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ORIGINAL ARTICLE

Prostate Cancer

Prostate volume does not provide additional predictive value to prostate health index for prostate cancer or clinically significant prostate cancer: results from a multicenter study in China

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To evaluate whether prostate volume (PV) would provide additional predictive utility to the prostate health index (phi) for predicting prostate cancer (PCa) or clinically significant prostate cancer, we designed a prospective, observational multicenter study in two prostate biopsy cohorts. Cohort 1 included 595 patients from three medical centers from 2012 to 2013, and Cohort 2 included 1025 patients from four medical centers from 2013 to 2014. Area under the receiver operating characteristic curves (AUC) and logistic regression models were used to evaluate the predictive performance of PV-based derivatives and models. Linear regression analysis showed that both total prostate-specific antigen (tPSA) and free PSA (fPSA) were significantly correlated with PV (all $P < 0.05$). [-2]proPSA (p2PSA) was significantly correlated with PV in Cohort 2 ($P < 0.001$) but not in Cohort 1 ($P = 0.309$), while no significant association was observed between phi and PV. When combining phi with PV, phi density (PHID) and another phi derivative (PHIV, calculated as phi/PV$^{0.5}$) did not outperform phi for predicting PCa or clinically significant PCa in either Cohort 1 or Cohort 2. Logistic regression analysis also showed that phi and PV were independent predictors for both PCa and clinically significant PCa (all $P < 0.05$); however, PV did not provide additional predictive value to phi when combining these derivatives in a regression model (all models *vs* phi were not statistically significant, all $P > 0.05$). In conclusion, PV-based derivatives (both PHIV and PHID) and models incorporating PV did not improve the predictive abilities of phi for either PCa or clinically significant PCa.
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Keywords: China; prostate cancer; prostate health index; prostate volume

INTRODUCTION

With the estimated 1 276 106 new cases and 358 989 deaths worldwide, prostate cancer (PCa) has become the second most common cancer and the fifth leading cause of cancer-specific death in males.[1] Along with widespread prostate-specific antigen (PSA) screening and an in-depth understanding of PCa, PSA has been gradually considered an unspecific tumor biomarker, leading to large numbers of unnecessary prostate biopsies.[2,3] Moreover, nonaggressive or low-grade PCa (also known as clinically insignificant disease) may not cause clinical consequences throughout the lifetime of a patient if left untreated or under surveillance, according to the results from several autopsy and active surveillance studies.[4–14] These clinical issues are also known as overdiagnosis and overtreatment.

To improve PSA-based diagnostic ability, the prostate health index (phi), derived from total PSA (tPSA), free PSA (fPSA), and [-2]proPSA (p2PSA), has been introduced and shown to be a better predictor than tPSA and %fPSA (fPSA/tPSA) for both PCa and clinically significant PCa. Using phi as a supplementary tool on tPSA may also reduce the number of unnecessary biopsies.[15–21]

Since many studies have reported that prostate volume (PV) is associated with prostate cancer and tPSA, PSA density (PSAD, tPSA/PV) was introduced to adjust this influence and was shown to have better predictive value for PCa.[22,23] However, phi, as a multivariable formula, did not include PV. Two previous single-center studies by Tosoian *et al.*[24] and Druskin *et al.*[25] demonstrated that phi density (PHID, calculated as phi/PV) outperformed phi in the diagnosis of clinically significant cancer (Gleason score, GS ≥7). A recent study by Vendrami *et al.*[26] demonstrated that PHID has a greater predictive value than phi when prostate biopsies were guided by image fusion of magnetic resonance (MR) and transrectal ultrasound. However, due to the

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relatively small sample sizes and the study design, the association between phi and PV was not clear enough in these studies. Therefore, we conducted this study to investigate the associations among p2PSA, phi, and PV. We also investigated whether PV would provide additional predictive utility when combined with phi in the Chinese population.

PARTICIPANTS AND METHODS

Study design and cohort

This study was a prospective, observational multicenter study in two prostate biopsy cohorts.[15,17] Cohort 1 recruited consecutive 635 patients from 2012 to 2013 in three tertiary hospitals in Shanghai, China (Huashan Hospital, Shanghai Cancer Center, and Xinhua Hospital). Cohort 2 recruited consecutive 1538 patients from 2013 to 2014 in four tertiary hospitals in Shanghai, China (the above three hospitals and Shanghai Changhai Hospital). All the patients underwent initial prostate biopsies. The indications for prostate biopsy were the same across different tertiary hospitals: (1) tPSA level >4.0 ng ml^{-1}; (2) %fPSA <0.16; and (3) presence of suspicious prostate nodules detected by digital rectal examination (DRE) or ultrasound. Transrectal ultrasound (TRUS)-guided biopsy was performed using a 10-core scheme in Cohort 1 and a 10- to 14-core scheme in Cohort 2. All biopsy specimens were reviewed in the Department of Pathology at each hospital. The study was approved by the institutional review board of each hospital, and written informed consent was obtained from each participant.

Patients were excluded in the present study if (1) there were no records of age and PV or (2) the records of any serum antigen levels (tPSA, fPSA, or p2PSA) were missing. Clinically significant PCa was defined as PCa with Gleason score (GS) ≥7.

Statistical analyses

Derivative variables were calculated as follows: (1) %fPSA: fPSA/tPSA; (2) PSAD: tPSA/PV; (3) %p2PSA: p2PSA/fPSA; (4) phi: (p2PSA/fPSA) × tPSA$^{0.5}$; (5) PHID: phi/PV; (6) PHIV: phi/PV$^{0.5}$

In univariate analysis, continuous variables were compared using a Mann–Whitney U test for nonnormal distributed variables or Student's *t*-test for normal distributed variables. Categorical variables were compared using a Chi-square test. Linear regression was used to measure the association between serum antigen levels (tPSA, fPSA, and p2PSA) and PV after log-transformation. In multivariate analysis, we performed four multivariate logistic regression (LR) models for predicting PCa and clinically significant PCa, including age, PV, and phi (or correlative serum antigen levels). Predictive abilities were evaluated using the area under the receiver operating characteristic curve (AUC). Statistical differences between AUCs were evaluated using the DeLong method.[27]

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

The characteristics of the two cohorts were described in our previous studies.[15,17] Based on the exclusion criteria, 40 and 513 patients were excluded from Cohort 1 and 2, respectively, because of incomplete records (**Supplementary Figure 1**). Finally, a total of 595 patients were included in Cohort 1 and 1025 patients were included in Cohort 2. The demographic information of the study populations is shown in **Supplementary Table 1**. Two hundred and fifty-five out of 595 patients were diagnosed with PCa (42.9%) and 193 patients were diagnosed with clinically significant PCa (32.4%) in Cohort 1. In Cohort 2, 437 (42.6%) patients were diagnosed with PCa and 346 (33.8%) with clinically significant PCa.

