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ORIGINAL ARTICLE

Prostate Cancer

The role of prostate-specific antigen density and negative multiparametric magnetic resonance imaging in excluding prostate cancer for biopsy-naïve men: clinical outcomes from a high-volume center in China

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This study aimed to assess the role of prostate-specific antigen density (PSAD) and negative multiparametric magnetic resonance imaging (mpMRI) in predicting prostate cancer for biopsy-naïve men based on a large cohort of the Chinese population. From a prostate biopsy database between March 2017 and July 2021, we retrospectively identified 240 biopsy-naïve patients with negative prebiopsy mpMRI (Prostate Imaging Reporting and Data System version 2 [PI-RADS v2] score <3). Logistic regression analysis was performed to select the potential predictors for clinically significant prostate cancer (csPCa). Receiver operating characteristic (ROC) curve analysis and area under the ROC curve (AUC) were performed to assess the diagnostic accuracy. The negative predictive values of mpMRI in excluding any cancer and csPCa were 83.8% (201/240) and 90.8% (218/240), respectively. ROC curve analysis indicated that PSAD was the most promising predictor, with an AUC value of 0.786 (95% confidence interval [CI]: 0.699–0.874), and multiparametric logistic regression analysis confirmed that higher PSAD remained a significant marker for predicting csPCa (odds ratio [OR]: 10.99, 95% CI: 2.75–44.02, $P < 0.001$). Combining negative mpMRI and PSAD below 0.20 ng ml^{-2} obviously increased the predictive value in excluding PCa (91.0%, 101/111) or csPCa (100.0%, 111/111). If a PSAD below 0.20 ng ml^{-2} was set as the criterion to omit biopsy, nearly 46.3% of patients (463 per 1000) with negative mpMRI could safely avoid unnecessary biopsy, with approximately 4.2% of patients (42 per 1000) at risk of missed diagnosis of PCa and no patients with csPCa missed. A PI-RADS v2 score <3 and a PSAD <0.20 ng ml^{-2} could be potential criteria for the Chinese population to omit prompt biopsy safely.
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Keywords: biopsy; magnetic resonance imaging; predictive value; prostate cancer; prostate-specific antigen density; transrectal ultrasound

INTRODUCTION

Prostate cancer (PCa) remains the most often diagnosed tumor among men worldwide, with regional differences in the prevalence and mortality rates.[1] The current diagnostic standard is 10- to 12-core systematic biopsy guided by transrectal ultrasound (TRUS);[2] however, some evidence indicates that transperineal biopsy reduces the infection risk compared with the transrectal approach.[3,4] The inevitable sampling errors of systematic biopsy and the low accuracy of gray scale ultrasound call for more accurate imaging to select patients with suspected PCa and lesions for biopsy.[5]

The development of prostate magnetic resonance imaging (MRI) in the early 1980s greatly improved our knowledge of the prostate.[6] Owing to the refinement of multiparametric sequences and the improvement of a reporting system to better identify suspicious lesions,[7,8] clinical results have confirmed that the multiparametric MRI (mpMRI) pathway has a positive impact on the early diagnosis of PCa.[9] Guidelines recommend scheduling mpMRI imaging before biopsy and prescribing MRI-targeted biopsy for patients with suspicious lesions on mpMRI.[2] However, there is no consensus on whether systematic biopsy can be omitted for patients with negative mpMRI results. A recent systematic review reported that the median negative predictive value (NPV) was 82.4% for excluding any PCa and 88.1% in clinically significant prostate cancer (csPCa) for a prebiopsy mpMRI. However, the predictive value varied regionally depending on cancer screening criteria, imaging

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protocols, and prevalence.[10] Simply assigning negative mpMRI to predict the absence of PCa seems insufficient, and supplementary risk stratification tools are warranted.

