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Utility of prostate-specific antigen derivatives to minimize unnecessary magnetic resonance imaging in patients with prior negative prostate biopsy

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Magnetic resonance imaging (MRI) has become an important tool for recommending prostate biopsy (PB) in prostate cancer (PCa) detection. However, the routine use of MRI in patients with previous negative PB remains debatable. This study aimed to evaluate the utility of prostate-specific antigen (PSA) derivatives to guide MRI use and reduce unnecessary scans in such cases. Receiver operating characteristic analysis identified a Prostate Imaging Reporting and Data System score ≥ 4 as the optimal threshold for predicting clinically significant PCa (Gleason score ≥ 7). A cohort of 251 patients with at least one prior negative PB who underwent serum PSA testing, free PSA, and MRI between October 2015 and June 2024 were analyzed. The optimal cutoff values for PSA, PSA density (PSAD), and free-to-total PSA ratio (%fPSA) were 11.87 ng/mL, 0.19 ng/mL^2, and 18.76%, respectively (all $p < 0.001$). Restricting MRI to patients with PSA < 11.87 ng/mL, PSAD < 0.19 ng/mL^2, or %fPSA > 18.76% could induce MRI use by 22.7% while missing only 9.1% of significant PCa cases on MRI-targeted PB.

Keywords Free-to-total PSA ratio, MRI, Negative biopsy, Prostate biopsy, Prostate cancer, Prostate-specific antigen density

Prostate cancer (PCa) is the most common malignancy and the second leading cause of cancer-related deaths among men worldwide[1]. Over the past few decades, serum prostate-specific antigen (PSA)–based screening and subsequent prostate biopsy (PB) have become standard diagnostic practices, despite challenges such as overdiagnosis and overtreatment[2,3].

Although transrectal ultrasonography (TRUS)–guided PB (TRUS-PB) has been in use since 1989[4], its false-negative rate ranges from 20 to 40%[5]. Consequently, managing patients with prior negative PB remains a significant challenge.

Magnetic resonance imaging (MRI) has emerged as a powerful tool to enhance diagnostic accuracy, particularly in patients with previous negative PB, by reducing unnecessary biopsies[6–8]. Combining MRI-targeted PB with systematic TRUS-PB has been shown to improve cancer detection[9].

There is a consensus to perform MRI and subsequent MRI-targeted PB in patients with prior negative PB but persistent clinical suspicion of PCa. The decision to perform an MRI on these patients should consider the results of other biomarkers and the financial burden of the examination [10]. Routine use of MRI could impose significant costs on patients and healthcare systems [7,11]. Furthermore, the recommendation to conduct MRI-targeted PB

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after initial negative TRUS-guided PB remains questionable, particularly for patients with PSA < 10 ng/mL, due to low cancer-specific mortality[12].

Detection rates for significant PCa on repeat PB following initial negative systematic and MRI-targeted PB range from 10 to 20%[13–16]. Therefore, determining appropriate MRI indications in patients with previous negative PB is essential. Although PSA and its derivatives, such as PSA density (PSAD) and the free-to-total PSA ratio (%fPSA), have been suggested as indicators for recommending PB[17,18], studies evaluating their utility in minimizing unnecessary MRI remain limited. This study aims to assess the effectiveness of PSA and its derivatives in reducing MRI usage without comprising the detection of PCa in patients with prior negative biopsies.

Materials and methods

Data collection

This single-institution retrospective study was approved by the Institutional Review Board (IRB No. B-2410-f933-105), with a waiver of informed consent. At our institution, all male patients presenting with lower urinary tract symptoms undergo serum PSA testing and TRUS as part of their initial diagnostic workup. An additional serum-free PSA test is reimbursed by Korea's national insurance when serum PSA levels exceed 2 ng/mL or PCa is suspected based on digital rectal examination or TRUS findings. Further MRI is performed following shared decision-making with the patient.

Between October 2015 and June 2024, 1,189 patients underwent repeated PB after serum PSA, free PSA testing, and MRI. Patients with a history of PCa, prostate surgery, prior PB, or use of medications affecting PSA levels (e.g., 5-α reductase inhibitors) were excluded. Ultimately, 251 patients with at least one previous negative PB were included in the study. A Gleason score ≥ 7 was classified as significant PCa.

