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The PRIMARY Score

Diagnostic Performance and Added Value Compared With MRI in Detecting Clinically Significant Prostate Cancer

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Purpose: Multiparametric MRI is the current standard for detecting clinically significant prostate cancer (csPCa). However, men with negative or equivocal MRI often undergo unnecessary biopsies due to concerns about false-negative results. The recently proposed ^{68}Ga-PSMA PET/CT-based PRIMARY score exhibited good diagnostic performance for csPCa. This study aimed to externally validate the performance of the PRIMARY score and evaluate its added diagnostic value to MRI triage in detecting csPCa.

Patients and Methods: This retrospective cohort study included 431 men who underwent both ^{68}Ga-PSMA PET/CT and MRI before biopsy. Performance was assessed using the area under the receiver operating characteristic curve and the decision curve analysis. The PRIMARY score + MRI was considered positive for either PRIMARY score 3–5 or Prostate Imaging Reporting and Data System (PI-RADS) 4/5.

Results: The prevalence of csPCa was 51.7% (223/431). The area under the receiver operating characteristic curve of the 5-level PRIMARY score for csPCa was significantly higher than that of MRI (0.873 vs 0.786, $P < 0.001$). For the entire group, sensitivity, specificity, positive predictive value, and negative predictive value of the PRIMARY score were 90.6%, 61.1%, 71.4%, and 85.8%, respectively, which outperformed 87.9%, 49.0%, 64.9%, and 79.1% of PI-RADS on MRI. The PRIAMRY score + MRI improved sensitivity (96.0% vs 87.9%, $P < 0.001$) and negative predictive value (91.5% vs 79.1%, $P < 0.001$) without compromising specificity and positive predictive value compared with MRI alone. This combined approach avoided 24.6% (106/431) of unnecessary biopsies, while missing 4.0% (9/223) of csPCa cases. The addition of the PRIMARY score in men with PI-RADS 1–3 showed a net benefit, but not in men with PI-RADS 4/5.

Conclusions: The PRIMARY score was superior to MRI in detecting csPCa, and its added diagnostic value was in men with negative or equivocal MRI results. The PRIMARY score + MRI improved negative predictive value and sensitivity for csPCa compared with MRI alone. Further prospective trials will validate whether men with clinical suspicion of csPCa but negative PRIMARY score + MRI can safely avoid unnecessary biopsies.

Key Words: PRIMARY score, PSMA PET/CT, prostate cancer, MRI, diagnosis

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Multiparametric MRI has emerged as the criterion standard for diagnosing prostate cancer (PCa).[1,2] In cases where a suspicious lesion is identified on the MRI, a combined targeted and systematic biopsy is recommended. However, if the MRI is negative and there is low clinical suspicion of PCa, the biopsy can be omitted through shared decision-making with the patient. An MRI-directed approach has been demonstrated to be more effective than transrectal template biopsy in reducing unnecessary biopsies and detecting clinically significant PCa (csPCa).[3,4] Nevertheless, despite the relatively high negative predictive value (NPV) of MRI, it can still miss up to 13% of csPCa cases.[5,6] Consequently, men with negative or equivocal MRI results may still undergo a biopsy due to concerns about false-negatives.

Prostate-specific membrane antigen (PSMA) PET/CT imaging has revolutionized the diagnostic pathway for PCa. Emmett et al[7] recently proposed a 5-point Likert PRIMARY score based on PSMA PET/CT that was introduced into the PCa molecular imaging standardized evaluation (PROMISE V2) criteria.[8] This score combines anatomic localization (peripheral, central, or transition zone), intraprostatic PSMA activity patterns (none, diffuse, or focal), and a very high SUV_{max} (>12) to enhance the accuracy of primary tumor diagnosis.

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Data Availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval: All procedures performed in studies 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. The institutional review board (Ethics Committees of Xijing Hospital, Fourth Military Medical University) approved this study, and all subjects signed a written informed consent.

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The PRIMARY score outperforms MRI alone in terms of diagnostic accuracy and interrater agreement, with a specificity of 64% and no sacrifice in sensitivity.

The aim of this study was to externally validate the performance of the PRIMARY score and evaluate its added diagnostic value to the MRI triage in the diagnosis of csPCa.

PATIENTS AND METHODS

Study Population

A total of 688 consecutive men who underwent both MRI and ^{68}Ga-PSMA PET/CT for suspected PCa were retrospectively reviewed between June 2017 and November 2022. The flowchart of screening was shown in Supplementary Figure S1, http://links.lww.com/CNM/A450. Finally, 431 men were enrolled for analysis. The institutional review board (Ethics Committees of Xijing Hospital, Fourth Military Medical University) approved this study, and all subjects signed a written informed consent. This study conforms with the Declaration of Helsinki and national regulations.

