Phi-based risk calculators performed better in the prediction of prostate cancer in the Chinese population

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Risk prediction models including the Prostate Health Index (phi) for prostate cancer have been well established and evaluated in the Western population. The aim of this study is to build phi-based risk calculators in a prostate biopsy population and evaluate their performance in predicting prostate cancer (PCa) and high-grade PCa (Gleason score ≥7) in the Chinese population. We developed risk calculators based on 635 men who underwent initial prostate biopsy. Then, we validated the performance of prostate-specific antigen (PSA), phi, and the risk calculators in an additional observational cohort of 1045 men. We observed that the phi-based risk calculators (risk calculators 2 and 4) outperformed the PSA-based risk calculator for predicting PCa and high-grade PCa in the training cohort. In the validation study, the area under the receiver operating characteristic curve (AUC) for risk calculators 2 and 4 reached 0.91 and 0.92, respectively, for predicting PCa and high-grade PCa, respectively; the AUC values were better than those for risk calculator 1 (PSA-based model with an AUC of 0.81 and 0.82, respectively) (all P < 0.001). Such superiority was also observed in the stratified population with PSA ranging from 2.0 ng ml−1 to 10.0 ng ml−1. Decision curves confirmed that a considerable proportion of unnecessary biopsies could be avoided while applying phi-based risk calculators. In this study, we showed that, compared to risk calculators without phi, phi-based risk calculators exhibited superior discrimination and calibration for PCa in the Chinese biopsy population. Applying these risk calculators also considerably reduced the number of unnecessary biopsies for PCa.

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INTRODUCTION
Prostate cancer (PCa) is the second most common cancer and one of the leading causes of cancer-related death among males worldwide.1 The incidence of PCa in China is relatively low compared to that in Western countries; however, it has been progressively rising in recent decades and has become the seventh most common cancer among Chinese males.2,3

Prostate-specific antigen (PSA) has been introduced to prostate cancer screening and clinical practice for decades and is still the most widely used biomarker for screening and early detection of PCa. However, PSA is organ specific rather than cancer specific; therefore, PSA screening has resulted in large numbers of unnecessary biopsies and overdiagnosis of indolent cancers.4,6

Existing studies in Caucasians with PSA levels ranging from 2.0 ng ml−1 to 10.0 ng ml−1 have shown that [-2]proPSA (p2PSA), an isoform of PSA, and its derivative Prostate Health Index (phi) might have a better discriminating ability in predicting PCa and high-grade PCa than PSA.7,8 Our previous study reported consistent results, and we found that phi performed better than PSA in discriminating PCa and non-PCa in patients with higher PSA levels in the Chinese population.9

Various risk calculators have been developed based on different clinical variables and have provided added value to the PSA test for predicting PCa or high-grade PCa. Among them, the Prostate Cancer Prevention Trial (PCPT) risk calculator10 and the European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator11 have been most widely used in Caucasians. It has been proven that these risk calculators can avoid 2%–20% unnecessary biopsies at a different threshold probability of PCa.12 The variables in the PCPT risk calculators include age, race, PSA, digital rectal examination (DRE), family history, and history of a previous negative prostate biopsy. The variables in the ERSPC risk calculators include PSA, DRE, the results of transrectal ultrasound (TRUS), prostate volume (PV), history of prostate biopsy, and the new version that incorporates...
The utility of these risk calculators for predicting PCa has been externally validated in the Western population,17,18 However, these two risk calculators are suitable for patients with PSA from 0 (or 0.5 ng ml$^{-1}$) to 50 ng ml$^{-1}$, and phi is only applicable when a patient had a recent DRE and had his PV measured using ERSPC risk calculator 3.

Most risk calculators (including PCPT and ERSPC risk calculators) were based on screening populations with low average PSA levels (most participants in PCPT had PSA below 6.0 ng ml$^{-1}$, and the participants in ERSPC had a mean PSA of 1.7 ng ml$^{-1}$).13,15,16 However, PSA screening is not often utilized in China, and most of the Chinese patients come to urologists for elevated PSA, lower urinary tract symptoms, and abnormal findings in DRE or TRUS in their comprehensive physical examination. Such population has a higher risk for PCa than the screening population. Therefore, these risk calculators might not be appropriate for such different clinical settings in China. In addition, according to a previous study, PCPT and ERSPC risk calculators overestimate the probability of PCa and high-grade disease (Gleason score $\geq 7$).19 Furthermore, we considered that phi might have more widespread use in Chinese biopsy populations according to our former study (e.g., for patients with PSA $\geq 10.0$ ng ml$^{-1}$).10 In consideration of the limited data on the performance of PCa risk calculators that include phi in the Chinese population, here, we built risk calculators (with or without phi) based on a prostate biopsy population and followed with an observational study to validate the performance of our risk calculators.