A visible lesion on MRI was defined as one with a Prostate Imaging Reporting and Data System version 2 (PI-RADSv2) score of ≥ 3, which served as the target for MRI-targeted biopsy. Patients with MRI-visible lesions underwent MRI-targeted transrectal (TR) PB in addition to a systematic 12-core TRUS-PB. Each targeted biopsy included a minimum of two cores per lesion. Patients without visible MRI lesions underwent only systematic 12-core TRUS-PB.

The MRI/TRUS fusion-guided PB protocol used in this study has been described previously[19]. All patients' prostate volumes were evaluated based on TRUS. All PB slides were reviewed by genitourinary pathologists with more than 10 yr of experience. The primary outcome was the predictive value of the Prostate Health Index (PHI) for PI-RADSv2 ≥ 3 lesions. Secondary outcomes included the diagnostic accuracy of PHI for overall PCa and significant PCa.

Statistical analysis

All statistical analyses were performed using the R statistical package (version 3.5.1; R Core Team, Vienna, Austria). Receiver operating characteristic (ROC) curves and areas under the curve (AUCs) were used to determine cutoff values for PI-RADSv2 in predicting overall and significant PCa. Cutoff values were defined using sensitivity analysis with the Youden index (sensitivity + specificity − 1). ROC curve analysis also determined optimal cutoff values for PSA and its derivatives in predicting MRI lesions. The DeLong test was used to assess statistical differences in AUCs. Multivariate logistic regression analyses were used to identify predictors for MRI lesions, overall PCa, and significant PCa on MRI-targeted PB cores. All p values were two-sided, with statistical significance set at $p < 0.05$.

Results

Table 1 presents the baseline demographic and clinicopathological characteristics of the patients. Among 251 patients, 127 (50.6%) patients had visible MRI lesions (PI-RADSv2 ≥ 3). Of these, 125 patients underwent MRI/TRUS fusion PB, while two patients with PI-RADSv2 ≥ 3 lesions and 124 patients without visible lesions underwent only systematic 12-core TRUS-PB. Patients with PI-RADSv2 < 3 lesions were older than those with PI-RADSv2 ≥ 3 (66.4 vs. 62.9 yr; $p = 0.001$). Higher PSA level (10.02 ± 9.31 ng/mL vs. 6.82 ± 5.39 ng/mL; $p = 0.001$) and PSAD level (0.26 ± 0.28 ng/mL^2 vs. 0.15 ± 0.11 ng/mL^2; $p < 0.001$) were observed in patients with PI-RADSv2 ≥ 3 (Table 1).

ROC curve analysis identified PI-RADSv2 ≥ 4 as the optimal cutoff value for predicting overall PCa (AUC = 0.73, $p < 0.001$) and significant PCa (AUC = 0.81, $p < 0.001$; Fig. 1). The optimal cutoff values for predicting PI-RADSv2 ≥ 4 lesions were 11.87 ng/mL for PSA (AUC = 0.63, $p < 0.001$), 0.19 ng/mL^2 for PSAD (AUC = 0.69, $p < 0.001$), and 18.76% for %fPSA (AUC = 0.63, $p < 0.001$; Fig. 2).

Multivariable regression analysis showed that older age (odds ratio [OR] = 1.04; 95% confidence interval [95% CI], 1.01–1.08; $p = 0.016$) and higher PSAD (OR = 154.44; 95% CI, 18.54–1,286.36; $p < 0.001$) were significantly associated with PI-RADSv2 ≥ 4 lesions (Table 2).

Among 125 patients who underwent combined MRI-targeted PB and systematic 12-core TRUS-PB, PSAD ≥ 0.19 ng/mL and PI-RADSv2 ≥ 4 were independent risk factors for overall PCa (OR = 2.90; 95% CI, 1.24–6.80; $p = 0.014$, and OR = 10.97; 95% CI, 3.08–39.09; $p < 0.001$, respectively) and significant PCa (OR = 3.27; 95% CI, 1.28–8.35; $p = 0.013$, and OR = 11.10; 95% CI, 2.44–50.46; $p = 0.002$, respectively; Table 3).