The correlations between serum antigen indices (tPSA, p2PSA, fPSA, and phi) and PV were evaluated by simple linear regression analysis (**Supplementary Table 2**). In Cohort 1, we found that both tPSA and fPSA were significantly correlated with PV ($P = 0.005$ and $P < 0.001$, respectively). However, no significant association was found between p2PSA and PV and between phi and PV ($P = 0.309$ and $P = 0.107$, respectively). In Cohort 2, tPSA, p2PSA, and fPSA were significantly correlated with PV (all $P < 0.001$). Similarly, no significant association was found between phi and PV ($P = 0.434$).

In the entire study population and separate cohorts, the median PV was approximately 40 ml (entire Cohort: 41 ml; Cohort 1: 42 ml; Cohort 2: 41 ml; **Supplementary Table 1**). We then performed a stratified analysis for patients with different PV (≤40 ml and >40 ml). When stratified using 40 ml as a threshold, patients with smaller PV had significantly lower tPSA, lower %fPSA, and higher %p2PSA in two separate cohorts (all $P < 0.05$, **Supplementary Table 3** and **4**). In Cohort 1, there was no significant difference in phi between the two volume groups ($P = 0.081$; **Supplementary Table 3**). However, marginally significant differences in phi were found between patients with PV ≤40 ml and >40 ml in Cohort 2 ($P = 0.047$; **Supplementary Table 4**).

The association between phi-PV derivatives and PCa or clinically significant PCa was also evaluated. In univariable logistic regression (**Table 1**), both PHID and PHIV (another phi derivative, calculated as phi/PV$^{0.5}$) were significantly associated with PCa and clinically significant PCa in the two cohorts (all $P < 0.001$). Notably, PHID had higher odds ratios (ORs) than phi when predicting PCa ($OR_{PHID} = 1.90$, $OR_{phi} = 1.02$) and clinically significant PCa ($OR_{PHID} = 1.43$, $OR_{phi} = 1.01$). Similar results were observed in Cohort 2 for PCa ($OR_{PHID} = 1.63$, $OR_{phi} = 1.02$) and clinically significant PCa ($OR_{PHID} = 1.37$, $OR_{phi} = 1.01$).

Multivariable LR showed that age, phi, and PV were all independent predictors for PCa and clinically significant PCa in both cohorts (all $P < 0.001$; **Table 2**). To evaluate whether PV would provide additional predictive value to phi, we established predictive models based on phi or phi-related variables (%p2PSA and tPSA), PV, and age in Cohort 1 and then validated the models in Cohort 2. The four LR models (LR-1, 2, 3, and 4) were described as follows: (a) model LR-1/LR-2 predicted PCa/clinically significant PCa using the variables of age, PV, and phi; (b) model LR-3/LR-4 predicted PCa/clinically significant PCa using the variables of age, PV, %p2PSA, and tPSA.

Comparisons of the AUCs among the phi-PV derivatives, models, and phi are shown in **Table 3** and **4**. Briefly, the AUCs of PHID and PHIV did not outperform phi for predicting PCa or clinically significant PCa (**Table 3** and **4**; ROC curves, **Supplementary Figure 2–4**). Despite the overfitting effect of the models in Cohort 1, all models in Cohort 2 did not outperform phi (all $P > 0.05$) for predicting either PCa or clinically significant PCa. Similar results are shown in **Supplementary Table 5** when predicting PCa with GS ≥8. These results indicated that PV would not provide additional predictive value to phi.

DISCUSSION

The objective of this study was to evaluate the association between phi and PV and to determine whether PV would provide additional predictive value to phi. We found that (1) p2PSA was significantly associated with PV, while there was no association between phi and PV, and (2) neither phi-PV derivatives (PHID or PHIV) nor phi-PV multivariate models outperformed phi for predicting PCa or clinically significant PCa. These results suggested that phi might not

Table 1: Univariable logistic regression models for the prediction of prostate cancer/clinically significant prostate cancer (Gleason score ≥7) in two cohorts

Variables	*Cohort 1 (n=595)*		*Cohort 2 (n=1025)*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
For PCa				
Age	1.06 (1.04–1.08)	<0.001	1.06 (1.05–1.08)	<0.001
PV	0.98 (0.97–0.99)	<0.001	0.99 (0.99–1.00)	0.010
tPSA	1.05 (1.04–1.06)	<0.001	1.04 (1.03–1.05)	<0.001
%fPSA*	0.98 (0.97–1.00)	0.028	0.90 (0.88–0.92)	<0.001
%p2PSA	1.05 (1.04–1.07)	<0.001	1.14 (1.12–1.17)	<0.001
PSAD*	1.03 (1.03–1.04)	<0.001	1.02 (1.01–1.02)	<0.001
phi	1.02 (1.01–1.02)	<0.001	1.02 (1.02–1.02)	<0.001
PHID	1.90 (1.65–2.18)	<0.001	1.63 (1.50–1.78)	<0.001
PHIV	1.11 (1.09–1.14)	<0.001	1.11 (1.09–1.14)	<0.001
For clinically significant PCa (GS ≥7)				
Age	1.05 (1.03–1.08)	<0.001	1.06 (1.04–1.08)	<0.001
PV	0.99 (0.98–1.00)	0.004	1.00 (0.99–1.00)	0.072
tPSA	1.03 (1.02–1.04)	<0.001	1.04 (1.03–1.04)	<0.001
%fPSA*	0.99 (0.97–1.01)	0.183	0.90 (0.88–0.92)	<0.001
%p2PSA	1.04 (1.02–1.05)	<0.001	1.08 (1.07–1.10)	<0.001
PSAD*	1.02 (1.01–1.02)	<0.001	1.02 (1.01–1.02)	<0.001
phi	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	<0.001
PHID	1.43 (1.32–1.55)	<0.001	1.37 (1.29–1.45)	<0.001
PHIV	1.06 (1.05–1.08)	<0.001	1.06 (1.05–1.07)	<0.001

