Prostate International 11 (2023) 167–172

Contents lists available at ScienceDirect

Prostate International

journal homepage: https://www.journals.elsevier.com/prostate-international

Research Article

How to avoid prostate biopsy in men with Prostate Image-Reporting and Data System 3 lesion? Development and external validation of new biopsy indication using prostate health index density

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ARTICLE INFO

Article history:
Received 30 May 2023
Received in revised form
24 June 2023
Accepted 5 July 2023
Available online 11 July 2023

Keywords:
Biopsy
Prostatic neoplasms
Prostate-specific antigen
Prostatic secretory proteins

ABSTRACT

Background: To develop a customized prostate biopsy indication using prostate health index density (PHID) combined with multiparametric magnetic resonance imaging (mpMRI) and assess the reliability of the PHID cutoff value in external populations.

Methods: A total of 521 cognitive MRI/ultrasonography fusion prostate biopsies and biomarker tests for prostate-specific antigen (PSA), free PSA, and PHI were performed after mpMRI. The predictive value for clinically significant prostate cancer (csPCa; Gleason score≥7) of PSA derivatives was examined using the ROC curve. We developed a new biopsy indication utilizing a PHID cutoff based on the Prostate Image-Reporting and Data System (PI-RADS) score, which was externally validated.

Results: The combination of PHID and mpMRI (AUC = 0.884) demonstrated the highest predictive ability for csPCa, although PHID (AUC = 0.843) and PI-RADS (AUC = 0.806) individually also showed a high diagnostic value. When a PHID cutoff of 0.75 was used in men with PI-RADS 3 lesions, the negative predictive value of csPCa was 100%, and approximately half of the biopsies could be safely avoided.

Conclusion: Compared to PHID or PI-RADS scores alone, the combination of PHID and PI-RADS scores increased the accuracy of csPCa detection and the number of cases in which biopsy could be avoided. In men with PI-RADS 3 lesions, the optimal PHID cutoff ≥0.75 can prevent half of the unnecessary biopsies without missing csPCa. In men with PI-RADS 4-5 lesions, biopsies are warranted regardless of PHID values because csPCa could be accompanied by low PHID.

1. Introduction

Elevated prostate-specific antigen (PSA) levels or abnormal digital rectal examination findings trigger a prostate biopsy to ascertain the presence of prostate cancer (PCa).[1] PSA, a key biomarker for several decades, is associated with a significant risk of false positives, although it is the most important in selecting candidates for prostate biopsy in asymptomatic patients.[2,3] Therefore, this strategy missed sometimes clinically significant prostate cancers (csPCa) and often detect clinically insignificant PCa.[4]

To complement this limitation, multiparametric magnetic resonance imaging (mpMRI) has recently been utilized before prostate biopsy to determine not only the likelihood of cancer but also its location.[3,5] These characteristics can be used in conjunction with target biopsy techniques.[6,7] Since the late 2010s, mpMRI has been validated in several large randomized controlled trials for its safety in delaying immediate biopsy.[4,8,9] However, these trials recommended that all mpMRI-visible lesions (PI-RADS ≥3) should be biopsied.[4] Notably, a PI-RADS 3 lesion is an equivocal lesion and has only a 12–17% detection rate of csPCa.[4,8] Therefore, the need for precise biopsy indications in this population is greater than in others.

New alternative biomarker, prostate health index (PHI), outperforms PSA and other biomarkers in identifying csPCa,[10] with PHI

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https://doi.org/10.1016/j.prnil.2023.07.001

density (PHID) proving even more precise in its detection than PHI itself.[11] However, the optimal criteria for delaying immediate biopsy using PHID in the mpMRI era are not yet established, necessitating further research.

This study aimed to evaluate the diagnostic potential of PHID in combination with mpMRI for predicting csPCa. We proposed an optimal PHID cutoff to avoid unnecessary biopsy in men with PI-RADS 3 lesions and assessed the reliability of this PHID cutoff value based on PI-RADS score in an external validation cohort.