Table 4 shows the predictive values of PSA and PSA derivatives for PI-RADSv2 ≥ 3 lesions. Although PSA < 11.87 ng/mL had the highest AUC, significant differences were observed between PSA < 11.87 and PSAD < 0.19 ng/mL^2 ($p = 0.612$) or %fPSA > 18.76% ($p = 0.062$). Avoiding MRI when PSA < 11.87 ng/mL would reduce MRI use by 45.8%, but 57.6% (19/33) of significant PCa cases could be missed. Using PSAD < 0.19 ng/mL^2 and %fPSA > 18.76% as criteria to omit MRI would reduce MRI use by 38.6% and 25.1%, respectively, with a risk of missing 29.5% and 22.7% of significant PCa cases. When combining each cutoff value of PSA and its

Variables	Overall	Invisible MRI lesion (PI-RADSv2 < 3)	Visible MRI lesion (PI-RADSv2 ≥ 3)	*p* value
Number of patients, *n* (%)	251 (100.0%)	124 (49.4%)	127 (50.6%)	
Age, yr	64.7 ± 8.5	62.9 ± 8.1	66.4 ± 8.5	0.001*
DRE abnormality, *n* (%)	7 (2.8%)	4 (3.2%)	3 (2.4%)	0.678
Prostate volume, mL	48.0 ± 22.0	50.0 ± 22.4	46.1 ± 21.4	0.164
PSA, ng/mL	8.44 ± 7.78	6.82 ± 5.39	10.02 ± 9.31	0.001*
PSAD, ng/mL^2	0.21 ± 0.22	0.15 ± 0.11	0.26 ± 0.28	< 0.001*
%fPSA, %	19.59 ± 12.97	20.16 ± 10.31	19.02 ± 15.14	0.485
PI-RADSv2 score, *n* (%)				
3			44 (34.6%)	
4			52 (40.9%)	
5			31 (24.4%)	
Location of MRI lesion, *n* (%)				
Transitional zone			65 (51.2%)	
Peripheral zone			50 (39.4%)	
Both			10 (7.9%)	
Unknown			2 (1.6%)	
Laterality of MRI lesion, *n* (%)				
Unilateral			114 (89.8%)	
Bilateral			13 (10.2%)	
Method of PB, *n* (%)				
Systematic 12-core PB	126 (50.2%)	124	2 (1.6%)	
MRI-targeted + systematic 12-core PB	125 (49.8%)	0	125 (98.4%)	
Number of PB	13.37 ± 1.11	12.78 ± 1.04	13.95 ± 0.84	< 0.001 *
Number of MRI-targeted biopsy			2.08 ± 0.47	
Patients with overall PB (*n* = 251)				
Benign	162 (64.5%)	85 (68.5%)	77 (60.6%)	
≤ GS 6	42 (16.7%)	21 (16.9%)	21 (16.5%)	0.231
≥ GS 7 (3 + 4)	47 (18.7%)	18 (14.5%)	29 (22.8%)	
Patients with systematic 12-core PB (*n* = 251)				
Benign	171 (68.1%)	99 (79.8%)	72 (56.7%)	
≤ GS 6	40 (15.9%)	19 (15.3%)	21 (16.5%)	< 0.001*
≥ GS 7 (3 + 4)	40 (15.9%)	6 (4.8%)	34 (26.3%)	
Patients with MRI-targeted biopsy (*n* = 125)				
Benign			81 (64.8%)	
≤ GS 6			11 (8.8%)	
≥ GS 7 (3 + 4)			33 (26.4%)	

Table 1. Comparison of baseline characteristics of patients with prior negative prostate biopsy (*n* = 251) according to the presence of visible lesions (PI-RADSv2 ≥ 3) on multiparametric magnetic resonance imaging. %fPSA, free-to-total PSA ratio; DRE, digital rectal examination; GS, Gleason score; MRI, magnetic resonance imaging; PB, prostate biopsy; PI-RADSv2, Prostate Imaging Reporting and Data System version 2; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density. All continuous data were described as mean ± standard deviation. We defined visible lesions on MRI as lesions with PI-RADSv2 score ≥ 3. *$p < 0.05$ (statistically significant differences).

derivatives, there were no significant differences in the AUC compared with PSA < 11.87 ng/mL alone. However, recommending MRI only for patients with PSA < 11.87 ng/mL, PSAD < 0.19 ng/mL^2, and %fPSA > 18.76% could reduce MRI utilization by 22.7%, with a minimal risk (9.1% or 3/33 cases) of missing significant PCa by omitting MRI-targeted PB.