The ratio of serum prostate-specific antigen (PSA) and prostate volume, namely PSA density (PSAD), has shown the ability to distinguish candidates for active surveillance or immediate interventions.[11,12] In the era of mpMRI, the use of PSAD to select patients for biopsy also shows promising results. Research has reported that negative mpMRI combined with low PSAD significantly improved the predictive value in excluding csPCa.[13–15] However, the cutoff values among studies varied, partly due to different study designs, cancer screening criteria, and imaging protocols.[16–19] More importantly, the significant regional disparity of PCa prevalence may also impact the role of mpMRI and PSAD in cancer risk stratification.[10] Therefore, we aimed to evaluate the role of PSAD and negative mpMRI in excluding PCa for biopsy-naïve men based on a large cohort from a high-volume center in China.

PATIENTS AND METHODS

Patients

This retrospective study received approval from the Research Ethics Committee of the West China Hospital of Sichuan University (Chengdu, China; No. 2019-869). Because of the anonymity of the data, written informed consent was not required. The hospital database was searched for patients who underwent prostate biopsy between March 2017 and July 2021 (4118 patients total), and 2259 consecutive men who underwent prebiopsy mpMRI followed by systematic biopsy were retrospectively identified. Our study included patients receiving a first biopsy with negative mpMRI. We excluded patients who had a previous biopsy, patients with either or both prebiopsy PSA and mpMRI performed elsewhere, and patients who had received any previous surgical treatment for their prostate.

Data collection

We collected baseline demographic and clinical data from our hospital database. Prebiopsy PSA and free-total PSA ratio (fPSA%) were collected within 30 days before biopsy. All included patients underwent mpMRI using a 3.0 Tesla machine (Skyra, Siemens, Munich, Germany; or GE Healthcare, Chicago, IL, USA) within 6 months before prostate biopsy. The Prostate Imaging Reporting and Data System (PI-RADS) version 2 scoring system was used to report the mpMRI results.[8] The imaging protocols for mpMRI are shown in **Supplementary Table 1**. Patients who had negative mpMRI (PI-RADS v2 <3) were reevaluated by one uroradiologist (Ling Yang) with >5 years of experience in evaluating prostate mpMRI (>200 MRIs per year). Prostate volume was determined on MRI using the standard ellipsoid formula. The PSAD was calculated using prebiopsy PSA and MRI prostate volume measurements. For all patients with negative mpMRI, 12-core TRUS-guided transperineal prostate biopsies were performed. Pathologic assessment was performed by a working group of experienced pathologists based on the 2014 International Society of Urological Pathology (ISUP) Consensus Conference.[20] The definition of csPCa was set as Gleason score (GS) ≥3 + 4.

Statistical analyses

We performed the Student's *t*-test or Mann–Whitney U test and the Chi-square or Fisher's exact test to compare statistical differences. Univariate and multivariate logistic regression analyses were performed to evaluate potential predictors for csPCa. The receiver operating characteristic (ROC) curve and area under the curve (AUC) were computed to establish the optimal cutoff values and to assess the model accuracy for diagnostic markers. The statistical software package R (http://www.R-project.org, The R Foundation, Boston, MA, USA) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA) were used to conduct statistical analyses. All results of the analysis were considered to be statistically significant with a two-sided $P < 0.05$.

RESULTS

A total of 240 patients with a negative mpMRI who received their first prostate biopsy were included (**Figure 1**). The mean age was 63.9 (standard deviation [s.d.]: 9.5) years; median PSA was 11.57 (interquartile range [IQR]: 6.98–16.60) ng ml^{-1}; median prostate volume was 49.66 (IQR: 33.47–77.26) ml; and median fPSA% was 0.14 (IQR: 0.09–0.18). Of the 240 patients, PCa was detected in 39 (16.3%) patients, of whom 17 patients had GS 3 + 3, 15 patients had GS 3 + 4, and 7 patients had GS > 3 + 4. Age, PSA level, and PSAD level were higher for patients diagnosed with csPCa, whereas the fPSA% and prostate volume were higher for patients diagnosed with benign or clinically insignificant prostate cancer (**Table 1**).

