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ORIGINAL ARTICLE

Prostate Cancer

Using the Prostate Imaging Reporting and Data System version 2 (PI-RIDS v2) to detect prostate cancer can prevent unnecessary biopsies and invasive treatment

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Prostate cancer (PCa) is one of the most common cancers among men globally. The authors aimed to evaluate the ability of the Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) to classify men with PCa, clinically significant PCa (CSPCa), or no PCa, especially among those with serum total prostate-specific antigen (tPSA) levels in the "gray zone" (4–10 ng ml^{-1}). A total of 308 patients (355 lesions) were enrolled in this study. Diagnostic efficiency was determined. Univariate and multivariate analyses, receiver operating characteristic curve analysis, and decision curve analysis were performed to determine and compare the predictors of PCa and CSPCa. The results suggested that PI-RADS v2, tPSA, and prostate-specific antigen density (PSAD) were independent predictors of PCa and CSPCa. A PI-RADS v2 score ≥4 provided high negative predictive values (91.39% for PCa and 95.69% for CSPCa). A model of PI-RADS combined with PSA and PSAD helped to define a high-risk group (PI-RADS score = 5 and PSAD ≥0.15 ng ml^{-1} cm^{-3}, with tPSA in the gray zone, or PI-RADS score ≥4 with high tPSA level) with a detection rate of 96.1% for PCa and 93.0% for CSPCa while a low-risk group with a detection rate of 6.1% for PCa and 2.2% for CSPCa. It was concluded that the PI-RADS v2 could be used as a reliable and independent predictor of PCa and CSPCa. The combination of PI-RADS v2 score with PSA and PSAD could be helpful in the prediction and diagnosis of PCa and CSPCa and, thus, may help in preventing unnecessary invasive procedures.
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INTRODUCTION

Prostate cancer (PCa) is the most common cancer among men in the United States, with 161 360 newly diagnosed cases in 2017 (19% of all diagnosed cancer cases).[1] Furthermore, the incidence and mortality of PCa in China have exhibited increasing trends during recent years.[2] Conventional screening and diagnostic techniques for PCa include digital rectal examination, prostate-specific antigen (PSA) testing, and transrectal ultrasound (TRUS)-guided biopsy. In addition, multiparametric magnetic resonance imaging (mpMRI) is useful for detecting PCa.[3–5]

In 2012, the European Society of Urogenital Radiology introduced the Prostate Imaging Reporting and Data System version 1 (PI-RADS v1) to classify mpMRI findings.[6,7] A meta-analysis revealed that PI-RADS v1 provided high accuracy for diagnosing PCa, although substantial heterogeneity was detected because of differences in the use of PI-RADS.[8] Thus, a standardized and globally acceptable second version (PI-RADS v2) was developed through an international collaboration of the American College of Radiology, European Society of Urogenital Radiology, and the AdMetech Foundation.[9–11] A comparison of the two versions revealed that PI-RADS v2 is simpler and more accurate for use in clinical practice[11] and has subsequently been validated in various clinical studies.[12–15]

However, there can be some pitfalls associated with PI-RADS v2 in the detection of PCa.[16] In addition, overdiagnosis and overtreatment are important problems for identifying and managing patients with PCa and clinically significant PCa (CSPCa).[17] To our knowledge, few studies have evaluated its performance among men exhibiting serum PSA levels in the "gray zone" (4–10 ng ml^{-1}).[18] Therefore, the present study examined the ability of PI-RADS v2 to identify PCa and CSPCa among men and those in the PSA gray zone. This information, in turn, may help prevent unnecessary invasive procedures.

PATIENTS AND METHODS

Patient population

The protocol for this retrospective single-center study was approved by the Ethics Committee of the Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China). All patients enrolled in the study signed a consent form for the procedure. Between January 2015 and July 2017, 334 patients underwent mpMRI at the Tongji Hospital and had available histopathological

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data. However, 26 patients were excluded because of previous prostate surgery (17 patients), biopsy before the mpMRI (3 patients), anti-androgen therapy at the time of biopsy (5 patients), and nonuse of PI-RADS v2 (1 patient). Thus, data from 308 consecutive patients (355 lesions) were included. The patients were divided into one of the three groups according to serum total PSA (tPSA) levels: normal (<4 ng ml^{-1}), gray zone (4–10 ng ml^{-1}), and high (>10 ng ml^{-1}). All clinical data of these patients were then analyzed.

MRI technique and reporting

All included patients underwent mpMRI, which involved T2-weighted imaging, diffusion-weighted imaging, and dynamic enhancement using a 3.0-T system (MAGNETOM Skyra; Siemens, Medical Solutions, Erlangen, Germany). The imaging was performed using an 18-element body coil above the pelvis and a spine coil underneath the pelvis. The mpMRI parameters are shown in **Supplementary Table 1**. The findings were re-reported and scored by a single experienced radiologist using PI-RADS v2.[9]

Pathology

All specimens were obtained after prostate surgery, which involved radical prostatectomy, transurethral resection of the prostate, transurethral enucleation and resection of the prostate, and/or TRUS-guided 12+X core biopsy (TRUS-guided 12-core systematic biopsy combined with TRUS-guided targeted biopsy and cognitive MRI fusion-guided targeted biopsy). TRUS-guided biopsy was performed using a 2102 BK Ultrasound system (BK Medical A/S, Herlev, Denmark). The specimens were fixed in 40% buffered formalin (AS1055A; Wuhan Aspen Biotechnology Co., ltd., Wuhan, China), embedded in paraffin (M5904; Shanghai Shanran Biotechnology Co., ltd., Shanghai, China), cut into 4-μm slices, and stained using hematoxylin and eosin (AS1018; Wuhan Aspen Biotechnology Co., ltd.). Experienced pathologists performed the histopathological assessments and categorized the results as PCa (with Gleason grade), atypical glands, or no cancer (*e.g.*, benign prostate tissue, benign prostatic hyperplasia, and prostatitis). The postoperative pathological report was considered to be the final pathological results for the patients who underwent both TRUS-guided biopsy and surgery. CSPCa was defined as a Gleason score of ≥3+4, tumor volume ≥0.5 cm^3, or tumor category ≥T3 according to the Epstein criteria.[19,20] The locations of the suspicious focal area of the mpMRI were compared with the site in the pathological section, and the PI-RADS v2 scores and pathological results of each focal area were determined and matched.