**PATIENTS AND METHODS**

**Cohort of the training study**

Subjects ($n = 635$) who underwent initial prostate biopsy from April 2012 to August 2013 in three tertiary medical centers in Shanghai (including Huashan Hospital, Fudan University; Shanghai Cancer Center, Fudan University; and Xinhua Hospital, Shanghai Jiao Tong University School of Medicine) were recruited as the training cohort. All clinical information was collected before biopsy. The patients were excluded if any essential clinical data on age, PSA, %fPSA (free PSA divided by PSA), p2PSA, or PV were missing. The characteristics of primary health institutes in China had been described in our previous study.10

**Cohort of the validation study**

Patients ($n = 1045$) who underwent initial prostate biopsy from August 2013 to December 2014 in four tertiary medical centers in Shanghai (including Huashan Hospital, Fudan University; Shanghai Cancer Center, Fudan University; Xinhua Hospital, Shanghai Jiao Tong University School of Medicine; and Changhai Hospital, the Second Military Medical University) were enrolled in our observational validation study. Participants who completed all the examinations (PSA, fPSA, p2PSA, and TRUS) were included in the final analysis. All clinical data were entered into the risk calculator to generate everyone’s risk index and were recorded. This process did not influence the decision-making for prostate biopsy in the validation population. In both the training and validation studies, all subjects underwent an ultrasound-guided transperineal needle prostate biopsy with 10–14 cores. The indications for prostate biopsy at our institute were the following: (1) PSA >10.0 ng ml$^{-1}$; (2) PSA >4.0 ng ml$^{-1}$ with confirmation after 2–3 months; (3) PSA level ranging from 4.0 ng ml$^{-1}$ to 10.0 ng ml$^{-1}$, with suspicious fPSA/PSA <0.16 or PSA density >0.15 (PSAD = PSA/PV, PV (ml) = height (cm) × length (cm) × width (cm) × 0.52); and (4) positive findings from a DRE, TRUS, or magnetic MRI with any level of PSA.

**Sample collection**

All biopsy specimens were diagnosed by pathologists from the pathology department of each hospital. All blood samples were collected before biopsy for the measurement of PSA, fPSA, and p2PSA using the Beckman Coulter DxI 800 Immunoassay System (Beckman Coulter, Brea, CA, USA). The protocol of the current study was reviewed and approved by the institutional review board of each hospital in Shanghai, China. Both written informed consent and verbal informed consent were obtained from the patients for their participation in the study.

**Statistical analyses**

Phi was calculated using the following formula: $(p2PSA/PSA) \times \sqrt{PSA}$. PSA and phi were log-transformed for further statistical analysis due to their nonnormalized distributions. Based on the training cohort ($n = 635$), we built four risk calculators. Risk calculator 1 (RC1) was built according to the rules of a logistic regression model based on age, lgPSA (logarithm of PSA), and %fPSA. Risk calculator 2 (RC2) was built according to the rules of a logistic regression model based on age and lgphi (logarithm of phi). Risk calculator 3 (RC3) was built according to the rules of a logistic regression model based on age, lgPSA, %fPSA, and PV. Risk calculator 4 (RC4) was built according to the rules of a logistic regression model based on age, lgPSA, %fPSA, and PV. Risk calculator 4 (RC4) was built according to the rules of a logistic regression model based on age, lgphi, and PV. Then, we evaluated the performances of phi, RC1, RC2, RC3, and RC4 in predicting PCa and high-grade PCa (Gleason score $\geq 7$) in the training cohort, the validation cohort, and their subgroups (i.e., the population with PSA ranging from 2.0 ng ml$^{-1}$ to 10.0 ng ml$^{-1}$).