2. Materials and methods

2.1. Patient and clinical data

We retrospectively reviewed 521 biopsy-naïve patients with suspected PCa due to elevated serum PSA levels (>4 ng/mL) or abnormal findings on digital rectal examination who underwent prostate biopsy after mpMRI at our institution. Exclusion criteria were other malignancies (n = 3), incomplete clinical data (n = 1), and acute urinary retention (n = 2). This study was conducted between July 2018 and October 2022. All patients underwent PSA, free PSA, and PHI analyses; transrectal ultrasonography; and prostate mpMRI before undergoing cognitive MRI/ultrasonography fusion-targeted prostate biopsy. The protocol was approved by the Ethics Committee of Pusan National University Yangsan Hospital Institutional Review Board (No. 04-2021-010). The clinicopathological data of 366 patients at Seoul Samsung Hospital were collected as an external validation cohort to validate the PHID cutoff value derived from the study cohort.

Clinical variables, such as age, serum PSA, [−2] proPSA (p2PSA), percentage free/total PSA (%fPSA), PHI, prostate volume, and digital rectal examination findings, were evaluated. Prostate volume was determined using transrectal ultrasonography and calculated with the standard ellipsoid formula. PHI was calculated using the formula [p2PSA/free PSA $\times$ $\sqrt{}$PSA].[12] Density values were determined by dividing the PSA derivative level by the volume of the prostate in milliliters.

2.2. mpMRI and biopsy protocol

All patients underwent mpMRI using a specialized six-channel phased-array coil and a 3.0-T MRI machine (Intera Achieva 3.0 T; Phillips Medical Systems, Best, Netherlands). The mpMRI protocol adhered to PI-RADS v2 guidelines and included T2-weighted imaging, dynamic contrast-enhanced imaging, and diffusion-weighted imaging with apparent diffusion coefficient reconstruction.

All patients underwent transrectal cognitive MRI/ultrasonography fusion-targeted prostate biopsies. At least three biopsy cores were obtained for each target lesion, and the index lesion data were analyzed as the target biopsy. At least 12 random cores were systematically obtained. If numerous lesions were detected using mpMRI, only the highest PI-RADS score was considered. The mpMRI results were interpreted by a urogenital radiologist who had more than 15 years of experience in the field.

Based on pathological evaluation, biopsy specimens were graded into three subgroups according to the International Society of Urological Pathology 2014/World Health Organization 2016 consensus guidelines.[13] csPCa was defined as a Gleason score $\geq$7 and non-clinically significant cancer (non-csPC) as a Gleason score of 6 or benign disease.

2.3. Statistical analysis

The medians and interquartile ranges (IQR) were used to report continuous variables, while proportions were used to report categorical variables. Continuous variables were compared between the csPC and non-csPC groups using an independent Student's t-test, and Pearson's chi-squared test was used to analyze categorical variables.

To assess the diagnostic performance of different biomarkers (PSA, PSAD, PHI, PHID, and %fPSA) and PI-RADS scores for csPCa, receiver operating characteristic (ROC) curve analysis was conducted. The area under the curve (AUC) was estimated along with a corresponding 95% confidence interval. The cutoff values of PHID ($\geq$0.50, 0.75, and 1.00) to determine the optimal diagnostic performance were evaluated. The sensitivity, specificity, and negative predictive values (NPV) at each cutoff were evaluated for the PI-RADS scores 1-2, 3, 4, and 5. All statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA) using a two-sided test with a 5% significance level.

3. Results

The clinicopathological characteristics of the patients are presented in Table 1. Among the 521 patients from our institution, adenocarcinoma was observed in 305 (58.5%) and csPCa in 243 (46.6%). The proportion of patients in the PI-RADS 1-2, 3, 4, and 5 groups were 6.1%, 26.3%, 41.5%, and 26.1%, respectively. The detection rates of csPCa in the PI-RADS 1-2, 3, 4, and 5 groups were 3.1%, 14.5%, 49.3%, and 85.3%, respectively. The median PSA, PSAD, PHI, and PHID values were significantly higher in patients with csPCa than in non-csPCa group. Abnormal digital rectal examination (60.9% vs. 21.2%, $P < 0.001$) and positive mpMRI (PI-RADS score $\geq$3 lesions) (99.6% vs 89.2%, $P < 0.001$) were more common in csPCa group than in non-csPCa group.

ROC curve analysis was used to measure the predictive capabilities of PSA and its derivatives (Fig. 1). PHID was the most accurate individual predictor among all the screening tools. PSAD (AUC = 0.806), PHI (AUC = 0.824), and PHID (AUC = 0.843) values outperformed PSA (AUC = 0.727) in predicting csPCa ($P = 0.038$). The combined assessment of PHID and PI-RADS scores (AUC = 0.884) ($P = 0.015$) was superior to the PHID and PI-RADS scores alone in detecting csPCa. The AUC of various PSA derivatives and PI-RADS scores are shown in Fig. 1.

