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The Prostate Health Index and multi-parametric MRI improve diagnostic accuracy of detecting prostate cancer in Asian populations

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Purpose: The aim of this study was to evaluate the effectiveness of the Prostate Health Index (PHI) and prostate multi-parametric magnetic resonance imaging (mpMRI) in predicting prostate cancer (PCa) and clinically significant prostate cancer (csPCa) during initial prostate biopsy.

Materials and Methods: In total, 343 patients underwent initial prostate biopsy and were screened by use of PHI and prostate-specific antigen (PSA) levels between April 2019 and July 2021. A subgroup of 232 patients also underwent prostate mpMRI. Logistic regression analysis was performed to evaluate the accuracies of PSA, PHI, and mpMRI as predictors of PCa or csPCa. These predictive accuracies were quantified by using the area under the receiver operating characteristic curve. The different predictive models were compared using the DeLong test.

Results: Logistic regression showed that age, PSA, PHI, and prostate volume were significant predictors of both PCa and csPCa. In the mpMRI subgroup, age, PSA level, PHI, prostate volume, and mpMRI were predictors of both PCa and csPCa. The PHI (area under the curve [AUC]=0.693) was superior to the PSA level (AUC=0.615) as a predictor of PCa (p=0.038). Combining PHI and mpMRI showed the most accurate prediction of both PCa and csPCa (AUC=0.833, 0.881, respectively).

Conclusions: The most accurate prediction of both PCa and csPCa can be performed by combining PHI and mpMRI. In the absence of mpMRI, PHI is superior to PSA alone as a predictor of PCa, and adding PHI to PSA can increase the detection rate of both PCa and csPCa.

Keywords: Multiparametric magnetic resonance imaging; Prostate cancer; Prostate Health Index

INTRODUCTION

The widespread use of prostate-specific antigen (PSA) to screen for prostate cancer (PCa) has led to a significant reduction in the incidence of metastatic disease and cancer-related mortality [1]. However, screening for total PSA continues to be highly controversial because of the limited specificity of this biomarker for clinically significant pros-

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tate cancer (csPCa). The low specificity often results in unnecessary biopsies for false-positive results, as well as the detection of indolent tumors that would not have caused harm during the patient's lifetime [2].

Given that incidence rates of age-specific PCa are increasing in parallel with increased life expectancies in many Asian countries, there is a need to identify accurate biomarkers to differentiate aggressive PCa from more favorable forms of PCa. This could allow clinicians to better counsel patients in selecting appropriate treatment options ranging from curative treatment to active surveillance on the basis of accurate risk estimation [3,4]. To overcome the limitations of PSA as a screening tool for PCa, the combined assessment of total and free PSA with [−2] proPSA (p2PSA) has been suggested. This information is used to derive the Prostate Health Index (PHI), which is calculated by using the formula: p2PSA/(free PSA)×√PSA. Several studies have found that the PHI is associated with better overall detection of aggressive PCa compared with the free/total PSA ratio (%fPSA) [5,6]. The PHI is also an accurate predictor of PCa in patients with total PSA levels between 2 and 10 ng/mL who fall into the "grey zone" [5]. Emphasis has also been placed on incorporating prostate multi-parametric magnetic resonance imaging (mpMRI) into existing diagnostic algorithms for PCa because of its value in pretreatment visualization [7,8]. However, the relatively high costs of the PHI and mpMRI limit their use as a routine component of PCa diagnostic algorithms. The accuracies of the PHI and mpMRI have not been rigorously evaluated in the Asian population.

In this study, we examined the accuracies of the PHI and mpMRI as predictors of PCa and csPCa in patients who underwent an initial prostate biopsy, with emphasis on their value in those in the PSA grey zone.