The baseline characteristics (age, PV, PSA, and %PSA) between two cohorts were compared using Student's $t$-test. The performance of each risk calculator was evaluated statistically on the basis of its discrimination and calibration according to established framework.21 Receiver operating characteristic (ROC) curves were used to measure the discriminating abilities of different predictors (phi and the four risk calculators). A $Z$-test was performed to evaluate the differences in area under the ROC curves (AUCs) for phi and the four risk calculators (RC1 was used as a reference). We performed a decision curve analysis (DCA) to evaluate the potential clinical usefulness of making decisions based on phi and the four risk calculators. A two-sided test with $P = 0.05$ was used. Statistical analyses were performed using SPSS 19.0 (Statistical Product and Service Solutions, IBM Corporation, Armonk, NY, USA) and R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

A total of 635 patients were included in the training study, and 1045 patients were enrolled in the validation study. The positive biopsy rates were 42.8% and 43.0% in the training and validation cohorts, respectively, which were comparable.

**Training study**

The characteristics of the cohort and the stratified subgroups (PSA ranging from 2.0 ng ml$^{-1}$ to 10.0 ng ml$^{-1}$) are shown in Table 1. In the training cohort and its subgroup with PSA ranging from 2.0 ng ml$^{-1}$ to 10.0 ng ml$^{-1}$, the mean age, PSA, and phi were statistically higher in men diagnosed with PCa than in men without PCa, whereas the mean PV and %fPSA were lower in the PCa group (all $P < 0.05$). When the patients were categorized by a Gleason score $\geq 7$ for high-grade PCa and others, the differences in age, PSA, phi, and PV remained significant, whereas the differences in %PSA were insignificant (data not shown).

Multivariate logistic regression analyses were performed to evaluate each factor in the training cohort. We observed that age, PSA, %fPSA, p2PSA, and PV were all associated with PCa (all $P < 0.01$), while %fPSA
was not associated with high-grade PCa. On the basis of the results from the multivariate logistic regression analyses and the consensus risk factors (i.e., age, PSA, %fPSA, p2PSA, and PV), we constructed the risk calculators as follows:

For PCa:

i. Risk calculator 1 (RC1): risk points = −4.928 + 0.023 × age + 2.789 × logPSA − 1.962 × %fPSA

ii. Risk calculator 2 (RC2): risk points = −9.597 + 0.026 × age + 4.154 × logphi

iii. Risk calculator 3 (RC3): risk points = −4.566 + 0.035 × age − 0.038 × PV + 3.236 × logPSA − 1.735 × %fPSA;

iv. Risk calculator II (RC4): risk points = −8.919 + 0.036 × age − 0.029 × PV + 4.147 × logphi.

For high-grade PCa:

i. Risk calculator 1 (RC1): risk points = −5.547 + 0.012 × age + 3.058 × logPSA

ii. Risk calculator 2 (RC2): risk points = −8.791 + 0.016 × age + 3.664 × logphi

iii. Risk calculator 3 (RC3): risk points = −5.193 + 0.021 × age + 3.351 × logPSA − 0.029 × PV

iv. Risk calculator II (RC4): risk points = −8.315 + 0.021 × age + 3.642 × logphi − 0.017 × PV.

In further analysis, the prediction accuracy of PSA, phi, and risk calculators 1–4 were evaluated in the training cohort. The AUCs of the different PCa risk calculators in the training cohorts and its subgroups are shown in Table 2. In the training cohort, when predicting PCa, the AUC for phi, RC2, and RC4 were 0.88, 0.89, and 0.90, respectively, which indicated that phi and phi-based risk calculators (RC2 and RC4) all performed better than RC1 (AUC = 0.83, all P < 0.05). When predicting high-grade PCa (a Gleason score ≥7), there was no significant difference among the AUCs of RC1 (AUC = 0.84), phi (AUC = 0.89), and RC2 (AUC = 0.89) in the training cohort, while RC4 (AUC = 0.89) performed better than RC1 (P < 0.05). However, phi, RC2, and RC4 did not outperform RC1 in the subgroup with PSA ranging from 2.0 ng ml⁻¹ to 10.0 ng ml⁻¹, and similar results were also observed when predicting high-grade PCa in the same subgroup (Table 3).

Validation study

In the subsequent validation study, we evaluated the predictive performance of PSA, phi, and RC1–4 in the validation cohort. The characteristics of the validation cohort and its subgroup (PSA ranging from 2.0 ng ml⁻¹ to 10.0 ng ml⁻¹) are shown in Table 4, and they were consistent with those of the training group.

When evaluating the prediction abilities of the risk calculators in the validation cohort and its subgroup, phi (Tables 2 and 3), RC2, and RC4 all outperformed RC1 (0.91, 0.91, and 0.91, respectively, vs 0.81 in the whole validation cohort and 0.89, 0.90, and 0.89, respectively, vs 0.71 in its subgroup) in predicting PCa (all P < 0.01). When predicting high-grade PCa, such superiority was still observed in the RCs that included phi. The calibration of the risk calculators was also assessed in the validation cohort (Table 5).

