a PI-RADS v2 score of <3 and PSAD of <0.3 ng/mL/mL could potentially avoid a prostate biopsy.

Keywords: Prostate cancer; Prostate Imaging Reporting and Data System score; Multiparametric magnetic resonance imaging; Transrectal ultrasound; Prostate biopsy; Prostate-specific antigen density

1. Introduction

Prostate cancer (PCa) is the fifth leading cause of cancer-related death in men, with an estimated 307,000 deaths per annum, accounting for 6.6% of the total male cancer mortality in Europe.[1] Although PCa can display heterogeneous clinical behaviors, early detection can alter its natural history and disease mortality.[2] Prostate cancer diagnosis has historically relied on prostate-specific antigen (PSA), digital rectal examination (DRE), transrectal ultrasound (TRUS), and systematic TRUS-guided biopsy. These diagnostic methods may be associated with the detection of indolent and clinically insignificant tumors, leading to overtreatment and increased morbidity.[3]

Transrectal ultrasound reported low sensitivity for PCa detection (0.17–0.57), and similarly, conventional TRUS-guided prostate biopsy achieved a PCa detection rate of 0.2 to 0.4.[4] Moreover, prostate biopsies are expensive and invasive and could be associated with severe complications.[5] In the last decade, prostate multiparametric magnetic resonance imaging (mpMRI) has emerged as a novel imaging technique for PCa detection, localization, staging, and treatment guidance, with specificity, sensitivity, and negative predictive value (NPV) of 0.88, 0.74, and 0.64 to 0.94, respectively.[6,7] With the aim to ensure standardization in mpMRI, the Prostate Imaging Reporting and Data System (PI-RADS) was developed in 2012 and revised in 2015 by the European Society of Urogenital Radiology and the American College of Radiology.[8] However, the use of the PI-RADS score has reported discordant results. The PI-RADS reported an NPV for PI-RADS <3 lesions of 0.98; nonetheless, the positive predictive value (PPV) for clinically significant PCa (csPCa) was 0.48 to 0.58. As a result, despite a PI-RADS score of <3, csPCa may have been missed.[9] Any additional stand-alone method that could improve the predictive performance of the PI-RADS score is worth considering, especially for dubious mpMRI or particular tumor localization.[10,11]

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This study aimed to establish the predictive values of PI-RADS, PSA level, PSA density (PSAD), DRE findings, and prostate volume, individually and in combination, for both general and csPCa, in biopsy-naive patients who have undergone a transrectal systematic prostate biopsy.

2. Materials and methods

This retrospective observational study was conducted at the Queen Elizabeth University Hospital, Glasgow, United Kingdom, according to the World Medical Association Declaration of Helsinki guidelines. A total of 836 patients underwent a transrectal prostate biopsy between January 2017 and December 2018. All patients provided written informed consent for the procedure. A total of 206 patients were excluded owing to the following exclusion criteria: absence of a previous prostate MRI (n = 127), duration of >6 months between prostate MRI and biopsy (n = 58), treatment with 5α-reductase inhibitors (as the prostate volume and PSA level would be underestimated) (n = 21). Finally, 630 patients were included.

2.1. Multiparametric magnetic resonance imaging protocol

Indications for mpMRI were based on clinical suspicion of PCa, PSA level of >4 ng/mL and positive DRE. Multiparametric MRI was performed using a 3-T MRI scanner to acquire axial and sagittal T1- and T2-weighted images and axial diffusion-weighted imaging. All mpMRI images were independently interpreted by 2 experienced genitourinary radiologists, each with at least 8 years of experience, according to PI-RADS version 2.0. Magnetic resonance imaging performed outside our institution was retrospectively reviewed by radiologists.

2.2. Prostate biopsy protocol

All biopsies were performed following a standardized protocol using TRUS guidance (BK Flex Focus 800 with an Endocavity biplane probe 8848 BK). Similar to mpMRI, indications for prostate biopsy were based on clinical suspicion of PCa, PSA level of >4 ng/mL, positive DRE, and/or PI-RADS score of ≥3. All patients were prescribed a prebiopsy dose of antibiotics (750 mg of oral ciprofloxacin). A periprostatic lidocaine infiltration nerve blockade was performed before biopsy, and a systematic biopsy protocol based on the European Association of Urology guidelines, including 12 cores, was completed for each patient. As no general agreement has been reported on the definition of csPCa, we defined csPCa as a Gleason score of ≥4 + 3 and/or a maximum cancer core length of ≥6 mm, in accordance with the Prostate MR Imaging Study, to avoid the underestimation of low-volume PCa. The highest Gleason score obtained at biopsy was cognitively and retrospectively paired with the PI-RADS score obtained on mpMRI by the urologist involved in prostate biopsy.