MATERIALS AND METHODS

1. Data collection

The present study enrolled 343 patients considered to be in the grey zone who underwent initial prostate biopsy and the PHI between April 2019 and July 2021. In addition, prostate mpMRI was performed in a subset of 232 of these patients (67.6%). We decided to exclude patients who had previously undergone a prostate biopsy; those using medications that can affect PSA levels (e.g., 5-α reductase inhibitors); and patients with a PSA level greater than 10 ng/mL. Clinical and pathological data, including age, PSA levels, the Prostate Imaging Reporting and Data System, version 2 (PI-RADS V2) scale, the PHI, and prostate biopsy results were collected. csPCa was defined as the presence of at least one sample with a Gleason score of 4 or 5 grade lesion (International Society of Urological Pathology Grade Group ≥2). Genitourinary pathologists with more than 10 years' experience reviewed all biopsy slides. Radical prostatectomy was performed using a robot-assisted approach by experienced urologists at our institution. Surgical specimens were processed and analyzed using a standardized technique by the same genitourinary pathologists who reviewed biopsy slides. The primary outcome was the detection rates of PSA, PHI, and mpMRI for PCa and csPCa; secondary outcomes included a comparison of the diagnostic accuracies of these screening modalities.

2. Transrectal ultrasound-guided biopsy and MRI-guided biopsy

Transrectal prostate biopsies were conducted in patients under local anesthesia by using an automatic biopsy gun and an 18-G needle under transrectal ultrasound (TRUS) guidance. In all, 12 cores (six in the peripheral zone, and six in the transitional zone) were taken in all patients. In the case of MRI-guided biopsy, at least two or more cognitive fusion-targeted or MRI/ultrasound image fusion (BioJet MRI-Ultrasound Fusion system with bk5000 ultrasound, BK medical, Burlington, MA, USA) biopsy cores were added for each lesion in patients with suspicious or equivocal lesions evident from mpMRI [9]. Two uroradiologists with more than 10 years' experience, including more than 1,000 pelvic MRIs read, graded the level of suspicion for csPCa from mpMRI mapping images using the PI-RADS V2 scale, scored from 1 to 5 [10].

3. Statistical analysis

All statistical analyses were conducted using the R statistical package (version 3.5.1) (R Core Team, Vienna, Austria, 2018) and IBM SPSS version 22.0 (IBM Corp, Armonk, NY, USA, 2013). Logistic regression analysis was performed to evaluate and compare the predictive accuracies of total PSA, the PHI, and mpMRI for PCa and csPCa confirmed on the basis of initial prostate biopsy. The individual predictors significant at the univariate level ($p<0.05$) were entered into a multivariate analysis used to define the best-fitting predictive models for PCa and csPCa [11]. Predictive accuracies were quantified using the area under the receiver operating characteristic (ROC) curve (AUC). The result of biopsy became the reference standard for creating the ROC. The DeLong test was used to examine significant differences between the AUCs for different predictive models [12].

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Table 1. Baseline characteristics of the study participants

Variable	Entire group (n=343)	MRI subgroup (n=232)
Age (y)	63.73±10.10	63.15±10.11
Prostate-specific antigen (ng/mL)	6.18±4.38	6.21±4.86
Prostate Health Index	60.82±32.66	61.56±35.39
Prostate volume (mL)	42.78±32.66	61.56±35.39
PI-RADS score		
1–2		115
3		37
4		52
5		28
Bx type		
12-core biopsy	120	9
MRI-fusion biopsy	223	223
Bx result (any PCa)		
Positive	145	88
Negative	198	144
Bx result (csPCa)		
Positive	103	62
Negative	240	170
Bx result (csPCa after RP)		
Positive	111	68
Negative	232	164

Values are presented as mean±standard deviation or number only.
MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging Reporting and Data System; Bx, biopsy; PCa, prostate cancer; csPCa, clinically significant prostate cancer; RP, radical prostatectomy.

4. Ethical statements

The Seoul National University Bundang Hospital Institutional Review Board (IRB) approved the study (IRB no. B-2201-734-103). Written informed patient consent was waived owing to the retrospective nature of study. All methods were conducted in accordance with relevant guidelines and regulations (the ethical standards of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards).

