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Diagnostic value of prostate health index in patients with no index lesion on mpMRI or negative previous combined biopsy

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Purpose: To assess the effectiveness of the prostate health index (PHI) in patients with no index lesions on multiparametric magnetic resonance imaging (mpMRI) or with negative findings on past prostate biopsy if there was an index lesion on mpMRI.

Materials and Methods: Patients without an index lesion on MRI or with a negative result on combined biopsy for index lesions were assessed. Patients who underwent transperineal mapping biopsy among those suspected of having prostate cancer (PCa) due to persistently elevated prostate-specific antigen (PSA) levels were analyzed.

Results: Of the 291 patients, 82 (28.2%) were diagnosed with PCa. Sixty-five of 291 patients had negative finding in previous combined biopsy. In total, 226 patients did not have any index lesions. The mean age of the PCa group was 64.33±8.88 years and that of the non-cancer group was 59.88±10.26 years (p<0.001). The PHI was 46.75±28.22 in the PCa group and 37.74±17.37 in the non-cancer group (p=0.001), and the prostate volume was 41.52±15.77 mL in the PCa group and 50.78±23.97 mL in the non-cancer group (p=0.001). In multivariate analysis, age (odds ratio [OR] 1.096, p<0.001), PHI (OR 1.021, p=0.005), and prostate volume (OR 0.954, p<0.001) were identified as significant factors for PCa detection. The optimal cutoff value of the PHI for PCa detection was 44.6 and the PHI density (PHID) was 0.88.

Conclusions: In patients with elevated PSA levels but no index lesions on mpMRI or negative biopsy findings, PHI and PHID demonstrated significant potential for improving PCa detection.

Keywords: Biopsy; Diagnosis; Prostate cancer

INTRODUCTION

Prostate cancer (PCa) is one of the most prevalent malignancies in men worldwide, and early diagnosis plays a critical role in improving patient outcomes [1]. Prostate-specific antigen (PSA) testing has long been the cornerstone of PCa screening [2]. While PSA is sensitive, its limited specificity often results in unnecessary biopsies and patient anxiety [3,4].

Multiparametric magnetic resonance imaging (mpMRI) has emerged as a powerful diagnostic modality for identify-

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ing clinically significant PCa [5]. mpMRI offers improved cancer localization and assists in risk stratification through the Prostate Imaging-Reporting and Data System (PI-RADS) [6]. mpMRI-based biopsy has been shown to increase the detection of significant PCa, while reducing the number of unnecessary biopsies in patients with low-risk disease [7]. However, despite its high negative predictive value, a significant number of patients with elevated PSA without an index lesion (PI-RADS ≥3) are diagnosed with PCa [8]. Moreover, if the PSA level is continuously elevated despite cancer not being diagnosed by combined biopsy, the cancer diagnosis rate at follow-up biopsy cannot be neglected. Unfortunately, diagnostic strategies for these patients have not been established.

The prostate health index (PHI) was introduced to enhance diagnostic accuracy [9]. PHI showed superior specificity in detecting clinically significant PCa compared with PSA alone. This advancement has reduced overdiagnosis and overtreatment, addressing a major drawback of PSA-based screening [10-12]. Moreover, PHI density (PHID) may further enhance the risk stratification, particularly in patients with borderline or ambiguous findings [13].

The present study investigated the utility of PHI and PHID in improving PCa detection using transperineal mapping biopsy in patients with elevated PSA levels but without index lesions on mpMRI or prior negative biopsy results.

MATERIALS AND METHODS

1. Study design and population

This retrospective cohort study was conducted at a single tertiary medical center (Samsung Medical Center, Seoul, Korea) between January 2019 and January 2023. A total of 291 patients with persistently elevated PSA levels (>3.0 ng/mL) were included. Eligible patients met one of the following criteria: (1) no index lesions (PI-RADS <3) on mpMRI [7] or (2) negative biopsy results despite the presence of suspicious findings. Patients with prior treatment for PCa or insufficient clinical data were excluded.

2. Data collection

Baseline demographic and clinical data were collected, including age, family history of PCa, PSA levels, free PSA, [-2]proPSA, PHI, and prostate volume measured via mpMRI. The PSA, free PSA, [-2]proPSA, and PHI were obtained within one month prior to biopsy. Additionally, all patients with a history of previous biopsies underwent transrectal combined (cognitive or fusion) biopsy.

