Evaluating the Role of Morphological Parameters in the Prostate Transition Zone in PHI-Based Predictive Models for Detecting Gray Zone Prostate Cancer

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ABSTRACT

BACKGROUND: The early detection of clinically significant prostate cancer (csPCa) through the integration of multidimensional parameters presents a promising avenue for improving survival outcomes for this fatal disease. This study aimed to assess the contribution of prostate transition zone (TZ) to predictive models based on the prostate health index (PHI), with the goal of enhancing early detection of csPCa in the prostate-specific antigen (PSA) gray zone.

METHODS: In this observational cross-sectional study, a total of 177 PSA gray zone patients (total prostate-specific antigen [tPSA] level ranging from 4.0 to 10.0 ng/mL) were recruited and received PHI detections from August 2020 to March 2022. Prostatic morphologies especially the TZ morphological parameters were measured by transrectal ultrasound (TRUS).

RESULTS: Univariable logistic regression indicated prostatic morphological parameters including total prostate volume (PV) indexes and transitional zone volume indexes were all associated with csPCa ($P < .05$), while the multivariable analysis demonstrated that C-reactive protein (CRP), PHI, PHI density (PHID), and PHI transition zone density (PHI-TZD) were the 4 independent risk factors. The receiver-operating characteristic (ROC) curve analysis suggested that integrated predictive models (PHID, PHI-TZD) yield area under the curves (AUCs) of 0.9135 and 0.9105 in csPCa prediction, which shows a relatively satisfactory predictive capability compared with other predictors. Moreover, the PHI-TZD outperformed PHID by avoiding 30 patients' unnecessary biopsies while maintaining 74.36% specificity at a sensitivity of 90%. Decision-curve analysis (DCA) confirmed the comparable performance of the multivariable full-risk prediction models, without the inclusion of the net benefit, thereby highlighting the superior diagnostic efficacy of PHID and PHI-TZD in comparison with other diagnostic models, in both univariable and multivariable models.

CONCLUSION: Our data confirmed the value of prostate TZ morphological parameters and suggested a significant advantage for the TZ-adjusted PHI predictive model (PHI-TZD) compared with PHI and PHID in the early detection of gray zone csPCa under specific conditions.

KEYWORDS: PSA gray zone, clinically significant prostate cancer, prostate health index, transition zone

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Introduction

Serum prostate-specific antigen (PSA) screening has been the widely used mainstay for prostate cancer (PCa) initial detection in the last decades.[1,2] The assessment of circulating total prostate-specific antigen (tPSA) levels, which encompasses a significant proportion of complexed PSA and the residual 5% to 20% of free prostate-specific antigen (fPSA), has been established and used as a customary clinical biomarker for prostate oncogenesis.[3] Despite the extensive comprehension of the heterogeneous nature of PCa and the need for a comprehensive risk-benefit analysis in invasive diagnosis, PSA screening has increasingly been recognized as a highly sensitive but poorly specific tool in practical settings. This inadequacy is particularly evident in the "PSA grey zone," where serum tPSA levels range from 4.0 to 10.0 ng/mL, and diagnostic specificity for identifying csPCa is low, ranging from 25% to 40%.[4,5] Therefore, changes in diagnostic strategies impetus the priorities, from overall tumor onset to precisely recognizing those clinically significant or aggressive PCa with higher risk.[6-8] Consequently, developing novel methods of risk stratification has become one of the main concerns in improving PSA-based PCa diagnostic models.