RESULTS

The baseline characteristics of the patient sample are presented in Table 1. In the total sample (n=343), biopsies confirmed that 145 patients (42.3%) tested positive, and 198 patients (57.7%) negative, for PCa. A total of 103 patients (30.0%) were diagnosed with csPCa. A total of 120 patients (35.0%) underwent TRUS-guided biopsy and 223 patients (65.0%) underwent MRI-guided biopsy. A subgroup of 232 patients underwent mpMRI. In this subgroup, 88 patients (37.9%) had PCa and 62 patients (26.7%) had csPCa.

Logistic regression analysis showed that age, PSA, PHI, and prostate volume were each associated with both PCa and csPCa (Supplementary Table 1). In patients who underwent mpMRI, age, PSA, PHI, prostate volume, and PI-RADS score were significantly associated with both PCa and csPCa (Table 2). Neither PSA nor the PHI was an independent predictor of csPCa after radical prostatectomy. Although it was not significantly associated with csPCa after radical prostatectomy, the overall trend for high PSA and high PHI predicting csPCa was consistent. Compared with patients with a PI-RADS score of 1 to 2, those with PI-RADS scores of 4 (odds ratio [OR], 7.3; 95% confidence interval [CI], 3.1–17.2; p<0.001) or 5 (OR, 14.4; 95% CI, 2.7–76.2; p=0.002) had higher odds of harboring PCa.

ROC curve analysis was then used to measure the predictive capabilities of the different screening tools. In the

Table 2. Multivariate logistic regression analysis to evaluate the predictive accuracies of each factor for PCa and csPCa in the MRI subgroup (n=232)

Variable	OR	95% CI	p-value
PCa			
Age	1.120	1.065–1.177	<0.001
PSA	1.208	0.997–1.508	0.044
PHI	1.024	1.009–1.038	0.001
Prostate volume	0.965	0.943–0.989	0.004
PI-RADS score			
3	0.964	0.324–2.868	0.948
4	7.253	3.052–17.234	<0.001
5	14.383	2.714–76.228	0.002
csPCa			
Age	1.100	1.040–1.163	0.001
PSA	1.226	0.997–1.508	0.053
PHI	1.014	1.002–1.026	0.025
Prostate volume	0.933	0.901–0.967	<0.001
PI-RADS score			
3	0.257	0.034–1.939	0.191
4	9.200	3.322–25.482	<0.001
5	15.445	3.808–62.652	<0.001
csPCa after RP			
Age	1.095	1.038–1.156	0.001
PSA	1.193	0.977–1.456	0.083
PHI	1.012	0.999–1.024	0.072
Prostate volume	0.934	0.902–0.967	<0.001
PI-RADS score			
3	0.826	0.186–3.669	0.802
4	11.696	4.237–32.283	<0.001
5	38.714	7.084–211.575	<0.001

PCa, prostate cancer; csPCa, clinically significant prostate cancer; MRI, magnetic resonance imaging; OR, odds ratio; CI, confidential interval; PSA, prostate-specific antigen; PHI, Prostate Health Index; PI-RADS, Prostate Imaging Reporting and Data System; RP, radical prostatectomy.