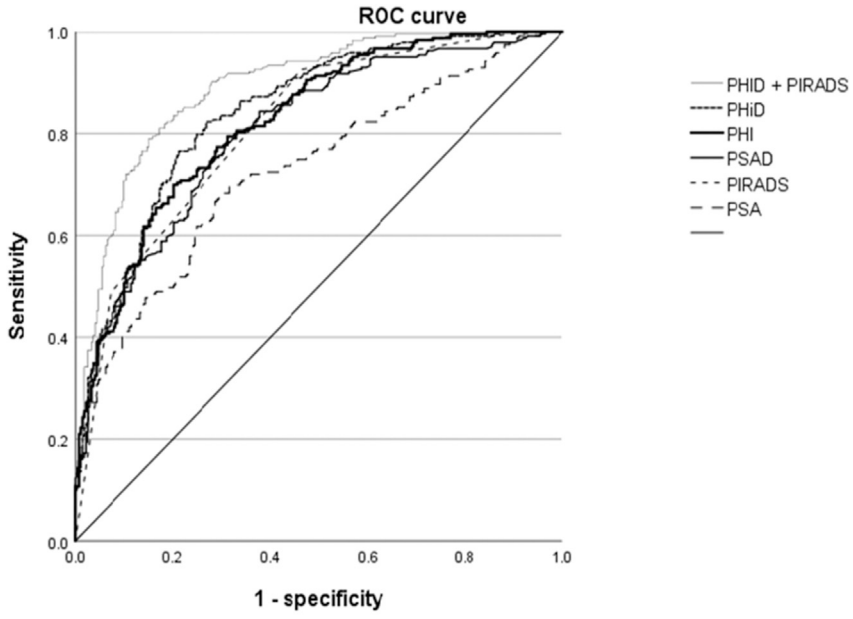
The NPV were evaluated at different PHID cutoff values ($\geq$0.50, 0.75, 1.00) for PI-RADS scores 1-2, 3, 4, and 5 lesions (Table 2). In men with a negative mpMRI (PI-RADS 1-2), a PHID cutoff of 1.00 detected 100% of csPCa, avoiding 62.5% of unnecessary biopsies. Only one patient with csPCa had a PHID value of 2.16. In men with PI-RADS 3 lesions, a PHID cutoff of 0.75 detected 100% of csPCa, while avoiding 45.9% of unnecessary biopsies. In men with PI-RADS 4 lesions, a PHID cutoff of 0.50 resulted in a 91.7% NPV with one missed csPCa (PHID, 0.40), while avoiding 10.2% of unnecessary biopsies. Using a PHID cutoff of 0.50 in men with PI-RADS 5 lesions, the rate of avoided biopsies was 2.2%, and an NPV of 100% was achieved. The distribution of PHID values according to the PI-RADS score is shown in Fig. 2.

Using the external validation cohort, a PHID cutoff of 0.75 for the PI-RADS 3 group detected 100% of csPCa and avoided 49.4% of unnecessary biopsies. In addition, we estimated the accuracy of the PHID cutoff values for the other PI-RADS scores. PHID cutoff 1.00 for the negative mpMRI (PI-RADS 1-2) group detected 100% of csPCa and avoided 62.5% of unnecessary biopsies. Using a PHID cutoff of 0.50 for the PI-RADS 4 group, 95% of the NPV (missed one csPCa) was estimated while avoiding only 2.8% of unnecessary biopsies. In addition, only 50% NPV was achieved in the PI-RADS 5 group, and 0.9% of biopsies were avoided. In men with PI-RADS 4-5 lesions, csPCa with a low PHID value was not rare. This finding is consistent with our data.