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Considering the special value of PSA in PCa diagnosis, several mathematical formulas with PSA derivates have been introduced to cancer prediction, including %fPSA (fPSA/tPSA), %p2PSA (p2PSA/fPSA), and PHI.[9-11] Among them, PHI has been confirmed to provide an unparalleled predictive utility for detecting overall PCa and csPCa in participants of different races or ethnicity worldwide.[12] Besides, to reduce the potential bias caused by serological category indicators alone, more researchers have searched for extra serum-based indices or brought prostatic morphological parameters from TRUS or multiparametric magnetic resonance imaging to optimize prediction models, including serum cytokines, PSA density (PSAD), PSAD modified by prostate transition zone volume (PSATZD), PHID, modified PHI density (mPHID), and other multivariable predictive models.[13-17] Noteworthy, several studies have reported that incorporating the prostate transition zone volume (PTZV) as a supplementary component of a PSA-based predictive model can effectively decrease the number of unnecessary biopsies while simultaneously maintaining a high level of sensitivity in detecting PCa.[15,18,19] The tPSA, however, is more prostate organ-specific rather than cancer-specific and is often associated with peripheral zone (PZ) cancer rather than TZ hyperplasia.[20,21] Thus, prior research asserting the superior diagnostic efficacy of TZ volume-adjusted indices for detecting cancer is subject to debate and requires further substantiation to evaluate the applicability of PTZV in PHI-based univariable and multivariable models for detecting gray zone PCa. Moreover, the introduction of prostatic indolent disease surrogate markers like benign prostatic hyperplasia (BPH)-related immunology indices into multivariate predictive models to enlarge the distinguishment between BPH and PCa may further increase the utility of the diagnostic model at this stage.[22]

Therefore, we conducted this cross-sectional study to investigate the additional diagnostic usefulness of prostate TZ morphological parameters and immunology-related indices. In addition, we aimed to compare the impact of PHI and its predictive models adjusted for prostatic volume on the detection of csPCa within the PSA gray zone.

Methods

Study design and cohort

This was an observational cross-sectional study conducted in a senile male cohort from August 2020 to March 2022 in Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. A final of 177 patients including 52 csPCa, 8 non-csPCa, and 117 BPH were confirmed to be recruited after getting written informed consent. All those participations were suspicious of gray zone PCa and corresponded to the following conditions: (1) tPSA level ranging from 4.0 to 10.0 ng/mL; (2) digital rectal examination (DRE) proved no abnormal finding existence; and (3) after collecting blood samples, each patient underwent a biopsy guided by TRUS with at least 12 cores. The gold standard was the pathology outcome of systematic prostate biopsies. The exclusion criteria were as follows: (1) incomplete records of demographics and clinical characteristics; (2) incomplete records of any serum antigen level (tPSA, fPSA, [−2] pro-prostate-specific antigen [p2PSA], PHI), pathology outcomes, or prostatic morphological parameters (especially prostate TZ-related indices); (3) previous history of PCa, treatment with 5-α reductase inhibitors; and (4) inability to sign an informed consent. Clinically significant PCa was defined as PCa with a Gleason score (GS) ⩾7. Once informed consent has been obtained, blood samples were collected for the measurement of PSAs before biopsies. Anonymized serum samples were aliquoted and stored. The prostate morphological parameters were obtained by TRUS before prostate biopsy.

Variables and outcomes

Beckman Coulter DxI800 Unicel Immunoassay system (Beckman Coulter, Shanghai, China) was used to perform the PHI including the tPSA, (p2PSA), and fPSA. The PHI score was determined by the PHI test: $PHI = (p2PSA/fPSA) \times \sqrt{tPSA}$. The prostate morphological parameters were measured by TRUS, including transverse diameter (TRD), longitudinal diameter (LD), anteroposterior diameter (APD), and total prostate volume (PV or TPV). We also measured TZ prostate morphological parameters including transition zone transverse diameter (TZ-TRD), transition zone longitudinal diameter (TZ-LD), transition zone anteroposterior diameter (TZ-APD), and transition zone prostate volume (PTZV). The standard ellipsoid formula ($[\pi/6] \times$ length $\times$ width $\times$ height) was used to estimate TPV and PTZV. Other derivative variables were calculated as follows: (1) PHI density (PHID): PHI/PV and (2) PHI transition zone density (PHI-TZD): PHI/PTZV.

Statistical analysis

This study employed univariate and multivariate logistic regression with binomial parameters to examine the relationship between covariates and csPCa. To assess the predictive accuracy of various models for csPCa in the PSA gray zone, Decision curve analysis (DCA), receiver-operating characteristic (ROC) curve analysis, and area under the receiver-operating characteristic curve (AUC) were used. The statistical analyses were performed using MedCalc (version 15.2.2) and R (version 4.0.0).

