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ORIGINAL ARTICLE

Prostate Cancer

Prostate Health Index (*phi*) and its derivatives predict Gleason score upgrading after radical prostatectomy among patients with low-risk prostate cancer

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To analyze the performance of the Prostate Health Index (*phi*) and its derivatives for predicting Gleason score (GS) upgrading between prostate biopsy and radical prostatectomy (RP) in the Chinese population, an observational, prospective RP cohort consisting of 351 patients from two medical centers was established from January 2017 to September 2020. Pathological reclassification was determined by the Gleason Grade Group (GG). The area under the receiver operating characteristic curve (AUC) and logistic regression (LR) models were used to evaluate the predictive performance of predictors. In clinically low-risk patients with biopsy GG ≤2, *phi* (odds ratio [OR] = 1.80, 95% confidence interval [95% CI]: 1.14–2.82, *P* = 0.01) and its derivative *phi* density (PHID; OR = 2.34, 95% CI: 1.30–4.20, *P* = 0.005) were significantly associated with upgrading to GG ≥3 after RP, and the results were confirmed by multivariable analysis. Similar results were observed in patients with biopsy GG of 1 for the prediction of upgrading to RP GG ≥2. Compared to the base model (AUC = 0.59), addition of the *phi* or PHID could provide additional predictive value for GS upgrading in low-risk patients (AUC = 0.69 and 0.71, respectively, both *P* < 0.05). In conclusion, *phi* and PHID could predict GS upgrading after RP in clinically low-risk patients.

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Keywords: Gleason score; prostate biopsy; prostate cancer; Prostate Health Index; radical prostatectomy; upgrading

INTRODUCTION

Discrepancies in the Gleason score (GS) between prostate biopsy and radical prostatectomy (RP) are common in prostate cancer (PCa) diagnosis.[1,2] A meta-analysis reported an overall GS upgrading rate of 38% among patients with low-grade (GS 2–6) biopsy after RP.[3] Unlike a decade prior, this problem has become increasingly critical in the era of active surveillance, as invasive treatment is not preferred for low-risk individuals.[4] In the Johns Hopkins Active Surveillance cohort, approximately 20% of patients received interventions within 2 years after diagnosis due to disease progression.[5] The biopsy results of the reclassified patients were highly suspicious, which could have been due to incomplete sampling. Therefore, additional tests, such as imaging techniques,[6,7] clinicopathological variables,[8–10] and novel biomarkers,[11,12] were applied to increase the accuracy of prostate biopsy as well as the predictive ability for GS upgrading.

[-2]proPSA (p2PSA), a precursor isoform of prostate-specific antigen (PSA), was introduced nearly a decade ago. The Prostate Health Index (*phi*), derived from total PSA (tPSA), free PSA (fPSA), and p2PSA, has shown significant benefits for predicting PCa as a supplement to PSAs.[13–15] Guazzoni *et al.*[16] revealed that p2PSA and *phi* were also strong predictors of PCa characteristics at final pathology after RP. In addition, several studies have suggested that *phi* could significantly contribute to the prediction of GS upgrading between biopsy and RP in Caucasian and Korean males.[16–19] Whether *phi* could predict pathological reclassifications after RP in Chinese patients has been poorly studied at this stage.

Therefore, the objective of the present study was to evaluate the predictive utility of p2PSA and *phi* in terms of pathological reclassifications in a Chinese PCa cohort. An exploratory evaluation of the density of biomarkers (divided by the prostate volume) was also applied.

PATIENTS AND METHODS

Study population

This was a prospective multicenter study in two PCa cohorts (Ruijin Hospital and Huashan Hospital, Shanghai, China). The study population included 351 consecutive PCa patients who were diagnosed by transrectal ultrasound-guided 12-core biopsies and then underwent laparoscopic RP between January 2017 and September 2020. Blood samples were collected for the measurement of PSAs prior to biopsies on the same day in a central laboratory as per the study protocol. All specimens were reviewed in the Department of Pathology at each hospital according to the new Gleason Grading System.[20] This study was approved by the institutional review board (IRB) of Ruijin Hospital

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and Huashan Hospital (central IRB No. KY2016-343, 24 Nov 2016, version 03), and written informed consent was obtained from each participant.