Statistical analyses

The factors evaluated for PCa and CSPCa included age, tPSA, prostate volume, PSA density (PSAD), and PI-RADS v2 score. Continuous data were reported as median and interquartile range, while categorical data were reported as number and percentage. Univariate and multivariate analyses were performed using logistic regression analysis to determine significant predictors of PCa and CSPCa. Diagnostic performance was evaluated using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy, which were reported with the 95% confidence intervals (CIs). Receiver operating characteristic (ROC) analysis was used to evaluate the area under the ROC curve (AUC). Mann–Whitney U-test was carried out to evaluate the detection rates of PI-RADS v2 scores.

For better application in individual risk evaluation, two predictive models were constructed to predict the presence of CSPCa in all patients (model 1) and patients in the PSA gray zone (model 2) based on multivariable logistic analysis. Model 1 was constructed by a statistical association including tPSA and PI-RADS v2 score, whereas model 2 included PSAD and PI-RADS v2 score. Decision curve analysis was performed using R version 3.1.3 (R foundation for Statistical Computing, Vienna, Austria). Other analyses were performed using IBM SPSS software (version 19.0; IBM Corp, Armonk, NY, USA), the MedCalc statistical software (version 15.2; MedCalc Software bvba, Ostend, Belgium) and the OpenEpi website (version 3.01).[21] $P < 0.05$ was considered statistically significant.

RESULTS

The 308 patients with 355 lesions included in the final analysis were grouped according to PSA level as follows: normal ($n = 35$ [44 lesions]), gray zone ($n = 80$ [102 lesions]), and high ($n = 193$ [209 lesions]). The characteristics of all patients and patients in the subgroups are shown in **Table 1**. The histopathological outcomes, stratified according to PI-RADS v2 score, and the detection rates of all patients and patients in the PSA gray zone for PCa and CSPCa are shown in **Supplementary Table 2** and **3**. Diagnostic performance for PCa and CSPCa in all patients and patients in the subgroups for two different cutoff points (PI-RADS v2 score 4 versus 5) is shown in **Supplementary Table 4**.

Univariate and multivariate analyses of risk factors for PCa and CSPCa

The univariate logistic regression analysis demonstrated that tPSA, PSAD, and PI-RADS v2 score demonstrated significant predictive value for PCa and CSPCa among all patients (**Table 2**). The tPSA and prostate volume data were excluded from the multivariate analysis to avoid confounding. The multivariate logistic regression analysis revealed that PI-RADS v2 score and PSAD were independent predictors of PCa and CSPCa (**Table 2**).

Performance of the PI-RADS v2 system among all patients

Among all patients, the pathological detection rates for PCa using PI-RADS v2 scores of 1–5 were 5.0%, 6.3%, 17.0%, 58.3%, and 95.1%, respectively. For CSPCa, the detection rates were 0, 2.8%, 10.6%, 54.2%, and 91.8%, respectively (**Supplementary Table 2**).

For PCa, the AUC of PI-RADS v2 was 0.932, which was slightly higher than that of PSAD (0.903) and tPSA (0.867), and noticeably higher than that of age (0.626) and prostate volume (0.596) (**Figure 1a**). For CSPCa, similar to the above result, the AUC of PI-RADS v2 (0.949) was slightly higher than that of PSAD (0.921) and tPSA (0.889), and noticeably higher than that of age (0.607) and prostate volume (0.584) (**Figure 1b**).

Results of the decision curve analysis demonstrated that the net benefit of PI-RADS v2 score was higher than tPSA ($P = 0.43$ and $P = 0.43$), PSAD ($P = 0.52$ and $P = 0.51$), prostate volume ($P = 0.02$ and $P = 0.02$), and age ($P = 0.03$ and $P = 0.02$), for PCa and CSPCa, respectively. Compared with these factors, model 1 had a superior net benefit, both for PCa and CSPCa (**Figure 2a** and **2b**).

A PI-RADS v2 score of ≥4 provided sensitivity for PCa of 87.84%, specificity of 92.27%, PPV of 89.04%, NPV of 91.39%, and diagnostic accuracy of 90.42%. For CSPCa, it provided sensitivity for PCa of 93.28%, specificity of 90.50%, PPV of 85.62%, NPV of 95.69%, and diagnostic accuracy of 91.55% (**Supplementary Table 4**).

Performance of the PI-RADS v2 system for patients in the PSA gray zone

Among patients in the PSA gray zone, the pathological detection rates for PCa using PI-RADS v2 scores of 1–5 were 0, 7.5%, 10.0%, 33.3%,