PSMA PET Protocol

Patients were prepared and images were acquired in accordance with standard clinical protocols. The ^{68}Ga PSMA-11 was radiolabeled using a previously described protocol.[9] All images were scanned with a Biograph 40 system (Siemens Medical Solutions, Erlangen, Germany). The whole-body PET scans were obtained 60 minutes after the IV injection of 1.8–2.2 MBq/kg ^{68}Ga-PSMA-11 according to the Joint EANM and SNMMI Procedure Guideline.[10] Low-dose CT scans (pitch 0.8, 50 mA, 120 kV [peak]) for PET attenuation were acquired (automatic mA, 120 keV, 512 × 512 matrix, 5-mm slice thickness, 1-second rotation time), followed by a PET scan with 5 bed positions (3 min/bed, from head to the proximal thighs) performed. All PET/CT images were sent to multimodal workstations for analysis.

PSMA PET/CT and PRIMARY Score Interpretation

All images were blinded reviewed by 2 experienced board-certified nuclear medicine specialists with 12 and 14 years of experience (F.K. and Z.Y.Q., respectively). Any discrepancy will be resolved by consensus with a third radiologist (W.J., with 20 years of experience in nuclear medicine). Within all the volumes of interest, SUV_{max} was measured. The PRIMARY score was evaluated according to the previous PRIMARY score study[7] and based on the following criteria: score 1, no dominant intraprostatic pattern on PSMA, low-grade activity; score 2, diffuse transition zone activity or symmetrical central zone activity that does not extend to the prostate margin on CT; score 3, focal transition zone activity visually twice above background transition zone activity; score 4, focal peripheral zone activity (no minimum intensity); and score 5, SUV_{max} >12. PRIMARY score 1–2 was defined as negative, and PRIMARY score 3–5 was defined as positive.

MRI Acquisition Protocol and Interpretation

All men received a pelvic MRI screening with a 3.0-T MR scanner (Signa; GE 750 Superconducting) through an 8-channel belly phased-control coils. The protocol consisted of T1-weighted imaging, T2-weighted imaging, and diffusion-weighted imaging (DWI) imaging sequences. All MRI scans were sent to the image postprocessing workstation (Advantage Workstation 4.6, GE Healthcare) and routinely reported by dedicated genitourinary radiologist according to the Prostate Imaging Reporting and Data System version 2 (Pl-RADS v2)[11] and, since 2019, PI-RADS v2.1.[12] For MRI alone, PI-RADS 1–2 was defined as negative, and PI-RADS 3–5 was defined as positive.

Combined PRIMARY Score + MRI

For analysis, the combination of PRIMARY score + MRI was considered negative for PRIMARY score 1–2 with PI-RADS 1–3 or positive for either PRIMARY score 3–5 or PI-RADS 4/5.

Histopathology Examination

All men received a transrectal ultrasound-guided 12-core systematic biopsy. Concurrent MRI-targeted biopsy was performed using cognitive fusion techniques when PI-RADS ≥3. For men who received radical prostatectomy, postoperative whole-mount pathological was used as pathological criterion instead. All pathology was processed and reported in accordance with 2014 International Society of Urological Pathology (ISUP) consensus guideline.[13] Clinically significant PCa was defined as the presence of any Gleason grade group (GG) ≥2 (Gleason score ≥3 + 4). Patients with a negative biopsy result had a follow-up performed within 6 months, including prostate-specific antigen (PSA) testing, MRI, necessary repeat biopsy, or transurethral resection prostate with histopathologic examination.

Statistical Analysis

Continuous variables were present as median and interquartile ranges, and the categorical variables were presented as frequencies and percentages. The areas under the receiver operating characteristic curve were used to evaluate the discriminative ability. For independent PRIMARY score, PRIMARY score ≥3 was defined as positive for analysis. For independent MRI, PI-RADS ≥3 was defined as positive for analysis. A net reclassification improvement (NRI) was calculated,[14] which quantify the extent to which individuals are more appropriately classified into risk categories using PRIMARY score versus PI-RADS. The comparison of sensitivity and specificity was performed with McNemar test. The comparison of positive predictive value (PPV) and NPV was assessed using relative predictive values,[15] and the R package DTComPair was used for analyses. Clinical utility was assessed by decision curve analysis (DCA).[16] Cohen κ with 95% confidence intervals (CIs) was used to evaluate the interrater agreement of PRIMARY score. The data were analyzed by IBM SPSS statistics software, version 26.0 (IBM, Inc, Chicago, IL), and R software, version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographics and Clinical Characteristics

