Original Article

Development and validation of multivariable biopsy-free nomograms to predict clinically significant prostate cancer in patients with prostate-specific antigen levels ≥20 ng/mL

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Background: Elevated prostate-specific antigen (PSA) levels often lead to prostate biopsies, which can result in overdiagnosis and complications, thereby increasing preoperative anxiety. This study aimed to develop and validate a novel biopsy-free diagnostic nomogram for accurate detection of clinically significant prostate cancer (csPCa) in patients with PSA levels ≥20 ng/mL.

Methods: The cohort of this retrospective analysis included patients with PSA levels ≥20 ng/mL who underwent evaluation including clinical variables, Prostate Imaging-Reporting and Data System (PI-RADS), prostate health index (PHI), and prostate-specific membrane antigen positron emission tomography-computed tomography (PSMA PET/CT). Nomogram performance was evaluated using the concordance index, calibration plot, decision curve analysis, and the area under the receiver operating characteristic curve (AUC).

Results: Of 684 patients, 478 and 206 were randomly assigned to the diagnostic and validation cohorts, respectively. Multivariable predictors of csPCa included age, PSA density, PI-RADS, location of suspicious lesion, %PSA variation ratio, and acute urinary retention. The foundational nomogram achieved AUCs of 0.930 and 0.911 for the training and validation sets, respectively. By integrating both PHI and PSMA maximum standardized uptake value (SUVmax), the diagnostic accuracy of the advanced nomogram improved significantly, with AUCs of 0.951 and 0.935 for the training and validation sets, respectively. Limitations included the lack of external validation and potential selection bias.

Conclusions: The biopsy-free nomogram presents a promising approach for accurate diagnosis of csPCa in patients with PSA levels ≥20 ng/mL. This non-invasive method can reduce unnecessary biopsies and enhance patient care by identifying those necessitating further evaluation and treatment.

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Introduction

Prostate cancer (PCa) is the most prevalent malignancy among males, accounting for the highest incidence and the second highest mortality rate. Screening of prostate-specific antigen (PSA) is pivotal for the diagnosis, staging, and surveillance of PCa. Elevated PSA levels, particularly ≥20 ng/mL, often indicate a higher tumor burden, which accounts for up to 70–89.8% of patients. However, traditional methods for screening of PSA frequently lack specificity, leading to overdiagnosis, unnecessary biopsies, and additional psychological and financial burdens to patients (1-3). Multiparametric magnetic resonance imaging (mpMRI) combined with the Prostate Imaging-Reporting and Data System (PI-RADS) version 2.1 has significantly enhanced assessment of clinically significant PCa (csPCa), although the limited positive predictive value still impacts overall effectiveness (4,5).

To address these challenges, emerging diagnostic modalities, such as the prostate health index (PHI), prostate-specific membrane antigen (PSMA), and positron emission tomography combined with computed tomography (PET/CT), can potentially improve the diagnostic accuracy of csPCa. The PHI is a more sensitive and specific diagnostic tool than total PSA, free PSA (fPSA), and [–2]proPSA [also known as p2PSA, a truncated form of proPSA (precursor PSA)]. Incorporation of the PHI into multivariable models has been reported to enhance detection of csPCa in patients with PSA levels of 4–20 ng/mL (6,7). Additionally, PSMA PET/CT, which utilizes radiolabeled small molecules targeting the cell surface glycoprotein overexpressed on PCa cells, provides whole body imaging specific for PCa. Quantitative assessment of PSMA expression in tumor tissues is a powerful tool for precise cancer localization and staging, as well as detection of disease recurrence and lymph node metastasis (8,9). Despite these advancements, there is still a scarcity of data on integrating multiple variables, including PI-RADS, PHI, and PSMA PET/CT, to predict suspected csPCa, especially for patients with PSA levels ≥20 ng/mL, for effective risk stratification and diagnosis to avoid unnecessary biopsies.

To address these clinical challenges, biopsy-free nomograms, incorporating clinical variables, PI-RADS grading, PHI, and maximum standardized uptake value (SUVmax) on PSMA PET/CT, were developed and validated to enhance the diagnosis of csPCa in highly

Highlight box

Key findings

- The development and validation of multivariable biopsy-free nomograms for predicting clinically significant prostate cancer (csPCa) in patients with prostate-specific antigen (PSA) levels ≥20 ng/mL present a promising approach to optimizing diagnosis and reducing unnecessary biopsies. By integrating clinical variables, imaging data, and biomarkers, this non-invasive method achieves high diagnostic accuracy, aiding in the precise identification of patients who require further evaluation and treatment.

What is known and what is new?

- Elevated PSA levels often lead to prostate biopsies, which can result in overdiagnosis, increased preoperative anxiety, and complications. Although there are existing methods for assessing prostate cancer risk, most involve invasive procedures.
- This study introduces a novel biopsy-free diagnostic nomogram capable of accurately detecting csPCa in patients with PSA levels ≥20 ng/mL. By combining clinical variables, Prostate Imaging-Reporting and Data System (PI-RADS) scores, prostate health index (PHI), and prostate-specific membrane antigen positron emission tomography-computed tomography (PSMA PET/CT), the nomogram significantly enhances diagnostic accuracy, achieving areas under the receiver operating characteristic curve (AUC) of 0.951 and 0.935 for the training and validation sets, respectively.