Discussion

Current guidelines recommend prostate MRI for patients with previous negative PB and ongoing suspicion of PCa[20]. A prior meta-analysis reported that the negative predictive value of MRI for detecting Gleason score ≥ 7 PCa was 90.8% when MRI-negative cases were defined as PI-RADSv2 < 3[21]. The current guideline[20] suggested that the cutoff value of Likert/PI-RADS ≥ 3 to recommend PB could reduce 30% of unnecessary PB while missing 11% of clinically significant PCa. For patients with previous negative PB, the incidences of clinically significant PCa were 5.6%, 13.6%, 33.6% and 70.3% in those with PI-RADS < 3, 3, 4, and 5 lesions[22].

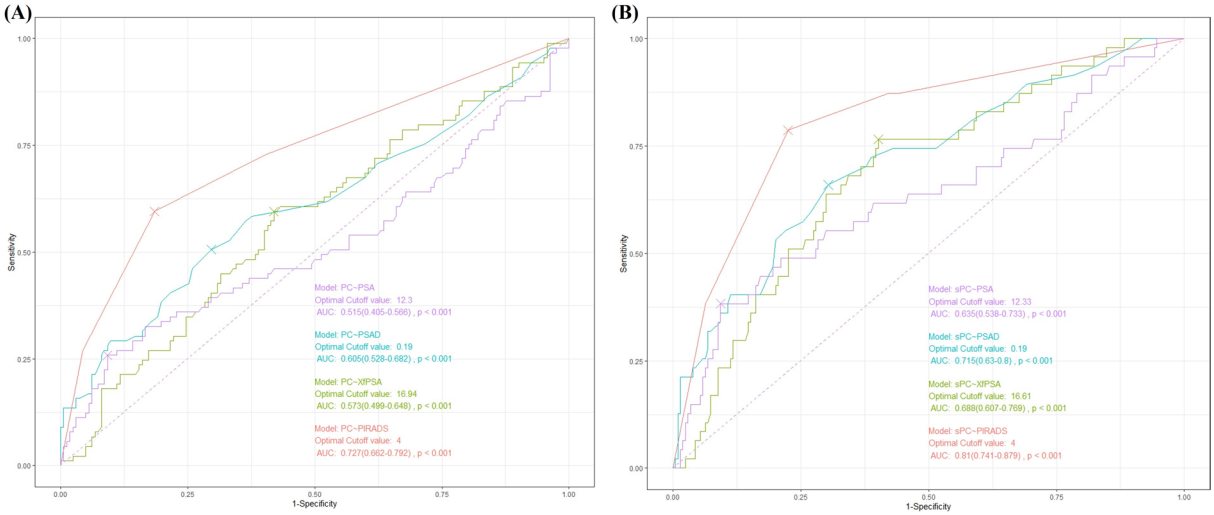


Fig. 1. Receiver operating characteristic curves of prostate-specific antigen (PSA) derivatives, including PSA density (PSAD) and the free-to-total PSA ratio (%fPSA), along with Prostate Imaging Reporting and Data System version 2 (PI-RADSv2) scores on multiparametric magnetic resonance imaging for predicting the presence of (**A**) overall prostate cancer and (**B**) clinically significant prostate cancer.

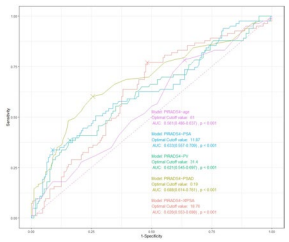


Fig. 2. Receiver operating characteristic curve of age, prostate-specific antigen (PSA), prostate volume, PSA density (PSAD), and the free-to-total PSA ratio (%fPSA) for predicting the presence of lesions on multiparametric magnetic resonance imaging with a Prostate Imaging Reporting and Data System version 2 (PI-RADSv2) score ≥ 4.

	Univariable analysis		Multivariable analysis	
Variables	**Odds ratio (95% CI)**	***p* value**	**Odds ratio (95% CI)**	***p* value**
Age	1.03 (1.00–1.06)	0.093	1.04 (1.01–1.08)	0.016*
Prostate volume	0.98 (0.97–1.00)	0.010*		
PSA	1.08 (1.03–1.13)	0.002*		
PSAD	104.52 (13.90–785.80)	< 0.001*	154.44 (18.54–1,286.36)	< 0.001*
%fPSA	0.98 (0.96–1.01)	0.112		

Table 2. Univariable and multivariable regression analysis for the prediction of lesions on multiparametric magnetic resonance imaging with Prostate Imaging Reporting and Data System score ≥ 4 in patients who underwent multiparametric magnetic resonance imaging. *Note*. %fPSA, free-to-total PSA ratio; 95% CI, 95% confidence interval; OR, odds ratio; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density. *$p < 0.05$ (statistically significant differences).