Clinical characteristics of 431 enrolled men were presented in Table 1. The prevalence of csPCa was 51.7% (223/431). The proportion of csPCa within PRIMARY score 1 to 5 was 6.3% (4/64), 20.2% (17/84), 31.6% (18/57), 70.8% (102/144), and 100% (82/82), respectively. The proportion of csPCa within PI-RADS 1 to 5 was 12.5% (5/40), 24.7% (22/89), 37.7% (29/77), 64.1% (75/117), and 85.2% (92/108), respectively. The increased levels of PRIMARY score and PI-RADS were associated with the increased detection rate of csPCa (Fig. 1).

Diagnostic Performance of Independent PRIMARY Score and MRI

The area under the receiver operating characteristic curve of the 5-level PRIMARY score in predicting csPCa was significantly higher than that of PI-RADS (0.873 vs 0.786, $P < 0.001$) (Fig. 2). For the entire group, sensitivity, specificity, PPV, and NPV of the PRIMARY score were 90.6%, 61.1%, 71.4%, and 85.8%, respectively, which outperformed 87.9%, 49.0%, 64.9%, and 79.1% of PI-RADS on MRI. Compared with MRI alone, the PRIMARY score exhibited a significant improvement in specificity ($P = 0.007$) and PPV ($P = 0.004$) (Table 2). In subgroup analyses stratified by age

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TABLE 1. Clinical Characteristics of 431 Patients

Variable	Median (Interquartile Range) or n (%)
Age, y	67 (62–73)
PSA, ng/mL	10.7 (7.1–18.4)
Prostate volume, mL	44.3 (32.6–66.0)
SUV_{max}	6.4 (4.4–9.8)
Gleason grade group	
No cancer	184 (42.7)
1	24 (5.6)
2	80 (18.6)
3	59 (13.7)
4	51 (11.8)
5	33 (7.7)
PRIMARY score	
1	64 (14.8)
2	84 (19.5)
3	57 (13.2)
4	144 (33.4)
5	82 (19.0)
PI-RADS	
1	40 (9.3)
2	89 (20.6)
3	77 (17.9)
4	117 (27.1)
5	108 (25.1)
PRIMARY score + MRI combined	
Negative	106 (24.6)
Positive	325 (75.4)

(Supplementary Table S1, http://links.lww.com/CNM/A450) and PSA (Supplementary Table S2, http://links.lww.com/CNM/A450), PRIMARY score also demonstrated high diagnostic accuracy.

In addition, the PRIMARY score demonstrated a positive NRI of 2.7% (95% CI, −2.4% to 7.9%; $P = 0.299$) for csPCa cases and 12.0% (95% CI, 3.5% to 20.4%; $P = 0.005$) for non-csPCa cases, resulting in an overall NRI of 14.7% (95% CI, 4.9% to 24.4%; $P = 0.003$) (Supplementary Table S3, http://links.lww.com/CNM/A450). This indicates that the PRIMARY score more accurately reclassifies non-csPCa cases into the lower-risk category compared with MRI.

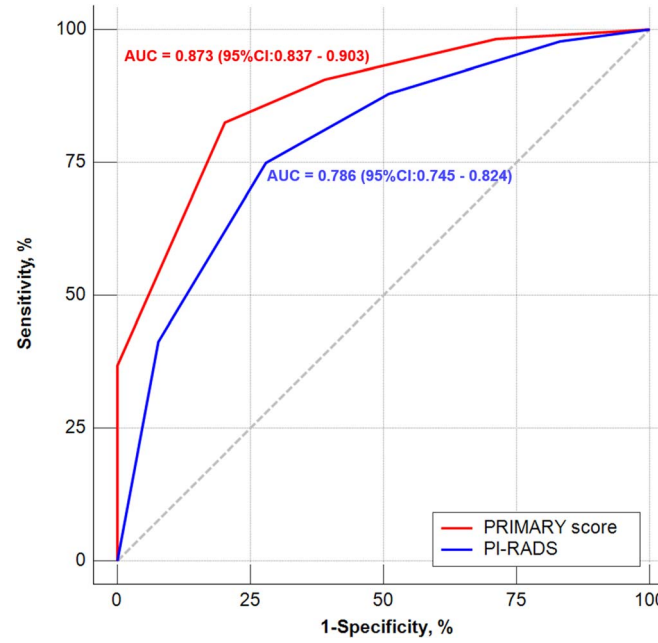

FIGURE 2. Receiver operating characteristic curve analysis for the 5-level PRIMARY score and PI-RADS to predict csPCa.