Univariate analysis revealed that older age ($P = 0.005$), higher PSA ($P = 0.001$) and PSAD ($P < 0.001$), and smaller prostate volume ($P = 0.039$) were the predictors of detecting csPCa. Multiparametric logistic regression analysis indicated that older age ($P = 0.002$) and higher PSAD ($P < 0.001$) were the significant markers for predicting csPCa (**Table 2**). Within the cohort, the median value of PSAD was 0.21 (IQR 0.14–0.34) ng ml^{-2}. The ROC curve analysis indicated that PSAD was the most promising predictive marker (AUC: 0.786; 95% CI: 0.699–0.874), as shown in **Figure 2** and **Supplementary Table 2**. The optimal threshold for PSAD predicting csPCa was established as 0.20 ng ml^{-2} to achieve the maximum diagnostic accuracy.

The NPVs of mpMRI to exclude any cancer and any csPCa in the 240 patients were 83.8% (201) and 90.8% (218), respectively. The combination of negative mpMRI and PSAD <0.20 ng ml^{-2} obviously increased the predictive value for excluding PCa or csPCa compared with negative mpMRI only (91.0% [101/111] *vs* 83.8% [201/240]; 100.0% [111/111] *vs* 90.8% [218/240], respectively). Patients with a negative prebiopsy mpMRI were divided into three groups based on their PSA and PSAD levels as low-, intermediate-, and high-risk groups. Further analysis revealed that most patients with csPCa (90.9%, 20/22) were diagnosed within the high-risk group (PSAD ≥0.20 ng ml^{-2} and PSA ≥10 ng ml^{-1}), whereas the predictive value of csPCa was only 6.7% (2/30) in patients with PSAD ≥0.20 ng ml^{-2} and PSA <10 ng ml^{-1}. When the PSAD cutoff value was established at 0.15 ng ml^{-2} or 0.10 ng ml^{-2}, the NPVs increased to 96.4% (53/55) or 97.6% (82/84), respectively,

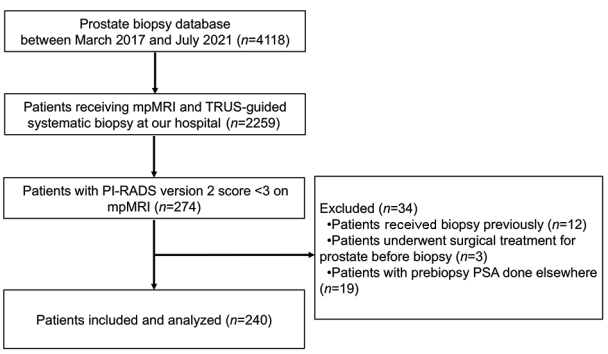

Figure 1: Patients selection flow chart. PI-RADS: Prostate Imaging-Reporting and Data System; mpMRI: multiparametric magnetic resonance imaging; TRUS: transrectal ultrasound; PSA: prostate-specific antigen.

Table 1: Patient demographics and biopsy results.

Characteristic	*All patients (n=240)*	*In-csPCa or benign patients (n=218)*	*csPCa patients (n=22)*	*P*
Age (year), mean±s.d.	63.9±9.5	63.3±9.5	69.4±8.1	0.005
PSA (ng ml^{-1}), median (IQR)	11.57 (6.98–16.60)	10.68 (6.80–16.31)	16.16 (12.69–24.08)	<0.001
fPSA (ng ml^{-1}), median (IQR)	1.31 (0.89–2.40)	1.31 (0.87–2.41)	1.61 (1.04–2.25)	<0.001
fPSA%, median (IQR)	0.14 (0.09–0.18)	0.14 (0.10–0.18)	0.11 (0.07–0.16)	0.196
PV (ml), median (IQR)	49.66 (33.47–77.26)	51.58 (33.69–81.22)	44.88 (30.71–57.09)	0.036
PSAD (ng ml^{-2}), median (IQR)	0.21 (0.14–0.34)	0.20 (0.14–0.33)	0.39 (0.24–0.94)	<0.001
Biopsy results, *n* (%)				
Gleason score <3+3	201 (83.8)	201 (92.2)		
Gleason score 3+3	17 (7.1)	17 (7.8)		
Gleason score 3+4	15 (6.3)		15 (68.2)	
Gleason score >3+4	7 (2.9)		7 (31.8)	