In this study, ROC curve analysis determined that the optimal PI-RADSv2 cutoff value for predicting both overall and significant PCa was 4, aligning with prior research findings[22]. Thus, we aimed to assess optimal PSA and PSA derivative cutoff values for identifying PI-RADSv2 ≥ 4 lesions on MRI. The cutoff values for predicting PI-RADSv2 ≥ 4 lesions were 11.87 ng/mL for PSA, 0.19 ng/mL^2 for PSAD, and 18.76% for %fPSA. Among these markers, PSAD demonstrated the highest AUC.

Multivariate logistic regression analysis indicated that PSAD and older age were associated with the presence of PI-RADSv2 ≥ 4 lesions. After adjusting for other clinicopathologic factors, PSAD ≥ 0.19 ng/mL and PI-

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Overall PCa at MRI-targeted PB core			–	
Age (≤ 60 yr vs. > 60 yr)	1.38 (0.55–3.47)	0.495		
DRE abnormality (no vs. yes)	< 0.001	0.999		
PSA (< 11.87 ng/mL vs. ≥ 11.87 ng/mL)	2.77 (1.21–6.33)	0.016*		
PSAD (< 0.19 ng/mL^2 vs. ≥ 0.19 ng/mL^2)	3.64 (1.67–7.93)	0.001*	2.90 (1.24–6.80)	0.014*
%fPSA (≥ 18.76% vs. < 18.76%)	2.46 (1.07–5.65)	0.034*		
Prostate volume (≥ 31.4 mL vs. < 31.4 mL)	0.32 (0.14–0.73)	0.006*		
PI-RADSv2 score				
3	Reference		Reference	
≥ 4	14.01 (4.01–48.92)	< 0.001*	10.97 (3.08–39.09)	< 0.001*
Location of MRI lesion				
Transitional zone	Reference			
Peripheral zone	1.01 (0.46–2.22)	0.972		
Both	1.91 (0.50–7.31)	0.345		
Laterality of MRI lesion				
Unilateral	Reference			
Bilateral	1.97 (0.60–6.53)	0.266		
Significant PCa at MRI-targeted PB core				
Age (≤ 60 yr vs. > 60 yr)	1.03 (0.39–2.72)	0.950		
DRE abnormality (no vs. yes)	< 0.001	0.999		
PSA (< 11.87 ng/mL vs. ≥ 11.87 ng/mL)	2.77 (1.21–6.33)	0.016*		
PSAD (< 0.19 ng/mL^2 vs. ≥ 0.19 ng/mL^2)	3.64 (1.67–7.93)	0.001*	3.27 (1.28–8.35)	0.013*
%fPSA (≥ 18.76% vs. < 18.76%)	2.46 (1.07–5.65)	0.034*		
Prostate volume (≥ 31.4 mL vs. < 31.4 mL)	0.48 (0.21–1.13)	0.093		
PI-RADSv2 score				
3	Reference		Reference	
≥ 4	14.01 (4.01–48.92)	0.001*	11.10 (2.44–50.46)	0.002*
Location of MRI lesion				
Transitional zone	Reference			
Peripheral zone	1.01 (0.46–2.22)	0.972		
Both	1.91 (0.50–7.31)	0.345		
Laterality of MRI lesion				
Unilateral	Reference			
Bilateral	1.97 (0.60–6.53)	0.266		

Table 3. Univariable and multivariable regression analysis for predicting overall prostate cancer and significant prostate cancer (≥ Gleason score 7) at magnetic resonance imaging targeted prostate biopsy cores. %fPSA, free-to-total PSA ratio; 95% CI, 95% confidence interval; DRE, digital rectal examination; MRI, magnetic resonance imaging; OR, odds ratio; PB, prostate biopsy; PCa, prostate cancer; PI-RADSv2, Prostate Imaging Reporting and Data System version 2; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density. *$p < 0.05$ (statistically significant differences).

RADSv2 ≥ 4 lesions were identified as independent risk factors for overall and significant PCa on MRI-targeted biopsy. These results are consistent with prior studies highlighting PSAD and MRI suspicion scores as significant predictors of cancer detection[23].