Table 1
The clinicopathologic characteristics of the patients

	Total (n = 521)	csPCa (n = 243)	non-csPCa (n = 278)	*P*-value
Age, years, median (IQR)	67 (62–74)	70 (65–76)	67 (60–71)	0.08
PSA, ng/ml, median (IQR)	7.3 (5.1–12.8)	10.1 (6.3–20.3)	7.3 (4.5–8.7)	<0.001
PSAD, ng/ml/ml, median (IQR)	0.2 (0.1–0.4)	0.3 (0.2–0.6)	0.2 (0.1–0.2)	<0.001
%free PSA, %, median (IQR)	13.8 (9.5–19.1)	12.0 (8.5–15.6)	15.2 (11.1–19.2)	0.196
PHI, median (IQR)	45.6 (32.1–80.9)	75.9 (45.4–119.5)	45.6 (25.7–48.1)	<0.001
PHID, median (IQR)	1.3 (0.7–2.4)	2.2 (1.4–3.6)	1.1 (0.5–1.3)	<0.001
Abnormal DRE, n (%)	207 (39.7%)	148 (60.9%)	59 (21.2)	<0.001
PI-RADS ≥3, n (%)	489 (93.9%)	242 (99.6%)	248 (89.2%)	<0.001

csPCa, clinically significant prostate cancer (Gleason score≥7); non-csPCa, Gleason score 6 cancer or no cancer; IQR, interquartile range; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; PHI, prostate health index; PHID, prostate health index density; DRE, digital rectal examination; PI-RADS, Prostate Image-Reporting and Data System.



	AUC (95% CI)	P-value
PSA	0.727 (0.684-0.771)	<0.001
PSAD	0.806 (0.796-0.859)	<0.001
PI-RADS	0.806 (0.769-0.843)	<0.001
PHI	0.824 (0.789-0.859)	<0.001
PHID	0.843 (0.810-0.876)	<0.001
PHID+PI-RADS	0.884 (0.856-0.913)	<0.001

Fig. 1. Receiver operating characteristic (ROC) curve and AUC of various PSA derivatives. AUC, area under curve; PSA, prostate-specific antigen; PSAD, PSA density; CI, confidence, interval; %fPSA, percent-free PSA; PHI, prostate health index; PI-RADS, Prostate Imaging-Reporting Data System.

4. Discussion

We investigated three PHID cutoff values (≥0.50, 0.75, and 1.00) to detect csPCa for PI-RADS scores of 1-2, 3, 4, and 5. To the best of our knowledge, our study is the second, only to Druskin et al. to combine PHID with mpMRI and biopsy results to diagnose csPCa.[11] Our research revealed a strong association between PHID and PI-RADS scores. Furthermore, we demonstrated that a cutoff of PHID ≥0.75 is the best predictor of csPCa for PI-RADS 3 lesions. The external validation model also confirmed PHID ≥0.75 as the optimal threshold for the detection of csPCa, with an NPV of 100 and a biopsy avoidance rate of 49.4%.

In our PI-RADS 1-2 group, 11 out of 32 (34.4%) patients had high PHID (>1.00), and 5 out of 32 (15.6%) patients had very high PHID (>2.00). Only one csPCa with PI-RADS 1-2 had very high PHID values of 2.16. Recent large RCTs, such as the PROMIS study, have concluded that biopsy is not necessary for PI-RADS 1-2 for detecting csPCa.[4] However, the findings of our study suggest that even in PI-RADS 1-2, if the PHID is significantly elevated (>2.00), the likelihood of csPCa is high, and biopsy is indicated.

In our PI-RADS 4 and 5 group, 49 out of 216 (22.8%) patients and 4 out of 136 (2.9%) patients had low PHID (<0.75), respectively. Furthermore, in PI-RADS 4 and 5 group, 22 out of 216 (10.2%) patients and 3 out of 136 (2.2%) patients had very low PHID (<0.50), respectively. Even though low incidence of low PHID in PI-RADS 4-5 group, csPCa was detected even at low PHID. These results suggest that selective biopsy based on PHID is not feasible in PI-RADS 4-5 group.

The optimal PHID threshold for a prostate biopsy remains a hotly debated topic. Ito et al. discovered that a threshold of 0.66 boasted a high sensitivity (95%); however, their study confined itself to PSA values within the 2–10 ng/mL range.[14] Ferro et al.

Table 2
Negative predictive value and number of biopsies avoided using various cutoffs of prostate health index density in the study cohort and the external validation cohort.