What is the implication, and what should change now?

- This biopsy-free method offers a more cost-effective and non-invasive solution, reducing unnecessary biopsies and improving the overall patient experience.
- Current medical practices should adopt this nomogram to more accurately identify patients requiring further evaluation and treatment, thereby enhancing prostate cancer management and patient care.
- Future external validation studies are essential to reinforce the clinical applicability and broader implementation of this model.

suspicious populations (PSA ≥20 ng/mL) to avoid unnecessary biopsies. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-533/rc).

Methods

Study population

The cohort of this retrospective study included 684 patients from two prospective trials (ChiCTR2200066455 and ChiCTR2000038696) conducted at The Second Hospital of Tianjin Medical University between January 2015 and July 2023. The inclusion criteria were: (I) age ≥18 years; (II) serum total PSA levels ≥20 ng/mL; (III) completion of mpMRI with PI-RADS version 2.1 of ≥3 lesions; and (IV) confirmed pathological results. The exclusion criteria were: (I) contraindications or inability to undergo prostate mpMRI; (II) previous history of PCa; (III) prior biopsy; and (IV) contraindication for biopsy or indeterminate pathological results. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The Second Hospital of Tianjin Medical University (No. KY2025K170) and individual consent for this retrospective analysis was waived due to the retrospective nature.

Collection of clinical information

The clinical information collected encompassed patient demographics, including age and body mass index (BMI), as well as medical history of hypertension, diabetes, and acute urinary retention (AUR) (within 1 month before biopsy). Additionally, data on prostate-specific parameters, such as prostate volume (PV), initial PSA within 1 month prior to biopsy, the last PSA measurement before biopsy, fPSA, the ratio of free to total PSA (f/tPSA), and PSA density (PSAD), were retrieved from medical records. Other recorded details comprised findings from a digital rectal examination (DRE), localization of suspicious lesions on mpMRI, PI-RADS score, PHI, SUVmax on PSMA PET/CT, and pathological outcomes. The %PSA variation ratio (PSAVR) was calculated as: (last PSA before biopsy – initial PSA)/initial PSA × 100%. Serum concentrations of total PSA, fPSA, and p2PSA were determined using the Access 2 analyzer (Beckman Coulter, Brea, CA, USA). The percentage of p2PSA (%p2PSA) was calculated as: p2PSA (pg/mL)/fPSA (μg/L) × 1,000 × 100. PHI was calculated using the formula: p2PSA/fPSA × √PSA. PV was calculated as (maximum anteroposterior diameter × maximum transverse diameter × maximum longitudinal diameter) × 0.52, as assessed by MRI.

Protocol for mpMRI and PSMA PET/CT

For all eligible patients, mpMRI examinations were conducted prior to biopsy using a 3.0T Avanto scanner (Siemens AG, Erlangen, Germany) without the use of an endorectal coil. Two urological radiologists, each with over 5 years of experience in analyzing prostate mpMRI and an annual workload of approximately 500 prostate MRIs, assessed the results. The recommended dosage of ^{68}Ga-PSMA-11 was typically 1.5–3.0 MBq/kg. The results of the PSMA PET examinations were interpreted by a minimum of two experienced nuclear medicine physicians, who considered various factors, including PSMA uptake patterns, areas exhibiting heightened PSMA uptake, as a potential indicator of PCa, and the intensity, pattern, and extent of ^{68}Ga-PSMA-11 uptake to gain insights into the nature of the malignancy, in addition to uptake in extraprostatic regions, such as the lymph nodes and other organs, suggestive of potential metastasis. SUVs were utilized as a common metric for quantification of PSMA uptake.

Histopathological analysis

Participants underwent either transperineal prostate biopsy, radical prostatectomy, or both procedures. The final ISUP score was determined as the highest score from either biopsy or radical prostatectomy. CsPCa was defined as prostate tissue samples with a Gleason score of ≥3+4. Because the Gleason score was our main indicator of clinical significance, cribriform pattern and intraductal carcinoma of the prostate were not included in the csPCa definition. Non-csPCa, defined as the absence of csPCa, included cases of benign prostatic hyperplasia, prostatitis, and normal prostate tissue with calcification. To ensure accuracy and consistency, at least two experienced uropathologists, blinded to both patient groups and biopsy methods, reviewed all pathology results. This approach minimized potential bias.