Table 1: The characteristics of all patients and each subgroup

Characteristics	*All patients (n=308) with 355 lesions*	*Normal PSA group (n=35, 11.4%) with 44 lesions (12.4%)*	*PSA gray zone group (n=80, 26.0%) with 102 lesions (28.7%)*	*High PSA group (n=193, 62.7%) with 209 lesions (58.9%)*
Age (year), median (IQR)	68 (63–74)	68 (61–75)	66 (60–72)	69 (64–75)
Prostate volume (cm^3), median (IQR)	46.73 (32.05–71.38)	37.63 (24.94–47.77)	47.51 (36.07–72.98)	49.65 (32.14–76.18)
tPSA (ng ml^{-1}), median (IQR)	14.23 (6.96–54.29)	2.67 (1.63–3.45)	6.91 (5.94–8.37)	37.11 (16.39–94.37)
PSAD (ng ml^{-1} cm^{-3}), median (IQR)	0.33 (0.13–1.33)	0.06 (0.04–0.09)	0.14 (0.10–0.21)	0.82 (0.34–2.14)
PI-RADS score, *n* (%)				
1	20 (5.6)	5 (11.4)	11 (10.8)	4 (1.9)
2	142 (40.0)	26 (59.1)	53 (52.0)	63 (30.1)
3	47 (13.2)	7 (15.9)	20 (19.6)	20 (9.6)
4	24 (6.8)	3 (6.8)	9 (8.8)	12 (5.7)
5	122 (34.4)	3 (6.8)	9 (8.8)	110 (52.6)
Method of obtaining pathological result, *n* (%)				
RP/TURP/TUERP	55 (15.5)/94 (26.5)/22 (6.2)	5 (11.4)/21 (47.7)/3 (6.8)	10 (9.8)/33 (32.4)/8 (7.8)	40 (19.1)/40 (19.1)/11 (5.3)
Biopsy	283 (79.7)	28 (63.6)	85 (83.3)	170 (81.3)
Pathological result, *n* (%)				
PCa	148 (41.7)	4 (9.1)	15 (14.7)	129 (61.7)
CSPCa	134 (37.7)	2 (4.5)	13 (12.7)	119 (56.9)
Non-PCa	207 (58.3)	40 (90.9)	87 (85.3)	80 (38.3)

CSPCa: clinically significant prostate cancer; IQR: interquartile range; PCa: prostate cancer; PI-RADS: Prostate Imaging Reporting and Date System; PSAD: prostate-specific antigen density; RP: radical prostatectomy; tPSA: total prostate-specific antigen; TUERP: transurethral enucleative resection of prostate; TURP: transurethral resection of prostate, PSA: prostate-specific antigen

Table 2: Univariate and multivariate logistic regression analyses to detect prostate cancer and clinically significant prostate cancer

Parameter	*Univariate*		*Multivariate*	
	Odds ratio (95% CI)	*P*	*Odds ratio (95% CI)*	*P*
For PCa				
Age (year)	1.055 (1.027–1.083)	<0.001	1.055 (1.009–1.103)	0.019
tPSA (ng ml^{-1})	1.070 (1.051–1.089)	<0.001	NA	NA
Prostate volume (ml)	0.995 (0.988–1.002)	0.131	NA	NA
PSAD (ng ml^{-1} cm^{-3})	21.387 (9.506–48.118)	<0.001	5.020 (2.105–11.973)	<0.001
PI-RADS v2 score	6.254 (4.552–8.592)	<0.001	4.142 (2.942–5.832)	<0.001
For CSPCa				
Age (year)	1.046 (1.019–1.074)	0.001	1.030 (0.982–1.081)	0.228
tPSA (ng ml^{-1})	1.068 (1.050–1.086)	<0.001	NA	NA
Prostate volume	0.996 (0.989–1.002)	0.222	NA	NA
PSAD (ng ml^{-1} cm^{-3})	19.429 (9.094–41.507)	<0.001	4.489 (1.990–10.127)	<0.001
PI-RADS v2 score	8.018 (5.487–11.715)	<0.001	5.201 (3.500–7.728)	<0.001

P<0.05 means statistically significant. CI: confidence interval; CSPCa: clinically significant prostate cancer; NA: not assessed; PCa: prostate cancer; PI-RADS v2: Prostate Imaging Reporting and Date System version 2; PSAD: prostate-specific antigen density; tPSA: total prostate-specific antigen

and 66.7%, respectively. For CSPCa, the detection rates were 0, 3.8%, 10.0%, 33.3%, and 66.7%, respectively (**Supplementary Table 3**).

The AUCs for PCa were 0.794 using PI-RADS v2 and 0.737 using PSAD, which were noticeably higher than the values for prostate volume (0.699), age (0.593), and tPSA (0.574) (**Figure 1c**). Similarly, for CSPCa, the AUC of PI-RADS v2 was 0.855, which was higher than that of PSAD (0.726) and noticeably higher than that of prostate volume (0.678), tPSA (0.617), and age (0.582) (**Figure 1d**).

The results of the decision curve analysis demonstrated that the net benefit of PI-RADS v2 score was slightly higher than PSAD ($P = 0.32$ and $P = 0.16$), prostate volume ($P = 0.48$ and $P = 0.20$), and age ($P = 0.0.33$ and $P = 0.17$), for PCa and CSPCa, respectively. And, model 2 had a similar net benefit to PI-RADS v2 score (**Figure 2c** and **2d**).

For patients in the PSA gray zone, a PI-RADS v2 score of ≥4 provided sensitivity for PCa of 60.00%, specificity of 89.66%, PPV of 50.00%, NPV of 92.86%, and diagnostic accuracy of 85.29%. For CSPCa, it provided sensitivity of 69.23%, specificity of 89.89%, PPV of 50.00%, NPV of 95.24%, and diagnostic accuracy of 87.25%. When we considered a PI-RADS v2 score of 5 as the threshold for CSPCa, it provided sensitivity of 46.15%, specificity of 96.63%, PPV of 66.67%, NPV of 92.47%, and diagnostic accuracy of 90.20% (**Supplementary Table 4**).