Patients were excluded if (1) the level of any serum antigen was unable to be tested due to poor serum sample quality ($n = 11$) or (2) had ever received neoadjuvant androgen deprivation therapy ($n = 14$).

Variables and outcomes

The clinicopathological variables included age, the number of biopsy-positive cores (>2 *vs* ≤2 [referent]), and the prostate volume (PV) which was measured by transrectal ultrasound and estimated using the prostate ellipsoid formula ([π/6] × length × width × height). Derivative variables were calculated as follows: (1) PSA density (PSAD): tPSA/PV; (2) p2PSAD: p2PSA/PV; (3) *phi*: (p2PSA/fPSA) × √tPSA; and (4) *phi* density (PHID): *phi*/PV.

Pathological reclassification between prostate biopsy and RP was determined by the Gleason Grade Group (GG, also known as GS pattern; **Table 1**). Outcomes were different across subsets: (1) GS upgrading was defined as the presence of RP GG ≥3 for patients with biopsy GG ≤2 (primary outcome) and RP GG ≥2 for patients with biopsy GG of 1 (secondary outcome); (2) GS downgrading was defined as RP GG ≤2 for patients with biopsy GG ≥3.

Statistical analysis

Baseline characteristics were compared using the Mann–Whitney U test (for continuous variables), Fisher's exact test (for categorical variables), and Cuzick's test (for trends across ordered groups, *e.g.*, GG). To identify the independent predictors of GS upgrading or downgrading, we performed univariate and multivariate logistic regression (LR) analyses and calculated the crude odds ratio (cOR) and adjusted odds ratio (aOR), 95% confidence interval (95% CI), and *P* value for each covariate. The base model included age, the number of positive cores (categorical), and logarithmically transformed tPSA as covariates. We constructed receiver operating characteristic (ROC) curves to analyze the predictive abilities of the predictors and multivariate models. The areas under the curve (AUC) were compared using the DeLong method.[21]

All statistical analyses were performed using Stata 15.1 Special Edition (StataCorp, College Station, TX, USA). A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

In this observational, prospective RP cohort, a total of 326 PCa patients were recruited based on the inclusion and exclusion criteria. The clinicopathological characteristics of the study cohort are shown in **Table 1**. Among 96 patients with biopsy GG of 1, 48 (50.0%) were reclassified to GG of 2 (3+4) after RP, and 16 (16.7%) were upgraded to high risk (GG ≥3). Among patients with biopsy GG of 2 ($n = 73$), 20 (27.4%) were upgraded after RP (**Table 1**).

Table 2 shows the baseline characteristics of patients with biopsy GG ≤2 with and without upgrading after RP. All the biomarkers and derivatives in the upgraded patients (from biopsy GG ≤2 to RP GG ≥3) were significantly higher than those in the nonupgraded patients (all $P < 0.05$; **Table 2**). However, in patients with biopsy GG of 1 (3+3), PHID was the only variable that remained significant upon comparison of the upgraded and nonupgraded groups (median: 1.4 *vs* 0.7, $P = 0.003$; **Table 2**).

Univariable and multivariable LR analyses were also performed to evaluate the associations between the predictors and pathological reclassifications (**Table 3**). After adjusting for age, the number of positive cores, and tPSA values, p2PSAD (aOR = 2.79, 95% CI: 1.20–6.51, $P = 0.02$), *phi* (aOR = 3.36, 95% CI: 1.34–8.38, $P = 0.009$), and PHID

Table 1: Clinicopathological characteristics in the study cohorts across biopsy Gleason Grade Groups