Statistical analysis

Participants were randomly allocated to the training group or validation group at a ratio of 7:3, followed by assessment of the comparability between the two groups. Non-

normally distributed counted data were analyzed using descriptive statistics and are presented as the median and interquartile range, while categorical data were presented as numbers (n) and percentages (%). Non-normally distributed and categorical data were analyzed using the Mann-Whitney *U* test, Wilcoxon rank-sum test, and Chi-squared test, respectively. The least absolute shrinkage and selection operator (LASSO) regression analysis was applied for variable selection and regularization. The optimal lambda value, crucial for constructing a model with optimal performance and minimal variables, was determined through 10-fold cross-validation with R software (https://www.r-project.org/). Subsequently, significant predictive factors identified by LASSO regression were incorporated into multivariate logistic regression analysis to establish the predictive model. A nomogram was developed using the model coefficients to predict the probability of specific outcomes, and the discriminatory capacity of the model was assessed using the receiver operating characteristic (ROC) curve, area under the curve (AUC), and concordance index (C-index). Data analysis was performed using IBM SPSS Statistics for Windows (version 23.0; IBM Corporation, Armonk, NY, USA) and R software (version 3.5.1). A probability (P) value <0.05 was considered statistically significant.

Results

Participant characteristics

Of the 684 study participants, 82.3% had csPCa (*Table 1* and Figure S1). The study participants were assigned to the training group (n=478) or the testing group (n=206) at a ratio of 7:3. There was no significant difference in clinical variables between these groups (Table S1). Among the 209 individuals who underwent PHI, PSMA PET/CT, and PI-RADS grading, the prevalence of csPCa was 68.9% (Table S2). Of these 209 individuals, 147 were assigned to the training group and 62 to the testing group. There was no significant difference in baseline characteristics between these groups (Table S3).

Development and validation of biopsy-free nomograms

For the fundamental model, LASSO regression identified six variables (age, PSAD, PI-RADS score, location, AUR, PSAVR, and PV) with non-zero coefficients (Figure S2). Subsequent multivariable logistic regression identified age, PSAD, PI-RADS score, PSAVR, location of suspicious lesion, and AUR as independent predictors of csPCa (*Table 2*). These independent predictors were then integrated into a nomogram for construction of a comprehensive model. The fundamental model demonstrated high diagnostic efficacy, with AUCs of 0.930 and 0.911 for the training and testing sets, respectively. These performance metrics exceeded those of predictions based solely on individual variables (*Figures 1*,*2*).

The advanced model identified PHI, PI-RADS, and PSMA SUVmax as independent predictive factors. The AUCs of the training and validation sets increased to 0.951 and 0.935, respectively. This significant improvement underscored the enhanced predictive accuracy of the advanced model as compared to the fundamental model (*Figures 1*,*2*). Throughout the validation process, calibration curves exhibited excellent consistency across both the training and testing sets, further affirming the robust performance of both the fundamental and advanced models (Figure S3).

Validation of the predictive model

Decision curve analysis (DCA) was employed to evaluate the clinical utility of the predictive model. The DCA curve illustrated the net benefit of using the model to predict csPCa across various threshold probabilities in both the training and testing datasets (*Figure 3*). Comprehensive analysis of various thresholds was conducted to determine the optimal cutoff values of PSAD, PHI, SUVmax, and nomograms to predict the occurrence of csPCa in highly suspicious patients with PSA levels ≥20 ng/mL (*Table 3*). Using a cutoff of 51.21% for the advanced model, 91.16% of patients were eligible for a biopsy-free approach, with a trade-off of missing 4.08% of patients with csPCa.

Discussion

Despite ongoing updates in prostate biopsy methods, a biopsy-free approach is increasingly being considered for high-risk PCa patients, such as those with PI-RAD score ≥4 or PSA ≥20 ng/mL (10,11). For instance, our recent study developed and validated three biopsy-free nomograms using various clinical variables, PHI, and SUVmax to more accurately predict csPCa in biopsy-naïve men with PI-RADS ≥4 lesions. The advanced nomogram, incorporating PHI and PSMA SUVmax, achieved an AUC of 0.955, potentially reducing unnecessary biopsies

Table 1 Patient characteristics (n=684)

Parameters	All patients (n=684)	csPCa (n=563)	Non-csPCa (n=121)	P
Age, years	71.00 (66.00–76.00)	72.00 (66.00–77.00)	70.00 (64.00–74.00)	<0.001*
BMI, kg/m^2	24.22 (22.32–26.41)	24.22 (22.31–26.30)	24.34 (22.36–27.24)	0.30
PSA, ng/mL	56.79 (30.95–145.37)	78.05 (37.50–184.60)	28.11 (23.16–37.56)	<0.001*
PV, mL	60.85 (41.45–82.67)	59.53 (40.99–79.98)	67.39 (50.19–100.42)	0.004*
PSAD, ng/mL^2	1.14 (0.57–2.65)	1.37 (0.72–3.23)	0.44 (0.30–0.64)	<0.001*
PSAVR, %	9.41 (4.88–18.77)	8.40 (4.05–15.22)	23.71 (10.99–39.16)	<0.001*
PI-RADS score				<0.001*
3	86 (12.6)	27 (4.8)	59 (48.8)	
4	136 (19.9)	93 (16.5)	43 (35.5)	
5	462 (67.5)	443 (78.7)	19 (15.7)	
Localization of suspicious lesion				<0.001*
PZ	317 (46.3)	229 (40.7)	88 (72.7)	
TZ	57 (8.3)	46 (8.2)	11 (9.1)	
PZ + TZ	270 (39.5)	260 (46.2)	10 (8.3)	
Others	40 (5.8)	28 (5.0)	12 (9.9)	
ISUP score				<0.001*
1	37 (5.4)	0	37 (30.6)	
2	28 (4.1)	28 (5.0)	0	
3	53 (7.7)	53 (9.4)	0	
4	234 (34.2)	234 (41.6)	0	
5	248 (36.3)	248 (44.0)	0	
DRE	587 (85.8)	489 (86.9)	98 (81.0)	0.09
AUR	188 (27.5)	124 (22.0)	64 (52.9)	<0.001*
Diabetes	135 (19.7)	114 (20.2)	21 (17.4)	0.50
Hypertension	277 (40.5)	239 (42.5)	38 (31.4)	0.03*