Results

The pathological outcome was a gold standard for the patient's diagnosis in this study. Altogether, the positive biopsy rate was 33.8% (60/177) in all participants with complete prostate TZ-related indices. Among 60 patients diagnosed with PCa, 8 (4.5%) men with GS 6 were diagnosed as non-csPCa while 52 (29.3%) men were diagnosed as csPCa according to the biopsy findings. Table 1 displays a comprehensive overview of the clinicopathologic characteristics of the participants. Notably,

Table 1. Clinical characteristics of the study cohorts.

MEDIAN (IQR)	TOTAL	CSPCA	BPH OR NON-CSPCA
Subjects, *n*	177	52	125
CRP, mg/mL	1 (1-4)	1 (1-3)	1 (1-7)
WBC, 10^9/L	5.75 (4.92-7.1)	6.11 (5.4-6.93)	5.61 (4.64-7.15)
Neutrophil, 10^9/L	3.54 (2.79-4.47)	3.92 (3.25-4.43)	3.36 (2.7-4.5)
Monocyte, 10^9/L	0.43 (0.34-0.51)	0.47 (0.34-0.55)	0.42 (0.33-0.5)
Lymphocyte, 10^9/L	1.59 (1.26-1.9)	1.63 (1.38-1.84)	1.57 (1.21-1.92)
Eosinophil, 10^9/L	0.16 (0.09-0.25)	0.14 (0.09-0.22)	0.17 (0.1-0.29)
Basophil, 10^9/L	0.03 (0.02-0.04)	0.02 (0.02-0.03)	0.03 (0.02-0.04)
Platelet, 10^9/L	183 (155-215)	184 (154-209)	181 (159-216)
% Neutrophil	60.9 (55.2-67.3)	63.5 (57.3-67.7)	59.8 (54.7-67.3)
% Lymphocyte	27.4 (22.3-33.3)	26 (21.9-30.7)	28.1 (22.6-33.9)
% Monocyte	7.2 (6-8.2)	6.9 (6-8.2)	7.3 (6-8.2)
% Eosinophil	2.7 (1.6-4.3)	2.2 (1.4-3.9)	2.7 (1.7-4.7)
% Basophil	0.4 (0.3-0.6)	0.4 (0.3-0.5)	0.5 (0.3-0.7)
tPSA, ng/mL	6.30 (5.00-7.98)	6.76 (5.47-8.68)	6.05 (4.92-7.54)
fPSA, ng/mL	1.03 (0.75-1.42)	0.83 (0.62-1.03)	1.13 (0.83-1.58)
%fPSA	0.17 (0.12-0.24)	0.13 (0.09-0.17)	0.19 (0.14-0.28)
p2PSA, pg/mL	14.40 (9.28-20.87)	16.14 (10.68-24.88)	13.90 (8.55-19.83)
PHI	33.6400 (24.2900-50.8000)	50.9498 (34.2374-77.6700)	29.0496 (19.8700-42.8300)
TRD, cm	5.3 (4.9-5.7)	4.9 (4.6-5.3)	5.4 (5.1-5.8)
APD, cm	4.3 (3.7-4.8)	3.5 (3.1-3.9)	4.6 (4-5)
LD, cm	5.3 (4.4-6)	4.2 (3.8-4.8)	5.6 (4.9-6.3)
PV, mL	61.37 (44.25-84.33)	36.56 (28.12-51.81)	71.84 (54.22-90.91)
PTZ-TRD, cm	4.6 (3.8-5.3)	3.5 (2.9-4.1)	5 (4.3-5.4)
PTZ-APD, cm	3.4 (2.7-3.9)	2.5 (2.2-3.1)	3.7 (3.2-4.1)
PTZ-LD, cm	4.2 (3.4-5)	3.2 (2.7-3.9)	4.5 (3.9-5.1)
PTZV, mL	34.54 (17.19-52.79)	14.19 (8.84-25.11)	42.16 (28.53-57.58)
PHID	0.5417 (0.3549-0.9655)	1.3078 (0.8432-1.8727)	0.4151 (0.2785-0.6162)
PHI-TZD	1.0175 (0.5559-2.3329)	3.4148 (1.7725-6.6761)	0.7607 (0.4646-1.1161)