Characteristic	*Overall*	*Biopsy GG (GS pattern)*				
		1 (≤6)	*2 (3+4)*	*3 (4+3)*	*4 (8)*	*5 (9–10)*	$^{a}P_{trend}$
Number of patients, *n* (%)	326 (100.0)	96 (29.4)	73 (22.4)	74 (22.7)	48 (14.7)	35 (10.7)	NA
Age (year), median (IQR)	69 (64–74)	67 (63–71)	70 (66–74)	70 (65–74)	72 (65–77)	69 (63–73)	0.103
Prostate volume (ml), median (IQR)	33.4 (25.1–46.5)	38.6 (25.5–50.7)	35.5 (25.8–48.7)	31.6 (25.1–46.0)	29.4 (23.5–44.0)	31.2 (23.9–44.5)	0.039
Total PSA (ng ml^{-1}), median (IQR)	15.0 (9.7–30.0)	10.9 (8.4–18.4)	14.9 (10.0–29.6)	15.8 (9.6–33.0)	18.7 (12.3–39.1)	31.9 (16.4–84.7)	<0.001
PSAD (ng ml^{-2}), median (IQR)	0.4 (0.3–0.9)	0.3 (0.2–0.5)	0.5 (0.3–0.9)	0.5 (0.3–1.0)	0.6 (0.3–1.0)	1.0 (0.5–2.0)	<0.001
p2PSA (pg ml^{-1}), median (IQR)	29.9 (16.5–65.3)	20.7 (13.7–38.9)	29.6 (19.3–52.3)	30.3 (15.7–65.5)	44.6 (17.5–115.7)	63.6 (29.9–238.5)	<0.001
p2PSAD (pg ml^{-2}), median (IQR)	0.8 (0.4–1.8)	0.5 (0.3–0.9)	0.8 (0.5–1.5)	0.9 (0.4–2.1)	1.4 (0.7–3.2)	2.0 (1.0–4.2)	<0.001
phi, median (IQR)	67.3 (41.8–126.5)	47.7 (33.9–69.1)	67.3 (45.2–118.5)	71.3 (40.5–127.9)	101.5 (59.9–144.3)	145.1 (75.8–247.4)	<0.001
PHID, median (IQR)	1.9 (1.0–3.6)	1.1 (0.7–2.0)	1.7 (1.0–2.9)	2.4 (1.2–4.4)	3.0 (1.5–4.9)	4.2 (2.5–5.8)	<0.001
Number of positive cores (*n*), median (IQR)	4 (2–7)	2 (1–3)	4 (3–7)	5 (2–6)	6 (3–8)	9 (6–11)	<0.001
RP GG, *n* (%)							
1 (≤6)	38 (11.7)	32 (33.3)	3 (4.1)	1 (1.4)	1 (2.1)	1 (2.9)	NA
2 (3+4)	130 (39.9)	48 (50.0)	50 (68.5)	25 (33.8)	7 (14.6)	0 (0)	NA
3 (4+3)	78 (23.9)	11 (11.5)	16 (21.9)	37 (50.0)	11 (22.9)	3 (8.6)	NA
4 (8)	26 (8.0)	2 (2.1)	3 (4.1)	5 (6.8)	13 (27.1)	3 (8.6)	NA
5 (9–10)	54 (16.6)	3 (3.1)	1 (1.4)	6 (8.1)	16 (33.3)	28 (80.0)	NA
Tumor volume (ml), median (IQR)	1.9 (0.6–6.0)	0.7 (0.2–2.8)	1.7 (0.6–6.0)	3.0 (1.0–6.0)	3.8 (0.8–9.6)	11.2 (5.0–22.5)	<0.001

^{a}P values were determined by Cuzick's test for trend. GG: Gleason Grade Group; GS: Gleason score; IQR: interquartile range; PSA: prostate-specific antigen; PSAD: PSA density; p2PSA: [-2]proPSA; p2PSAD: p2PSA density; *phi*: Prostate Health Index; PHID: *phi* density; RP: radical prostatectomy; NA: not analyzed

Table 2: Descriptive characteristics of low-risk patients (biopsy Gleason Grade Group ≤2) with and without upgrading after radical prostatectomy