Negative and Positive Results of csPCa in Independent PRIMARY Score and MRI

The false-negative rate for PRIMARY score was 14.2% (21/148), which was lower than 20.9% (27/129) for MRI. In men with csPCa, there were 6 cases diagnosed as negative on both independent PRIMARY score and MRI, of which 5 cases were GG 2 and 1 case was GG 3. Among the remaining 217 csPCa cases, 181 were positive on both modalities, 21 cases were positive on the PRIMARY score but negative on MRI, and 15 cases were negative on the PRIMARY score but positive on MRI (Table 3 and Supplementary Fig. S2, http://links.lww.com/CNM/A450). The PRIMARY score was positive in 92.8% (155/167) of csPCa cases with PI-RADS 4/5 and in 83.9% (47/56) of csPCa cases with PI-RADS 1–3.

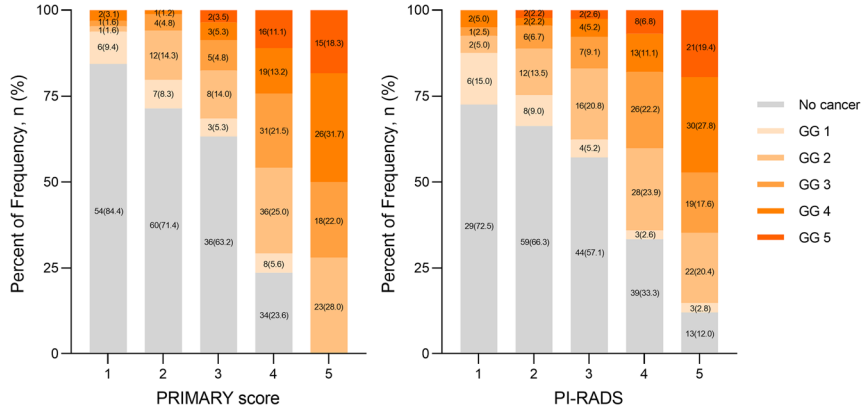

FIGURE 1. Bar chart showing the distribution of Gleason grade groups (GG) in each PRIMARY score and PI-RADS. Data were presented as frequency and percentage.

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TABLE 2. Diagnostic Performance* of MRI, PRIMARY Score, and PRIAMRY Score + MRI for csPCa

	MRI		PRIMARY Score		PRIMARY Score + MRI	
	Negative	Positive	Negative	Positive	Negative	Positive
Non-csPCa	102	106	127	81	97	111
csPCa	27	196	21	202	9	214
Sensitivity (%)	87.9 (82.7–91.7)		90.6 (85.8–93.9)		96.0 (92.2–98.0)	
Ratio to MRI			Ratio = 1.03, $P = 0.317$		Ratio = 1.09, $P < 0.001$	
Specificity (%)	49.0 (42.1–56.0)		61.1 (54.0–67.7)		46.6 (39.7–53.7)	
Ratio to MRI			Ratio = 1.24, $P = 0.007$		Ratio = 0.95, $P = 0.50$	
PPV (%)	64.9 (59.2–70.2)		71.4 (65.7–76.5)		65.8 (60.4–70.9)	
Ratio to MRI			Ratio = 1.10, $P = 0.004$		Ratio = 1.01, $P = 0.565$	
NPV (%)	79.1 (70.8–85.5)		85.8 (78.9–90.8)		91.5 (84.1–96.0)	
Ratio to MRI			Ratio = 1.09, $P = 0.082$		Ratio = 1.16, $P < 0.001$	

*The comparison of sensitivity and specificity was performed with McNemar test; the comparison of PPV and NPV was assessed using relative predictive value approach.

Diagnostic Performance of Combined PRIMARY Score With MRI

The combination of PRIMARY score + MRI demonstrated a significant improvement in sensitivity (96.0% vs 87.9%, $P < 0.001$) and NPV (91.5% vs 79.1%, $P < 0.001$) for detecting csPCa compared with MRI alone, without compromising specificity (46.6% vs 49.0%, $P = 0.50$) and PPV (65.8% vs 64.9%, $P = 0.565$) (Table 2). In subgroup analyses stratified by age (Supplementary Table S1, http://links.lww.com/CNM/A450) and PSA (Supplementary Table S2, http://links.lww.com/CNM/A450), PRIMARY score + MRI also improved sensitivity and NPV compared with MRI, except for men with PSA < 10 ng/mL.