Establishment and evaluation of the prediction model

Figure 3 shows the detection rates of CSPCa in each category classified according to tPSA (normal, gray zone, and high), PSAD (<0.15 ng ml^{-1} cm^{-3} or ≥0.15 ng ml^{-1} cm^{-3} in gray zone PSA group), and PI-RADS v2 score. The categories of PI-RADS score 5 and PSAD ≥0.15 ng ml^{-1} cm^{-3} with tPSA in the gray zone (4–10 ng ml^{-1}), or PI-RADS score ≥4 with high tPSA level (>10 ng ml^{-1}) were defined as the high-risk group (red zones) with detection rates of 75%–95% for CSPCa. In contrast, the categories of PI-RADS score <4 with normal tPSA level (0–4 ng ml^{-1}), PI-RADS score <4 and PSAD <0.15 ng ml^{-1} cm^{-3} with tPSA in the gray zone, PI-RADS score <3 and PSAD ≥0.15 ng ml^{-1} cm^{-3} with tPSA in

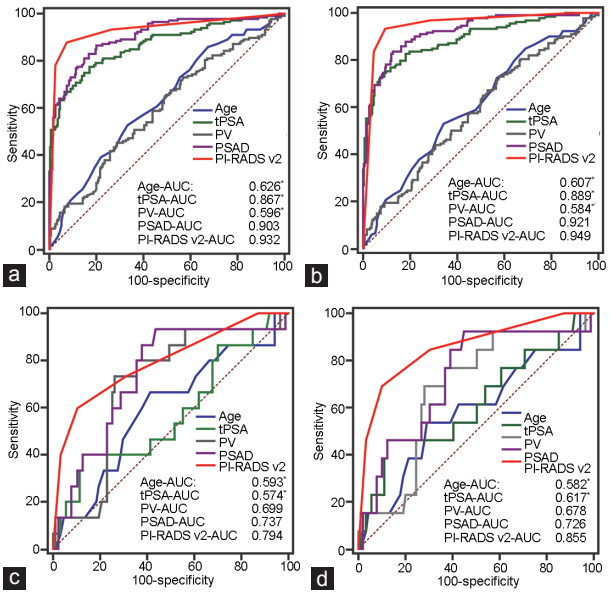

Figure 1: ROC analyses of each factor in all patients for (**a**) PCa and (**b**) CSPCa, and in patients with PSA in gray zone for (**c**) PCa and (**d**) CSPCa. ROC curves show diagnostic accuracy of age (blue line), tPSA (green line), prostate volume (gray line), PSAD (purple line), and PI-RADS v2 score (red line). *There was a significant difference compared with the AUC of PI-RADS v2. AUC: area under the ROC curve; CSPCa: clinically significant prostate cancer; PCa: prostate cancer; PI-RADS v2: Prostate Imaging Reporting and Data System version 2; PSAD: prostate-specific antigen density; PV: prostate volume; ROC: receiver operating characteristic; tPSA; total prostate-specific antigen.

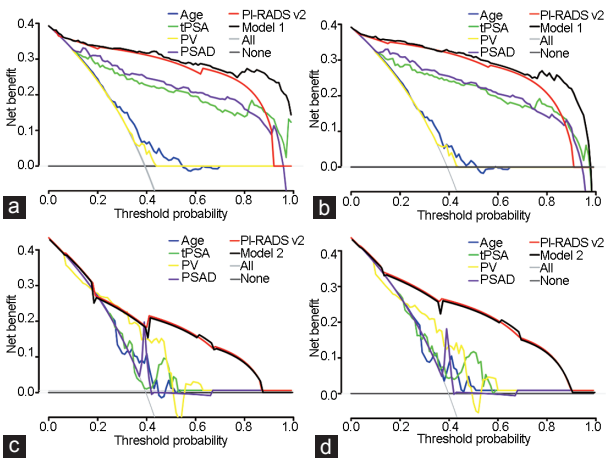

Figure 2: Decision curve analysis of each factor in all patients for (**a**) PCa and (**b**) CSPCa, and in patients with PSA in gray zone for (**c**) PCa and (**d**) CSPCa. DCA curves show net benefit of age (blue line), tPSA (green line), prostate volume (yellow line), PSAD (purple line), PI-RADS v2 score (red line), and model 1 and model 2 (black line). Model 1 is constructed by a statistical association including tPSA and PI-RADS v2 score, whereas model 2 includes PSAD and PI-RADS v2 score. CSPCa: clinically significant prostate cancer; DCA: decision curve analysis; PCa: prostate cancer; PI-RADS v2: Prostate Imaging Reporting and Data System version 2; PSAD: prostate-specific antigen density; PV: prostate volume; tPSA: total prostate-specific antigen.

the gray zone, or PI-RADS score <3 with high tPSA level were defined as low-risk (green zones), with detection rates of 0–8% for CSPCa. Others were defined as moderate risk (yellow zones), with detection rates of 15%–40% for CSPCa. The detection rates for PCa and CSPCa of patients with low, moderate, and high risk were 6.1% and 2.2%, 29.2% and 22.9%, and 96.1% and 93.0%, respectively.

PSA group	PSAD level (ng ml^{-1}cm^{-3})	PI-RADS v2 score				
		1	2	3	4	5
Normal (*n*=44)	-	0 (*n*=5)	0 (*n*=26)	0 (*n*=7)	33% (*n*=3)	33% (*n*=3)
Gray zone (*n*=102)	<0.15	0 (*n*=7)	0 (*n*=29)	0 (*n*=10)	25% (*n*=4)	33% (*n*=3)
	≥0.15	0 (*n*=4)	8% (*n*=24)	20% (*n*=10)	40% (*n*=5)	83% (*n*=6)
High (*n*=209)	-	0 (*n*=4)	3% (*n*=63)	15% (*n*=20)	75% (*n*=12)	95% (*n*=110)

Figure 3: Clinically significant prostate cancer detection rates stratified by the combination of PI-RADS v2 score, tPSA, and PSAD. Green, yellow, and red zones indicate low-, moderate- and high-risk groups, respectively. PI-RADS v2: Prostate Imaging Reporting and Data System version 2; PSAD: prostate-specific antigen density; tPSA: total prostate-specific antigen.