Characteristic	*Biopsy GG ≤2*			*Biopsy GG=1*		
	Upgrading (RP GG ≥3)	*Nonupgrading (RP GG ≤2)*	[a]*P*	*Upgrading (RP GG ≥2)*	*Nonupgrading (RP GG=1)*	[a]*P*
Patients, *n*/total (%)	36/169 (21.3)	133/169 (78.7)	NA	64/96 (66.7)	32/96 (33.3)	NA
Age (year), median (IQR)	68 (66–74)	69 (63–72)	0.45	67 (63–70)	69 (62–74)	0.70
Prostate volume (ml), median (IQR)	30.9 (23.4–45.8)	37.4 (28.8–52.1)	0.10	39.3 (23.6–49.0)	38.0 (33.2–53.0)	0.27
Number of positive cores ≥3, *n*/total (%)	18/71 (25.4)	53/71 (74.6)	0.22	21/25 (84.0)	4/25 (16.0)	0.18
Total PSA (ng ml^{-1}), median (IQR)	15.5 (11.8–24.9)	11.4 (8.7–20.9)	0.02*	11.1 (8.3–18.4)	10.7 (8.5–20.2)	0.80
PSAD (ng ml^{-2}), median (IQR)	0.5 (0.3–0.9)	0.3 (0.2–0.5)	0.02*	0.3 (0.2–0.5)	0.3 (0.2–0.4)	0.33
p2PSA (pg ml^{-1}), median (IQR)	37.6 (19.1–60.2)	22.7 (15.1–44.5)	0.01*	21.0 (12.09–34.3)	20.3 (15.8–46.0)	0.60
p2PSAD (pg ml^{-2}), median (IQR)	1.13 (0.61–1.62)	0.56 (0.34–0.93)	0.005*	0.56 (0.34–0.97)	0.38 (0.27–0.56)	0.07
phi, median (IQR)	67.3 (47.2–125.4)	53.2 (34.2–83.8)	0.005*	49.2 (36.1–67.6)	42.5 (28.9–78.3)	0.41
PHID, median (IQR)	2.5 (1.1–3.2)	1.2 (0.8–2.0)	0.004*	1.4 (0.9–2.2)	0.7 (0.5–1.1)	0.003*

[a]*P* values were determined by Mann–Whitney U test for continuous variables, and Fisher's exact test for categorical variables. *Statistically significant ($P < 0.05$). IQR: interquartile range; PSA: prostate-specific antigen; PSAD: PSA density; p2PSA: [-2]proPSA; p2PSAD: p2PSA density; *phi*: Prostate Health Index; PHID: *phi* density; RP: radical prostatectomy; NA: not analyzed; GG: Gleason Grade Group

Table 3: Univariable and multivariable logistic regression analyses for prediction of upgrading after radical prostatectomy[a]

Predictor	*Biopsy GG ≤2 (univariable analysis)*		*Biopsy GG ≤2 (multivariable analysis[b])*		*Biopsy GG=1 (univariable analysis)*		*Biopsy GG=1 (multivariable analysis[b])*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*
Age	1.02 (0.96–1.09)	0.44	1.04 (0.97–1.13)	0.27	0.99 (0.93–1.06)	0.84	1.01 (0.91–1.11)	0.89
Prostate volume	0.40 (0.14–1.19)	0.10	Not applicable		0.47 (0.14–1.61)	0.23	Not applicable	
Number of positive cores ≥3	1.70 (0.75–3.85)	0.21	0.87 (0.33–2.33)	0.79	2.42 (0.73–8.10)	0.15	4.56 (0.91–22.93)	0.07
Total PSA	1.48 (0.95–2.30)	0.08	0.25 (0.05–1.38)	0.11	0.75 (0.40–1.39)	0.36	0.26 (0.04–1.58)	0.15
PSAD	1.57 (0.96–2.57)	0.07	2.98 (0.87–10.18)	0.08	1.16 (0.58–2.33)	0.67	1.55 (0.38–6.23)	0.54
p2PSA	1.39 (0.99–1.95)	0.06	2.06 (0.88–4.80)	0.10	0.81 (0.55–1.19)	0.29	1.54 (0.60–3.97)	0.37
p2PSAD	1.94 (1.17–3.22)	0.01*	2.79 (1.20–6.51)	0.02*	1.58 (0.80–3.12)	0.19	1.85 (0.81–4.22)	0.14
phi	1.80 (1.14–2.82)	0.01*	3.36 (1.34–8.38)	0.009*	0.99 (0.60–1.62)	0.96	7.95 (2.03–31.18)	0.003*
PHID	2.34 (1.30–4.20)	0.005*	2.73 (1.29–5.77)	0.009*	2.31 (1.10–4.85)	0.03*	2.91 (1.18–7.14)	0.02*