*%fPSA and PSAD were transformed with per 1% change in case of inflated ORs. OR: odds ratio; PV: prostate volume; PSA: prostate-specific antigen; tPSA: total PSA; fPSA: free PSA; p2PSA: [-2]proPSA; PSAD: PSA density; phi: prostate health index; PHID: phi density; PHIV: phi/$PV^{0.5}$; PCa: prostate cancer; GS: Gleason score; CI: confidence interval

Table 2: Multivariable logistic regression including age, prostate volume, and prostate health index for the prediction of prostate cancer/clinically significant prostate cancer (Gleason score ≥7)

Variable	*Cohort 1 (PCa versus non-PCa)*		*Cohort 2 (PCa versus non-PCa)*		*Cohort 1 (GS ≥7 versus else)*		*Cohort 2 (GS ≥7 versus else)*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*
Age	1.07 (1.05–1.10)	<0.001	1.06 (1.04–1.08)	<0.001	1.06 (1.03–1.09)	<0.001	1.05 (1.03–1.07)	<0.001
PV	0.97 (0.95–0.98)	<0.001	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)	<0.001
phi	1.01 (1.01–1.02)	<0.001	1.02 (1.01–1.02)	<0.001	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	<0.001

All variables were log-transformed before modeling. OR: odds ratio; PV: prostate volume; phi: prostate health index; PCa: prostate cancer; GS: Gleason score; CI: confidence interval

be influenced by PV and adding PV might not provide additional predictive value to phi.

A single-center study[24] demonstrated that PHID outperformed phi in predicting clinically significant PCa. The highest discriminative ability was observed for PHID in predicting clinically significant disease (with an AUC of 0.84), which was significantly higher than phi (AUC = 0.76). That study only included 118 men with elevated PSA and negative DRE who underwent a phi test and prostate biopsy, while all patients had a phi test in our study. In our multicenter study, with a two-step external validation, PHID did not significantly outperform phi for predicting PCa or clinically significant PCa. The differences observed by Tosoian *et al.*[24] might be due to its relatively small sample size.

Based on our results, PV would not improve the predictive abilities of phi, suggesting that regardless of PV, phi alone could independently predict PCa and clinically significant PCa. Although the molecular mechanisms are not clear, there are several assumptions that might explain these results. First, p2PSA is considered a "prostate cancer-specific antigen" rather than a prostate-specific antigen. One study[28] showed that p2PSA had higher immunostaining in prostate tumor tissues than in benign prostate tissues. Therefore, tumor volume rather than PV would be a major factor for p2PSA value. Second, both tPSA and fPSA have a positive linear association with PV. However, the influence of PV might have been partially adjusted using $tPSA^{0.5}$/fPSA.

There were several limitations of this study. First, the PVs were all calculated through a transrectal approach (TRUS), which might cause subjective error among different ultrasonologists. However, all volumes of prostate were measured by skilled ultrasonologists, with a minimum of 5 years of working experience in our study. A recent study demonstrated that PHID appears to have greater predictive performance than phi when prostate biopsies were guided by image fusion of MR and transrectal ultrasound.[26] However, we were not able to perform similar analyses in the present study due to the lack of MRI data from our study subjects. MR-TRUS fusion biopsy will be applied in future studies to address this problem. Second, all medical centers participating in the present study were located in Shanghai, a large city in East China, which may cause selection bias. However, individuals all over the country seek the services of these tertiary hospitals.

In conclusion, PV-based derivatives (both PHIV and PHID) and correlative models do not improve the predictive abilities of phi for both PCa and clinically significant PCa.

AUTHOR CONTRIBUTIONS

RN, DFX, JFX, and YHS conceived and designed the study. DWY, JQ, FL, BTH, SLZ, and QD contributed materials and collected the data.

Table 3: Area under receiver operating characteristic curves of different measurements for predicting prostate cancer in entire cohorts and subsets grouped by total prostate-specific antigen

Measurements	*Cohort 1 (entire, n=595)*		*Cohort 2 (entire, n=1025)*		*Cohort 1 (tPSA 2–10 ng ml^{-1}, n=211)*		*Cohort 2 (tPSA 2–10 ng ml^{-1}, n=433)*		*Cohort 1 (tPSA 10–20 ng ml^{-1}, n=171)*		*Cohort 2 (tPSA 10–20 ng ml^{-1}, n=243)*	
	AUC (95% CI)	*P**	*AUC (95% CI)*	*P**	*AUC (95% CI)*	*P**	*AUC (95% CI)*	*P**	*AUC (95% CI)*	*P**	*AUC (95% CI)*	*P**
tPSA	0.82 (0.78–0.85)		0.78 (0.76–0.81)		0.56 (0.45–0.66)		0.58 (0.52–0.64)		0.60 (0.51–0.69)		0.59 (0.52–0.67)	
%fPSA	0.65 (0.60–0.69)		0.71 (0.68–0.74)		0.58 (0.48–0.68)		0.73 (0.68–0.78)		0.61 (0.53–0.70)		0.60 (0.52–0.67)	
%p2PSA	0.84 (0.81–0.88)		0.87 (0.84–0.89)		0.68 (0.57–0.80)		0.88 (0.84–0.92)		0.78 (0.71–0.85)		0.81 (0.75–0.87)	
PSAD	0.86 (0.83–0.89)	0.095	0.82 (0.79–0.85)	<0.001	0.65 (0.56–0.75)	0.578	0.67 (0.61–0.73)	<0.001	0.74 (0.67–0.82)	0.279	0.68 (0.61–0.75)	<0.001
phi	0.88 (0.85–0.91)	Reference	0.91 (0.89–0.93)	Reference	0.69 (0.58–0.81)	Reference	0.89 (0.85–0.93)	Reference	0.79 (0.72–0.86)	Reference	0.82 (0.77–0.88)	Reference
PHID	0.89 (0.86–0.92)	0.471	0.89 (0.87–0.91)	0.001	0.72 (0.62–0.82)	0.334	0.84 (0.81–0.88)	0.004	0.80 (0.74–0.87)	0.443	0.79 (0.73–0.85)	0.061
PHIV	0.89 (0.86–0.92)	0.040	0.91 (0.89–0.92)	0.311	0.72 (0.61–0.83)	0.125	0.88 (0.84–0.91)	0.219	0.80 (0.74–0.87)	0.170	0.81 (0.75–0.87)	0.286
LR-1	0.91 (0.88–0.93)	0.001	0.90 (0.89–0.92)	0.542	0.78 (0.69–0.88)	0.023	0.88 (0.84–0.91)	0.387	0.84 (0.78–0.90)	0.016	0.82 (0.77–0.88)	0.983
LR-3	0.91 (0.89–0.94)	0.002	0.90 (0.88–0.92)	0.198	0.78 (0.69–0.87)	0.043	0.86 (0.82–0.90)	0.112	0.84 (0.78–0.90)	0.034	0.81 (0.76–0.87)	0.738