Data are presented as median (IQR) or n (%). The P values were calculated using the Chi-squared test (categorical variables) and Mann-Whitney *U* test (continuous variables). *, P values <0.05. Others: lesions beyond the peripheral and transition zones. AUR, acute urinary retention; BMI, body mass index; csPCa, clinically significant prostate cancer; DRE, digital rectal examination; IQR, interquartile range; ISUP, International Society of Urological Pathology; PCa, prostate-specific antigen; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; PSAVR, %PSA variation ratio; PV, prostate volume; PZ, peripheral zone; TZ, transition zone.

by 92.41% while only missing 1.53% of csPCa cases (12). Furthermore, in this study, we created two biopsy-free prostate nomograms—the fundamental and the advanced—using clinical data and imaging parameters from patients with PSA ≥20 ng/mL. The fundamental nomogram included six parameters: age, PSAD, PI-RADS score, PSAVR, location of the suspicious lesion, and AUR. These parameters are straightforward and suitable for primary healthcare settings. For instance, age is a significant factor; the probability of PCa increases with age, while younger patients have a lower detection rate (13,14). Prostate tumors are primarily located in the peripheral zone, which mpMRI can easily detect. However, radiation oncologists may be more interested in the dominant intraprostatic lesion than

Table 2 Multivariable logistic regression analysis to predict clinically significant prostate cancer

Parameters	Model 1			Model 2		
	β-coefficient	OR (95% CI)	P	β-coefficient	OR (95% CI)	P
Age, years						
<60		Reference		–	–	–
60–80	0.835	2.31 (0.76–7.01)	0.10	–	–	–
>80	1.957	7.08 (1.26–39.58)	0.03*	–	–	–
PHI	–	–	–	0.014	1.014 (1.005–1.024)	0.005*
PSMA PET/CT SUVmax	–	–	–	0.165	1.179 (1.068–1.303)	0.001*
AUR						
No		Reference		–	–	–
Yes	–1.047	0.351 (0.17–0.725)	0.01*	–	–	–
PSAD, ng/mL^2						
0-0.499		Reference			Reference	
0.500–0.999	1.308	3.80 (1.59–8.58)	0.002*	–0.208	0.813 (0.183–3.602)	0.80
1.000–1.999	2.191	8.94 (8.79–28.63)	<0.001*	1.454	4.280 (0.602–30.440)	0.10
≥2.000	3.274	26.41 (5.04–138.33)	<0.001*	–0.762	0.467 (0.022–10.013)	0.60
%PSA variation ratio						
≤10		Reference		–	–	–
>10	–0.792	0.453 (0.22–0.91)	0.03*	–	–	–
PI-RADS score						
3		Reference			reference	
4	1.278	3.58 (1.53–8.44)	0.003*	0.502	1.652 (0.355–7.687)	0.50
5	2.552	12.84 (5.36–30.75)	<0.001*	1.879	6.544 (1.254–34.145)	0.03*
Localization of suspicious lesion						
PZ		Reference		–	–	–
TZ	–0.088	0.92 (0.33–2.52)	0.90	–	–	–
PZ + TZ	1.493	4.45 (1.59–12.43)	0.004*	–	–	–
Others	0.447	1.56 (0.41–5.99)	0.50	–	–	–

*, P values <0.05. Model 1: fundamental model; Model 2: advanced model. Others: lesions beyond the peripheral and transition zones. AUR, acute urinary retention; CI, confidence interval; csPCa, clinically significant prostate cancer; OR, odds ratio; PET, positron emission tomography; PHI, prostate health index; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; PSMA, prostate-specific membrane antigen; PZ, peripheral zone; SUVmax, maximum standardized uptake value; TZ, transition zone.

just csPCa. Multivariate analysis revealed that AUR and % variation ratio were protective factors for csPCa, and these factors should be noted when taking the medical history. Hypertension and diabetes were not significantly associated with csPCa, and family history was not included in this study. Traditional markers like PSA are widely used but lack precision in identifying aggressive PCa, especially in patients with enlarged PVs (15,16). Therefore, PSAD