[a]Upgrading was defined as the presence of RP GG ≥3 for patients with biopsy GG ≤2 (primary outcome), and RP GG ≥2 for patients with biopsy GG of 1 (secondary outcome). [b]Adjusted for age, number of positive cores (≤2 *vs* ≥3), and logarithmically transformed total PSA. *Statistically significant ($P < 0.05$). PSA: prostate-specific antigen; PSAD: PSA density; p2PSA: [-2]proPSA; p2PSAD: p2PSA density; *phi*: Prostate Health Index; PHID: *phi* density; RP: radical prostatectomy; NA: not analyzed; GG: Gleason Grade Group; OR: odds ratio; CI: confidence interval

(aOR = 2.73, 95% CI: 1.29–5.77, $P = 0.009$) were found to be independent predictors for upgrading after RP among patients with biopsy GG ≤2 (**Table 3**). However, in patients with biopsy GG = 1, only *phi* (aOR = 7.95, 95% CI: 2.03–31.18, $P = 0.003$) and PHID (aOR = 2.91, 95% CI: 1.18–7.14, $P = 0.02$) remained significant and independent predictors for upgrading in the multivariable analysis (**Table 3**). In contrast, p2PSA, p2PSAD, *phi*, and PHID were all independent protective factors (aOR <1, all $P < 0.05$) for the prediction of downgrading after RP (from biopsy GG ≥3 to RP GG ≤2; **Supplementary Table 1**).

ROC curve analyses were then performed to evaluate the predictive abilities of different predictors and models in patients with biopsy GG ≤2 (**Figure 1**). The AUCs of PSAD, *phi*, and PHID were all higher than those of PSA but did not reach statistical significance (0.66, 0.67, and 0.69, respectively, compared to 0.61 [referent], all $P > 0.05$; **Figure 1a**). However, the multivariable LR models incorporating *phi* or PHID significantly outperformed the base model (all $P < 0.05$; **Figure 1b**). Among patients with biopsy GG of 1, both *phi* and PHID had significantly higher AUCs than PSA for predicting upgrading after RP (0.70 and 0.71, respectively, compared to 0.50 [referent], both $P < 0.05$; **Figure 2a**), but incorporation of the *phi* or PHID did not improve the overall predictive values of the base model in the multivariable analysis (both $P > 0.05$; **Figure 2b**). Neither *phi* nor PHID significantly outperformed PSA or provided additional value to the base model for the prediction of downgrading (**Supplementary Figure 1**).

Upgrading rates were compared between the groups stratified by different cutoff values of *phi* and PHID (**Figure 3**). Among patients with biopsy GG ≤2, men with a *phi* ≥35 had a 3.3-fold higher risk of upgrading after RP than those with a *phi* <35 (25.4% *vs* 7.7%, $P = 0.02$). Similarly, patients with PHID ≥1.0 had a 3.2-fold higher risk of upgrading than others (25.6% *vs* 8.0%, $P = 0.01$; **Figure 3a**). Similar results were found for PHID in patients with biopsy GG of 1, but no significant difference in upgrading rates was observed when using the commonly used cutoffs of *phi* (**Figure 3b**).

DISCUSSION

The present study investigated the association between *phi*, as well as its derivative PHID, and pathological reclassification after RP. We found that *phi* and PHID could well predict GS upgrading in the Chinese population. Despite the low utilization of active surveillance in China,[22,23] the results are critical to low-risk patients with biopsy GG ≤2 for classification as those at "real" clinical risk.

Three previous studies in Caucasians reported that *phi* was a valuable independent predictor of GS upgrading (from GS 6 to GS ≥7) after RP.[16–18] Moreover, addition of the *phi* might increase the predictive accuracy of a base multivariable model by 5.0%–5.7%.[16,17] However, Park *et al.*[19] revealed an increase in the AUC of up to 13.1% in Koreans, consistent with our results based on the Chinese population (0.79 *vs* 0.66; **Figure 2b**). Furthermore, this was the first study to estimate the predictors of GG reclassification between biopsy and RP