2.3. Statistical analysis

The factors evaluated and recorded included age, PSA level, PSAD, DRE findings, PI-RADS score, and prostate volume (on both MRI and ultrasound).[12] Descriptive statistics included the mean and SD for continuous variables, whereas frequencies and percentages were obtained for categorical variables. A best-fit receiver operating characteristic (ROC) curve was calculated using the area under the ROC curve (AUC) estimates and 95% confidence intervals (CIs). Univariate and multivariate analyses were performed with logistic regression analysis to obtain odds ratios and 95% CIs, whereas Pearson χ^2 test was performed for categorical variables to obtain detection rates. Statistical analysis was performed using the Statistical Product and Service Solutions software for Windows (version 25.0; IBM Corp, Armonk, NY), with $p < 0.05$ as statistically significant.

3. Results

3.1. Demographic data

The descriptive statistics of the 630 patients included in this study are reported in Table 1. The median patient age was 70 years (interquartile range, 63–75 years). The median PSA level was 8.6 ng/mL, and the median PSAD was 0.18 ng/mL/mL. A total of 374 (59.6%) patients were diagnosed with PCa, whereas only 275 (44.4%) reported a positive or suspicious DRE. Multiparametric MRI scans reported PI-RADS 4 or 5 lesions in 34.3% of patients, whereas PI-RADS 2 and 3 lesions occurred in 11.8% and 19.5% of patients, respectively.

3.2. Prostate cancer risk factor assessment

The ROC curve analysis for total PCa prediction showed AUC values for PSAD and PI-RADS score of 0.739 (95% CI, 0.69–0.789; $p < 0.0001$) and 0.717 (95% CI, 0.665–0.768; $p < 0.0001$), respectively, higher than those for PSA (0.643; 95% CI, 0.588–0.698; $p < 0.0001$), age (0.640; 95% CI, 0.583–0.697; $p < 0.0001$), and DRE (0.616; 95% CI, 0.56–0.673; $p < 0.0001$). Transrectal ultrasound and MRI prostate volumes reported low and comparable AUC values of 0.316 (95% CI, 0.261–0.371; $p < 0.0001$) and 0.317 (95% CI, 0.263–0.372; $p < 0.0001$, respectively).

3.3. Prostate cancer univariate and multivariate analyses

Univariate logistic regression analysis revealed a statistically significant risk of PCa related to increased PSA level, PSAD, age, DRE, or PI-RADS score. In particular, a PSA level of >10 ng/mL, PSAD of >0.151 ng/mL/mL, and age older than 65 years were associated with an increased risk of PCa. Similar results were reported for positive DRE and PI-RADS score of >3, whereas prostate volume was inversely correlated with PCa. The PSA level and prostate volume were excluded from the multivariate analysis to avoid repetition of data, as they were already considered in the PSAD. Multivariate logistic regression confirmed that the PI-RADS score and PSAD were independent predictors of total PCa (Table 2).

Table 1

Descriptive characteristics of the patients involved.

	Median	IQR
Age, yr	70	63–75
PSA, ng/mL	8.6	5.7–15.6
PSA density, ng/mL/mL	0.18	0.11–0.36
mpMRI prostate volume, mL	44	33–62
TRUS prostate volume, mL	41	31–57
	No. patients	**Percent, %**
Positive DRE	275	44.4
PI-RADS 2	66	11.8
PI-RADS 3	109	19.5
PI-RADS 4	192	34.3
PI-RADS 5	192	34.3
Positive biopsy	374	59.6

DRE = digital rectal examination; IQR = interquartile range; mpMRI = multiparametric magnetic resonance imaging; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

Table 2

Univariate and multivariate logistic regression analyses for total prostate cancer risk.