The ROC curves for phi and RC 1–4 in predicting PCa in two cohorts and in the subgroups with PSA ranging from 2.0 ng ml⁻¹ to 10.0 ng ml⁻¹ are shown in Supplementary Figure 1. The DCA revealed that any phi-based risk calculator performed better than PSA-based RC1 in both training and validation cohorts (Supplementary Figures 2 and 3). A potential net reduction in the number of biopsies was seen in PCa risk thresholds of approximately 20% for PCa in both cohorts.

Table 1: Clinical characteristics of the training cohort

| Variables          | All PSA | PCa | Non-PCa | P*   | All PSA | PCa | Non-PCa | P*   |
|--------------------|---------|-----|---------|------|---------|-----|---------|------|
| Patient (n)        | 635     | 272 | 363     |      | 222     | 39  | 183     |      |
| Age (year, median (IQR)) | 69.0 (61.0–76.0) | 72.0 (65.0–78.0) | 66.0 (59.0–74.0) | 5.11×10⁻¹⁰ | 65.0 (58.8–72.2) | 69.0 (63.0–75.0) | 65.0 (58.0–72.0) | 0.015 |
| Volume (ml), median (IQR) | 41.0 (32.0–56.1) | 38.0 (29.0–51.0) | 45.0 (34.0–62.0) | 1.44×10⁻⁶ | 40.0 (33.0–50.0) | 36.0 (27.0–43.0) | 40.0 (33.0–51.0) | 6.0×10⁻¹³ |
| PSA (ng ml⁻¹), median (IQR) | 13.3 (7.6–31.5) | 31.8 (14.0–145.7) | 9.4 (6.2–15.1) | 3.06×10⁻⁵ | 6.4 (4.7–8.1) | 6.9 (5.2–8.4) | 6.6 (4.7–8.1) | 0.55 |
| %fPSA (%), median (IQR) | 14.0 (10.0–21.0) | 12.0 (9.0–16.0) | 17.0 (11.0–23.0) | 3.55×10⁻¹⁰ | 16.6 (11.6–22.0) | 13.7 (11.3–19.7) | 17.0 (12.4–22.2) | 0.09 |
| phi, median (IQR) | 48.4 (30.6–143.5) | 158.7 (64.6–448.7) | 34.0 (25.9–47.4) | 1.44×10⁻⁶ | 33.2 (24.5–41.5) | 44.4 (33.3–64.5) | 31.6 (23.9–39.3) | 3.9×10⁻⁴ |

The P values were calculated using Mann–Whitney U test to observe whether there is any significant difference between the distributions of two groups. PCa: prostate cancer; IQR: interquartile range; PSA: prostate-specific antigen; %fPSA: percentage of free prostate-specific antigen; phi: prostate health index

Table 2: Evaluation of the area under the receiver operation curves of different risk calculators in all patients

| Calculators | PCa (n=268)* | High-grade PCa (n=207)* | PCa (n=438)* | High-grade PCa (n=347)* |
|-------------|--------------|-------------------------|--------------|-------------------------|
| phi         | 0.85         | 0.85                    | 0.89         | 0.89                    |
| RC1         | 0.83         | 0.83                    | 0.84         | 0.84                    |
| RC2         | 0.89         | 0.89                    | 0.89         | 0.89                    |
| RC3         | 0.86         | 0.86                    | 0.86         | 0.86                    |
| RC4         | 0.895        | 0.895                   | 0.895        | 0.895                   |

*P referred to the significance between RC1 and other risk calculator, in training cohort (n=635); in validation cohort (n=1045); RC1 was built in the rule of logistic regression based on age, PSA, and %fPSA ( %fPSA were excluded while predicting high-grade PCa); RC2 was built in the rule of logistic regression RC based on age and phi; %fPSA was built in the rule of logistic regression RC based on age, PSA, %fPSA ( %fPSA were excluded while predicting high-grade PCa), and prostate volume; RC4 was built in the rule of logistic regression RC based on age, phi, and prostate volume. PCa: prostate cancer; PSA: prostate-specific antigen; phi: prostate health index; AUC: area under the receiver operating characteristic curve; CI: confidence interval; NA: not available; RC: risk calculator; %fPSA: percentage of free prostate-specific antigen.
We specifically evaluated the potential reduction of unnecessary biopsies using phi-based risk calculators compared with RC1 at the PCA risk threshold of 40% (approximately the positive biopsy rate in the Chinese biopsy population) (Table 6). For instance, with a sensitivity of 90%, phi, RC2, and RC4 could spare 28.0%, 27.8%, and 25.6%, respectively, of the patients in the validation cohort who did not have PCa from undergoing an unnecessary invasive procedure.