Abbreviations: % Basophil, Basophil/WBC; % Eosinophil, Eosinophil/WBC; % Lymphocyte, Lymphocyte count/WBC; % Monocyte, Monocyte/WBC; % Neutrophil, Neutrophil count/WBC; %fPSA, fPSA/tPSA; APD, anteroposterior diameter; BPH, benign prostatic hyperplasia; CRP, C-reactive protein; csPCa, clinically significant prostate cancer; fPSA, free prostate-specific antigen; IQR, interquartile range; data are given as median (IQR), unless otherwise indicated; LD, longitudinal diameter; non-csPCa, non-clinical significant prostate cancer; p2PSA, [−2] pro-PSA; PHI, prostate health index, PHI = (p2PSA/fPSA) × √tPSA; PHID, PHI density, PHID = PHI/PV; PHI-TZD, PHI transition zone density, PHI-TZD = PHI/PTZV; PTZ-APD, prostate transition zone anteroposterior diameter; PTZ-LD, prostate transition zone longitudinal diameter; PTZ-TRD, prostate transition zone transverse diameter; PTZV, prostate transition zone volume; PV, prostate volume; tPSA, total prostate-specific antigen; TRD, transverse diameter; WBC, white blood cell.

individuals diagnosed with csPCa exhibited elevated levels of various immunology-related indices in comparison with those with BPH and non-csPCa including total cell counts of white blood cell (WBC), neutrophil, monocyte, and lymphocyte. Meanwhile, most PSA-based indices, excluding fPSA and %fPSA, presented higher levels. Furthermore, all prostate morphological parameters including PV, APD, TRD, LD, and TZ prostate morphological parameters PTZV, TZ-APD,

TZ-TRD, and TZ-LD presented much smaller levels among men with csPCa than patients with indolent disease.

To estimate the probability of csPCa, univariate and multivariate logistic regression models were used to screen for independent risk factors. In univariable logistic regression, the result was as follows: Immunology-related indices except for CRP were not significantly associated with csPCa in our cohort ($P > .05$). Meanwhile, PSA-based biomarkers except for tPSA were all associated with csPCa ($P < .05$). Among them, p2PSA (odds ratio [OR] = 1.04, 95% CI = [1.02-1.07], $P < .001$) and PHI (OR = 1.07, 95% CI = [1.04-1.09], $P < .0001$) were positively correlated with csPCa. Moreover, prostatic morphological parameters including total prostate volume indexes (PV, LD, TRD, APD) and transitional zone volume indexes (PTZV, PTZ-LD, PTZ-TRD, PTZ-APD) were all associated with csPCa ($P < .05$) and were all independent protective factors of csPCa. Furthermore, the multivariable analysis demonstrated that CRP, PHI, PHID, and PHI-TZD were the 4 independent risk factors but other indices from univariable logistic regression analysis were excluded (Table 2). Cutoff, specificity, and unnecessary biopsies of indolent disease of various parameters at the fixed sensitivity of 80%, 90%, and 95% are shown in Table 3. When the p2PSA and PTZV were used for unnecessary biopsies, about 60% of men would have avoided unnecessary biopsies with 95% sensitivity, whereas PHI-TZD had a significantly high specificity at 65.81% despite a relatively low biopsy avoided rate. When sensitivity was fixed at 90%, the specificity of PHID (70.94%) and PHI-TZD (74.36%) was dramatically higher than other predictors. Although only approximately 20% of unnecessary biopsies could be avoided, PHID and PHI-TZD can minimize the missed diagnosis of csPCa as far as possible while maintaining a high level of sensitivity. When the sensitivity was set lower than 90%, the likelihood of increasing the unnecessary biopsy rate by sacrificing the sensitivity of total detectable PCa was not so considerable (Table 3).