	Univariate logistic regression				Multivariate logistic regression			
		95% CI				95% CI		
	OR	Lower	Upper	*p*	OR	Lower	Upper	*p*
Age, yr								
≤65				<0.0001				0.001
66–70	2.510	1.585	3.974	<0.0001	2.850	1.633	4.973	<0.0001
71–75	2.157	1.400	3.322	<0.0001	1.642	0.959	2.810	0.070
>75	2.822	1.798	4.429	<0.0001	2.340	1.307	4.191	0.004
PSA, ng/mL								
≤6				<0.0001				
6.1–8	1.781	1.101	2.881	0.019				
8.1–10	1.920	1.143	3.225	0.014				
>10	3.701	2.454	5.582	<0.0001				
PSA density, ng/mL/mL								
≤0.15				<0.0001				<0.0001
0.151–0.29	3.012	1.989	4.561	<0.0001	2.350	1.501	3.680	<0.0001
0.3–0.44	5.857	2.852	12.028	<0.0001	3.887	1.797	8.406	0.001
>0.45	16.343	8.081	33.049	<0.0001	9.445	4.341	20.547	<0.0001
TRUS prostate volume, mL								
<20				<0.0001				
21–30	1.118	0.456	2.743	0.808				
31–40	1.184	0.503	2.787	0.698				
>40	0.342	0.155	0.753	0.008				
mpMRI prostate volume, mL								
<20				<0.0001				
21–30	1.207	0.423	3.443	0.726				
31–40	0.528	0.199	1.404	0.201				
>40	0.288	0.114	0.727	0.008				
DRE								
Positive	3.031	2.150	4.274	<0.0001	1.357	0.880	2.093	0.167
PI-RADS score								
PI-RADS 2				<0.0001				<0.0001
PI-RADS 3	1.333	0.707	2.516	0.374	1.242	0.613	2.516	0.547
PI-RADS 4	2.534	1.413	4.544	0.002	2.077	1.090	3.957	0.026
PI-RADS 5	10.264	5.391	19.540	<0.0001	4.847	2.357	9.970	<0.0001

CI = confidence interval; DRE = digital rectal examination; mpMRI = multiparametric magnetic resonance imaging; OR = odds ratio; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

3.4. Clinically significant prostate cancer univariate and multivariate analyses

Univariate analysis for csPCa reported that age older than 70 years, PSA level of >10 ng/mL, and PSAD of >0.151 ng/mL/mL were associated with an increased risk of csPCa, as well as positive DRE and PI-RADS score of >3. Multivariate logistic regression confirmed that the PSAD and PI-RADS score were independent predictors of csPCa (Table 3).

3.5. Prediction of clinically significant prostate cancer

Table 4 shows the csPCa detection rate stratified according to PI-RADS score and PSAD. When a PI-RADS score of ≥3 was considered positive, the sensitivity, specificity, PPV, and NPV for csPCa were 0.84, 0.98, 0.98, and 0.89, respectively. Of the 23 patients with a PI-RADS score of <3 (6.7% of all PI-RADS scores), 17.4% had csPCa.

Similarly, when a PSAD of ≥0.15 ng/mL/mL was considered positive, the sensitivity, specificity, PPV, and NPV for csPCa were 0.59, 0.92, 0.89, and 0.68, respectively. Thirty-six (17%) of 215 patients with a PSAD of <0.15 ng/mL/mL had csPCa. Finally, when considering the detection rate of csPCa using the 16 categories classified by PI-RADS score and PSAD, it is possible to define high- and low-risk groups. A PI-RADS score of 5 with either PSAD, or a PI-RADS score of 4 plus a PSAD of <0.3 ng/mL/mL, was associated with the highest csPCa detection rate (36.1%–82.1%) and referred to as the high-risk group. On the other hand, a PI-RADS score of 2 plus a PSAD of <0.3 or >0.45 ng/mL/mL, or a PI-RADS score of 3 plus a PSAD between 0.151 and 0.29 or >0.45 ng/mL/mL, yielded the lowest csPCa detection rate (0%–8.3%) and was categorized as the low-risk group (χ^2_9 [n = 271] = 43.6, p < 0.0001).