A. Study cohort (n = 521)

Cutoff	PI-RADS score 1-2 (n = 32)			PI-RADS score 3 (n = 135)			PI-RADS score 4 (n = 216)			PI-RADS score 5 (n = 136)		
	NPV (%)	n. (%) avoided biopsy	n. cancers missed	NPV (%)	n. (%) avoided biopsy	n. cancers missed	NPV (%)	n. (%) avoided biopsy	n. cancers missed	NPV (%)	n. (%) avoided biopsy	n. cancers missed
0.50	100	9 (28.1)	0	100	28 (20.7)	0	91.7	22 (10.2)	1	100	3 (2.2)	0
0.75	100	17 (53.1)	0	100	62 (45.9)	0	86.0	49 (22.8)	7	44.4	4 (2.9)	5
1.00	100	21 (65.6)	0	97.6	80 (59.3)	2	74.4	64 (29.8)	22	41.7	5 (3.77)	7

B. External validation cohort (n = 366)

Cutoff	PI-RADS score 1-2 (n = 72)			PI-RADS score 3 (n = 85)			PI-RADS score 4 (n = 108)			PI-RADS score 5 (n = 101)		
	NPV (%)	n. (%) avoided biopsy	n. cancers missed	NPV (%)	n. (%) avoided biopsy	n. cancers missed	NPV (%)	n. (%) avoided biopsy	n. cancers missed	NPV (%)	n. (%) avoided biopsy	n. cancers missed
0.50	100	18 (25)	0	100	21 (24.7)	0	95	3 (2.8)	1	50	1 (0.9)	1
0.75	100	36 (50)	0	100	42 (49.4)	0	88	22 (20.4)	3	40	4 (3.9)	6
1.00	100	45 (62.5)	0	98.2	56 (65.9)	1	83.3	30 (27.8)	6	41.7	5 (4.9)	7

PI-RADS, Prostate Imaging-Report and Data System; NPV, negative predictive value; PHI, prostate health index; PHID, prostate health index density; PSAD, prostate-specific antigen density; %fPSA, percent of free prostate-specific antigen.

suggested a heightened PHID threshold of 0.781 could improve the accuracy of PCa detection. However, in a study of 196 men, this threshold yielded a sensitivity of only 81.7%, indicating a higher risk of missing a cancer.[12] Druskin et al. used PHID in conjunction with mpMRI and a prior negative biopsy status to identify significant cancers.[11] Their findings were encouraging in that PHID $\geq$0.44 and PI-RADS 1-2 lesions had a 100% sensitivity in csPCa detection, with 7.7% of missed cancers.[11] Similarly, our results demonstrated a 100% cancer detection rate at a PHID cutoff of 0.50 in PI-RADS 1-2 lesions.

In our investigation, the AUC value for PHID emerged as 0.843, outperforming all other parameters like PHI and total PSA, which stood at 0.824 and 0.727, respectively. Mearini et al. initially evaluated the value of PHID for PCa detection and reported a high diagnostic sensitivity.[15] Their analysis of PHID in 275 patients revealed an AUC of 0.77, significantly outpacing that of total PSA (AUC = 0.54).[15] Subsequent studies have consistently attested to the high AUC values of PHID in ROC analyses.[16,17] Filella et al. validated this finding by calculating the AUC of PHID (0.760) for intermediate- and high-risk csPCa.[16] Tosoian et al. calculated the most significant AUC for PHID (0.84), outperforming all other parameters such as PHI and %fPSA.[17]

Numerous studies have scrutinized the effectiveness of PCa biomarkers in men with PI-RADS 3 lesions, likely due to the csPCa detection rate in PI-RADS 3 lesions fluctuating between 2% and 23%.[18–22] Thus, the management of PI-RADS 3 lesions varies widely among institutions.[18–20] Previous studies of PI-RADS 3 lesions with prostate biopsy results showed that PSAD $\geq$0.30 was associated with the highest csPCa detection rate.[21] Lee et al. found that PHI $\geq$30 was associated with an accurate diagnosis of PCa and csPCa.[22] Our study showed that PHID can also aid in the decision-making to perform biopsies for PI-RADS 3 lesions. Future prospective studies should combine PHID with objective imaging criteria to maximize the diagnostic performance.