In-csPCa: clinically insignificant prostate cancer; csPCa: clinically significant prostate cancer; s.d.: standard deviation; IQR: interquartile range; PSA: prostate-specific antigen; fPSA%: free-total PSA ratio; PV: prostate volume; PSAD: prostate-specific antigen density; fPSA: free PSA

Table 2: Univariate and multivariate logistic regression analyses for potential predictors of clinically significant prostate cancer in men with negative multiparametric magnetic resonance imaging

Characteristic	*Univariate analysis*		*Multivariate analysis*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
Age (year)	1.08 (1.02–1.14)	0.005	1.12 (1.05–1.21)	0.002
PSA (ng ml^{-1})	1.04 (1.02–1.07)	0.001	1.00 (0.94–1.07)	0.918
fPSA%	0.01 (0–12.90)	0.196		
PV (ml)	0.98 (0.96–1.00)	0.039	0.99 (0.96–1.02)	0.363
PSAD (ng ml^{-2})	17.12 (4.32–67.84)	<0.001	10.99 (2.75–44.02)	<0.001

CI: confidence interval; PSA: prostate-specific antigen; fPSA%: free-total PSA ratio; PV: prostate volume; PSAD: prostate-specific antigen density; OR: odds ratio

in the intermediate-risk group; in the high-risk group, the NPVs increased from 79.8% (79/99) to 83.1% (98/118) and 85.2% (115/135), respectively (**Table 3**).

DISCUSSION

In the era of precision medicine, the mpMRI pathway is being increasingly used for the detection of PCa.[21] For patients with suspicious lesions on mpMRI, guidelines recommend combining systematic biopsy, mpMRI and MRI-targeted biopsy.[2] However, for men with negative prebiopsy mpMRI results, whether systematic biopsy can be omitted remains controversial.[10] Previous studies reported combining low PSAD and negative mpMRI to exclude patients with PCa; however, the predictive role and optimal cutoff values varied regionally.[13,15,17] Our study revealed that a PI-RADS v2 score <3 combined with a PSAD <0.20 ng ml^{-2} might be a potential criterion for the Chinese population to safely omit prompt prostate biopsy. Patients with negative prebiopsy mpMRI may be further stratified by PSA and PSAD levels.

In the mid-1980s, mpMRI was first introduced for PCa diagnosis, mainly with T1- and T2-weighted sequences.[6] The additional imaging sequences and the use of structured reporting systems further improved the accuracy and popularity of mpMRI.[22] In 2012, the initial version for the PI-RADS classification system (PI-RADS version 1) was released, which provided promising accuracy in detecting PCa (sensitivity: 0.78, and specificity: 0.79).[7,23] The updated version published 2 years later (PI-RADS version 2) and aimed to simplify the time-consuming flow charts and decrease variability in examination performance and showed better sensitivity (0.95 *vs* 0.88) and similar specificity (0.73 *vs* 0.75) compared with PI-RADS version 1.[8,24,25] Notably, despite the iteration of updated reporting systems and the improved ability to detect and localize PCa on mpMRI, it is currently insufficiently accurate