PRIMARY Score in PI-RADS 1–3 Triage Population

The clinical characteristics of 206 patients with PI-RADS 1–3 were presented in Supplementary Table S4, http://links.lww.com/CNM/A450. Among these, 48.5% (100/206) were categorized as positive based on PRIMARY scores of 3–5. Among the positive group, 47% (47/100) were diagnosed with csPCa, and their median PSA level was 11.8 (7.9–22.4) ng/mL. A total of 106 cases (51.5%) were classified as negative, including 9 cases (8.4%) of csPCa (6 with GG 2 and 3 with GG 3), accounting for 4.0% (9/223) of all csPCa cases. Men with a positive PRIMARY score exhibited higher SUV_{max} ($P < 0.001$), lower prostate volume ($P = 0.015$), and higher PSA density ($P = 0.044$) compared with men with a negative

TABLE 3. Clinical Characteristics of Patients With csPCa* in Total and Positive on MRI and/or PRIMARY Score

	csPCa (n = 223)	Both PRIMARY Score and MRI (n = 181)	MRI Only (n = 15)	PRIMARY Score Only (n = 21)
Age, y	68 (63–74)	68 (64–74)	62 (61–71)	69 (64–72)
PSA, ng/mL	14.0 (8.4–21.9)	14.5 (8.7–22.5)	8.6 (5.2–16.4)	11.8 (9.9–27.1)
Prostate volume, mL	35.3 (27.5–50.3)	36.0 (28.5–50.0)	26.5 (20.8–50.3)	34.3 (26.1–57.0)
SUV_{max}	8.9 (6.2–17.6)	10.1 (6.9–18.7)	3.6 (3.3–4.4)	15.4 (6.4–23.4)
PI-RADS				
1	5 (2.2)	0	0	4 (19.0)
2	22 (9.9)	0	0	17 (81.0)
3	29 (13.0)	26 (14.4)	3 (20.0)	0
4	75 (33.6)	68 (37.6)	7 (46.7)	0
5	92 (41.3)	87 (48.1)	5 (33.3)	0
PRIMARY score				
1	4 (1.8)	0	4 (26.7)	0
2	17 (7.6)	0	11 (73.3)	0
3	18 (8.1)	16 (8.8)	0	2 (9.5)
4	102 (45.7)	95 (52.5)	0	7 (33.3)
5	82 (36.8)	70 (38.7)	0	12 (57.1)
Gleason grade group				
2	80 (35.9)	58 (32.0)	8 (53.3)	9 (42.9)
3	59 (26.5)	48 (26.5)	4 (26.7)	6 (28.6)
4	51 (22.9)	44 (24.3)	3 (20.0)	4 (19.0)
5	33 (14.8)	31 (17.1)	0	2 (9.5)

*Six csPCa cases (5 IUSP 2 and 1 ISUP 3) were diagnosed as negative on both independent MRI and PRIMARY score.

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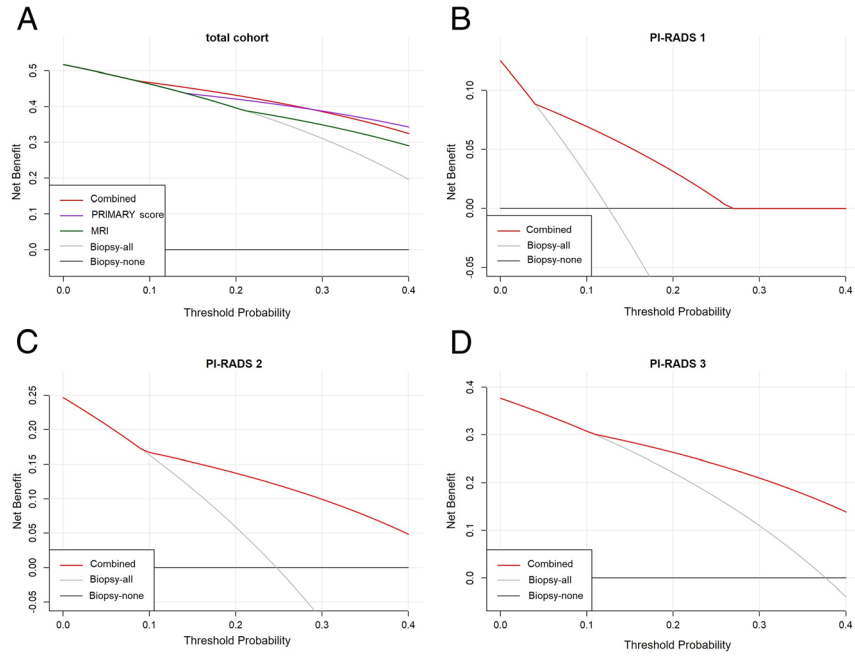