DISCUSSION

The present study revealed that the PI-RADS v2 score was an independent predictor for both PCa and CSPCa, and a PI-RADS v2 score ≥4 was useful for PCa screening, based on high values for sensitivity, specificity, PPV, and NPV. Furthermore, ROC curve analysis revealed that PI-RADS v2 was slightly more effective than PSA or PSAD for screening (**Figure 1**). This conclusion was similar to those of several previous studies.[11,15,22–24] Subsequently, the patients were divided into one of three groups according to tPSA level and we found that in both the normal PSA and high PSA groups, the parameters of the diagnostic performance were high for both PCa and CSPCa (**Supplementary Table 4**). This suggests that PI-RADS v2 has a good predictive value for PCa after preliminary screening of PSA levels.

Particularly, among patients in the PSA gray zone, PI-RADS v2 retained its good diagnostic performance with a high diagnostic accuracy. Using a PI-RADS v2 score ≥4 provided high specificity (89.66% and 89.89%) and NPV (92.86% and 95.24%), with moderate sensitivity (60.00% and 69.23%) and low PPV (50.00% and 50.00%), for PCa and CSPCa, respectively. Furthermore, despite a lower sensitivity (46.15%), changing the threshold to 5 provided the persistently high specificity (96.63%) and NPV (92.47%) for CSPCa. This finding highlights the possibility that CSPCa can be ruled out in a large number of patients, which can prevent unnecessary invasive treatment for patients in the PSA gray zone and PI-RADS v2 score ≤4.

It is worth noting that the sensitivity was unexpectedly low in patients with PSA levels in the gray zone. This may be related to the composition of the study group. Abnormal PSA levels may be caused by many conditions such as prostatitis and hemorrhage, among others, resulting in the low specificity and high false positive rate for PSA.[25] On the other hand, prostatitis, granuloma, abscess, and hemorrhage may represent pitfalls in prostate mpMRI, which leads to the results of PI-RADS inconsistent with reality.[16] Among the 102 lesions in patients in the PSA gray zone group, 66 were histopathologically diagnosed as benign prostatic hyperplasia, 3 prostatitis, 9 benign prostatic hyperplasia with prostatitis, 1 granuloma, and 1 hemorrhage. This may not only lead to an elevation in PSA levels but also lead to higher PI-RADS scores, resulting in an increase in the false positive rate and a decrease in the sensitivity of PI-RADS. This, therefore, requires clinicians and radiologists to make a comprehensive judgment based on other clinical features and to further evaluate and modify the PI-RADS score and diagnosis.

Mertan *et al*.[14] prospectively evaluated the detection rates for various PI-RADS v2 scores, and reported that a PI-RADS v2 score of

5 had a better detection rate (78%), compared to a score of 4 (30%). The detection rates in the present study were higher (95.1% for a score of 5 and 58.3% for a score of 4), which may be related to differences in PCa staging between the Chinese and Western populations. For example, most Chinese patients present with mid-to-late stage PCa,[26] which would be associated with clearer and more typical lesions that are assigned higher scores. Nevertheless, the detection rates for CSPCa using a score of 3 were relatively low in both Mertan *et al*.'s[14] study and the present study. This finding is not in agreement with the system's design which indicates that "clinically significant cancer is equivocal,"[9] and similar findings were reported by Mertan *et al*.[14] Thus, PI-RADS v2 should not be confined to its description in the clinical setting. Woo *et al*.[27] investigated the number of patients who were downgraded after radical prostatectomy in each PI-RADS score group and reported that 4/8 (50.0%), 4/49 (8.2%), and 2/47 (4.3%) of patients were downgraded with PI-RADS scores 3, 4, and 5, respectively, meaning that one-half of patients with a PI-RADS score of 3 may be candidates for active surveillance. The present study revealed a CSPCa detection rate of 10.6% among all patients and 10.0% among patients in the PSA gray zone, supporting a similar conclusion. The PI-RADS v2 scoring system no longer included clinical factors, and was completely dependent on mpMRI,[28] which made the report and score more objective. However, in practice, clinicians should take clinical factors into consideration, regard the score as one of the risk stratification indicators, and devote special attention to patients with a PI-RADS score of 3.

The insignificant lesions (Gleason score 6) appear to be clinically indolent and could be considered as "low-risk" PCa.[27] Active surveillance, which monitors for signs of progression rather than immediately treating the disease after diagnosis, can be a feasible and safe option for patients with insignificant lesions.[27,29,30] Recently, the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) panel develops recommendations for MRI to assess the natural history of MRI findings and, thus, facilitate the determination of thresholds that identify radiologically significant disease in men undergoing active surveillance for PCa so that these patients can receive the appropriate treatment.[31] A few groups have reported that improved diagnostic performance and avoidance of unnecessary biopsy can be achieved by combining PI-RADS with other markers, such as PSAD,[32] lesion volume,[33] and the prostate cancer antigen 3 (*PCA3*) gene.[34,35] For this purpose, we stratified patients according to serum tPSA levels, followed by the prediction and diagnosis of PCa based on mpMRI findings and PI-RADS v2 reports. Notably, the present study revealed that PI-RADS was useful among patients in the PSA gray zone with high diagnostic accuracy and NPV for CSPCa, suggesting that the PI-RADS v2 score system can help to prevent unnecessary invasive treatment among patients in the PSA gray zone. Nevertheless, PSA remains an important marker for identifying men with an increased risk for PCa.[36] Thus, we confidently recommend active surveillance for patients in the PSA gray zone with a PI-RADS v2 score of 4, while care is needed to detect CSPCa in patients with a score of 5, although there was no significant difference between detection rates of PI-RADS v2 scores 4 and 5 ($P = 0.221$). This approach may be effective for identifying the candidate for active surveillance without overdiagnosis and overtreatment, although it should be verified in further prospective studies.