3. Biopsy protocol

All patients underwent systematic transperineal mapping biopsy using a 5-mm template grid under general anesthesia. This method ensures comprehensive sampling of the prostate gland and improves cancer detection rates [14]. Biopsies were performed by experienced urologists or residents, and specimens were analyzed by dedicated genitourinary pathologists.

4. Statistical analysis

Patients were categorized into two groups based on their biopsy results: PCa and non-cancer. Descriptive statistics were calculated for demographic and clinical variables, and group comparisons were performed using Fisher's exact test for categorical variables and Student's t-test for continuous variables. Logistic regression analysis was conducted to identify the independent predictors of PCa. Receiver operating characteristic (ROC) curves were generated to evaluate the diagnostic performance of the PHI and PHID, and the area under the curve (AUC) was calculated. The optimal cutoff values for PHI and PHID were determined using Youden's index.

Statistical significance was defined as $p<0.05$. All analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp.).

5. Ethical considerations

This study was approved by the Institutional Review Board of Samsung Medical Center (approval number: 2024-12-026), and the need for informed consent was waived due to the retrospective nature of the study. All the procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki (2013).

RESULTS

1. Patient characteristics

A total of 291 patients were included in the study, of whom 82 (28.2%) were diagnosed with PCa and 209 (71.8%) without cancer. Sixty-five of 291 patients had index lesions on pre-biopsy MRI; however, the prostate was not diagnosed because of a previous combined biopsy. In total, 226 patients did not have any index lesions. Among 226 patients with no index lesions on pre-biopsy mpMRI, 57 (25.2%) were diagnosed with PCa.

The mean age of the PCa group was significantly higher than that of the non-cancer group (64.33±8.88 years vs. 59.88±10.26 years, $p<0.001$). The number of previous biopsies was also significantly greater in the PCa group (0.89±0.88 vs.

Table 1. Baseline characteristics

Parameter	Prostate cancer (n=82)	No-cancer (n=209)	p-value
Age (y)	64.33±8.88	59.88±10.26	<0.001[a]
Familial history	4 (4.9)	8 (3.8)	0.685[b]
5ARI administration	4 (4.9)	3 (1.4)	0.085[b]
Number of past biopsies	0.89±0.88	0.65±0.89	0.034[a]
PSA (ng/mL)	7.32±5.59	7.29±5.04	0.974[a]
Free PSA (ng/mL)	1.34±3.77	1.05±0.76	0.294[a]
p2PSA (pg/mL)	16.91±13.66	14.65±10.14	0.178[a]
Prostate health index	46.75±28.22	37.74±17.37	0.001[a]
Prostate volume (mL)	41.52±15.77	50.78±23.97	0.001[a]

Values are presented as mean±standard deviation or number (%).
5ARI, 5 alpha reductase inhibitors; PSA, prostate specific antigen; p2PSA, [-2]proPSA.
[a]:Based on Student t-test. [b]:Based on Fisher's exact test.

Table 2. Logistic regression and multivariable analysis for prostate cancer

Parameter	Odds ratio	95% CI		p-value	Odds ratio	95% CI		p-value
		Lower	Upper			Lower	Upper	
Age	1.049	1.020	1.080	0.001	1.096	1.058	1.135	<0.001
Familial history	1.288	0.377	4.401	0.686				
5ARI administration	3.521	0.771	16.092	0.104				
Number of past biopsies	1.343	1.018	1.772	0.037	1.371	0.990	1.899	0.057
PSA	1.001	0.953	1.051	0.973				
Free PSA	1.060	0.937	1.199	0.356				
p2PSA	1.017	0.995	1.039	0.130				
Prostate health index	1.019	1.006	1.032	0.003	1.021	1.006	1.037	0.005
Prostate volume	0.976	0.961	0.991	0.002	0.954	0.936	0.973	<0.001

CI, confidence interval; 5ARI, 5 alpha reductase inhibitors; PSA, prostate specific antigen; p2PSA, [-2]proPSA.

0.65±0.89, p=0.034). While PSA levels did not differ significantly between groups (p=0.974), the PCa group exhibited significantly higher PHI values (46.75±28.22 vs. 37.74±17.37, p=0.001), and smaller prostate volumes (41.52±15.77 mL vs. 50.78±23.97 mL, p=0.001) (Table 1).