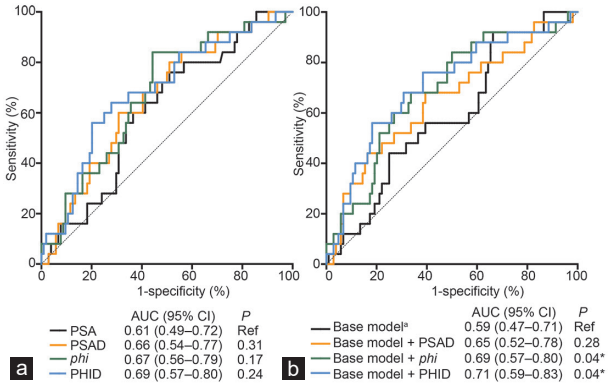

Figure 1: ROC curves of (**a**) predictors and (**b**) multivariable models for prediction of upgrading after RP in patients with biopsy GG ≤2. *Statistically significant ($P < 0.05$). Upgrading was defined as the presence of RP GG ≥3. [a]Base model = age + number of positive cores (categorical) + logarithmically transformed total PSA. ROC: receiver operating characteristic; RP: radical prostatectomy; AUC: area under ROC curve; 95% CI: 95% confidence interval; PSA: prostate-specific antigen; PSAD: PSA density; *phi*: Prostate Health Index; PHID: *phi* density; ref: reference; GG: Gleason Grade Group.

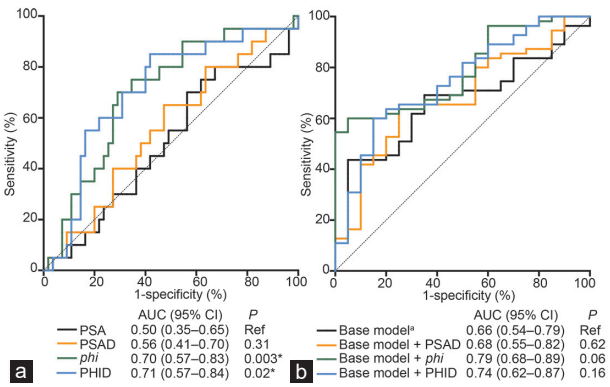

Figure 2: ROC curves of (**a**) predictors and (**b**) multivariable models for prediction of upgrading after RP in patients with biopsy GG of 1. *Statistically significant ($P < 0.05$). Upgrading was defined as the presence of RP GG ≥2. [a]Base model = age + number of positive cores (categorical) + logarithmically transformed total PSA. The definitions of the abbreviations are shown in the legend of **Figure 1**.

(from GG ≤2 to ≥3). Due to the significantly better prognosis of GG 2 (3+4) than GG 3 (4+3), the results of the present study might be important to current clinical practice.

Phi profiling has yet to be applied for patients undergoing active surveillance. Nearly 20% of patients fail to remain in active surveillance due to progression within 2 years.[5] The clinical risk of these patients could be misclassified by sampling bias associated with prostate biopsy. Our results, together with those from previous studies, provide preliminary evidence that patients with elevated *phi* values are at a higher risk of GS upgrading after RP. We also evaluated the reclassification effects at a specific cutoff of *phi* or PHID. The results might indicate that patients under active surveillance with a high *phi* or PHID should reconsider their strategy for disease management. We believe that this topic is important and worth investigating in an active surveillance cohort in future.

Several limitations should be noted. First, the sample size of the present study was relatively small. However, it is thus far the largest observational prospective study in a Chinese cohort. Confirmation