**P* value, statistical analysis (DeLong method) between AUCs of different variables. ROC: receiver operating characteristic; AUCs: area under ROC curves; PSA: prostate-specific antigen; tPSA: total PSA; fPSA: free PSA; p2PSA: [-2]proPSA; PSAD: PSA density; phi: prostate health index; PHID: phi density; PHIV: phi/PV$^{0.5}$; LR-1: the first logistic regression model; LR-3: the third logistic regression model; CI: confidence interval

Table 4: Area under receiver operating characteristic curves of different measurements for predicting clinically significant prostate cancer (Gleason score ≥7) in entire cohorts and subsets grouped by total prostate-specific antigen

Measurements	*Cohort 1 (entire, n=595)*		*Cohort 2 (entire, n=1025)*		*Cohort 1 (tPSA 2–10 ng ml^{-1}, n=211)*		*Cohort 2 (tPSA 2–10 ng ml^{-1}, n=433)*		*Cohort 1 (tPSA 10–20 ng ml^{-1}, n=171)*		*Cohort 2 (tPSA 10–20 ng ml^{-1}, n=243)*	
	AUC (95% CI)	*P**	*AUC (95% CI)*	*P**	*AUC (95% CI)*	*P**	*AUC (95% CI)*	*P**	*AUC (95% CI)*	*P**	*AUC (95% CI)*	*P**
tPSA	0.85 (0.81–0.88)		0.81 (0.79–0.84)		0.59 (0.44–0.73)		0.60 (0.53–0.67)		0.63 (0.54–0.73)		0.59 (0.50–0.67)	
%fPSA	0.64 (0.59–0.68)		0.70 (0.67–0.74)		0.58 (0.47–0.70)		0.68 (0.61–0.75)		0.63 (0.52–0.73)		0.63 (0.55–0.70)	
%p2PSA	0.83 (0.79–0.87)		0.87 (0.84–0.89)		0.72 (0.59–0.86)		0.88 (0.85–0.92)		0.72 (0.62–0.81)		0.81 (0.75–0.87)	
PSAD	0.87 (0.84–0.90)	0.415	0.84 (0.82–0.87)	<0.001	0.59 (0.46–0.73)	0.134	0.71 (0.65–0.78)	<0.001	0.80 (0.73–0.87)	0.120	0.67 (0.60–0.75)	<0.001
phi	0.88 (0.85–0.91)	Reference	0.92 (0.90–0.93)	Reference	0.73 (0.61–0.86)	Reference	0.90 (0.87–0.94)	Reference	0.73 (0.64–0.82)	Reference	0.82 (0.76–0.88)	Reference
PHID	0.88 (0.85–0.91)	0.801	0.90 (0.88–0.92)	<0.001	0.74 (0.63–0.85)	0.895	0.87 (0.83–0.91)	0.043	0.77 (0.69–0.86)	0.023	0.79 (0.73–0.86)	0.163
PHIV	0.89 (0.86–0.92)	0.304	0.91 (0.90–0.93)	0.297	0.75 (0.63–0.87)	0.522	0.90 (0.87–0.93)	0.586	0.77 (0.68–0.85)	0.005	0.81 (0.75–0.87)	0.490
LR-2	0.90 (0.87–0.92)	0.016	0.92 (0.90–0.93)	0.990	0.80 (0.70–0.90)	0.155	0.91 (0.87–0.94)	0.931	0.79 (0.72–0.86)	0.006	0.83 (0.77–0.89)	0.698
LR-4	0.90 (0.88–0.93)	0.040	0.90 (0.89–0.92)	0.067	0.77 (0.67–0.87)	0.549	0.88 (0.84–0.92)	0.298	0.81 (0.74–0.88)	0.006	0.81 (0.75–0.87)	0.651

**P* value, statistical analysis (DeLong method) between AUCs of different variables. ROC: receiver operating characteristic; AUC: area under ROC curve; PSA: prostate-specific antigen; tPSA: total PSA; fPSA: free PSA; p2PSA: [-2]proPSA; PSAD: PSA density; phi: prostate health index; PHID: phi density; PHIV: phi/PV$^{0.5}$; LR-2: the second logistic regression model; LR-4: the fourth logistic regression model; CI: confidence interval

DH, YSW, RN, and DFX analyzed the data. DH, YSW, RN, and DFX wrote the manuscript. RN, DFX, JFX, and YHS supervised the study. DH and YSW contributed equally to this study. All authors have read and approved the final manuscript.