The ROC curve analysis of univariable logistic regression indicated that integrated predictive models (PHID, PHI-TZD) yield AUCs of 0.9135 and 0.9105 in csPCa prediction among these PSA gray zone participations, which shows a relatively satisfactory predictive capability compared with other single-dimension predictors (Figure 1A). Meanwhile, DCA suggested a higher net benefit of PHID and PHI-TZD than other predictors, which superior discriminative capability (Figure 1B). However, when we constructed the ROC curve analysis of multivariable logistic regression, the introduction of immunology-related indices' CRP into the full-risk models (PHID or PHI-TZD) did not show higher accuracy or AUC (Figure 1C). DCA also affirmed the almost identical value of the multivariable full-risk prediction models without the additional net benefit (Figure 1D). In summary, our findings indicate that, when evaluating predictive models for the detection of csPCa within the PSA gray zone, the diagnostic efficacy of PHID and PHI-TZD surpasses that of other extant diagnostic models, in both univariable and multivariable models. Furthermore, our analysis incorporates morphological parameters of the TZ prostate in the assessment of PHI diagnostic utility and risk evaluation. At a sensitivity level of 90%, PHI-TZD exhibits superior diagnostic performance compared with PHID and other models by obviating the need for 30 unnecessary biopsies in our cohort, while concurrently maintaining a specificity rate of 74.36%, which aligns with the findings of Ito et al.[15] Our work confirmed the value of prostate TZ morphological parameters for gray zone PCa detection. PHI-based predictive models with TZ parameters, especially PHI-TZD, presented paralleled diagnostic performance with PHID, even preferable outcomes on certain conditions. Despite this, further validation is urgently needed.

Discussion

Considering that as early and accurate prediction as possible for the occurrence of PCa is the essential means to face the outburst of PCa in the rapidly aging society in the future. Currently, clinical urologists face the challenge of distinguishing the heterogeneity of PCa biology through both morphological and molecular means, with a focus on identifying high-risk PCa or csPCa for personalized treatment. In the past decade, significant progress has been made in comprehending the histological and molecular distinctions of PCa, owing to the advent of innovative serological models and imaging-based morphological parameters. Nonetheless, in practice, the clinical decision-making process for PCa primarily relies on patients' PSA fluctuations and pathological findings, leaving ample opportunity for enhancing the identification of high-risk PCa through an examination of the spatial distribution and molecular heterogeneity of tumorigenesis. Besides, describing the characteristics and differences of PCa progression among these histological zones based on an in-depth understanding of the unique molecular, genomic, and histological features has become a hard but important way to annotate the origin of PCa.

Previous research classified the human prostate as the PZ, the TZ, and the central zone (CZ) according to histological features and highlighted the morphological differences of tumorigeneses such as differentiation degree and distant invasion.[23-25] Given the multifocality and scattered spatial distribution of PCa progression, the establishment of a simple zonal boundary definition appears to encounter difficulties in identifying the early onset of PCa. Therefore, comprehensive analysis of morphological and molecular biology research can improve the understanding of PCa oncogenesis with variable prognosis in the clinic. For clinical utility, subsequent studies have focused on the combination of serological indices' PSA and prostate morphological parameters. Ito et al[15] demonstrated that serological indices containing p2PSA, particularly PHI, have significantly greater specificity for PCa detection

Table 2. Univariable and multivariable logistic regression analysis testing variables as independent risk factors of csPCa.