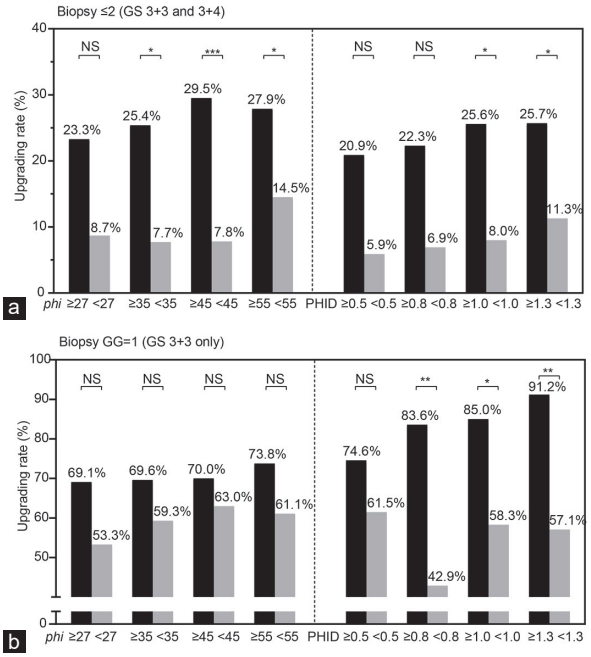

Figure 3: Upgrading rates for patients with biopsy (**a**) GG ≤2 and (**b**) GG = 1 under different cutoff values of *phi* or PHID. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Upgrading was defined as the presence of RP GG ≥3 for patients with biopsy GG ≤2 (primary outcome), and RP GG ≥2 for patients with biopsy GG of 1 (secondary outcome). RP: radical prostatectomy; GG: Gleason Grade Group; GS: Gleason score; *phi*: Prostate Health Index; PHID: *phi* density; NS: no statistical significance.

of the study results in a large-scale cohort is necessary before further application. Second, due to the low utilization rate of active surveillance for clinically low-risk PCa patients in China,[22,23] it is difficult to evaluate the association between *phi* or PHID and pathological reclassification in these patients. Such an evaluation is critical for the further implementation of our findings and application of *phi* testing for patients under active surveillance as a monitoring method.

CONCLUSION

Phi and its derivative PHID could predict GS upgrading in clinically low-risk patients with biopsy GG ≤2. Our findings might have clinical significance for treatment decisions in patients with low-risk PCa classified by biopsy results.

AUTHOR CONTRIBUTIONS

RN and YSW conceived and designed the study. JQY, DH, XLL, ZJF, YG, and HWJ contributed materials and collected data. DH, JQY, JYH, XHR, and RN analyzed the data. DH and JQY drafted the manuscript. RN, DFX, and YSW revised the manuscript. All authors have read and approved the final manuscript and agree with the order of presentation of the authors.

COMPETING INTERESTS

In the present study, we declare that Beckman Coulter, Inc., provided the tests for tPSA, fPSA, and p2PSA, but did not participate in the study design, data analysis and interpretation, and manuscript writing. There are no other potential competing interests to be declared.

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Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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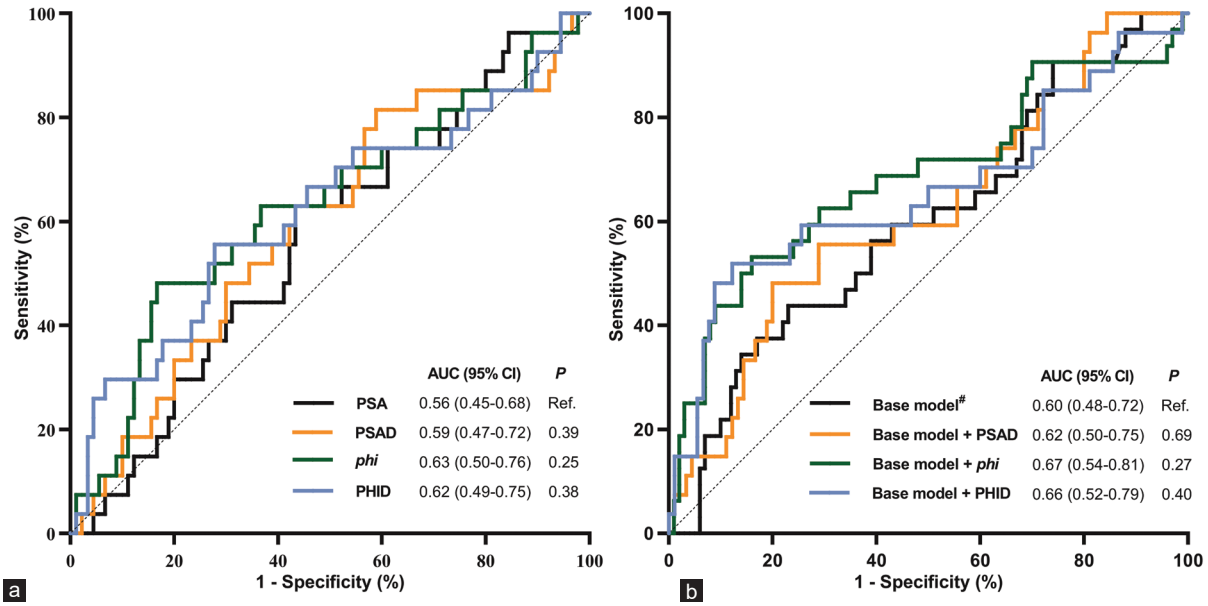