COMPETING INTERESTS

In the present study, we declare that Beckman Coulter, Inc., provided the tests for tPSA, fPSA, and p2PSA. All the sample tests, data analyses, and manuscript writing were performed by the researchers, independent from Beckman Coulter, Inc. 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 Table 1: Characteristics of Cohort 1 and 2 and comparison of each variable between cohorts

Variables	*Entire cohort (n=1620)*	*Cohort 1 (n=595)*	*Cohort 2 (n=1025)*	*P*
		Median (range)		
Age (year)	69 (62–74)	69 (62–76)	68 (62–74)	0.014
PV (ml)	41 (31–58)	42 (33–57)	41 (31–59)	0.045
tPSA (ng ml^{-1})	12.16 (7.29–26.60)	13.14 (7.60–30.62)	11.65 (7.08–25.51)	0.031
p2PSA (pg ml^{-1})	21.68 (12.43–58.30)	23.74 (13.21–84.89)	20.78 (12.02–48.44)	0.001
%fPSA	0.14 (0.10–0.20)	0.14 (0.10–0.21)	0.13 (0.09–0.19)	0.121
%p2PSA	14.99 (9.70–24.00)	15.33 (10.28–25.61)	14.79 (9.47–22.6)	0.031
phi	46.35 (28.94–108.37)	48.45 (30.81–139.70)	44.73 (27.47–98.07)	0.009
		# (%) of positive		
PCa	692 (42.7)	255 (42.9)	437 (42.6)	0.930
PCa (GS ≥7)	539 (33.3)	193 (32.4)	346 (33.8)	0.587
PCa (GS ≥8)	287 (17.7)	102 (17.1)	185 (18.0)	0.645

PV: prostate volume; PSA: PSA: prostate-specific antigen; tPSA: total PSA; fPSA: free PSA; p2PSA: [-2]proPSA; phi: prostate health index; PCa: prostate cancer; GS: Gleason score

Supplementary Table 2: Simple linear regression between serum indices and prostate volume in entire cohort and two separate cohorts

Variables	*Cohort*	*n*	*Coefficient (95% CI)*	R^2	*P*
tPSA	1	595	0.359 (0.107–0.611)	0.013	0.005
	2	1025	0.501 (0.359–0.642)	0.045	<0.001
	Entire	1620	0.469 (0.343–0.594)	0.032	<0.001
p2PSA	1	595	0.169 (–0.157–0.495)	0.002	0.309
	2	1025	0.566 (0.382–0.751)	0.034	<0.001
	Entire	1620	0.470 (0.307–0.633)	0.020	<0.001
fPSA	1	595	0.544 (0.299–0.789)	0.031	<0.001
	2	1025	0.759 (0.629–0.889)	0.114	<0.001
	Entire	1620	0.709 (0.591–0.827)	0.079	<0.001
phi	1	595	–0.195 (–0.433–0.042)	0.004	0.107
	2	1025	0.058 (–0.087–0.202)	0.0006	0.434
	Entire	1620	–0.004 (–0.128–0.119)	3.0×10^{-6}	0.944

PSA: prostate-specific antigen; tPSA: total PSA; fPSA: free prostate-specific antigen; p2PSA: [-2]proPSA; phi: prostate health index; CI: confidence interval

Supplementary Table 3: Characteristics of Cohort 1 and comparison of each variable between different groups by prostate volume

Variables	*Entire cohort (n=595)*	*Volume (ml)*		*P**
		≤40 (n=275)	*>40 (n=320)*	
		Median (range)		
Age (year)	69 (62–76)	69 (60–75)	70 (63–77)	0.017
tPSA (ng ml^{-1})	13.14 (7.60–30.62)	12.11 (6.64–24.22)	14.34 (8.44–38.21)	0.003
p2PSA (pg ml^{-1})	23.74 (13.21–84.89)	21.87 (11.73–73.66)	25.73 (14.38–114.46)	0.062
%fPSA	0.14 (0.10–0.21)	0.13 (0.09–0.18)	0.15 (0.11–0.22)	0.001
%p2PSA	15.33 (10.28–25.61)	18.53 (11.81–26.07)	13.58 (8.91–24.01)	<0.001
phi	48.45 (30.81–139.70)	58.78 (32.93–136.53)	43.30 (30.19–146.57)	0.081
		# (%) of positive		
PCa	255 (42.9)	137 (49.8)	118 (36.9)	0.001
PCa (GS ≥7)	193 (32.4)	101 (36.7)	92 (28.8)	0.038
PCa (GS ≥8)	102 (17.1)	50 (18.0)	52 (16.3)	0.533

*Difference in continuous variables is evaluated by Mann–Whitney U-test, and categorical variables by Chi-squared test. PSA: prostate-specific antigen; tPSA: total PSA; fPSA: free PSA; p2PSA: [-2]proPSA; phi: prostate health index; PCa: prostate cancer; GS: Gleason score

Supplementary Table 4: Characteristics of Cohort 2 and comparison of each variable between different groups by prostate volume

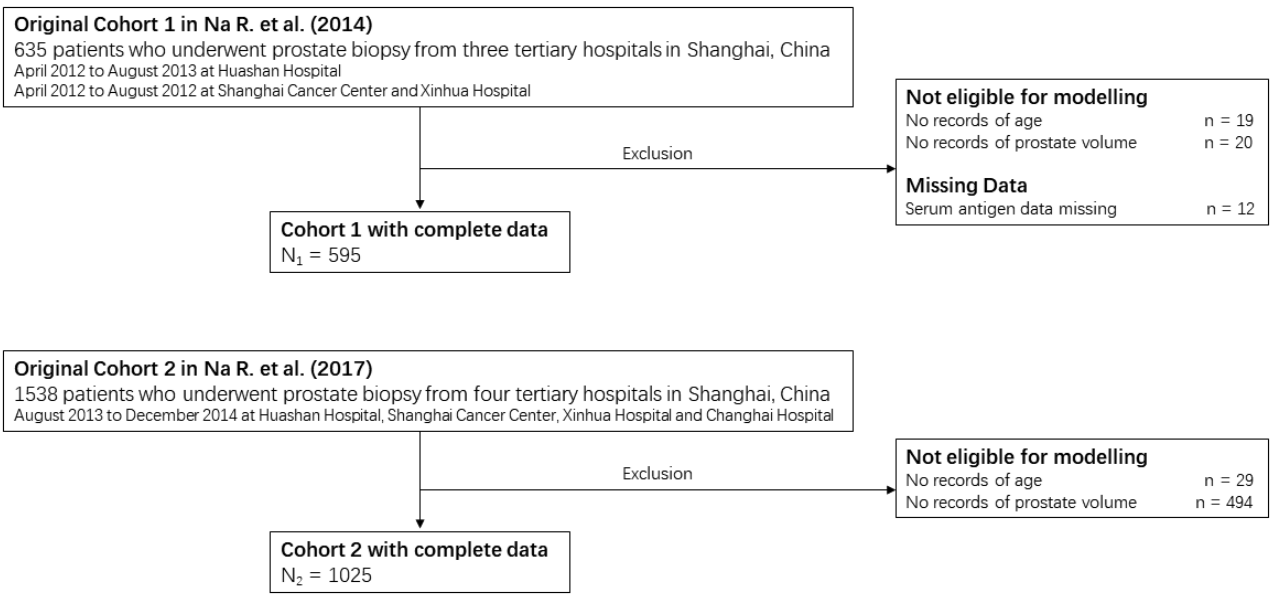
Variables	*Entire cohort (n=1025)*	*Volume (ml)*		*P**
		≤40 (n=500)	*>40 (n=525)*	
		Median (range)		
Age (year)	68 (62–74)	68 (61–73)	68 (63–74)	0.011
tPSA (ng ml^{-1})	11.65 (7.08–25.51)	10.68 (5.96–22.83)	12.48 (8.19–28.13)	<0.001
p2PSA (pg ml^{-1})	20.78 (12.02–48.44)	18 (10.32–44.91)	23.23 (14.99–52.61)	<0.001
%fPSA	0.13 (0.09–0.19)	0.12 (0.08–0.16)	0.15 (0.11–0.22)	<0.001
%p2PSA	14.79 (9.47–22.6)	17.01 (11.18–24.42)	12.49 (8.61–21.21)	<0.001
phi	44.73 (27.47–98.07)	49.75 (29.46–98.06)	42.35 (25.93–98.07)	0.047
		# (%) of positive		
PCa	437 (42.6)	239 (47.8)	198 (37.7)	0.001
PCa (GS ≥7)	346 (33.8)	188 (37.6)	158 (30.1)	0.011
PCa (GS ≥8)	185 (18.0)	92 (18.4)	93 (17.7)	0.775