FIGURE 3. Decision curve analysis for the (**A**) total cohort, (**B**) PI-RADS 1 only patients, (**C**) PI-RADS 2 only patients, and (**D**) PI-RADS 3 only patients. "Biopsy-all" and "Biopsy-none" were used as reference. Combined indicates PIRMARY score + MRI.

PRIMARY score. However, PSA levels did not exhibit a statistically significant difference between the 2 groups ($P = 0.457$).

Impact on Biopsy

According to DCA (Fig. 3), the combination of PRIMARY score + MRI exhibited a higher net benefit than the individual PRIMARY score and MRI in the risk threshold range of 9% to 28%. Addition of the PRIMARY score for PI-RADS 1–3 patients demonstrated a net benefit. However, for men with PI-RADS 4/5, no net benefit was observed at any threshold probability (Supplementary Fig. S3, http://links.lww.com/CNM/A450). The net benefit and reduction in unnecessary biopsies within different risk threshold were shown in Supplementary Table S5, http://links.lww.com/CNM/A450. By abstaining from performing biopsies on men with a negative PRIMARY score + MRI, it would be possible to avoid 24.6% of unnecessary biopsies while only missing 4.0% of csPCa cases (Table 4, Fig. 4).

Interrater Agreement of PRIMARY Score

Two further nuclear medicine specialists evaluated the PRIMARY score of randomly selected 130 cases (50.8% with csPCa). Cohen κ for the 5-point PRIMARY score was 0.799 (95% CI, 0.718–0.880) for reader 1 and 0.776 (95% CI, 0.692–0.861) for reader 2. Cohen κ for negative against positive PRIMARY score (1–2 vs 3–5) for reader 1 was 0.818 (95% CI, 0.715–0.921) and 0.793 (95% CI, 0.683–0.903) for reader 2.

DISCUSSION

The present study externally confirmed that the PRIMARY score was superior to MRI in the diagnosis of csPCa, and its added diagnostic value was in men with negative or equivocal MRI results. The combination of PRIMARY score + MRI significantly improved the NPV and sensitivity for csPCa compared with MRI alone, while maintaining specificity and PPV. Our result provides compelling evidence for the potential role of PRIMARY score + MRI in guiding biopsy decisions. Further prospective trials will validate whether men with clinical suspicion of csPCa but negative PRIMARY score + MRI can safely avoid unnecessary biopsies.

The PI-RADS scoring system distinguishes among the peripheral, central, and transitional zones of the prostate, while incorporating semiquantitative measurements such as apparent diffusion coefficient maps and DWI. It is important to note that the occurrence of PCa is associated with specific anatomical zones. The majority of malignancy cases (68%) originate from the peripheral zone, whereas a small percentage (8%) is found in the central zone.[17]

Similar to PI-RADS, the PRIMARY score takes into account zonal localization, intraprostatic PSMA patterns, and a very high SUV_{max} to improve the diagnostic accuracy for csPCa. This approach overcomes the limitations of relying solely on SUV_{max}, which can result in misinterpretation due to variations in optimal SUV_{max} cutoff values caused by different PET cameras and PSMA ligands. For instance, although the PRIMARY trial used an optimal cutoff value of 4.0, other studies have reported values ranging from 5 to 9.[18–21] Furthermore, previous research has shown a positive correlation between PSMA intensity and Gleason grade group, suggesting that focal activity of PSMA predicts a higher likelihood of csPCa.[22] As a result, the utilization of the 5-point PRIMARY score, incorporating zonal location and PSMA patterns, can optimize diagnostic accuracy.