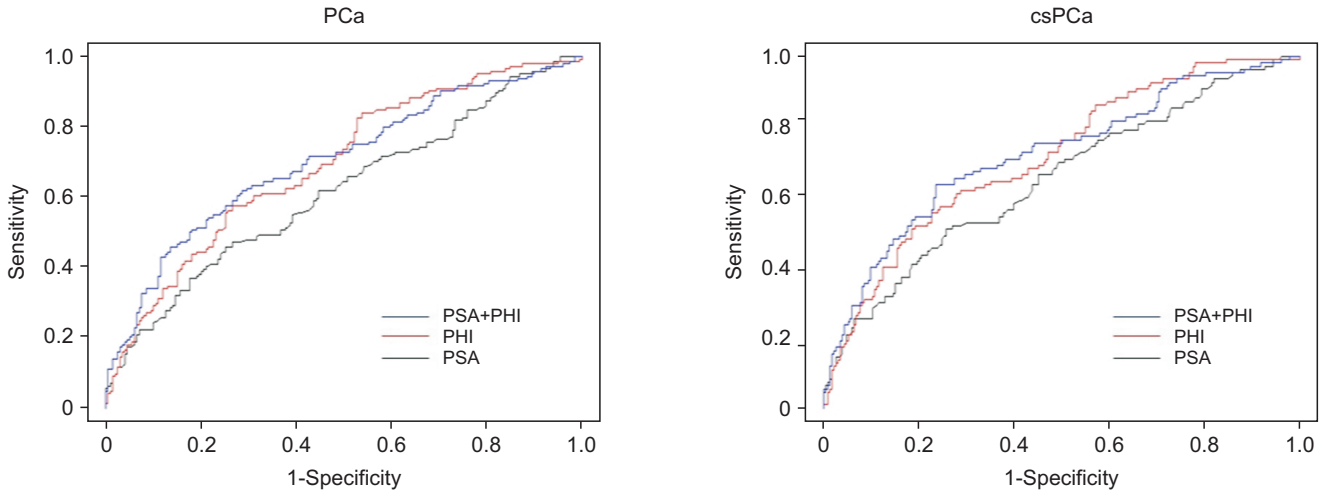

Fig. 1. Receiver operating characteristic curves of prostate-specific antigen (PSA), Prostate Health Index (PHI), and PSA+PHI for prostate cancer (PCa) and clinically significant prostate cancer (csPCa) in the entire group (n=343).

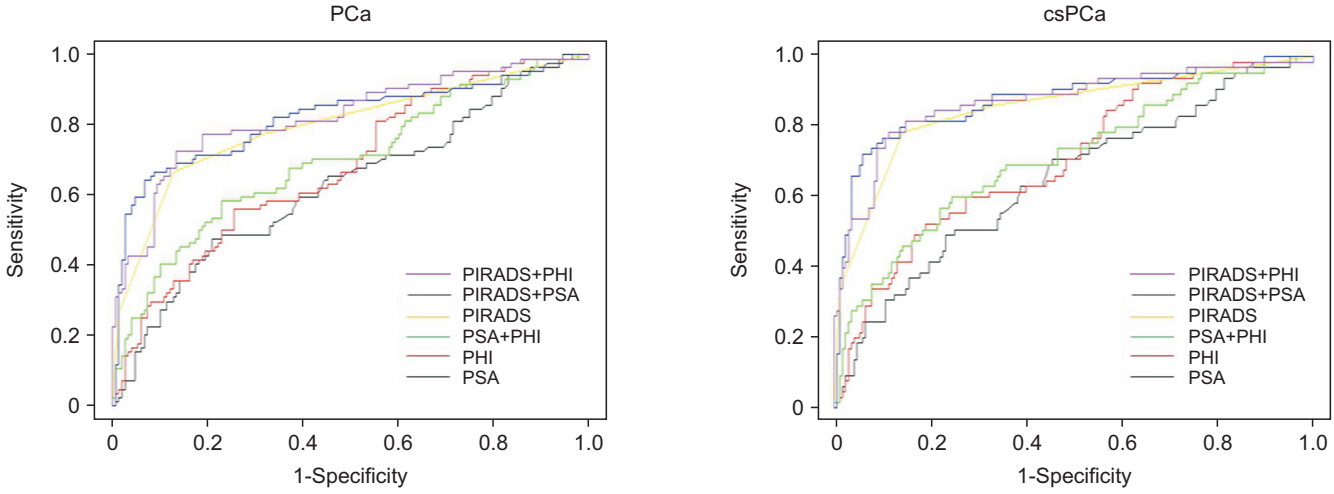

Fig. 2. Receiver operating characteristic curves of prostate-specific antigen (PSA), Prostate Health Index (PHI), PSA+PHI, Prostate Imaging Reporting and Data System (PI-RADS), PI-RADS+PSA, PI-RADS+PHI in the magnetic resonance imaging subgroup (n=232). PCa, prostate cancer; csPCa, clinically significant prostate cancer.