*Difference in continuous variables is evaluated by Mann–Whitney U-test, and categorical variables by Chi-squared test. PSA: prostate-specific antigen; tPSA: total PSA; fPSA: free PSA; p2PSA, [-2]proPSA; phi: prostate health index; PCa: prostate cancer; GS: Gleason score

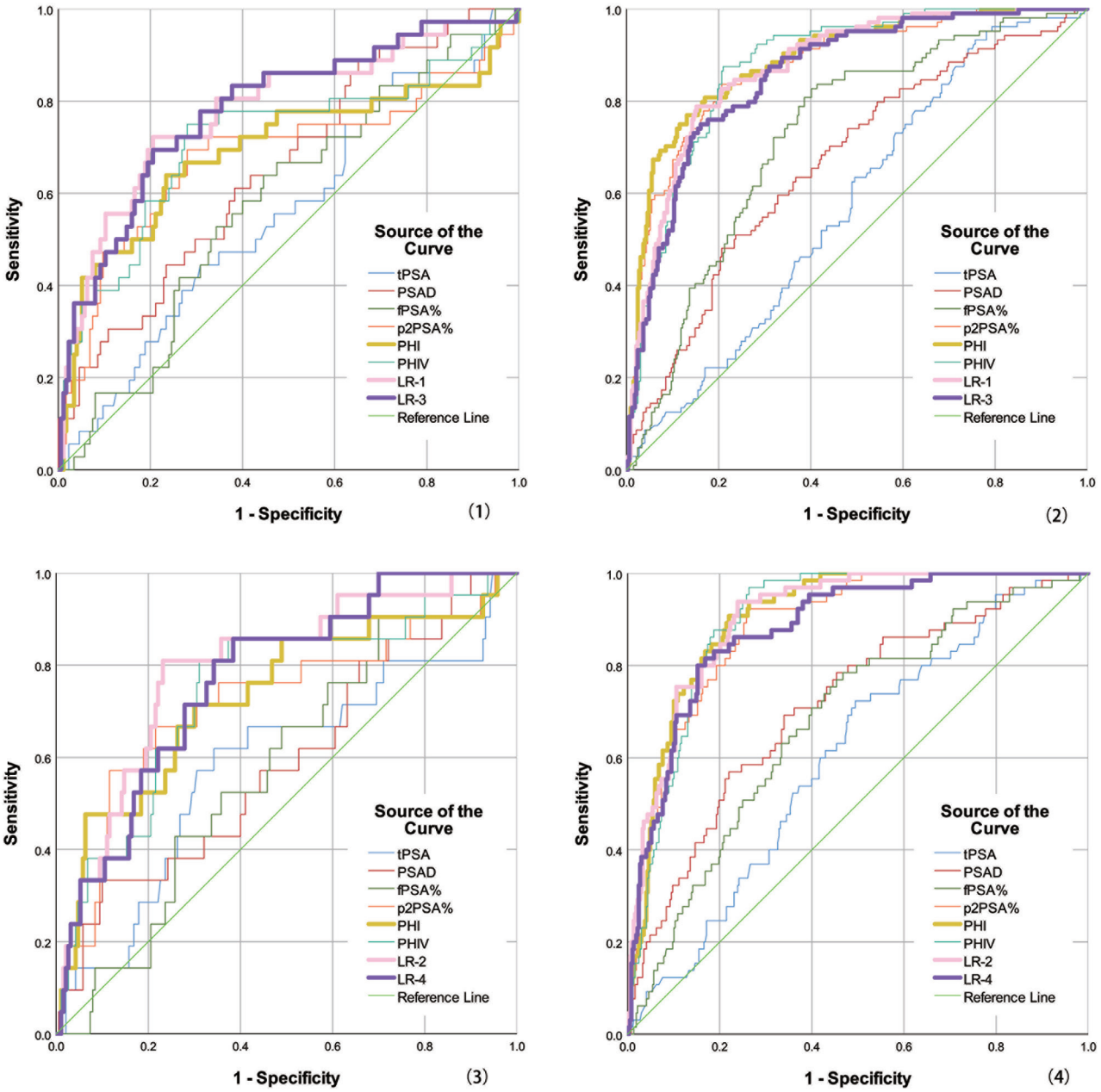
Supplementary Table 5: Area under receiver operating characteristic curves of different measurements for predicting prostate cancer (Gleason score ≥8) in entire cohorts and subsets grouped by total prostate-specific antigen