Consistent with the original study of PRIMARY score,[7] our findings externally confirmed that the PRIMARY score outperforms MRI alone in detecting csPCa, and the agreement between raters is higher compared with previous reports on MRI.[23] The PRIMARY

TABLE 4. Number of Patients Who Avoided Unnecessary Biopsies and Missed csPCa Under Different Biopsy Strategies

Biopsy Strategy	Avoided Biopsies	Missed csPCa
PRIMARY score ≥3	34.3% (148/431)	9.4% (21/223)
PI-RADS ≥3	29.9% (129/431)	12.1% (27/223)
PRIMARY score + MRI	24.6% (106/431)	4.0% (9/223)

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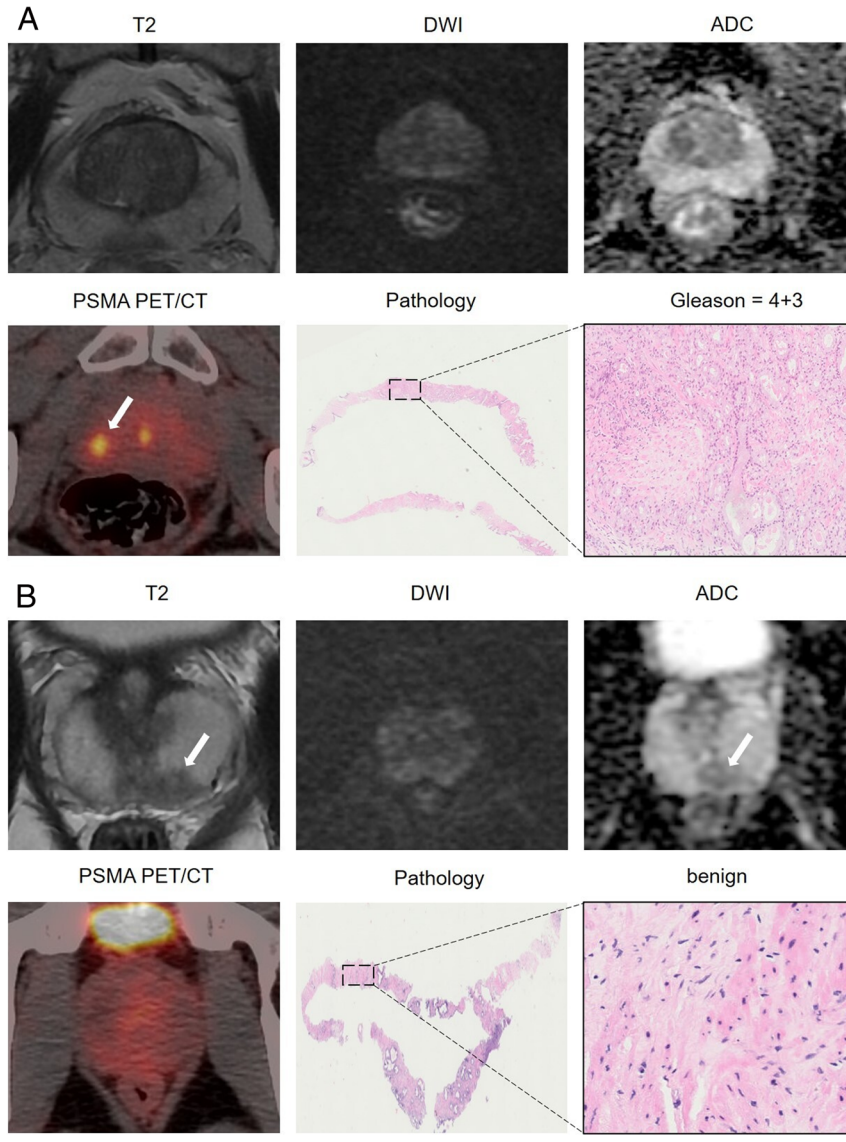

FIGURE 4. **A**, A 73-year-old man was defined as PI-RADS 1 on MRI. The corresponding ^{68}Ga-PSMA PET/CT showed a focal PSMA activity lesion (arrow) involving the right peripheral zone (SUV_{max}, 6.9), defined as PRIMARY score 4 and confirmed to be ISUP 3 on biopsy pathology. This case can be correctly diagnosed as positive by the combination of PRIMARY score + MRI to avoid the false-negative of MRI. **B**, A 56-year-old man was defined as PI-RADS 3 on MRI. The corresponding ^{68}Ga-PSMA PET/CT showed diffuse PSMA uptake without any focal activity (SUV_{max}, 3.6), defined as PRIMARY score 2 and confirmed to be benign on biopsy pathology. This case can be correctly diagnosed as negative by the combination of PRIMARY score + MRI to avoid unnecessary biopsy. ADC indicates apparent diffusion coefficient.

score improved specificity from 49.0% to 61.1% without sacrificing sensitivity and showed more accuracy in reclassifying non-csPCa to the lower-risk category when compared with MRI. In subgroup analyses, particularly when PSA ≥10 ng/mL, sensitivity, specificity, PPV, and NPV of the PRIMARY score were higher than that of MRI. In addition, the false-negative rate is lower with the PRIMARY score compared with MRI. In fact, the false-negative cases were identified by alternative modalities in all except 6 cases who were negative on both independent modalities.