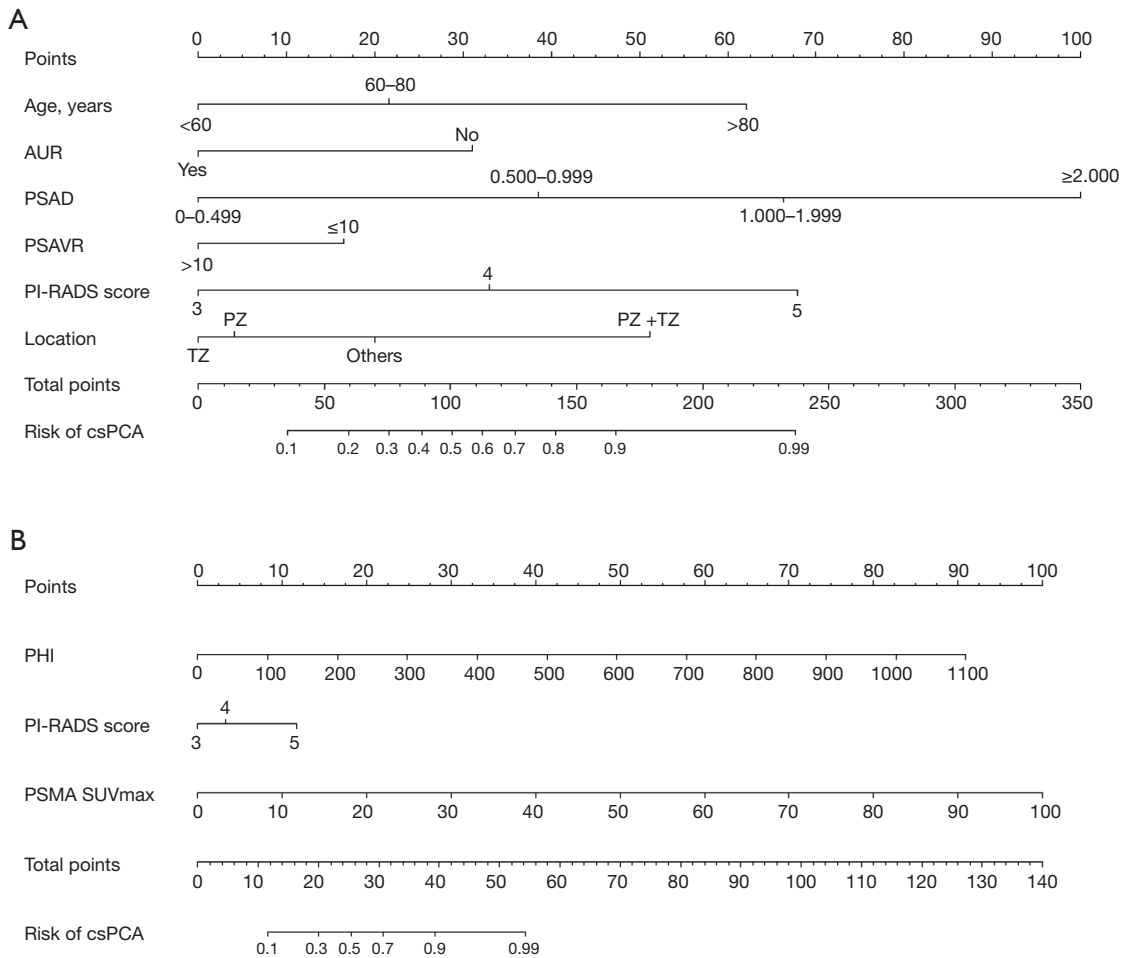

Figure 1 The biopsy-free nomograms for clinically significant prostate cancer in the fundamental (A) and advanced (B) models. AUR, acute urinary retention; csPCa, clinically significant prostate cancer; PHI, prostate health index; PI-RADS, Prostate Imaging-Reporting and Data System; PSAD, prostate-specific antigen density; PSAVR, %PSA variation ratio; PSMA, prostate-specific membrane antigen; PZ, peripheral zone; SUVmax, maximum standardized uptake value; TZ, transition zone.

was included in the fundamental model to estimate csPCa. In contrast, the advanced nomogram incorporates medical technologies such as PHI and PSMA PET/CT, which are mainly applicable in larger medical centers. PSA derivatives like PHI have been developed to improve specificity. Studies have demonstrated PHI's potential in differentiating benign and malignant diseases (17,18). PHI, PI-RADS, and PSMA SUVmax were identified as key predictive factors in the advanced model. PHI, ranked second in importance, has a value close to that of PSMA PET/CT. Removing PHI from the advanced model reduced the AUC from 0.951 to 0.892, underscoring its critical role in diagnostic accuracy. The true value of PHI, apart from the two imaging modalities, will be further investigated in future cohorts. For example, in 2021, Stejskal *et al.* reported an AUC of 0.697 for PHI to predict csPCa, surpassing PSA (0.595), PI-RADS (0.625), and PSAD (0.649), with a significant improvement in predictive accuracy when combined with PI-RADS (19). Zhou *et al.* developed a diagnostic model incorporating PHI and PI-RADS in a multicenter prospective study, achieving an AUC of 0.89 for csPCa detection in the validation cohort, thereby avoiding 55.91% of biopsies while only missing 1.82% of csPCa cases (20). A meta-analysis comprising 60 studies involving 14,255 patients found that the sensitivity and specificity of PHI to predict csPCa were 87.4% and 56.9%, respectively (6). These studies collectively suggest the potential of incorporating PHI with predictive tools to enhance prediction of csPCa.