Measurements	*Cohort 1 (entire, n=595)*		*Cohort 2 (entire, n=1025)*		*Cohort 1 (tPSA 2–10, n=211)*		*Cohort 2 (tPSA 2–10, n=433)*		*Cohort 1 (tPSA 10–20, n=171)*		*Cohort 2 (tPSA 10–20, n=243)*	
	AUC (95% CI)	*P**	*AUC (95% CI)*	*P**	*AUC (95% CI)*	*P**	*AUC (95% CI)*	*P**	*AUC (95% CI)*	*P**	*AUC (95% CI)*	*P**
tPSA	0.88 (0.85–0.91)		0.87 (0.84–0.90)		0.75 (0.48–1.00)		0.65 (0.50–0.80)		0.693 (0.537–0.849)		0.65 (0.53–0.77)	
%fPSA	0.59 (0.52–0.65)		0.66 (0.63–0.70)		0.63 (0.37–0.89)		0.51 (0.37–0.66)		0.589 (0.402–0.775)		0.62 (0.49–0.75)	
%p2PSA	0.81 (0.76–0.86)		0.83 (0.80–0.87)		0.59 (0.26–0.92)		0.67 (0.49–0.86)		0.666 (0.503–0.829)		0.76 (0.65–0.87)	
PSAD	0.89 (0.86–0.92)	0.148	0.87 (0.84–0.90)	0.033	0.94 (0.89–0.99)	0.007	0.61 (0.47–0.76)	0.433	0.831 (0.753–0.910)	0.116	0.75 (0.66–0.85)	0.679
phi	0.87 (0.83–0.91)	Reference	0.90 (0.87–0.92)	Reference	0.51 (0.16–0.86)	Reference	0.70 (0.53–0.88)	Reference	0.689 (0.527–0.852)	Reference	0.78 (0.68–0.88)	Reference
PHID	0.87 (0.83–0.91)	0.981	0.88 (0.85–0.91)	0.003	0.69 (0.44–0.94)	0.003	0.67 (0.50–0.83)	0.240	0.740 (0.590–0.890)	0.216	0.80 (0.71–0.89)	0.412
PHIV	0.87 (0.83–0.91)	0.474	0.89 (0.86–0.92)	0.163	0.61 (0.29–0.93)	<0.001	0.69 (0.51–0.86)	0.345	0.724 (0.570–0.878)	0.200	0.80 (0.71–0.90)	0.228
LR-2	0.87 (0.83–0.91)	0.807	0.89 (0.86–0.92)	0.281	0.72 (0.47–0.98)	0.008	0.72 (0.56–0.88)	0.434	0.742 (0.609–0.874)	0.265	0.79 (0.70–0.89)	0.770
LR-4	0.89 (0.86–0.92)	0.058	0.89 (0.87–0.92)	0.715	0.84 (0.68–0.99)	0.004	0.74 (0.60–0.88)	0.439	0.780 (0.681–0.880)	0.150	0.80 (0.71–0.89)	0.713

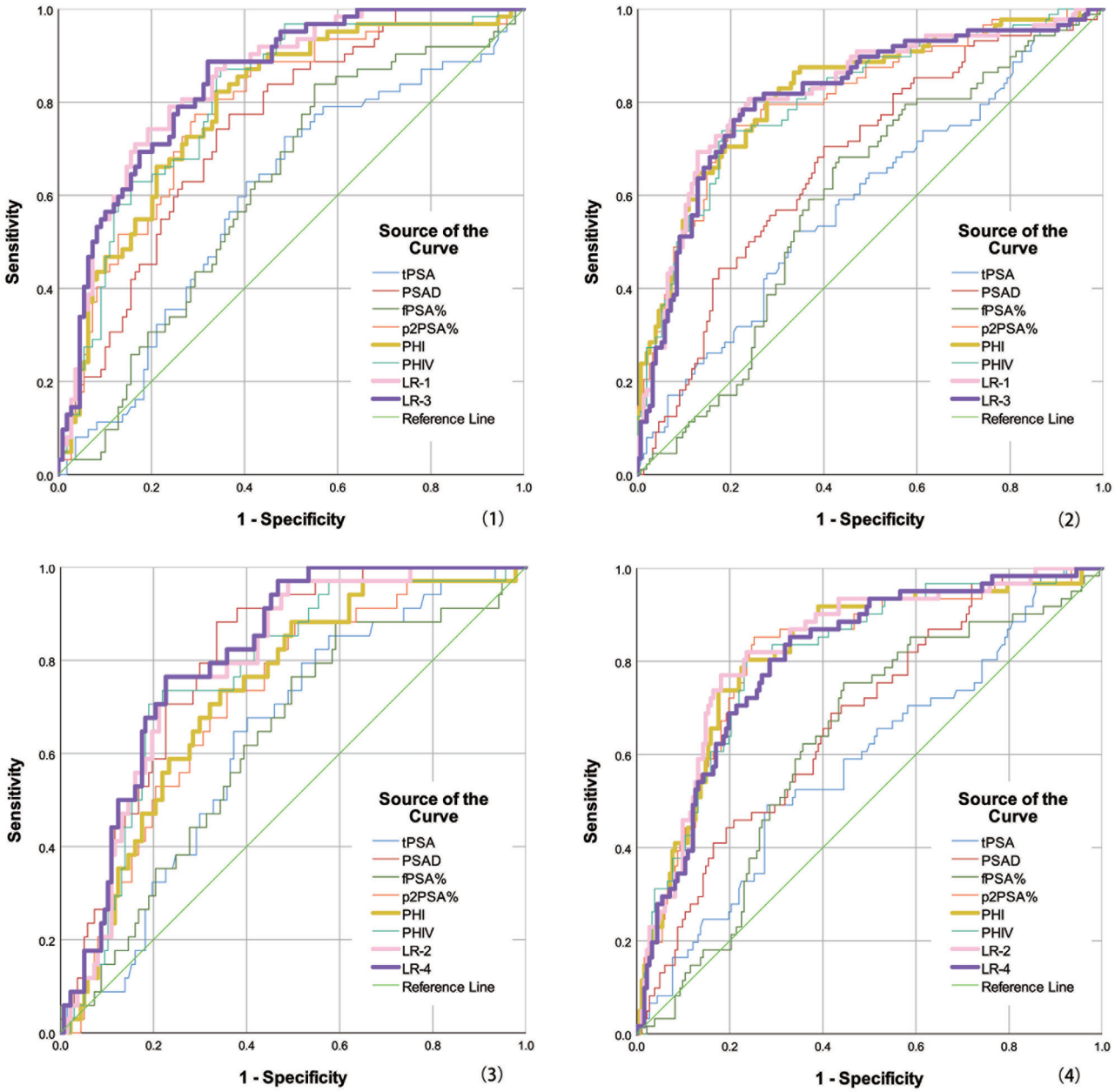
**P*: *P* value, statistical analysis (DeLong Method) between AUCs of different variables. PSA: prostate-specific antigen; tPSA: total prostate-specific antigen; fPSA: free prostate-specific antigen; p2PSA: [-2]proPSA; PSAD: PSA density; phi: prostate health index; PHID: phi density; PHIV: phi/$PV^{0.5}$; LR-n: the nth logistic regression model; PCa: prostate cancer; GS: Gleason score; CI: confidence interval; ROC: receiver operating characteristic; AUC: area under ROC curve