entire sample, the PHI (AUC=0.693) was superior to PSA (AUC=0.615) in predicting PCa (p=0.038). The predictive capabilities of the PHI (AUC=0.718) compared with PSA (AUC=0.666) were, however, similar in predicting csPCa (p=0.171). Fig. 1 shows the ROC curves of PSA, PHI, and PSA+PHI for PCa and csPCa in the entire sample. We also performed a subanalysis in patients who underwent mpMRI (n=232). Fig. 2 shows the ROC curves of PSA, PHI, PI-RADS, PSA+PHI, PSA+PI-RADS, and PHI+PI-RADS in this subgroup. The PI-RADS score was the most accurate individual predictor of both PCa (AUC=0.810) and csPCa (AUC=0.856) and outperformed both PSA and the PHI. The combined assessment of PSA and PHI (PSA+PHI) was superior to either measure in isolation for both PCa (AUC=0.709) and csPCa (AUC=0.723) (p<0.001).

Table 3 shows the calculated thresholds, sensitivity, and specificity for each parameter in the ROC curve analysis. The combination of PHI and mpMRI showed the greatest accuracy for the prediction of both PCa (AUC=0.833) and csPCa (AUC=0.881) (p<0.001). Table 4 shows the results of the DeLong analysis of statistically significant differences between the AUCs for each factor. The combination of PI-RADS and PHI (PI-RADS+PHI) performed better than PI-RADS alone for both PCa and csPCa statistically (both p<0.001). However, the diagnostic power of PI-RADS+PSA and PI-RADS+PHI was similar for PCa and csPCa (p=0.758, p=0.842, respectively).

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Table 3. AUC of each parameter to predict PCa and csPCa with threshold, specificity, and sensitivity

Variable	AUC	Threshold	Specificity	Sensitivity
Entire group, PCa				
PSA	0.615 (0.555–0.676)	6.340	0.749	0.458
PHI	0.693 (0.637–0.749)	61.120	0.734	0.576
PSA+PHI	0.701 (0.634–0.768)	5.40, 62.78	0.714	0.618
Entire group, csPCa				
PSA	0.650 (0.586–0.713)	6.320	0.742	0.509
PHI	0.714 (0.657–0.771)	61.160	0.755	0.598
PSA+PHI	0.721 (0.651–0.791)	5.70, 66.51	0.764	0.636
MRI subgroup, PCa				
PSA	0.641 (0.566–0.717)	6.320	0.792	0.500
PHI	0.692 (0.622–0.762)	61.980	0.743	0.580
PI-RADS	0.810 (0.752–0.868)	3.000	0.868	0.693
PSA+PHI	0.709 (0.640–0.777)	3.08, 93.53	0.785	0.591
PSA+PI-RADS	0.828 (0.748–0.908)	3.98, 3.00	0.924	0.682
PHI+PI-RADS	0.833 (0.752–0.914)	158.14, 1.00	0.819	0.795
MRI subgroup, csPCa				
PSA	0.659 (0.580–0.738)	6.320	0.762	0.515
PHI	0.715 (0.639–0.791)	67.450	0.800	0.565
PI-RADS	0.856 (0.797–0.914)	2.500	0.835	0.839
PSA+PHI	0.723 (0.654–0.792)	8.40, 32.89	0.738	0.647
PSA+PI-RADS	0.876 (0.791–0.961)	4.58, 3.00	0.939	0.765
PHI+PI-RADS	0.881 (0.796–0.966)	32.75, 4.00	0.884	0.824

Values are presented as mean (range) or number only.
AUC, area under curve; PCa, prostate cancer; csPCa, clinically significant prostate cancer; PSA, prostate-specific antigen; PHI, Prostate Health Index; MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging Reporting and Data System.