	UNIVARIABLE ANALYSIS		MULTIVARIABLE ANALYSIS	*P*
	OR (95% CI)	*P*	OR (95% CI)	
CRP, mg/mL	0.95 (0.91-0.99)	**.039**	0.94 (0.87-1.01	.089
WBC, 10^9/L	1.01 (0.86-1.18)	.936	/	/
Neutrophil, 10^9/L	1.05 (0.85-1.31)	.652	/	/
Monocyte, 10^9/L	3.8 (0.43-33.89)	.232	/	/
Lymphocyte, 10^9/L	0.92 (0.65-1.3)	.623	/	/
Eosinophil, 10^9/L	0.41 (0.03-5.41)	.5	/	/
Basophil, 10^9/L	0 (0-167627.15)	.419	/	/
Platelet, 10^9/L	1 (0.99-1)	.416	/	/
% Neutrophil	1.01 (0.98-1.05)	.419	/	/
% Lymphocyte	0.99 (0.95-1.02)	.46	/	/
% Monocyte	1.1 (0.93-1.3)	.263	/	/
% Eosinophil	0.95 (0.81-1.11)	.528	/	/
% Basophil	0.43 (0.12-1.45)	.172	/	/
tPSA, ng/mL	1.14 (1-1.3)	.055	/	/
fPSA, ng/mL	0.56 (0.33-0.95)	**.03**	1.09 (0.46-2.58)	.852
%fPSA	0 (0-0.01)	**<.0001**	/	/
p2PSA, pg/mL	1.04 (1.02-1.07)	**.001**	0.98 (0.91-1.04)	.442
PHI	1.07 (1.04-1.09)	**<.0001**	1.08 (1.02-1.15)	**.013**
TRD, cm	0.25 (0.13-0.48)	**<.0001**	/	/
APD, cm	0.15 (0.08-0.29)	**<.0001**	/	/
LD, cm	0.23 (0.14-0.37)	**<.0001**	/	/
PV, mL	0.95 (0.93-0.97)	**<.0001**	0.91 (0.85-0.98)	**.019**
PTZ-TRD, cm	0.26 (0.16-0.4)	**<.0001**	/	/
PTZ-APD, cm	0.15 (0.08-0.27)	**<.0001**	/	/
PTZ-LD, cm	0.27 (0.17-0.42)	**<.0001**	/	/
PTZV, mL	0.93 (0.91-0.96)	**<.0001**	1.07 (0.98-1.16)	.133
PHID	32.73 (10.35-103.51)	**<.0001**	0.12 (0-2.97)	.194
PHI-TZD	4.05 (2.52-6.51)	**<.0001**	3.11 (1.07-8.99)	**.036**

Bold values indicate significant difference.
Abbreviations: % Basophil, Basophil/WBC; % Eosinophil, Eosinophil/WBC; %fPSA, fPSA/tPSA; % Lymphocyte, Lymphocyte count/WBC; % Monocyte, Monocyte/WBC; % Neutrophil, Neutrophil count/WBC; APD, anteroposterior diameter; CI, confidence interval; CRP, C-reactive protein; csPCa, clinical significant prostate cancer; fPSA, free prostate-specific antigen; LD, longitudinal diameter; p2PSA, [−2] pro-PSA; PHI, prostate health index, PHI = (p2PSA/fPSA) × $\sqrt{}$tPSA; PHID, PHI density, PHID = PHI/PV; PHI-TZD, PHI transition zone density, PHI-TZD = PHI/PTZV; PTZ-APD, prostate transition zone anteroposterior diameter; PTZ-LD, prostate transition zone longitudinal diameter; PTZ-TRD, prostate transition zone transverse diameter; PTZV, prostate transition zone volume; PV, prostate volume; tPSA, total prostate-specific antigen; TRD, transverse diameter; WBC, white blood cell.

compared with %f-PSA in the 2.0 to 10.0 ng/mL range. They also demonstrated that PTZV -adjusted indices could perform a better utility at a high sensitivity of more than 90%. Moreover, Yan et al[26] gave the heterogeneity between aged prostate peripheral and transitional zone based on single-cell RNA

Table 3. Cutoff, specificity, and likelihood of detecting csPCa of various parameters at the fixed sensitivity of 80%, 90%, and 95% ($n = 177$).