Although PSAD < 0.19 ng/mL^2 had the highest AUC for predicting PI-RADSv2 ≥ 4 lesions, using this criterion to omit MRI could reduce MRI use by 38.6% but carried a 30.3% risk of missing significant PCa. Including %fPSA > 18.76% alongside PSAD < 0.19 ng/mL^2 as a triage tool showed no significant change in AUC for predicting PI-RADSv2 ≥ 4 but reduced the risk of missing significant PCa to 9.1% while decreasing MRI use by 23.1%. Recommending MRI for patients with PSA ≥ 11.87 ng/mL, PSAD ≥ 0.19 ng/mL^2, or %fPSA ≤ 18.76% resulted in a 22.7% reduction in MRI use, with a 9.1% risk of missing significant PCa.

The result of our study is comparable to those of previous studies. For overall population, the triage strategy utilizing PSA and its derivatives to recommend MRI could reduce 24.6–33.9% of MRI, with the risk of missing 4.2–9.5% of clinically significant PCa[24]. In addition, a recent study based on the Prostate Cancer Disease Observation (PRECISION) cohort[25] reported that utilizing Rotterdam Prostate Cancer Risk Calculator (RPCRC) could reduce 34.9% of unnecessary MRI at the cost of missing 15.7% of clinically significant PCa. For patients with previous negative PB, utilizing RPCRC could reduce 51% of MRI at the cost of missing 10% of high-grade PCa[24].

Cutoff value for the omission of MRI	All patients who underwent MRI ($n=251$)						MRI/TRUS fusion PB group ($n=125$)	
	AUC (95% CI)	*p* value	Sensitivity of visible lesion on MRI (PI-RADSv2 ≥ 3)	Specificity of visible lesion on MRI (PI-RADSv2 ≥ 3)	Avoidable MRI (% of all MRI; 251)	Unnecessary MRI avoided (% of PI-RADSv2 < 3)	Missed PCa at MRI-targeted core (% of all PCa)	Missed significant PCa at MRI-targeted core (% of all significant PCa)
PSA < 11.87 ng/mL	0. 67 (0.60–0.74)	Reference	26.8% (34/127)	92.7% (115/124)	45.8% (115/251)	92.7% (115/124)	61.4% (27/44)	57.6% (19/33)
PSAD < 0.19 ng/mL^2	0.65 (0.59–0.71)	0.612	48.8% (62/127)	78.2% (97/124)	38.6% (97/251)	78.2% (97/124)	29.5% (13/44)	30.3% (10/33)
%fPSA > 18.76%	0.58 (0.52–0.64)	0.062	65.4% (83/127)	50.8% (63/124)	25.1% (63/251)	50.8% (63/124)	22.7% (10/44)	21.2% (7/33)
PSA < 11.87 ng/mL + PSAD < 0.19 ng/mL^2	0.66 (0.60–0.72)	0.808	52.8% (67/127)	77.4% (96/124)	38.2% (96/251)	77.4% (63/124)	27.3% (12/44)	27.3% (9/33)
PSAD < 0.19 ng/mL^2 + fPSA > 18.76%	0.61 (0.54–0.67)	0.183	73.2% (93/127)	46.8% (58/124)	23.1% (58/251)	46.8% (58/124)	11.4% (5/44)	9.1% (3/33)
PSA < 11.87 ng/mL + PSAD < 0.19 ng/mL^2 + %fPSA > 18.76%	0.62 (0.56–0.68)	0.267	75.6% (96/127)	46.0% (57/124)	22.7% (57/251)	46.0% (57/124)	11.4% (5/44)	9.1% (3/33)

Table 4. Comparison of area under the curve, sensitivity, and specificity to predict visible lesions on multiparametric magnetic resonance imaging (MRI) (PI-RADSv2 score ≥ 3) and risk of missing overall prostate cancer/clinically significant prostate cancer at MRI targeted biopsy cores according to each cutoff value of prostate-specific antigen (11.87 ng/mL), prostate-specific antigen density (0.19 ng/mL^2), and %fPSA (18.76%). %fPSA, free-to-total PSA ratio; AUC, area under the curve; MRI, magnetic resonance imaging; PB, prostate biopsy; PCa, prostate cancer; PI-RADSv2, Prostate Imaging Reporting and Data System version 2; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; TRUS, transrectal ultrasonography.