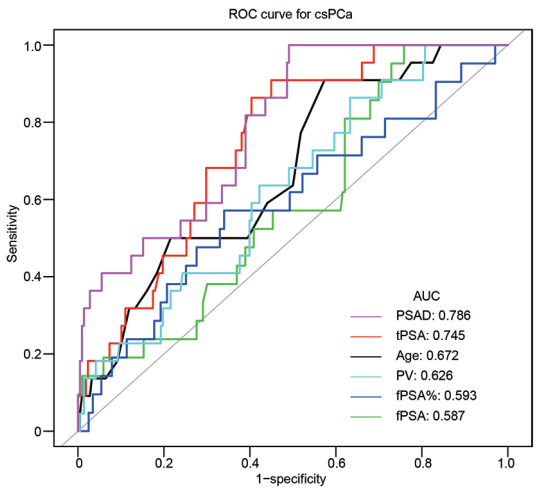

Figure 2: ROC curve analysis of the AUC was used to assess model accuracy for diagnostic markers. csPCa: clinically significant prostate cancer; PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; tPSA: total prostate-specific antigen; fPSA%: free-total PSA ratio; PV: prostate volume; fPSA: free PSA; ROC: receiver operating characteristic; AUC: area under the ROC curve.

to use a negative mpMRI scan to omit prostate biopsy.[10,26] Galosi *et al.*[27] found that mpMRI may miss cribriform cancer and low-volume high-grade cancers. The consensus also showed that positive digital rectal examination (DRE) is still an indication for biopsy, irrespective of PSA values and imaging results.[28] In addition, PCa discovered with DRE only is frequently correlated with adverse pathology.[2]

Because using PSA to detect csPCa has low predictive value and specificity, and high-grade cancer may produce less PSA than differentiated cancers,[29] the use of PSAD which combines the predictive information of serum PSA and prostate volume together has a promising value for predicting disease progression with active surveillance.[12] EAU Guidelines have assigned a PSAD <0.15 ng ml^{-2} as part of the criteria for delayed invasive intervention for patients already diagnosed with PCa.[2] Researchers have also started to apply PSAD as an indicator to stratify patients with negative mpMRI before prostate biopsy. Pagniez *et al.*[30] systematically reviewed the literature and concluded that a PSAD <0.15 ng ml^{-2} combined with negative prebiopsy mpMRI is the most powerful tool to identify men without csPCa who may avoid biopsy. However, none of the studies included in the review focused on Asian men. Recently, Norris *et al.*[31]

Table 3: Negative predictive value of multiparametric magnetic resonance imaging for prostate cancer in different patient groups stratified by prostate-specific antigen density and prostate-specific antigen

PSAD value (ng ml^{-2})	*PCa*	*csPCa*		
		Total	*PSA <10 ng ml^{-1}*	*PSA ≥10 ng ml^{-1}*
<0.20, % (*n*/total)	91.0 (101/111)	100.0 (111/111)	100.0 (71/71)[a]	100.0 (40/40)[a]
≥0.20, % (*n*/total)	77.5 (100/129)	82.9 (107/129)	93.3 (28/30)[b]	79.8 (79/99)[c]
<0.15, % (*n*/total)	94.0 (63/67)	100.0 (67/67)	100.0 (46/46)[a]	100.0 (21/21)[a]
≥0.15, % (*n*/total)	79.8 (138/173)	87.3 (151/173)	96.4 (53/55)[b]	83.1 (98/118)[c]
<0.10, % (*n*/total)	85.7 (18/21)	100.0 (21/21)	100.0 (17/17)[a]	100.0 (4/4)[a]
≥0.10, % (*n*/total)	83.6 (183/219)	90.0 (197/219)	97.6 (82/84)[b]	85.2 (115/135)[c]