PREDICTOR	AT 95% SENSITIVITY		% OF BIOPSY AVOIDED AT THE CUTOFF MAINTAINING 95% SENSITIVITY	AT 90% SENSITIVITY		% OF BIOPSY AVOIDED AT THE CUTOFF MAINTAINING 90% SENSITIVITY	AT 80% SENSITIVITY		% OF BIOPSY AVOIDED AT THE CUTOFF MAINTAINING 80% SENSITIVITY
	CUTOFF	SPECIFICITY%		CUTOFF	SPECIFICITY%		CUTOFF	SPECIFICITY%	
CRP, mg/mL	⩽13.00	18.80 (12.2-27.1)	53.6 (95/177)	⩽8.00	21.37 (14.3-29.9)	51.9 (92/177)	⩽3.00	29.06 (21.0-38.2)	46.8 (83/177)
fPSA, ng/mL	⩽1.84	17.95 (11.5-26.1)	54.2 (96/177)	⩽1.42	30.77 (22.6-40.0)	45.7 (81/177)	⩽1.25	40.17 (31.2-49.6)	39.5 (70/177)
p2PSA, pg/mL	>5.74	8.55 (4.2-15.2)	60.4 (107/177)	>7.07	12.82 (7.4-20.3)	57.6 (102/177)	>10.60	38.46 (29.6-47.9)	40.6 (72/177)
PHI	>26.61	40.17 (31.2-49.6)	39.5 (70/177)	>29.62	57.26 (47.8-66.4)	28.2 (50/177)	>33.34	63.25 (53.8-72.0)	24.2 (43/177)
PV, mL	⩽80.72	38.46 (29.6-47.9)	40.6 (72/177)	⩽78.50	43.59 (34.4-53.1)	37.2 (66/177)	⩽66.83	56.41 (46.9-65.6)	28.8 (51/177)
PTZV, mL	⩽80.72	38.46 (29.6-47.9)	59.8 (106/177)	⩽44.04	46.15 (36.9-55.6)	35.5 (63/177)	⩽38.01	58.12 (48.6-67.2)	27.6 (49/177)
PHID	>0.39	47.01 (37.7-56.5)	35.0 (62/177)	>0.53	70.94 (61.8-79.0)	19.2 (34/177)	>0.70	88.03 (80.7-93.3)	7.9 (14/177)
PHI-TZD	>0.89	65.81 (56.5-74.3)	22.6 (40/177)	>1.03	74.36 (65.5-82.0)	16.9 (30/177)	>1.36	88.03 (80.7-93.3)	7.9 (14/177)

Abbreviations: CRP, C-reactive protein; csPCa, clinical significant prostate cancer; fPSA, free prostate-specific antigen; p2PSA, [−2] pro-PSA; PHI, prostate health index, PHI = (p2PSA/fPSA) × √tPSA; PHID, PHI density, PHID = PHI/PV; PHI-TZD, PHI transition zone density, PHI-TZD = PHI/PTZV; PTZV, prostate transition zone volume; PV, prostate volume.
Biopsy avoided was restricted to patients with predictor value lesser than cutoff (predictor value greater than cutoff in p2PSA, PHI, PHID, and PHI-TZD) and divided by the number of total enrolled patients; data are given as percentage (%), unless otherwise indicated.