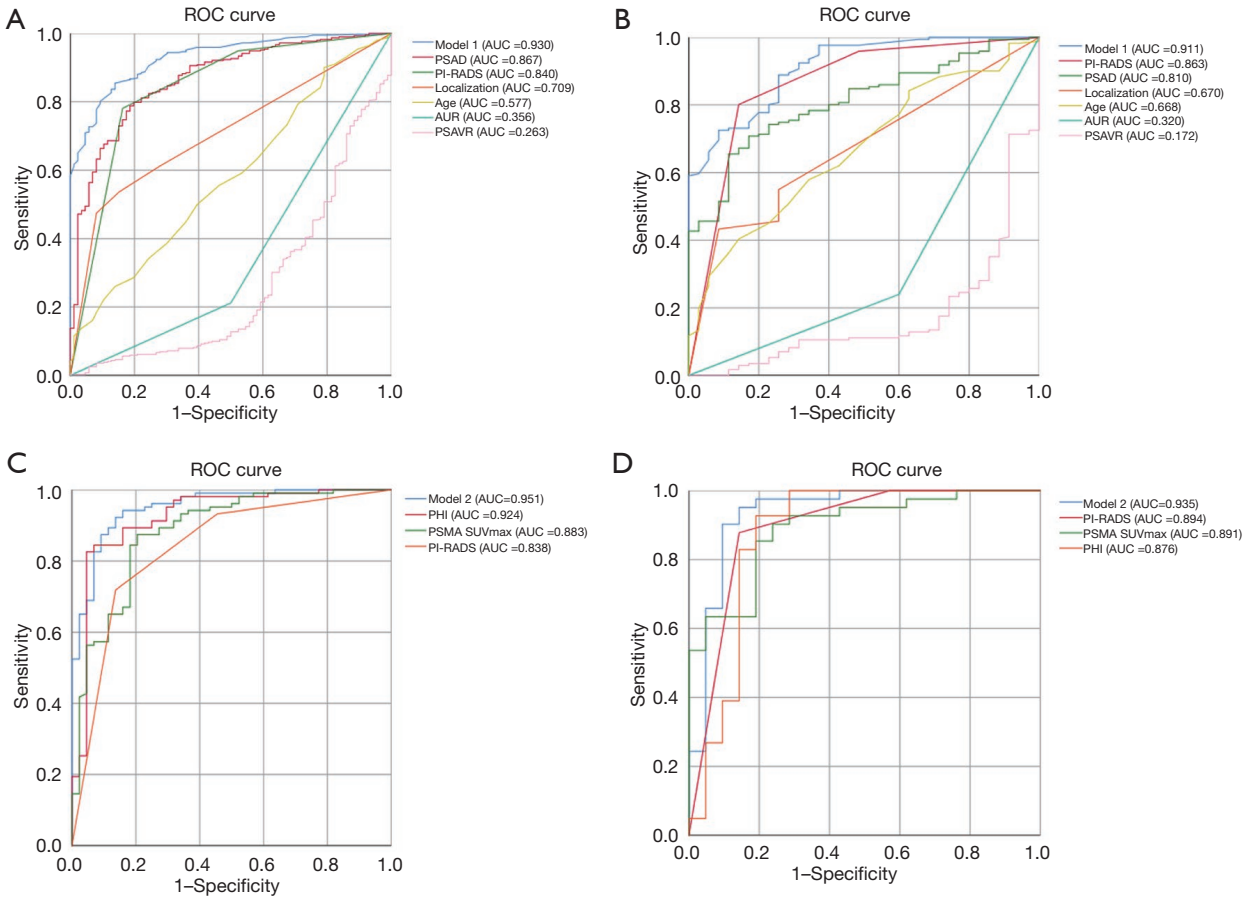

Figure 2 AUC of two nomograms for both the training and validation sets for highly suspected PCa (PSA ≥20 ng/mL). (A,B) The fundamental model includes age, PSAD, PSAVR, PI-RADS, and localization of suspicious lesion. (C,D) The advanced model includes PHI, PI-RADS, and SUVmax. Model 1: fundamental model; Model 2: advanced model. AUC, area under the curve; AUR, acute urinary retention; PCa, prostate cancer; PHI, prostate health index; PI-RADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; PSAVR, %PSA variation ratio; PSMA, prostate-specific membrane antigen; ROC, receiver operating characteristic; SUVmax, maximum standardized uptake value.