[a]Low-risk group; [b]intermediate-risk group; [c]high-risk group. PSAD: prostate-specific antigen density; PSA: prostate-specific antigen; PCa: prostate cancer; csPCa: clinically significant prostate cancer

indicated that the combination of the PSAD threshold altered the rates of undetected csPCa in patients with negative mpMRI (PI-RADS versions 1 and 2). They showed that using a PSAD cutoff values of 0.15 ng ml^{-2} and 0.1 ng ml^{-2} reduced the missed diagnosis rate of csPCa among 331 patients to 9% (30 patients; 95% CI: 6.2%–13%) and 3% (11 patients; 95% CI: 1.7%–5.9%), respectively. Based on our study results, if a PSAD <0.20 ng ml^{-2} was established as the criterion to omit biopsy, almost 463 of every 1000 patients could safely avoid unnecessary biopsy, with no patients at risk of missed diagnosis of csPCa (per 1000 patients, 279 patients had PSAD of 0.15 ng ml^{-2} and 88 patients had PSAD of 0.10 ng ml^{-2}). Because PSAD is a low-cost and reliable marker to predict cancer on biopsy, its usefulness can be extended to patients in active surveillance. Roscigno *et al*.[32] observed that the use of PSAD ≥0.20 ng ml^{-2} improved the predictive accuracy of mpMRI for reclassifying patients in active surveillance. Therefore, the results of our study could also be evaluated in other clinical scenarios, such as active surveillance and previous negative biopsy.

Our study revealed that the highest csPCa detection rate was found among men with PSAD ≥0.20 ng ml^{-2} and PSA ≥10 ng ml^{-1} (csPCa detection rate: 20.2%), followed by the group of men with PSAD ≥0.20 ng ml^{-2} and PSA <10 ng ml^{-1} (csPCa detection rate: 6.7%). In clinical practice, once diagnosed with PCa, those patients harboring PSA >10 ng ml^{-1} would be categorized into the intermediate- or high-risk group based on the increasing risk of biochemical recurrence after curative treatment. We assumed that the more precise stratification based on mpMRI results (negative or positive), PSAD (<0.20 ng ml^{-2} or ≥0.20 ng ml^{-2}) and PSA (<10 ng ml^{-1} or ≥10 ng ml^{-1}) may help classify patients into different risk groups before biopsy and thus play a role in informing prostate biopsy decisions. However, multicenter designed studies are warranted to validate our results.

Our study had several limitations. Firstly, the sample size was relatively small, and the strict inclusion criteria for biopsy-naïve patients further limited our cohort size; however, these results were consistent with those of other studies.[13,17] In addition, DRE results were not included in our study. Secondly, systematic biopsy results rather than radical prostatectomy specimens or saturation biopsy settings were used as the reference standard, which may have overestimated the NPV of mpMRI, whereas 12-core mapping biopsy may also be considered undersampling in large PVs, leading to underdetection.[33] Nevertheless, patients without cancer on biopsy do not undergo surgery, and 18- to 24-core saturation biopsies may lead to overdiagnosis of low-risk tumors as well as increased complication rates. Moreover, 12-core systematic biopsy currently remains the most prevalent standard for prostate biopsy worldwide. Furthermore, the overall NPV of mpMRI in our study seemed lower compared with other cohorts. This finding is likely due to the prebiopsy triage and was also observed in the PRIMARY trial.[34] Thirdly, a number of urologists, radiologists and pathologists become involved in the biopsy process, which may cause internal variation. However, this approach reflected real-world practice, and all procedures (imaging reporting, pathology assessment, and biopsy performance) were performed in line with published guidelines.[2,8,20] Finally, our results were limited by the retrospective and single-center study design. The diagnostic information for patients who had negative MRI results and refused to undergo biopsy was not available. However, as Donato *et al*.[35] reported in their mpMRI-based triage pathway, in which the decision to biopsy was at the discretion of the treating urologist assisted by multiple variables, patients with negative mpMRI who chose not to undergo biopsy had significantly lower PSAD. Such facts may help us affirm the hypothesis that the unavailable data in our study would have little impact on our results because the patients with lower PSAD may have a lower risk of invasive cancer and are more likely to choose not to undergo an immediate biopsy.

CONCLUSIONS

In conclusion, PSAD in combination with negative mpMRI can facilitate evaluating the necessity of prostate biopsy. A PI-RADS v2 score <3 combined with a PSAD <0.20 ng ml^{-2} could be potential criteria for the Chinese population to safely omit prompt biopsy. Multicenter studies are warranted to validate whether our results may be extrapolated to other scenarios.