4. Discussion

We analyzed and established the predictive values of PI-RADS, PSA level, PSAD, DRE findings, and prostate volume, individually and in combination, in relation to the risk of being diagnosed with PCa after a systematic transrectal prostate biopsy from our cohort of patients. Both general PCa and csPCa risks were considered. We focused our attention on PI-RADS and PSAD, the only factors included in our multivariate analysis, to eliminate possible confounding factors and correlate with current literature findings.[13,14]

In our study, when a PI-RADS score of ≥3 was considered positive, the sensitivity, specificity, PPV, and NPV were 0.84, 0.98, 0.98, and 0.89, respectively. These results are comparable with

those described in the literature, as reported by de Rooij et al.[7] in a recent meta-analysis that demonstrated the sensitivity, specificity, and NPV of 0.74 (95% CI, 0.66–0.81), 0.88 (95% CI, 0.82–0.92), and 0.64–0.94, respectively.[7,15,16] Despite the good performance of PI-RADS in terms of low NPV and improved concordance with histologic reports, mpMRI alone does not help the clinician to decide which patients should be spared from unnecessary biopsies. [17–19] Referring to our series, if patients with a PI-RADS score of ≤2 avoided biopsy, 17.4% of csPCa would have been missed. The understaging of csPCa on the MRI—and consequently the generally low NPV associated with the PI-RADS score—could be explained by the correlation between tumor volume/grade and PI-RADS score.[20,21] As a result, a tumor with a low volume, even if clinically significant, could be underscored or missed by mpMRI owing to technical limitations. A workaround to improve the predictive value of PI-RADS could therefore be the combined use with PSAD.[22,23] The importance of PSAD has been thoroughly described in the literature, as it is included in the Epstein criteria and correlated with PCa aggressiveness.[24,25] In our study, PSAD was an independent predictor of PCa and csPCa. When a PSAD of ≥0.15 ng/mL/mL was considered positive, the sensitivity, specificity, PPV, and NPV for csPCa were 0.59, 0.92, 0.89, and 0.68, respectively. Veneziano et al.[26]

Table 4

Cancer detection rate stratified by PI-RADS, PSA density, and combined score ($p < 0.001$).

Cancer detection rate				
PI-RADS	2	3	4	5
PCa	35.4%	42.2%	58.1%	84.9%
csPCa	17.4%	41.3%	56.8%	81.0%
PSA density	≤0.15	0.151–0.29	0.3–0.44	>0.45
PCa	38.9%	65.7%	78.8%	91.2%
csPCa	42.9%	63.5%	63.4%	80.8%
csPCa detection rate (%)				
PSA density	PI-RADS			
	2	3	4	5
<0.15	5.6%	19.4%	38.9%	36.1%
0.151–0.29	0.0%	8.2%	41.1%	50.7%
0.3–0.44	8.3%	16.7%	20.8%	54.2%
>0.45	0.0%	2.4%	15.5%	82.1%

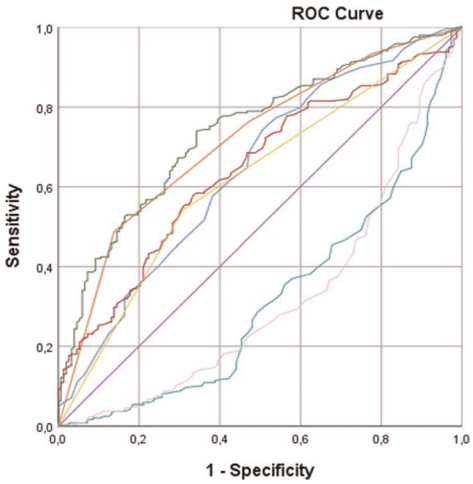
Green, low-risk group; yellow, intermediate-risk group; red, high-risk group.
csPCa = clinically significant PCa; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen.

Table 3

Univariate and multivariate logistic regression analyses for clinically significant prostate cancer.