However, there is not yet a consensus on a cutoff value for PHI, as values range from 21.33 to 63.9 across studies due to substantial heterogeneity (6). Nevertheless, for patients with PSA levels exceeding 20 ng/mL, effective utilization of PHI should be considered to guide diagnostic and therapeutic decisions. Based on the calculated Youden index, a PHI cutoff value of 149.23 exhibited a sensitivity of 82.6% and specificity of 92.3%, enabling avoidance of 92.3% of biopsies while only missing 17.36% of csPCa cases. This outcome is encouraging, as current practices primarily employ PHI to differentiate patients in the PSA gray zone, whereas this study provides evidence for the use of PHI to guide diagnosis and treatment decisions for individuals with elevated PSA levels.

In addition to serum biomarkers, mpMRI is a recognized standard for diagnosis of csPCa. In this study, we utilized mpMRI-related parameters, such as PV, PSAD, PI-RADS score, and tumor location. Other mpMRI parameters, like the apparent diffusion coefficient (ADC) value, may also hold significant diagnostic value. However, the high false positive rate remains problematic for predicting low-to-intermediate-risk lesions within the prostate. For instance, the detection rates of csPCa in patients with PI-RADS scores of 3, 4, and 5 were reportedly 21%, 39%, and 73%, respectively (21,22). PSMA PET/CT has gained substantial support for staging csPCa and treating post-recurrence cases. It can detect a significant number of patients with lymph node and bone metastases, which can negatively

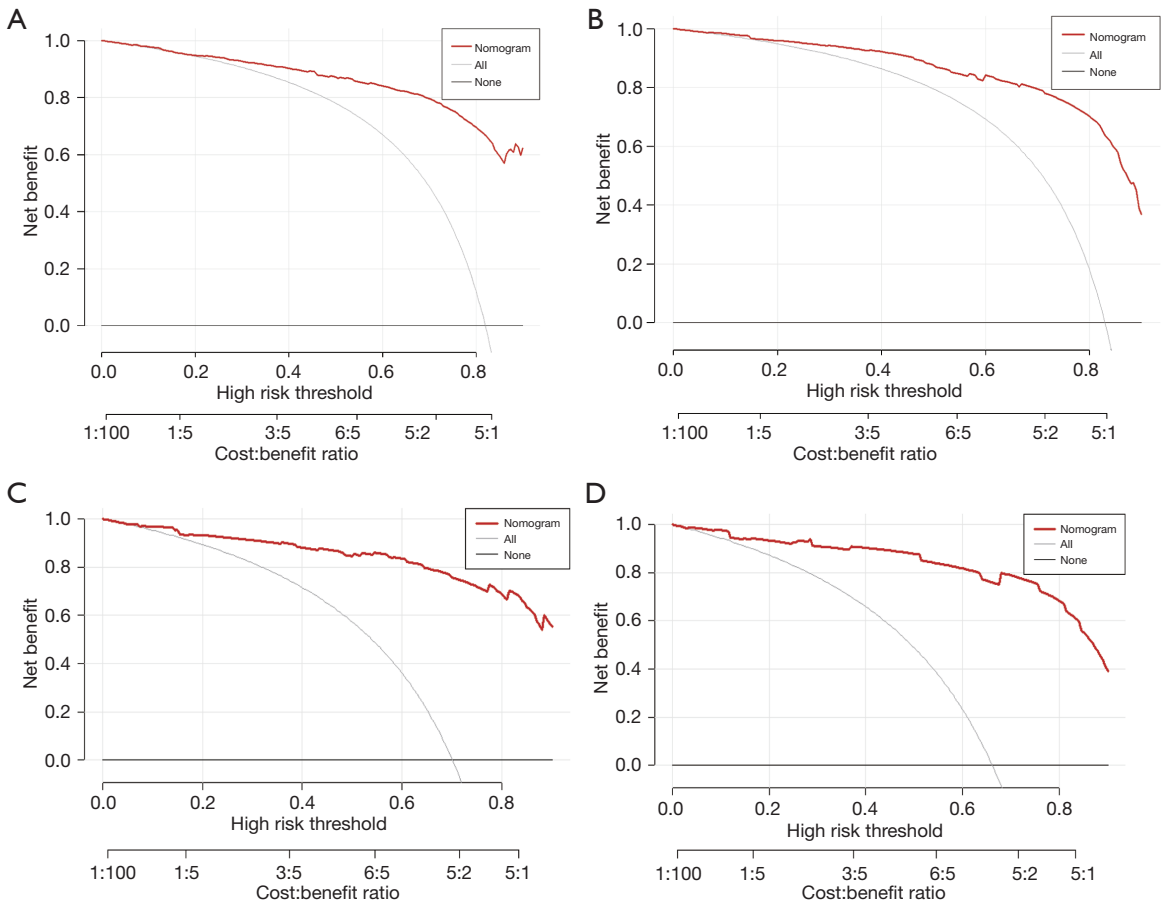

Figure 3 DCA for two nomograms to predict csPCa in the both training and validation sets. (A,B) DCA of nomogram 1 predictions in the training and validation sets. (C,D) DCA of nomogram 2 predictions in the training and validation sets. csPCa, clinically significant prostate cancer; DCA, decision curve analysis.