Although the risk of PCa in patients with previously negative PB is relatively lower than PB-naive men[22], MRI and subsequent targeted PB should be determined based on patient shared decision making, considering the risk of missing clinically significant PCa.

The findings of this study should be interpreted cautiously due to several limitations, including the retrospective, single-institution design. Interobserver variability in MRI interpretation using PI-RADS remains a concern, recommending the agreement among well-experienced radiologists[26]. Although the radiologists in our institution are well-experienced over 20 years, the possibility of interobserver discrepancy highlights the need for multicenter studies with centralized MRI interpretation review system to validate our results. Additionally, novel biomarkers such as the PHI, PHI density[27], and PCa antigen 3 gene[28] were not evaluated. Considering that those novel biomarkers showed superiority to conventional PSA derivatives in prediction of PCa, the combination of such biomarkers into criteria might enhance the negative predictive value, minimizing the potential risk to miss clinically significant PCa. Further study including such novel biomarkers should be performed. Meanwhile, all biopsies in this study were performed via the TR route, which may have influenced the detection accuracy. Previous research suggests that transperineal (TP) biopsy offers equal or superior detection rates compared with TR biopsy and TP biopsy could potentially reduce unnecessary MRIs[29,30]. Furthermore, given the low cancer-specific mortality in patients with prior negative biopsies[12], longer followup studies are needed to evaluate ultimate cost-effectiveness and survival analysis of clinical progression. Despite these limitations, this study is, to the best of our knowledge, the first to evaluate the use of PSA and PSA derivatives as a triage tool to reduce unnecessary MRI in patients with prior negative biopsy.

Conclusions

In patients with prior negative prostate biopsy, limiting MRI to cases with PSA < 11.87 ng/mL, PSAD < 0.19 ng/mL, and %fPSA > 18.76% can reduce MRI use by 22.7%, with a 9.1% risk of missing significant PCa. However, those criteria for MRI recommendation should be adjusted based on the other novel biomarkers or individual patient characteristics and preferences.

Data availability

The materials datasets used and/or analyzed during this study are available from the corresponding author upon reasonable request.

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References

1. Bray, F. et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **74**, 229–263 (2024).
2. Welch, H. G. et al. Reconsidering prostate cancer mortality—The future of PSA screening. *N. Engl. J. Med.* **382**, 1557–1563 (2020).
3. Van Poppel, H. et al. Serum PSA-based early detection of prostate cancer in Europe and globally: Past, present and future. *Nat. Rev. Urol.* **19**, 562–572 (2022).
4. Hodge, K. K. et al. Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. *J. Urol.* **142**, 71–74 (1989).