Furthermore, we designed a prediction model that combines PI-RADS, tPSA, and PSAD. It showed that the low-risk group yielded detection rates of 6.1% and 2.2%, the moderate-risk group yielded detection rates of 29.2% and 22.9%, and the high-risk group yielded detection rates of 96.1% and 93.0% for PCa and CSPCa, respectively. This indicated that this model could predict the presence of PCa and CSPCa well, which provided a more certain way of predicting the presence of PCa. In the future, combining various clinical factors with PI-RADS score may better identify patients who can avoid unnecessary invasive procedures.

This study had several limitations, the first of which was its retrospective design, which is associated with a risk for selection bias. Second, various approaches were used to obtain the pathological specimens because some of the patients did not conform to surgical indications due to metastasis, old age, or patient refusal. We attempted to minimize the risk for bias using whole-mount pathology as the reference standard, and the biopsies as a supplement to more closely reflect the patient's structure. Third, the number of patients included in our study was small, which may have underpowered the predictive value and, thus, larger-scale data are needed to validate our findings. Fourth, the PI-RADS v2 scores were assigned only by a single radiologist, although that person had 17 years' experience in uroradiology, and previous studies have indicated that PI-RADS v2 has good interobserver agreement.[11,15,37,38]

CONCLUSIONS

The PI-RADS v2 demonstrated good performance for detecting PCa among all patients and those in the PSA gray zone; thus, PI-RADS v2 may be useful in preventing unnecessary invasive procedures. Furthermore, our results suggest that the PI-RADS score should not be confined to its description, and the combination of PI-RADS v2 score with PSA and PSAD could be helpful for the prediction and diagnosis of PCa and CSPCa.

AUTHOR CONTRIBUTIONS

CL and XYZ designed the retrospective analysis. CL, XYZ, SLL, ZXW, KY, CXF, and ZK collected, analyzed, and interpreted the clinical data and wrote and revised the manuscript. LW revised the manuscript. XYZ supervised the project and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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

REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017; 67: 7–30.
2 Chen W, Zheng R, Baade PD, Zhang S, Zeng H, *et al*. Cancer statistics in China, 2015. *CA Cancer J Clin* 2016; 66: 115–32.
3 Radtke JP, Kuru TH, Boxler S, Alt CD, Popeneciu IV, *et al*. Comparative analysis of transperineal template saturation prostate biopsy versus magnetic resonance imaging targeted biopsy with magnetic resonance imaging-ultrasound fusion guidance. *J Urol* 2015; 193: 87–94.
4 Fütterer JJ, Briganti A, De Visschere P, Emberton M, Giannarini G, *et al*. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. *Eur Urol* 2015; 68: 1045–53.
5 Hoeks CM, Barentsz JO, Hambrock T, Yakar D, Somford DM, *et al*. Prostate cancer: multiparametric MR imaging for detection, localization, and staging. *Radiology* 2011; 261: 46–66.
6 Bjurlin MA, Meng X, Le Nobin J, Wysock JS, Lepor H, *et al*. Optimization of prostate biopsy: the role of magnetic resonance imaging targeted biopsy in detection, localization and risk assessment. *J Urol* 2014; 192: 648–58.
7 Hassanzadeh E, Glazer DI, Dunne RM, Fennessy FM, Harisinghani MG, *et al*. Prostate imaging reporting and data system version 2 (PI-RADS v2): a pictorial review. *Abdom Radiol (NY)* 2016; 42: 278–89.
8 Hamoen EH, de Rooij M, Witjes JA, Barentsz JO, Rovers MM. Use of the prostate imaging reporting and data system (PI-RADS) for prostate cancer detection with