2. Predictors of PCa

Univariate logistic regression analysis revealed age (odds ratio [OR] 1.049, p=0.001), number of previous biopsies (OR 1.343, p=0.037), PHI (OR 1.019, p=0.003), and prostate volume (OR 0.976, p=0.002). In the multivariate model, age (OR 1.096, p<0.001), PHI (OR 1.021, p=0.005), and prostate volume (OR 0.954, p<0.001) remained independent predictors of PCa detection (Table 2).

3. Diagnostic performance of PHI and PHID

ROC curve analysis showed that the AUC for PHI was 0.602 (p=0.007), while that for PHID was slightly higher at 0.641 (p<0.001) (Fig. 1). The optimal cutoff value for PHI to predict PCa was determined to be 44.60, with a sensitivity of 43% and a specificity of 79%. For PHID, the optimal cutoff was 0.88, with sensitivity and specificity values of 61% and 61%, respectively (Table 3).

DISCUSSION

PCa is one of the most common malignancies among men worldwide and poses a significant public health burden. PCa ranks among the top causes of cancer-related morbidity and mortality in men, with its incidence steadily increasing owing to aging populations and the widespread adoption of PSA screening [15]. PSA has high sensitivity, but low specificity [16]. Despite these limitations, PSA testing has persisted as a reliable and widely used biomarker for PCa detection. It has become a cornerstone of early diagnosis, enabling timely intervention and improving patient outcomes [17].

Biopsy remains the only definitive method for the detection of PCa. However, the high rate of unnecessary biopsies owing to PSA's limited specificity of PSA has significant consequences. Complications of prostate biopsy, such as hematuria, infection, and sepsis, are relatively uncommon and contribute substantially to patient morbidity and healthcare

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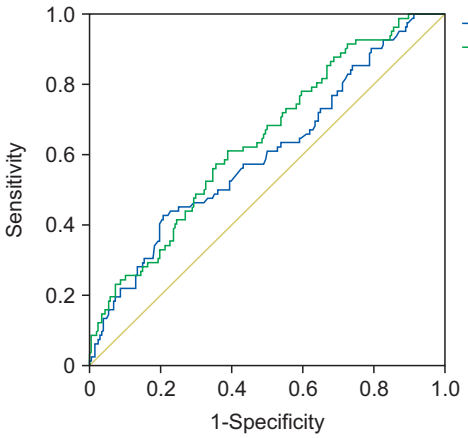

	AUC	95% CI		p-value
		Lower	Upper	
PHI	0.602	0.528	0.675	0.007
PHID	0.641	0.571	0.710	<0.001

Fig. 1. Area under cover (AUC) of prostate health index (PHI) and PHI density (PHID) for prostate cancer. CI, confidence interval.

Table 3. Cutoff value for prostate cancer

	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy	Youden's index
PHI	44.60	0.43	0.79	0.46	0.68	0.62	0.22
PHID	0.88	0.61	0.61	0.61	0.61	0.72	0.22

PHI, prostate health index; PHID, prostate health index density; PPV, positive predictive value; NPV, negative predictive value.

costs [18]. Furthermore, Rosario et al. [19] emphasized the psychological burden of repeated biopsies, which can cause considerable distress and reduce the patients' quality of life. These issues underscore the pressing need to minimize unnecessary biopsies using improved diagnostic approaches. The introduction of mpMRI has significantly advanced PCa diagnostics by enhancing the detection of clinically significant PCa while reducing unnecessary biopsies. The high negative predictive value of mpMRI allows for more selective biopsies, thereby reducing the number of unnecessary procedures without compromising the diagnostic accuracy [20].

However, management of patients with elevated PSA levels and negative mpMRI findings remains unclear. Additionally, patients with index lesions (PI-RADS 3 to 5) on mpMRI who have negative combined biopsy results lack standardized follow-up strategies, leaving a diagnostic gap in clinical practice [21].

PHI represents a promising advancement in PCa diagnosis. PHI, which combines total PSA, free PSA, and [-2] proPSA, provides superior specificity compared to PSA alone [9]. Furthermore, PHID, which incorporates prostate volume into the calculation, offers additional stratification benefits, particularly in patients with intermediate PSA levels [22].