Our study has several limitations. Owing to its retrospective design, this study was subject to bias. Moreover, our analysis may be underpowered by the relatively small sample size of the external validation group compared to that of the study population. Even though previous studies have developed nomograms to detect significant cancers, we did not create a multivariable nomogram incorporating PHID. Given the complexity of applying nomograms in clinical practice, we sought to provide a simpler cutoff value to guide biopsy indications. Theoretically, transrectal cognitive biopsy using an end-fire-type probe has a low accurate sampling rate for anterior transition zone lesions, especially for small lesions. To overcome the shortcomings of this procedure, the authors recognized the distorted position, that is, posterior lesions appearing more rostral on transrectal ultrasonography and anterior lesions appearing more caudal. In addition, we actively utilized the sagittal view for visual estimation. Lastly, prostate volume is a crucial aspect to consider when assessing the diagnostic performance of PCa biomarkers. Although large prostate does not need more number of biopsy cores,[23] patients with a small prostate volume ($\leq$35 cc) exhibited higher AUC values for PHI, %p2PSA, %fPSA, and total PSA than those with a larger prostate volume (>50 cc).[24] Thus, additional analysis is necessary to ascertain the diagnostic value of PHID in relation to prostate volume.

In conclusion, the combination of PHID and PI-RADS scores improved the accuracy of csPCa detection compared to PHID or PI-RADS scores individually. By utilizing a PHID cutoff of 0.75 in men with PI-RADS 3 lesions, we can potentially avoid half of the unnecessary biopsies without missing csPCa detection. This PHID cutoff demonstrated 100% sensitivity and NPV in external validation. Although PI-RADS 1-2 lesions are predominantly benign, they may harbor significant cancer if the PHID value is extremely high. In the case of men with PI-RADS 4-5 lesions, csPCa might be present

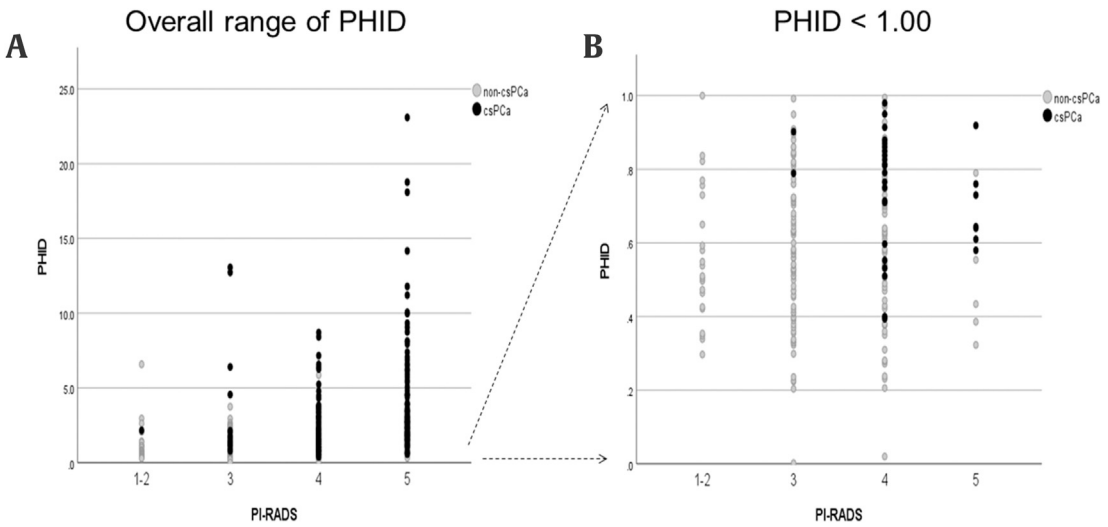


Fig. 2. Distribution of prostate health index density according to Prostate Image-Report and Data System score. Black spot indicated clinically significant cancer. Gray spot indicated benign or Gleason 6 cancer. (A) Distribution of overall PHID according to PI-RADS score; (B) distribution of PHID range of 0 to 1 according to PI-RADS score.

even with a low PHID value; hence, biopsies should be performed irrespective of the PHID value. To prevent unnecessary biopsies, an individualized approach considering the PHID cutoff based on the PI-RADS score should be contemplated.

Funding

None.

Authors' contributions

JY Kim: project development, data collection, data analysis, manuscript writing and editing.

SS Jeon: project development, data collection. JH Chung: data collection. SS Lee: data collection. SW Park: project development, data collection, data analysis, manuscript writing and editing.

Ethics statement

This retrospective, single-center study was approved by the Pusan National University Yangsan Hospital institutional review board (No. 04-2021-010). As all data were analyzed retrospectively after de-identification, the requirements for review and informed consent were waived.

Declaration of competing interest

None of the contributing authors have any conflicts of interest, including specific financial interests, relationships, or affiliations relevant to the subject matter or materials discussed in the manuscript.

Acknowledgments

None.

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