multiparametric magnetic resonance imaging: a diagnostic meta-analysis. *Eur Urol* 2015; 67: 1112–21.
9 AdMetech Foundation. PI-RADSv2: Prostate Imaging and Reporting and Data System; 2015. Available from: https://www.acr.org/-/media/ACR/Files/RADS/Pi-RADS/PIRADS-V2.pdf. [Last accessed on 2018 Jan 30].
10 Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, *et al*. PI-RADS prostate imaging-reporting and data system: 2015, version 2. *Eur Urol* 2016; 69: 16–40.
11 Tewes S, Mokov N, Hartung D, Schick V, Peters I, *et al*. Standardized reporting of prostate MRI: comparison of the prostate imaging reporting and data system (PI-RADS) version 1 and version 2. *PLoS One* 2016; 11: e0162879.
12 Schieda N, Quon JS, Lim C, El-Khodary M, Shabana W, *et al*. Evaluation of the European Society of Urogenital Radiology (ESUR) PI-RADS scoring system for assessment of extra-prostatic extension in prostatic carcinoma. *Eur J Radiol* 2015; 84: 1843–8.
13 Vargas HA, Hötker AM, Goldman DA, Moskowitz CS, Gondo T, *et al*. Updated prostate imaging reporting and data system (PIRADS v2) recommendations for the detection of clinically significant prostate cancer using multiparametric MRI: critical evaluation using whole-mount pathology as standard of reference. *Eur Radiol* 2016; 26: 1606–12.
14 Mertan FV, Greer MD, Shih JH, George AK, Kongnyuy M, *et al*. Prospective evaluation of the prostate imaging reporting and data system version 2 for prostate cancer detection. *J Urol* 2016; 196: 690–6.
15 Feng ZY, Wang L, Min XD, Wang SG, Wang GP, *et al*. Prostate cancer detection with multiparametric magnetic resonance imaging: prostate imaging reporting and data system version 1 versus version 2. *Chin Med J (Engl)* 2016; 129: 2451–9.
16 Panebianco V, Giganti F, Kitzing YX, Cornud F, Campa R, *et al*. An update of pitfalls in prostate mpMRI: a practical approach through the lens of PI-RADS v. 2 guidelines. *Insights Imaging* 2018; 9: 87–101.
17 Loeb S, Bjurlin MA, Nicholson J, Tammela TL, Penson DF, *et al*. Overdiagnosis and overtreatment of prostate cancer. *Eur Urol* 2014; 65: 1046–55.
18 Wang R, Wang J, Gao G, Hu J, Jiang Y, *et al*. Prebiopsy mp-MRI can help to improve the predictive performance in prostate cancer: a prospective study in 1,478 consecutive patients. *Clin Cancer Res* 2017; 23: 3692–9.
19 Van der Kwast TH, Roobol MJ. Defining the threshold for significant versus insignificant prostate cancer. *Nat Rev Urol* 2013; 10: 473–82.
20 Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA* 1994; 271: 368–74.
21 Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version 3.01. Available from: http://www.Awww.OpenEpi.com. [Last updated on 2013 Apr 06; Last accessed on 2017 Aug 25].
22 Seo JW, Shin SJ, Taik Oh Y, Jung DC, Cho NH, *et al*. PI-RADS version 2: detection of clinically significant cancer in patients with biopsy gleason score 6 prostate cancer. *AJR Am J Roentgenol* 2017; 209: W1–9.
23 Cash H, Maxeiner A, Stephan C, Fischer T, Durmus T, *et al*. The detection of significant prostate cancer is correlated with the prostate imaging reporting and data system (PI-RADS) in MRI/transrectal ultrasound fusion biopsy. *World J Urol* 2016; 34: 525–32.
24 Baldisserotto M, Neto EJ, Carvalhal G, de Toledo AF, de Almeida CM, *et al*. Validation of PI-RADS v.2 for prostate cancer diagnosis with MRI at 3T using an external phased-array coil. *J Magn Reson Imaging* 2016; 44: 1354–9.
25 Schröder FH, Carter HB, Wolters T, van den Bergh RC, Gosselaar C, *et al*. Early detection of prostate cancer in 2007. Part 1: PSA and PSA kinetics. *Eur Urol* 2008; 53: 468–77.
26 Na R, Jiang H, Kim ST, Wu Y, Tong S, *et al*. Outcomes and trends of prostate biopsy for prostate cancer in Chinese men from 2003 to 2011. *PLoS One* 2012; 7: e49914.
27 Woo S, Kim SY, Lee J, Kim SH, Cho JY. PI-RADS version 2 for prediction of pathological downgrading after radical prostatectomy: a preliminary study in patients with biopsy-proven Gleason Score 7 (3+4) prostate cancer. *Eur Radiol* 2016; 26: 3580–7.
28 Dola EF, Nakhla OL, Genidi EA. Assessing the validity of prostate imaging reporting and data system version 2 (PI-RADS v2) scoring system in diagnosis of peripheral zone prostate cancer. *Eur J Radiol Open* 2017; 4: 19–26.
29 Tosoian JJ, Trock BJ, Landis P, Feng Z, Epstein JI, *et al*. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol* 2011; 29: 2185–90.
30 Eggener SE, Mueller A, Berglund RK, Ayyathurai R, Soloway C, *et al*. A multi-institutional evaluation of active surveillance for low risk prostate cancer. *J Urol* 2013; 189: S19–25.
31 Moore CM, Giganti F, Albertsen P, Allen C, Bangma C, *et al*. Reporting magnetic resonance imaging in men on active surveillance for prostate cancer: the PRECISE recommendations – A Report of a European School of Oncology Task Force. *Eur Urol* 2017; 71: 648–55.
32 Washino S, Okochi T, Saito K, Konishi T, Hirai M, *et al*. Combination of PI-RADS score and PSA density predicts biopsy outcome in biopsy naïve patients. *BJU Int* 2017; 119: 225–33.
33 Martorana E, Pirola GM, Scialpi M, Micali S, Iseppi A, *et al*. Lesion volume predicts prostate cancer risk and aggressiveness: validation of its value alone and matched with prostate imaging reporting and data system score. *BJU Int* 2017; 120: 92–103.
34 Lanz C, Cornud F, Beuvon F, Lefèvre A, Legmann P, *et al*. Gleason score determination with transrectal ultrasound-magnetic resonance imaging fusion guided prostate biopsies-are we gaining in accuracy? *J Urol* 2016; 195: 88–93.
35 Kaufmann S, Bedke J, Gatidis S, Hennenlotter J, Kramer U, *et al*. Prostate cancer gene 3 (PCA3) is of additional predictive value in patients with PI-RADS grade III (intermediate) lesions in the MR-guided re-biopsy setting for prostate cancer. *World J Urol* 2016; 34: 509–15.
36 Alberts AR, Schoots IG, Roobol MJ. Prostate-specific antigen-based prostate cancer screening: past and future. *Int J Urol* 2015; 22: 524–32.
37 Rosenkrantz AB, Ginocchio LA, Cornfeld D, Froemming AT, Gupta RT, *et al*. Interobserver reproducibility of the PI-RADS version 2 lexicon: a multicenter study of six experienced prostate radiologists. *Radiology* 2016; 280: 793–804.
38 Muller BG, Shih JH, Sankineni S, Marko J, Rais-Bahrami S, *et al*. Prostate cancer: interobserver agreement and accuracy with the revised prostate imaging reporting and data system at multiparametric MR imaging. *Radiology* 2015; 277: 741–50.