Our study highlighted the advantages of the PRIMARY score in men with negative or equivocal MRI results. Among men categorized as PI-RADS 1–3, the prevalence of csPCa was 27.2% (56/206), and the PRIMARY score successfully identified 83.9% (47/56) of these malignancies. Furthermore, 51.5% (106/206) of men with PI-RADS 1–3 had a negative PRIMARY score, of which 91.5% (97/106) were non-csPCa cases. According to DCA, the addition of PRIMARY score provides a net benefit for men with PI-RADS 1–3, whereas no net benefit was observed for men with PI-RADS 4–5.

Being a newly proposed scoring system, there is limited research exploring the disparity in PSA levels between individuals with a positive PRIMARY score and those with a negative PRIMARY score within the PI-RADS 1–3 triage population. The present study revealed that there was no statistically significant difference in PSA levels between the 2 groups. From a pathophysiological perspective, it is important to note that PSA serves as an organ-specific biomarker rather than a tumor-specific one. Apart from PCa, other benign

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prostate conditions such as benign prostatic hyperplasia and prostatitis can also lead to elevated PSA levels.[24,25] When PSA values fall within the diagnostic gray zone (4 ng/mL to 10 ng/mL), the biopsy-based detection rate of csPCa only ranges between 4.1% and 25%.[26,27] In the existing literature, median PSA levels in men with negative or equivocal MRI results (PI-RADS 1–3) predominantly fall within the diagnostic gray zone,[28–30] which is consistent with the findings in our current study (9.8 ng/mL). Consequently, the non–tumor-specific nature of PSA and its limited diagnostic accuracy at lower levels may account for the lack of a statistically significant difference in PSA levels between the 2 groups, even when stratified according to the PRIMARY score.

The previous PRIMARY trial showed that PSMA + MRI improved sensitivity and NPV but decreased specificity compared with MRI alone.[31] However, in our study, the combination of PRIMARY score + MRI not only improved sensitivity and NPV but also maintained the same level of specificity and PPV. According to DCA, the PRIMARY score + MRI outperformed individual imaging modalities. By avoiding biopsies in men with a negative PRIMARY score + MRI, it was possible to avoid 24.6% of unnecessary biopsies while only missing 4.0% (9/223) of csPCa cases, including 6 cases of GG2 and 3 cases of GG 3. In a subanalysis of the Prostate Cancer Prevention Trial, it was found that the prevalence of high-grade cancer was 5.2% in men with normal digital rectal examination and a PSA level of 2.1–4.0 ng/mL.[32] Another study reported a 9% prevalence of undiagnosed high-grade cancer in autopsies of unscreened men.[33] Therefore, the missing 4.0% of csPCa cases in immediate prostate biopsies seemed to be acceptable in this study, especially considering the majority of missed cancers were low-grade features. Given the high sensitivity and NPV of the PRIMARY score + MRI in detecting csPCa, and the fact that the majority of missed tumors were low-grade features, avoiding biopsy in men with negative PRIMARY score + MRI results seems to be a feasible strategy.

The present study had certain limitations. First, it was a retrospective analysis and conducted in a highly specialized single tertiary referral center. PSMA PET was not the standard of care for detecting intraprostatic malignancies during the study period, and patients undergoing MRI may not have had PSMA PET screening before biopsy, resulting in a potential selection bias. Second, it was not feasible to perform radical prostatectomy in men with negative biopsies, resulting in a lack of whole-mount pathology specimens as reference criteria for all men and introducing an imperfect-standard bias. Third, the PSMA ligand used in our study was ^{68}Ga, and it would be meaningful to validate the diagnostic value of the PRIMARY score for variable PSMA ligands (eg, ^{18}F) in future studies. Finally, despite the great potential for clinical application of the PRIMARY score, the risk-benefit ratio, cost-effectiveness, and long-term clinical outcomes will be key end points to be evaluated in future prospective trials.

CONCLUSIONS

The PRIMARY score was superior to MRI in detecting csPCa, and its added diagnostic value was in men with negative or equivocal MRI results. The PRIMARY score + MRI improved NPV and sensitivity for csPCa compared with MRI alone. Further prospective trials will validate whether men with clinical suspicion of csPCa but negative PRIMARY score + MRI can safely avoid unnecessary biopsies.

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