Table 3 Predictive performance of different cut-off values of PSAD, PHI, SUVmax, and nomogram

Nomogram	Decision to biopsy	Sensitivity, %	Specificity, %	PPV, %	NPV, %	% avoided biopsy	% missed csPCa
Model 1	PSAD† ≥0.67 ng/mL^2	78.83	81.40	95.08	45.75	79.29	17.36
	PSAD‡ ≥0.33 ng/mL^2	97.19	34.88	87.19	73.17	85.98	2.30
	NP† ≥80.00%	85.46	86.05	96.54	56.49	85.56	11.92
	NP‡ ≥57.41%	94.39	69.77	93.43	73.17	89.96	4.60
Model 2	PHI† ≥147.28	82.52	95.45	97.70	70.00	86.40	12.24
	PHI‡ ≥77.09	98.10	65.90	87.10	93.54	88.44	1.36
	SUVmax† ≥8.21	87.38	79.55	90.91	72.91	85.03	8.84
	SUVmax‡ ≥6.86	94.17	63.64	85.84	82.35	85.03	4.08
	NP† ≥53.55%	92.23	86.36	94.06	82.61	90.48	5.44
	NP‡ ≥51.21%	94.17	84.09	93.27	86.05	91.16	4.08

†, first threshold (cut-off value at maximum Youden index); ‡, second threshold (cut-off value at maximum accuracy csPCa). Model 1: fundamental model; Model 2: advanced model. csPCa, clinically significant prostate cancer; NP, nomogram points; NPV, negative predictive value; PHI, prostate health index; PPV, positive predictive value; PSAD, prostate-specific antigen density; SUVmax, maximum standardized uptake value.

impact survival beyond just identifying csPCa. PSMA expression levels have been correlated with elevated PSA levels and higher Gleason scores (23-25). A cross-sectional study conducted by Matushita *et al.* reported that the sensitivity and specificity of ^{68}Ga-PSMA PET were 0.90 and 0.90, respectively, for diagnosis of csPCa, and 0.93 and 0.96, respectively, for staging (26). The PRIMARY study found that the negative predictive value and sensitivity of mpMRI were improved by combining PSMA PET/CT (91% *vs.* 72% and 97% *vs.* 83%, respectively) (27). Additionally, a robust correlation was identified between very high SUVmax values and csPCa, underscoring the significance of utilizing SUVmax with PSMA PET/CT as a preliminary diagnostic and prognostic tool (28). The AUCs of the PRIMARY and PI-RADS scoring systems were 0.85 [95% confidence interval (CI): 0.81–0.89] and 0.76 (95% CI: 0.71–0.81), respectively, indicating superior accuracy of the PRIMARY score for clinical diagnosis of csPCa (29). In the present study, the AUC of PSMA SUVmax was 0.883 for patients with PSA levels of 20 ng/mL. When employing an SUVmax cutoff of 8.21, the sensitivity and specificity were 97.38% and 79.55%, respectively, thus avoiding 85.03% of csPCa diagnoses while missing only 8.84%.

There has been no report on simultaneous integration of PHI and PSMA PET/CT for diagnosis of csPCa, especially for patients with highly suspicious PCa seeking a biopsy-free approach. In contemporary clinical practice, PHI testing can distinguish patients with ambiguous PSA levels, while PSMA PET/CT is indispensable for postoperative staging and detection of biochemical recurrence. However, elevated PSA levels, particularly exceeding 20 ng/mL, reliably indicate csPCa (2,3). Consequently, we propose synergizing PHI and PSMA PET/CT to formulate a biopsy-free nomogram to predict csPCa in highly suspicious PCa patients to avoid unnecessary biopsies. For this purpose, two nomograms were developed and validated: one incorporating age, PSAD, changes, PI-RADS, and MRI location, and another focusing on PHI, PI-RADS, and SUVmax. These nomograms demonstrated robust predictive ability for high-risk patients, amalgamating traditional and advanced factors for well-informed decision-making for management of PCa.

While these findings are promising, there are several limitations in this study that warrant acknowledgment. First, the retrospective nature of the study may have introduced patient selection bias. Second, the reliance on a small sample size from a single center is also a notable constraint. Third, the interpretation of MRI and PSMA results was performed by experienced radiologists, thus affecting generalizability. Additionally, variations in PSMA tracer uptake may also affect SUVmax values. To enhance generalizability, future prospective, multi-center, randomized, clinical trials should be undertaken, employing standardized MRI and PSMA protocols. Fourth, external validation using independent datasets is essential to ensure the reliability and applicability of the developed models across diverse patient populations.

Conclusions

A biopsy-free diagnostic model that integrated both PHI and PSMA PET/CT was developed and validated to minimize unnecessary biopsies for csPCa in patients with PSA levels exceeding 20 ng/mL. These findings underscored the potential of this approach to enhance diagnostic accuracy and streamline patient management, presenting a promising avenue to reduce dependence on invasive procedures and improve patient care for evaluation of csPCa.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-533/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-533/coif). The authors

have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of The Second Hospital of Tianjin Medical University (No. KY2025K170) and individual consent for this retrospective analysis was waived due to the retrospective nature.

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