Supplementary Table 1: Parameters of multiparametric magnetic resonance imaging

Characteristics	*T2WI*	*DWI*	*DCE*
Repetition time (ms)	6500–6874	4500	5.08
Echo time (ms)	104	85	1.77
Section thickness (mm)	3	3	3.5
Field of view (mm)	180×180	214×171	260×260
Matrix	384×346	90×72	192×154
Flip angle (°)	160	90	15
b values (s mm^{-2})	-	0, 200, 400, 800, 1000, 1500	-
Temporal resolution (s)	-	-	8

T2WI: T2-weighted imaging; DWI: diffusion-weighted imaging; DCE: dynamic enhancement; -: not applicable

Supplementary Table 2: The histopathological outcomes of all patients stratified by Prostate Imaging Reporting and Data System version 2 score and the detection rates of prostate cancer and clinically significant prostate cancer

Histopathological diagnoses	*PI-RADS v2 score*					*Total*	*P*
	1	*2*	*3*	*4*	*5*		
PCa							
Significant PCa	0	4	5	13	112	134	-
Insignificant PCa	1	5	3	1	4	14	-
Atypical glands	1	0	2	2	0	5	-
No cancer	18	133	37	8	6	202	-
Total	20	142	47	24	122	355	-
PCa DRs (%)	5.0	6.3	17.0	58.3	95.1		<0.001
CSPCa DRs (%)	0	2.8	10.6	54.2	91.8		<0.001

P-values compare the significance between DRs of PI-RADS v2 4 and 5 scores. *P*<0.05 means statistically significant. CSPCa: clinically significant prostate cancer; DRs: detection rates; PCa: prostate cancer; PI-RADS v2: Prostate Imaging Reporting and Data System version 2; -: not applicable

Supplementary Table 3: The histopathological outcomes of patients in the prostate-specific antigen gray zone stratified by Prostate Imaging Reporting and Data System version 2 score and the detection rates of prostate cancer and clinically significant prostate cancer

Histopathological diagnoses	*PI-RADS v2 score*					*Total*	*P*
	1	*2*	*3*	*4*	*5*		
PCa							
Significant PCa	0	2	2	3	6	13	-
Insignificant PCa	0	2	0	0	0	2	-
Atypical glands	0	0	1	2	0	3	-
No cancer	11	49	17	4	3	84	-
Total	11	53	20	9	9	102	-
PCa DRs (%)	0	7.5	10.0	33.3	66.7		0.221
CSPCa DRs (%)	0	3.8	10.0	33.3	66.7		0.221

P-values compare the significance between DRs of PI-RADS v2 4 and 5 scores. *P*<0.05 means statistically significant. PI-RADS v2: Prostate Imaging Reporting and Data System version 2; PCa: prostate cancer; CSPCa: clinically significant prostate cancer; DRs: detection rates; -: not applicable

Supplementary Table 4: The diagnostic performance of prostate cancer and clinically significant prostate cancer in each groups for cutoff point of Prostate Imaging Reporting and Data System version 2 score 4 and 5

Cutoff point	*tPSA level (ng ml^{-1})*	*Performance parameter for PCa/CSPCa*				
		SEN (95% CIs), %	*SPE (95% CIs), %*	*PPV (95% CIs), %*	*NPV (95% CIs), %*	*DA (95% CIs), %*
PI-RADS v2 score 4	<4	75.00 (30.06–95.44) /100 (34.24–100)	92.50 (80.14–97.42) /90.48 (77.93–96.23)	50.00 (18.76–81.24) /33.33 (9.68–70.00)	97.37 (86.50–99.53) /100 (90.82–100)	90.91 (78.84–96.41) /90.91 (78.84–96.41)
	4–10	60.00 (35.75–80.18) /69.23 (42.37–87.32)	89.66 (81.49–94.46) /89.89 (81.89–94.59)	50.00 (29.03–70.97) /50.00 (29.03–70.97)	92.86 (85.28–96.69) /95.24 (88.39–98.13)	85.29 (77.15–90.88) /87.25 (79.41–92.40)
	>10	91.47 (85.38–95.17) /95.80 (90.54–98.19)	95.00 (87.84–98.04) /91.11 (83.43–95.43)	96.72 (91.87–98.72) /93.44 (87.59–96.64)	87.36 (78.76–92.79) /94.25 (87.24–97.52)	92.82 (88.50–95.60) /93.78 (89.65–96.33)
	All	87.84 (81.59–92.17) /93.28 (87.73–96.43)	92.27 (87.81–95.19) /90.50 (85.91–93.70)	89.04 (82.94–93.14) /85.62 (79.01–90.40)	91.39 (86.80–94.48) /95.69 (92.02–97.72)	90.42 (86.91–93.07) /91.55 (88.19–94.02)
PI-RADS v2 score 5	<4	50.00 (15.00–85.00) /50.00 (9.45–90.55)	97.50 (87.12–99.56) /95.24 (84.214–98.68)	66.67 (20.77–93.85) /33.33 (6.15–79.23)	95.12 (83.86–98.65) /97.56 (87.40–99.57)	93.18 (81.77–97.65) /93.18 (82.77–97.65)
	4–10	40.00 (19.82–64.25) /46.15 (23.21–70.86)	96.55 (90.35–98.82) /96.63 (90.55–98.85)	66.67 (35.42–87.94) /66.67 (35.42–87.94)	90.32 (82.62–94.82) /92.47 (85.27–96.31)	88.24 (80.55–93.14) /90.20 (82.89–94.59)
	>10	83.72 (76.39–89.10) /88.24 (81.22–92.86)	97.50 (91.34–99.31) /94.44 (87.65–97.60)	98.18 (93.61–99.50) /95.45 (89.80–98.04)	78.79 (67.74–85.69) /85.86 (77.65–91.39)	89.00 (84.03–92.55) /90.91 (86.24–94.10)
	All	78.38 (71.07–84.25) /83.58 (76.39–88.90)	97.10 (93.82–98.66) /95.48 (91.87–97.52)	95.08 (89.68–97.73) /91.80 (85.57–95.49)	86.27 (81.25–90.10) /90.56 (86.12–93.68)	89.30 (85.65–92.10) /90.99 (87.55–93.54)

PCa: prostate cancer; CSPCa: clinically significant prostate cancer; PI-RADS v2: Prostate Imaging Reporting and Data System version 2; tPSA: total prostate-specific antigen; SEN: sensitivity; SPE: specificity; PPV: positive predictive value; NPV: negative predictive value; DA: diagnostic accuracy; CIs: confidence intervals