	Univariate logistic regression				Multivariate logistic regression			
		95% CI				95% CI		
	OR	Lower	Upper	*p*	OR	Lower	Upper	*p*
Age, yr								
≤65				0.002				0.177
66–70	1.189	0.659	2.145	0.565	1.280	0.648	2.528	0.478
71–75	2.514	1.364	4.635	0.003	1.921	0.955	3.865	0.067
>75	2.521	1.377	4.617	0.003	1.970	0.956	4.059	0.066
PSA, ng/mL								
≤6				<0.0001				
6.1–8	0.632	0.322	1.241	0.182				
8.1–10	0.652	0.320	1.329	0.239				
>10	2.093	1.180	3.713	0.012				
PSA density, ng/mL/mL								
≤0.15				<0.0001				0.034
0.151–0.29	2.317	1.304	4.119	0.004	1.765	0.940	3.317	0.077
0.3–0.44	2.311	1.072	4.984	0.033	1.391	0.591	3.276	0.450
>0.45	5.600	2.919	10.74	<0.0001	2.895	1.399	5.988	0.004
TRUS prostate volume, mL								
<20				0.166				
21–30	0.306	0.092	1.024	0.055				
31–40	0.513	0.157	1.672	0.268				
>40	0.351	0.111	1.113	0.075				
mpMRI prostate volume, mL								
<20				0.220				
21–30	0.657	0.217	1.991	0.457				
31–40	0.454	0.153	1.349	0.155				
>40	0.419	0.148	1.182	0.100				
DRE								
Positive	2.924	1.878	4.552	<0.0001	1.61	0.95	2.71	0.077
PI-RADS score								
PI-RADS 2				<0.0001				<0.0001
PI-RADS 3	3.343	0.979	11.408	0.054	3.46	0.97	12.38	0.056
PI-RADS 4	6.234	1.990	19.527	0.002	5.81	1.78	19	0.004
PI-RADS 5	20.226	6.424	63.684	<0.0001	12.68	3.85	41.8	<0.0001

CI = confidence interval; DRE = digital rectal examination; mpMRI = multiparametric magnetic resonance imaging; OR = odds ratio; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.



Variable	AUC	95% Confidence Interval		P value
		Lower Bound	Upper Bound	
Age	0.640	0.583	0.697	<0.0001
PSA	0.643	0.588	0.698	<0.0001
PSA density	0.739	0.690	0.789	<0.0001
DRE	0.616	0.560	0.673	<0.0001
PIRADS score	0.717	0.665	0.768	<0.0001
TRUS Prostate Volume (cc)	0.316	0.261	0.371	<0.0001
MRI Prostate volume (cc)	0.317	0.263	0.372	<0.0001

Figure 1. ROC curve and analysis. AUC = area under the curve; DRE = digital rectal examination; MRI = magnetic resonance imaging; PIRADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; ROC = receiver operating characteristic; TRUS = transrectal ultrasound.

reported a specificity of 0.63 and sensitivity of 0.79 when the threshold value was set to 0.15 ng/mL/mL. Similarly, with a cutoff of 0.15 ng/mL/mL, Washino et al.[14] described a sensitivity and specificity of 0.99 and 0.34, respectively. Compared with the available results, our data showed a lower sensitivity, although with higher specificity. However, the reasons for these discrepancies include differences in the demographics and biopsy settings.

Although we reported similar sensitivity, specificity, NPV, and PPV for PSAD and PI-RADS alone, the combined use of these parameters yielded significant results. When the PSAD and PI-RADS score were ≤0.15 ng/mL/mL and 2, respectively, the csPCa detection rate was 5.6%, whereas a PSAD of >0.45 ng/mL/mL and PI-RADS score of 5 yielded an 82.1% detection rate. The combination of PI-RADS score and PSAD could be a useful tool to predict biopsy outcome and guide treatment.[14,22]

To the best of our knowledge, our study is one of the largest of this nature. Our results are consistent with those available in the literature, supplementing the idea of combining mpMRI findings with PSAD in deciding whether a patient should undergo prostate biopsy. Different limitations have to be reported: absence of a worldwide-accepted definition for csPCa; retrospective study; different urologists performing prostate biopsies; Gleason scores retrospectively paired to the PI-RADS score; and utilization of biopsy-derived Gleason scores, which are prone to sampling error, reader error, and understaging. Finally, another limitation is the absence of blinding between the radiologist and urologist and the lack of radiologists' concordance analysis.

5. Conclusions

The combination of PI-RADS score and PSAD could prove to be a helpful and reliable diagnostic tool before prostate biopsy, in both the detection and follow-up of PCa. In particular, patients with a PI-RADS score of <3 and PSAD of <0.3 ng/mL/mL could avoid potential unnecessary biopsies.

Acknowledgments

None.

Statement of ethics

Being a retrospective study, the study did not require another ethical approval and participants' consent, according to the ethical guidelines of the Queen Elizabeth University Hospital. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest statement

No conflict of interest has been declared by the authors.

Availability of data and materials

Data are available on request.

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Author contributions

MM, AI, PA, BJR: Project development;
MM, VR, RS, DL, UM, SJ: Data collection;
MM, VR, RS: Manuscript writing;
BB, CG: Data analysis;
CF, BB, CG, PA, BJR: Manuscript editing.

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