Table 4. DeLong analysis of statistically significant differences between the AUCs for each factor

Group	p-value	
	PCa	csPCa
Entire group		
PSA vs. PHI	0.038	0.171
PSA vs. PSA+PHI	<0.001	<0.001
Magnetic resonance imaging subgroup		
PSA vs. PHI	0.299	0.370
PSA vs. PI-RADS	<0.001	<0.001
PHI vs. PI-RADS	0.005	<0.001
PSA vs. PSA+PHI	<0.001	<0.001
PSA vs. PI-RADS+PHI	<0.001	<0.001
PHI vs. PHI+PI-RADS	<0.001	<0.001
PI-RADS vs. PI-RADS +PHI	<0.001	<0.001
PI-RADS+PSA vs. PI-RADS+PHI	0.758	0.842

AUC, area under curve; PCa, prostate cancer; csPCa, clinically significant prostate cancer; PSA, prostate-specific antigen; PHI, Prostate Health Index; PI-RADS, Prostate Imaging Reporting and Data System.

DISCUSSION

Although many studies have been conducted on the PHI, relatively little is known about its role as a predictor of PCa or csPCa in the South Korean population, especially for patients in the grey zone. This might be attributed in part to the high cost of the PHI and insurance issues related to coverage of those costs in South Korea. To the best of our knowledge, this is one of the largest studies to examine the PHI with the inclusion of PI-RADS findings to evaluate predictive performance for PCa and csPCa for Asian men in the PSA grey zone. We compared the predictive capabilities of different noninvasive modalities, including PSA, the PHI, and the PI-RADS score, in the diagnostic workup of PCa and csPCa in patients at the time of the initial biopsy.

In a meta-analysis of 2,919 patients enrolled across 8 studies, Filella and Giménez [13] demonstrated the superiority of the PHI over both PSA and the %fPSA in the detection of PCa (sensitivity: 90%, specificity: 31.6%). Loeb and Catalona [2] reviewed the efficacy of the PHI and described it as a simple and cost-effective blood test, which outperforms total PSA in the detection of PCa and which should form part of a multivariable approach to screening. In a subsequent study, Loeb and colleagues [14] advocated for the addition of the PHI to predictive models (PCPT [Prostate

Cancer Prevention Trial] and ERSCP [European Randomized study of Screening for Prostate Cancer]) to improve their accuracies in the detection of PCa. Stejskal et al. [15] also found that PHI is an accurate method for predicting csPCa, with similar efficacy compared with prostate mpMRI. The authors also suggested that a combination of the PHI, PI-RADS, and PSA density could provide the most accurate prediction of PCa in all patients.

Several recent studies also support the growing use of mpMRI as the most sensitive and specific imaging tool for the detection, lesional characterization, and staging of PCa. For example, Numao et al. [16] showed that prebiopsy prostate mpMRI combined with the assessment of prostate volume decreases the number of initial prostate biopsies by discriminating between PCa and csPCa in men with PSA levels below 10 ng/mL and normal findings on digital rectal examination. Men with negative prostate mpMRI results had a lower frequency of csPCa, whereas men with positive mpMRI results had a higher frequency of csPCa. Boesen et al. [17] discovered that mpMRI performed before repeated biopsies improves the detection rate of csPCa and enables a more accurate estimation of Gleason score by combining standard TRUS-biopsy with MRI-fusion biopsies under visual TRUS-guidance. The authors concluded that mpMRI may provide valuable information about the histopathological aggressiveness of PCa lesions and the tumor stage with possible extracapsular extension. Another study [18] conducted by the same author identified that the AUC for bi-parametric MRI alone was 0.84 and the model that combined PI-RADS, age, tumor stage, and PSA density had the highest discriminatory power (AUC=0.89). van Leeuwen et al. [19] also demonstrated that adding age, results of the digital rectal examination, prostate volume, and PI-RADS score to PSA increased the AUC dramatically for predicting clinically significant PCa from 0.598 to 0.883.

Our results are congruent with those reported in prior studies, because the PHI was superior to PSA in predicting PCa. In addition, mpMRI emerged as the most accurate predictor of both PCa and csPCa, outperforming PSA and the PHI (AUC=0.810, 0.856, respectively). It is still controversial whether PSA and the PHI can predict csPCa [6]. In our study, PSA and the PHI were not significant predictors of csPCa. Although the PHI alone was not statistically significant for csPCa in our study, we determined that adding the PHI to PSA could detect csPCa better than the PHI alone.