5. Perera, M. et al. Management of men with previous negative prostate biopsy. *Curr. Opin. Urol.* **26**, 481–487 (2016).
6. Abd-Alazeez, et al. The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level—can it rule out clinically significant prostate cancer?. *Urol. Oncol.* **32**(45), e17-22 (2014).
7. Hutchinson, R. C. et al. The economic effect of using magnetic resonance imaging and magnetic resonance ultrasound fusion biopsy for prostate cancer diagnosis. *Urol. Oncol.* **34**, 296–302 (2016).
8. Kim, E. H. et al. Should men undergo MRI before prostate biopsy—CON. *Urol. Oncol.* **41**, 92–95 (2023).
9. Ahdoot, M. et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. *N Engl. J. Med.* **382**, 917–928 (2020).
10. Rosenkrantz, A. B. et al. Prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a prior negative biopsy: A consensus statement by AUA and SAR. *J. Urol.* **196**, 1613–1618 (2016).
11. Kim, S. J. et al. Challenges in adopting level 1 evidence for multiparametric magnetic resonance imaging as a biomarker for prostate cancer screening. *JAMA Oncol.* **4**, 1663–1664 (2018).
12. Kawa, S. M. et al. A Nationwide analysis of risk of prostate cancer diagnosis and mortality following an initial negative transrectal ultrasound biopsy with long-term follow-up. *J. Urol.* **208**, 100–108 (2022).
13. Venderink, W. et al. Yield of repeat targeted direct in-bore magnetic resonance-guided prostate biopsy (MRGB) of the same lesions in men having a prior negative targeted MRGB. *Korean J. Radiol.* **19**, 733–741 (2018).
14. Pepe, P. et al. Early second round targeted biopsy of PI-RADS score 3 or 4 in 256 men with persistent suspicion of prostate cancer. *In Vivo* **33**, 897–901 (2019).
15. Wallstrom, J. et al. Prostate cancer screening with magnetic resonance imaging: Results from the second round of the Goteborg prostate cancer screening 2 trial. *Eur. Urol. Oncol.* **5**, 54–60 (2022).
16. Barletta, F. et al. How to optimize follow-up in patients with a suspicious multiparametric MRI and a subsequent negative targeted prostate biopsy. Results from a large, single-institution series. *Urol. Oncol.* **40**, 103 (2022).
17. Djavan, B. et al. Optimal predictors of prostate cancer on repeat prostate biopsy: A prospective study of 1051 men. *J. Urol.* **163**, 1144–1148 (2000) (**discussion 1148–1149**).
18. Ploussard, G. et al. Risk of repeat biopsy and prostate cancer detection after an initial extended negative biopsy: Longitudinal follow-up from a prospective trial. *BJU Int.* **111**, 988–996 (2013).
19. Hwang, S. I. et al. Value of MR-US fusion in guidance of repeated prostate biopsy in men with PSA < 10 ng/mL. *Clin. Imaging.* **53**, 1–5 (2019).
20. Mottet, N. et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on prostate cancer-2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur. Urol.* **79**, 243–262 (2021).
21. Sathianathen, N. J. et al. Negative predictive value of multiparametric magnetic resonance imaging in the detection of clinically significant prostate cancer in the prostate imaging reporting and data system era: A systematic review and meta-analysis. *Eur. Urol.* **78**, 402–414 (2020).
22. Patel, H. D. et al. Risk of prostate cancer for men with prior negative biopsies undergoing magnetic resonance imaging compared with biopsy-naive men: A prospective evaluation of the PLUM cohort. *Cancer* **128**, 75–84 (2022).
23. Vourganti, S. et al. Multiparametric magnetic resonance imaging and ultrasound fusion biopsy detect prostate cancer in patients with prior negative transrectal ultrasound biopsies. *J. Urol.* **188**, 2152–2157 (2012).
24. Soeterik, T. F. W. et al. Personalised prostate cancer diagnosis: Evaluating biomarker-based approaches to reduce unnecessary magnetic resonance imaging and biopsy procedures. *Eur. Urol. Open Sci.* **75**, 106–119 (2025).
25. Remmers, S. et al. Reducing biopsies and magnetic resonance imaging scans during the diagnostic pathway of prostate cancer: Applying the Rotterdam prostate cancer risk calculator to the PRECISION trial data. *Eur. Urol. Open Sci.* **36**, 1–8 (2021).
26. Rosenkrantz, A. B. et al. Interobserver reproducibility of the PI-RADS version 2 Lexicon: A multicenter study of six experienced prostate radiologists. *Radiology* **280**, 793–804 (2016).
27. Liu, A. Q. et al. Initial prostate health index (PHI) and PHI density predicts future risk of clinically significant prostate cancer in men with initial negative prostate biopsy: A 6-year follow-up study. *Prostate Cancer Prostatic. Dis.* **25**, 684–689 (2022).
28. Pagniez, M. A. et al. Predictive factors of missed clinically significant prostate cancers in men with negative magnetic resonance imaging: A systematic review and meta-analysis. *J. Urol.* **204**, 24–32 (2020).
29. Kaneko, M. et al. Transperineal vs transrectal magnetic resonance and ultrasound image fusion prostate biopsy: A pair-matched comparison. *Sci. Rep.* **13**, 13457 (2023).
30. Oderda, M. et al. Transrectal versus transperineal prostate fusion biopsy: A pair-matched analysis to evaluate accuracy and complications. *World J. Urol.* **42**, 535 (2024).

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Author contributions

S.L. and B.S. contributed to project development. S.L and B.S. conducted data analysis. S.L., H.R., and B.S. were responsible for manuscript writing and editing. S.H.S., S.I.H., and H.J.L. managed data collection and analysis. S.K.H., and S.S.B. performed the critical review. B.S. supervised the study.

Declarations

Competing interests

The authors declare no competing interests.

Research involving human participants and/or animals

This study was approved by the Seoul National University Bundang Hospital Institutional Review Board (IRB No. B-2410-933-105). It did not involve animal subjects. All procedures followed the ethical standards of the institutional and national research committees and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

Due to the retrospective nature of the study, Seoul National University Bundang Hospital Institutional Review Board waived the need of obtaining informed consent.

Additional information

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