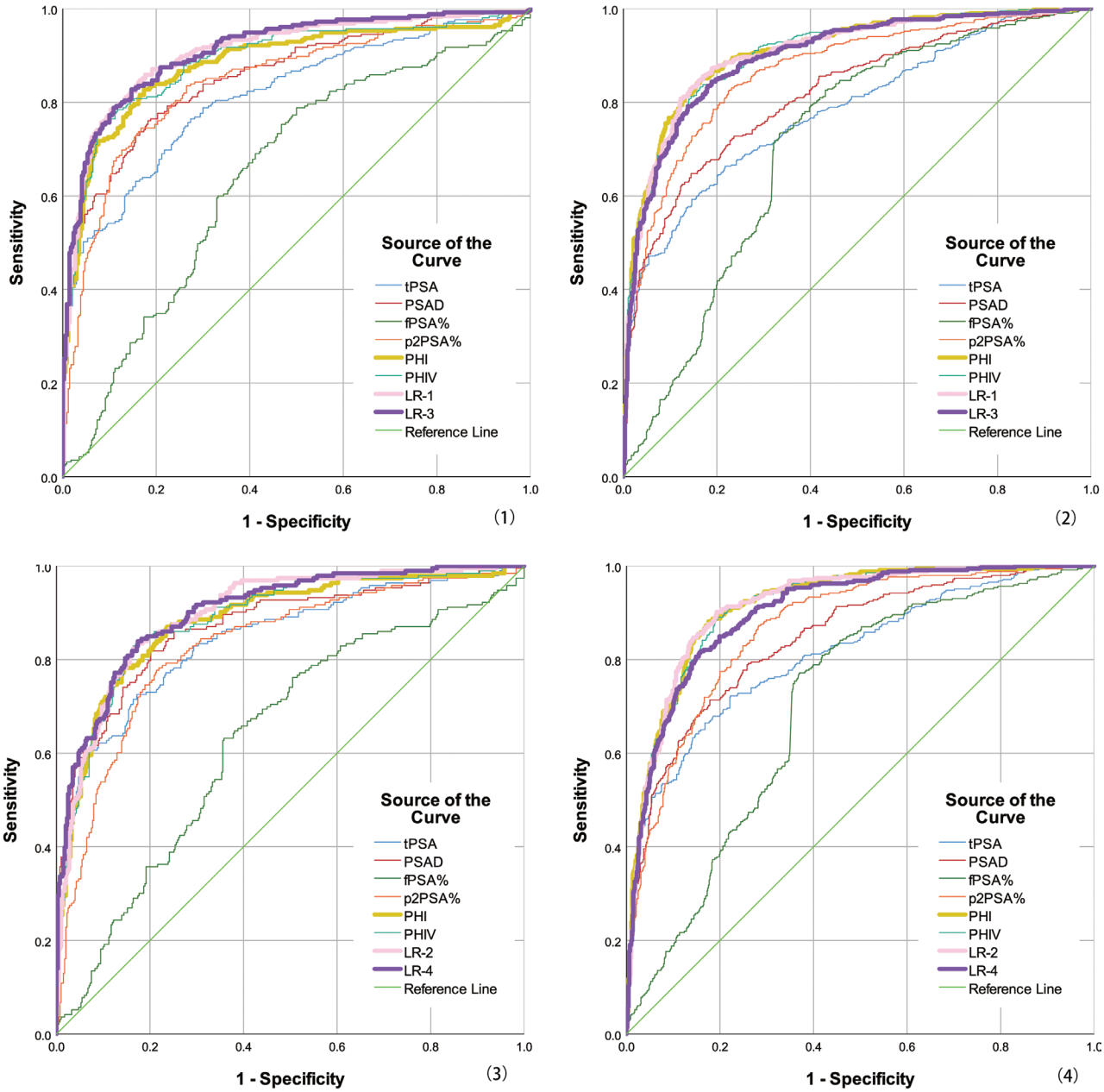
Supplementary Figure 1: Flowchart of study population enrollment based on inclusion and exclusion criteria.



Supplementary Figure 2: ROC curves of different measurements in a subset (tPSA 2–10 ng ml^{-1}) (1) for PCa in Cohort 1; (2) for PCa in Cohort 2; (3) for PCa (GS ≥7) in Cohort 1; (4) for PCa (GS ≥7) in Cohort 2. PCa: prostate cancer; PSA: prostate-specific antigen; ROC: receiver operating characteristic; GS: Gleason score.



Supplementary Figure 3: ROC curves of different measurements in a subset (tPSA 10–20 ng ml^{-1}) (1) for PCa in Cohort 1; (2) for PCa in Cohort 2; (3) for PCa (GS ≥7) in Cohort 1; (4) for PCa (GS ≥7) in Cohort 2. PCa: prostate cancer; PSA: prostate-specific antigen; ROC: receiver operating characteristic; GS: Gleason score.



Supplementary Figure 4: ROC curves of different measurements in entire cohorts (1) for PCa in Cohort 1; (2) for PCa in Cohort 2; (3) for PCa (GS ≥7) in Cohort 1; (4) for PCa (GS ≥7) in Cohort 2. PCa: prostate cancer; ROC: receiver operating characteristic; GS: Gleason score.