In patients with persistently elevated PSA levels but no index lesions on mpMRI, or those with negative combined biopsy results despite suspicious lesions, PHI may serve as a valuable tool to guide decision-making. Schoots et al. [23] reported cases where mpMRI failed to detect clinically significant cancers, suggesting that reliance on imaging alone may not suffice. The present study supports the use of PHI to determine the necessity of follow-up or repeat biopsies in these challenging patient populations. Specifically, the findings of this study indicate that PHI and PHID are independent predictors of PCa detection, with optimal cutoff values that can guide clinical decision-making. In the absence of standardized follow-up guidelines for patients with negative mpMRI or combined biopsy results, the PHI provides a clinically actionable parameter to address this gap. The findings of this study suggest that performing biopsies in patients with elevated PSA levels and negative mpMRI findings or prior negative biopsies is a prudent approach when guided by PHI. Moreover, Wang et al. [24] conducted a study on the cancer prediction ability of serum biomarkers in patients with a history of negative prostate biopsy. Similar to the findings of present study, their research also reported the highest AUCs for PHI and PHID, which were 0.73 and 0.70, respectively. However, their study did not propose cutoff values for PCa biopsy or cancer detection.

The prevalence of PCa increases with age [25]. Consistently, the present study showed that age is a significant risk factor for PCa. The prostate volume has also been found to be associated with cancer detection. This finding suggests the usefulness of PSA density and PHID, which evaluate PSA or PHI per unit volume, as predictive markers for assessing PCa risk [26].

In this study, transperitoneal template-guided mapping biopsy was performed, and 24-core or 36-core biopsy was per-

formed depending on prostate size. Although mpMRI-based combined biopsy is recommended for its superior cancer detection rate, transperitoneal template-guided mapping biopsy is expected to have a superior cancer detection rate than traditional extended sextant systematic biopsy in patients without an index lesion or those who were not diagnosed with cancer in a previous combined biopsy, which were the subjects of this study.

As this was a single-center retrospective study, the findings may not be generalizable to broader populations. The time between the previous biopsy and the transperineal mapping biopsy could not be analyzed. Furthermore, the moderate AUC values for PHI and PHID suggested that these biomarkers should not replace other established diagnostic tools. However, this study suggested a cutoff value for patients who did not have a strategy for prostate biopsy. Future research should focus on prospective multicenter studies to validate these findings and explore the integration of PHI and PHID with other emerging biomarkers, such as PCA3 or genomic tests, to further enhance diagnostic accuracy. Moreover, establishing separate cutoff values for patients without an index lesion and those with previous combined biopsy-negative results in a large-scale cohort study would provide more clinical utility.

CONCLUSIONS

This study highlights the diagnostic utility of PHI and PHID in patients with elevated PSA levels but without mpMRI-detected lesions or prior negative combined biopsy findings. Based on the results of this study, the cutoff values of PHI and PHID for biopsy are presented for these patients. By providing actionable thresholds, it offers a practical approach to address an unmet need in PCa diagnostics.

CONFLICTS OF INTEREST

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AUTHORS' CONTRIBUTIONS

Research conception and design: Seong Soo Jeon and Jae Hoon Chung. Data acquisition: Jae Hoon Chung and Wan Song. Statistical analysis: Jae Hoon Chung. Data analysis and interpretation: Seong Soo Jeon and Jae Hoon Chung. Drafting of the manuscript: Seong Soo Jeon and Jae Hoon Chung. Critical revision of the manuscript: Wan Song, Minyong Kang, Byeong Chang Jeong, and Seong Il Seo. Obtaining funding: Seong Soo Jeon. Administrative, technical, or material support: Hyun Hwan Sung and Hwang Gyun Jeon. Supervision: Seong Soo Jeon and Jae Hoon Chung. Approval of the final manuscript: all authors.

REFERENCES

1. Chung JH, Yu J, Song W, Kang M, Sung HH, Jeon HG, et al. Strategy for prostate cancer patients with low prostate specific antigen level (2.5 to 4.0 ng/mL). J Korean Med Sci 2020;35:e342.
2. Verma A, St Onge J, Dhillon K, Chorneyko A. PSA density improves prediction of prostate cancer. Can J Urol 2014;21:7312-21.
3. Etzioni R, Cha R, Feuer EJ, Davidov O. Asymptomatic incidence and duration of prostate cancer. Am J Epidemiol 1998;148:775-85.
4. Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. J Natl Cancer Inst 2009;101:374-83.
5. Rouvière O, Puech P, Renard-Penna R, Claudon M, Roy C, Mège-Lechevallier F, et al.; MRI-FIRST Investigators. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019;20:100-9.
6. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS prostate imaging - reporting and data system: 2015, version 2. Eur Urol 2016;69:16-40.
7. Hugosson J, Månsson M, Wallström J, Axcrona U, Carlsson SV, Egevad L, et al.; GÖTEBORG-2 Trial Investigators. Prostate cancer screening with PSA and MRI followed by targeted biopsy only. N Engl J Med 2022;387:2126-37.
8. Emmett L, Buteau J, Papa N, Moon D, Thompson J, Roberts MJ, et al. The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentre study. Eur Urol 2021;80:682-9.