**DISCUSSION**

Our previous study showed that %p2PSA and its derivative phi provide additional value to predicting PCa and high-grade PCa in the Chinese biopsy population.\(^{10}\) This is the first study evaluating phi-based risk calculators for PCa in the Chinese population. All risk calculators were constructed based on the same previous population and were validated in an independent multicenter population. Our results indicated that the phi-based risk calculators (RC2 and RC4) exhibited superior discrimination and calibration in predicting PCa and high-grade PCa compared to the risk calculators without phi (RC1 and RC3). In addition, we also demonstrated that phi-based risk calculators provided added value for sparing unnecessary biopsies through a DCA.

The goal of the PCA diagnosis is to identify the presence of clinically significant disease while minimizing unnecessary biopsies. Combining PSA, PSA derivatives, other PCa biomarkers and patients’ clinical information would predict the risk of PCa much more precisely than using PSA alone. Risk calculators for PCa had been developed and...
Table 6: Number of unnecessary biopsies reduced by different prostate cancer risk calculators comparing with risk calculator 1

| RCs       | Biopsies reduced in training cohort (%) | Biopsies reduced in validation cohort* |
|-----------|----------------------------------------|---------------------------------------|
|           | Sensitivity=90%                         | Sensitivity=95%                        |
| Phi       | 21.00                                  | 28.00                                 |
| RC2       | 19.50                                  | 27.80                                 |
| RC3       | 8.90                                   | 9.80                                  |
| RC4       | 25.90                                  | 25.60                                 |

*The numbers of biopsies reduced were calculated at the sensitivity of 90 and 95 with the PCa risk threshold of 40. 1RC1 was built in the rule of logistic regression RC based on age, PSA, and IPSS (IPSS were excluded while predicting high-grade PCa); 2RC2 was built in the rule of logistic regression RC based on age and phi; 3RC3 was built in the rule of logistic regression RC based on age, PSA, IPSS (IPSS were excluded while predicting high-grade PCa), and prostate volume; 4RC4 was built in the rule of logistic regression RC based on age, phi, and prostate volume. PCa: prostate cancer; PSA: prostate-specific antigen; IPSS: International Prostate Symptom Score; RCs: risk calculators.

The phi-based risk calculators performed better than PSA-based risk calculators and demonstrated the net reduction in the number of biopsies. The net reduction in the number of biopsies was observed at PCa risk thresholds of approximately 20%, and it would be higher in a population with a higher risk of PCa. This indicates that these risk calculators might be suitable for clinically based cohorts.

## Author Contributions

YSW, QD, JX, and YHS conceived and designed the study. RN, XLL, FL, and HWJ contributed materials and analysis tools. YSW, JQ, HWJ, and YHS read and approved the final version of the manuscript. All authors declared no competing interests.

## Competing Interests

All authors declared no competing interests.
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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 phi, RC1, RC2, RC3, and RC4 for predicting prostate cancer in two cohorts and in subgroups with PSA ranged from 2.0 ng ml\(^{-1}\) to 10.0 ng ml\(^{-1}\). (a) ROC curves of phi, RC1, RC2, RC3, and RC4 for predicting prostate cancer in the training cohort. (b) ROC curves of phi, RC1, RC2, RC3, and RC4 for predicting prostate cancer in the validation cohort. (c) ROC curves of phi, RC1, RC2, RC3, and RC4 for predicting prostate cancer in the subgroup of the training cohort with PSA ranging from 2.0 ng ml\(^{-1}\) to 10.0 ng ml\(^{-1}\). (d) ROC curves of phi, RC1, RC2, RC3, and RC4 for predicting prostate cancer in the subgroup of the validation cohort with PSA ranging from 2.0 ng ml\(^{-1}\) to 10.0 ng ml\(^{-1}\). ROC: receiver operating characteristic; PSA: prostate-specific antigen.

Supplementary Figure 2: Net benefits of phi and phi-based risk calculators for predicting prostate cancer in the training cohort.
Supplementary Figure 3: Net benefits of phi and phi-based risk calculators for predicting prostate cancer in the validation cohort.