Supplementary Figure 1: ROC curves of (a) predictors and (b) multivariable models for prediction of downgrading[a] after RP in patients with biopsy GG ≥3. [a]Downgrading was defined as the presence of RP GG ≤2. [#]Base model = age + no. of positive cores (categorical) + logarithmically transformed total PSA. ROC: receiver operating characteristic; RP: radical prostatectomy; AUC: area under ROC curve; 95% CI: 95% confidence interval; PSA: prostate-specific antigen; PSAD: PSA density; *phi*: prostate health index; PHID: *phi* density.

Supplementary Table 1: Descriptive characteristics of high-risk patients (biopsy Gleason Grade Groups 3-5) and logistic regression analyses for prediction of downgrading after radical prostatectomy[a]

Characteristics	*Nondowngrading (RP GG ≥3)*	*Downgrading (RP GG ≤2)*	*P*[b]	*Univariable analysis*		*Multivariable analysis*[c]	
				OR (95% CI)	*P*	*OR (95% CI)*	*P*
Patients, *n*/total (%)	122/157 (77.7)	35/157 (22.3)	NA	NA	NA	NA	NA
Age (year)	71 (64–75)	69 (65–74)	0.63	1.00 (0.95–1.05)	0.94	1.02 (0.96–1.09)	0.57
Prostate volume (ml)	30.2 (23.9–42.2)	34.7 (24.9–51.7)	0.30	2.02 (0.75–5.44)	0.16	NA	NA
Number of Pos cores ≥3, *n*/total (%)	84/105 (80.0)	21/105 (20.0)	0.04*	0.36 (0.15–0.90)	0.03*	0.36 (0.12–1.09)	0.07
Total PSA (ng ml^{-1})	19.3 (11.8–43.3)	16.3 (9.8–33.0)	0.27	0.91 (0.67–1.23)	0.53	2.82 (0.76–10.53)	0.12
PSAD (ng ml^{-2})	0.6 (0.3–1.2)	0.5 (0.3–0.8)	0.27	0.92 (0.65–1.29)	0.62	0.68 (0.24–1.92)	0.47
p2PSA (pg ml^{-1})	41.7 (19.6–119.4)	33.7 (13.6–68.3)	0.04*	0.67 (0.47–0.95)	0.02*	0.52 (0.30–0.91)	0.02*
p2PSAD (pg ml^{-2})	1.4 (0.7–2.6)	0.9 (0.3–2.8)	0.09	0.65 (0.42–0.99)	0.05*	0.52 (0.30–0.91)	0.02*
phi	101.5 (61.5–168.0)	66.7 (35.3–129.9)	0.02*	0.62 (0.41–0.95)	0.03*	0.41 (0.20–0.83)	0.01*
PHID	2.9 (1.6–4.9)	1.8 (0.7–4.9)	0.11	0.65 (0.42–1.01)	0.06	0.51 (0.28–0.93)	0.03*

[a]Downgrading was defined as the presence of RP GG ≤2 for patients with biopsy GG ≥3, [b]*P* values were determined by Mann–Whitney U-test for continuous variables, and Fisher's exact test for categorical variables, [c]Adjusted for age, number of positive cores (≤2 *vs* ≥3), and logarithmically transformed total PSA. *Statistically significant ($P<0.05$). PSA: prostate-specific antigen; PSAD: PSA density; p2PSA: [-2]proPSA; p2PSAD: p2PSA density; *phi*: Prostate Health Index; PHID: *phi* density; RP: radical prostatectomy; NA: not analyzed; GG: Gleason Grade Groups; OR: odds ratio; CI: confidence interval; Pos: positive