https://doi.org/10.4111/icu.20250007

9. Lazzeri M, Haese A, Abrate A, de la Taille A, Redorta JP, McNicholas T, et al. Clinical performance of serum prostate-specific antigen isoform [-2]proPSA (p2PSA) and its derivatives, %p2PSA and the prostate health index (PHI), in men with a family history of prostate cancer: results from a multicentre European study, the PROMEtheuS project. BJU Int 2013;112:313-21.
10. Stephan C, Vincendeau S, Houlgatte A, Cammann H, Jung K, Semjonow A. Multicenter evaluation of [-2]proprostate-specific antigen and the prostate health index for detecting prostate cancer. Clin Chem 2013;59:306-14.
11. Yu GP, Na R, Ye DW, Qi J, Liu F, Chen HT, et al. Performance of the Prostate Health Index in predicting prostate biopsy outcomes among men with a negative digital rectal examination and transrectal ultrasonography. Asian J Androl 2016;18:633-8.
12. Chiu PK, Ng CF, Semjonow A, Zhu Y, Vincendeau S, Houlgatte A, et al. A multicentre evaluation of the role of the Prostate Health Index (PHI) in regions with differing prevalence of prostate cancer: adjustment of PHI reference ranges is needed for European and Asian settings. Eur Urol 2019;75:558-61.
13. Boo Y, Chung JH, Kang M, Sung HH, Jeon HG, Jeong BC, et al. Comparison of prostate-specific antigen and its density and prostate health index and its density for detection of prostate cancer. Biomedicines 2023;11:1912.
14. Kanthabalan A, Abd-Alazeez M, Arya M, Allen C, Freeman A, Jameson C, et al. Transperineal magnetic resonance imaging-targeted biopsy versus transperineal template prostate mapping biopsy in the detection of localised radio-recurrent prostate cancer. Clin Oncol (R Coll Radiol) 2016;28:568-76.
15. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
16. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. J Natl Cancer Inst 2006;98:529-34.
17. Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev 2013;2013:CD004720.
18. Peyromaure M, Ravery V, Messas A, Toublanc M, Boccon-Gibod L, Boccon-Gibod L. Pain and morbidity of an extensive prostate 10-biopsy protocol: a prospective study in 289 patients. J Urol 2002;167:218-21.
19. Rosario DJ, Lane JA, Metcalfe C, Donovan JL, Doble A, Goodwin L, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. BMJ 2012;344:d7894.
20. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al.; PROMIS study group. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815-22.
21. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Brunckhorst O, Darraugh J, et al. EAU-EANM-ESTRO-ESUR-ISUP-SIOG guidelines on prostate cancer-2024 update. Part I: screening, diagnosis, and local treatment with curative intent. Eur Urol 2024;86:148-63.
22. Wu B, Shao Y, Lin X, Hasi C, Jia W, Wang D, et al. Comparisons of the diagnostic accuracy across prostate health index, prostate health index density, and percentage free prostate-specific antigen for clinically significant prostate cancer: a prospective diagnostic study. Transl Androl Urol 2023;12:425-32.
23. Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink MG. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol 2015;68:438-50.
24. Wang Z, Chan MT, Tsang WC, Chiong E. Utility of serum biomarkers for predicting cancer in patients with previous negative prostate biopsy. World J Urol 2022;40:2255-60.
25. Şahin B, Çelik S, Sözen S, Türkeri L, Aslan G, Yazıcı S, et al.; Members of Turkish Urooncology Association. A new parameter to increase the predictive value of multiparametric prostate magnetic resonance imaging for clinically significant prostate cancer in targeted biopsies: lesion density. Prostate Int 2024;12:145-50.
26. Chen Y, Xu D, Ruan M, Li H, Lin G, Song G. A prospective study of the prostate health index density and multiparametric magnetic resonance imaging in diagnosing clinically significant prostate cancer. Investig Clin Urol 2023;64:363-72.