By use of the DeLong test, we found that adding the PHI to parameters like PSA can be effective for predicting PCa and csPCa. Although mpMRI is a powerful diagnostic tool, adding the PHI can provide more accuracy in predicting both PCa and csPCa ($p<0.001$ in the DeLong test). In the AUC curve analysis, the detection rate for PCa and csPCa also significantly increased (AUC=0.833, 0.881, respectively).

In terms of cost and insurance issues, PSA is routinely performed in South Korea. The PHI and MRI are performed selectively at the individual urologist's discretion. Although many studies have shown that a combination of current diagnostic modalities increases the detection rate of PCa, relatively less has been done concerning the PHI. In our study, the PHI alone was not enough for PCa screening compared with current competitive diagnostic modalities such as mpMRI. When mpMRI was performed, no significant differences were found between PSA and the PHI in terms of diagnosing PCa and csPCa ($p=0.758$, $p=0.842$, respectively). This was primarily due to the powerful diagnostic capabilities of mpMRI in terms of diagnosing PCa and csPCa (AUC values of 0.810 and 0.856, respectively, with mpMRI alone). However, it is practically difficult for all patients with suspected PCa to undergo mpMRI. In this study cohort, only 232 of 343 patients underwent mpMRI. Compared with mpMRI, the PHI is a relatively simple and inexpensive blood test. In the absence of mpMRI, the combination of the PHI with PSA rather than PSA alone helps in the diagnosis of both PCa and csPCa in a statistically significant way. In addition, for all PCa patients in the entire group, the PHI showed better diagnostic ability than PSA ($p=0.038$).

Our study has several limitations. First, it was a retrospective study that included patients of a single ethnicity. Further prospective studies are therefore needed. The PHI is not yet reimbursed by national insurance in Korea. As a result, the total number of PHI tests was low. Second, our study was conducted with different biopsy methods. MRI-guided biopsy and conventional 12-core TRUS-guided biopsy were combined, which could be a factor affecting the cancer detection rate. In addition, a global consensus has not yet been reached on the definition of csPCa. We used a Gleason score of greater than six to define csPCa; however, maximum core length is also often used in the definition of csPCa [20,21]. This measure was not available for all patients; however, so we did not include it in the final analysis. Finally, since our study analyzed the association between biomarkers (e.g., total PSA or PHI) and PCa, it lacked data on survival analysis, as it was initiated less than 5 years ago and long-term follow-up data are scarce.

Nevertheless, we compared various combinations of parameters to identify the most appropriate diagnostic tools in biopsy-naïve patients within the PSA grey zone. The important clinical question was whether the PHI can provide additional insight into the diagnosis and prediction of PCa.

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Since active surveillance can be considered a treatment option for low-grade PCa, our result can be applied to physician counseling in South Korean patients [22].

CONCLUSIONS

The most accurate prediction of both PCa and csPCa can be performed by combining the PHI and mpMRI. In the absence of mpMRI, the PHI is superior to PSA alone as a predictor of PCa, and adding the PHI to PSA can increase the detection rate of both PCa and csPCa. Further long-term prospective studies related to the PHI and mpMRI are required.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Changhee Ye and Sangchul Lee. Data acquisition: Changhee Ye, Hyungwoo Ahn, Sung Il Hwang, Hak Jong Lee, Jin-Nyoung Ho, and Dan Hyo Kim. Statistical analysis: Changhee Ye, Sang Hun Song, and Hwanik Kim. Data analysis and interpretation: Changhee Ye, Sang Hun Song, Hwanik Kim, and Sangchul Lee. Drafting of the manuscript: Changhee Ye. Critical revision of the manuscript: Sang Hun Song, Sangchul Lee, Sung Kyu Hong, and Seok-Soo Byun. Obtaining funding: Sangchul Lee. Administrative, technical or material support: Hakmin Lee and Seong Jin Jeong. Supervision: Sangchul Lee, Sung Kyu Hong, and Seok-Soo Byun. Approval of the final manuscript: all authors.

SUPPLEMENTARY MATERIAL

Supplementary material can be found via https://doi.org/10.4111/icu.20220056.

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