AUTHOR CONTRIBUTIONS

XT, THL, and Lu Y designed the study; XT and CCZ wrote this article in cooperation; XT and CCZ performed the data analyses; Lu Y and QW were responsible for study supervision and were the guarantor of the article; DMC, Ling Y and LN got involved in the biopsy procedure (ultrasound imaging, MRI imaging and pathology assessment); and XT, SQ, ZHL, KJ, JKL, and XYX collected the data. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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Supplementary Table 1: Sequence parameters of multiparametric magnetic resonance imaging protocol

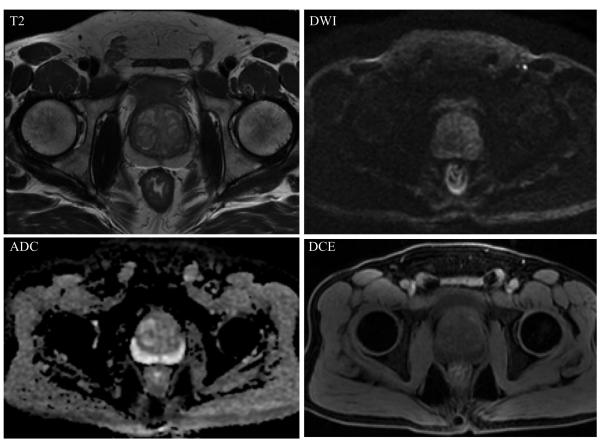
Sequence	*Siemens*			*GE Healthcare*		
	T2 TSE axial	*EPI DWI axial*	*DCE axial*	*T2 TSE axial*	*EPI DWI axial*	*DCE axial*
TR (ms)	6220	5100	4.29	3253	3635	4.088
TE (ms)	101	89	2.14	129.1	81.5	1.788
Flip angle (°)	160	180	9	103.5	90	12
Freq FOV (mm; phase FOV)	200	256	256	248	260	380
Slices/thickness (mm)	3	3	2	4	4	2
Voxel size (mm)	0.6×0.6	1.6×1.6	0.8×0.8	0.6×0.6	1.6×1.6	0.7×0.7
Averages/NEX	2	b50-2, b400-3, b800-4, b1400-6	1	2.5	b50-2, b200-3, b1400-16	1
b values (s/mm^2; directions)		50/200/800/1400			50/200/1400	
Time	02:25	04:17	04:27	02:07	04:10	04:19

TR: repetition time; TE: echo time; FOV: field of view; EPI: echo planar imaging; TSE: turbo-spin echo; DCE: dynamic contrast enhancement; NEX: number of excitation; DWI: diffusion-weighted imaging

- 9 patients (9/249, 3.6%) were reclassified as PI-RADS >2 after expert uroradiologist review

Example:

A 61-year-old patient (PSA: 8.63 ng/mL, fPSA: 1.32 ng/mL, fPSA/PSA: 0.153, mpMRI-derived prostate volume: 60.43 cm^3, PSAD: 0.14 ng/mL/cm^3) had a prebiopsy MRI that detected abnormal nodules at the transition zone of the prostate (PI-RADS 2)



Supplementary Table 2: Details of receiver operating characteristic curve

Parameter	*AUC, CI 95%*	*P*
PSAD	0.786 (0.699–0.874)	
tPSA	0.746 (0.655–0.835)	0.264
Age	0.672 (0.560–0.783)	0.104
PV	0.623 (0.511–0.741)	<0.01
f/t PSA	0.593 (0.456–0.730)	<0.01
fPSA	0.587 (0.469–0.706)	<0.01

PSAD: prostate-specific antigen density; tPSA: total prostate-specific antigen; PV: prostate volume; f/t PSA: free-total PSA ratio; AUC: area under the curve; fPSA: free PSA; CI: confidence interval