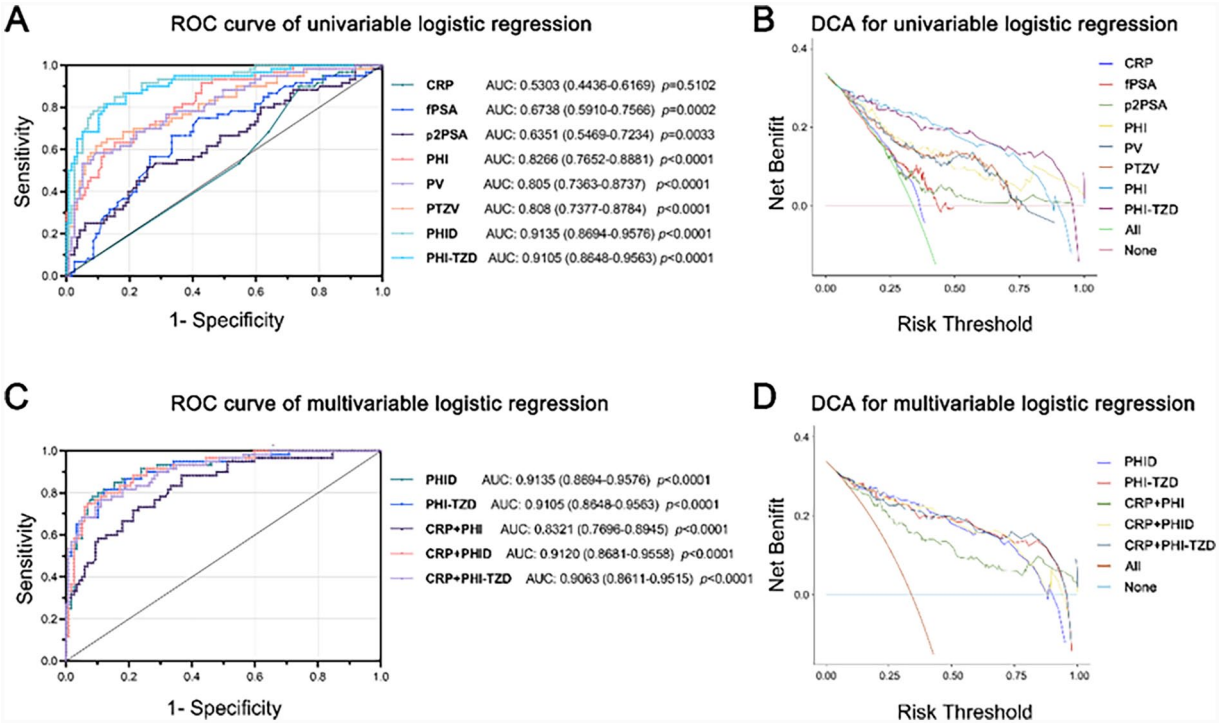

Figure 1. (A) ROC curve of the univariable logistic regression shows the area under the ROC curve for csPCa prediction on prostate biopsy. (B) DCA showing the net benefit and diagnostic performance of each prediction model for csPCa in univariable logistic regression. The PHID and PHI-TZD score demonstrated separation from the other biomarkers across a wide range of threshold values. (C) ROC curve of the multivariable logistic regression shows the area under the ROC curve for csPCa prediction on prostate biopsy. (D) DCA showing the net benefit and diagnostic performance of each prediction model for csPCa in multivariable logistic regression.
CRP indicates C-reactive protein; csPCa, clinically significant prostate cancer; DOC, decision-curve analysis; fPSA, free prostate-specific antigen; p2PSA, [–2] pro-PSA; PHI, prostate health index, PHI = (p2PSA/fPSA) × √tPSA; PHID, prostate health index density, PHID = PHI/PV; PHI-TZD, PHI transition zone density, PHI-TZD = PHI/PTZV; PTZV, prostate transition zone volume; PV, prostate volume; ROC, receiver-operating characteristic.

sequencing, which could help to understand the underlying mechanism of prostate disease origin.

To evaluate the role of TZ volume in PHI-based predictive models for PSA gray zone PCa detection, we conducted this study. Based on our results, the volume and 3 diameters (LD, TRD, and APD) of the TZ are significantly correlated with the PCa occurrence in patients according to univariable logistic regression analysis and they are also independent protective indexes to predict the probability of csPCa. In theory, the presence of abnormal transitional zone-related indices in patients with PSA levels falling within the reference range of the gray zone typically signifies the manifestation of indolent ailments, such as benign prostate hyperplasia and inflammation, that do not pose a threat to the patients' life expectancy or comorbidity status.[24] In consideration of the fact in the real world, the positive rate of prostate biopsy for PCa diagnosis is about 25%, which means most biopsy-taker are nontumor patients only with elevated serum tPSA levels, also leading to the unnecessary excessive diagnosis and wasting in the health care resource. However, our results indicated that in most cases the combination of TZ indices and PHI (PHI-TZD) performed a similar diagnostic utility in gray zone csPCa detection compared with PHID, despite presenting preferable outcomes when the diagnostic sensitivity was fixed at 90%. Although the specific mechanisms are not clear, the assumptions that gray zone patients' tumors in the prostate TZ are mostly low-risk and tumor focal occurrence across 3 histological zones might explain this result.

Since the varying incidence, prognosis, and outcomes of PCa across histological zones, it is imperative to ascertain the precise location and pathological type of each sample. Regrettably, our current cross-sectional study is unable to provide further localization of tumors within each prostate zone. We acknowledge the presence of potential limitations and biases in our study. We acknowledged that there might be several limitations and biases in this study. Hence, more work and validation are required to further explain the specific reason and underlying mechanism of TZ volume indices in providing better adjustment value for PHI-based comprehensive multivariate predictive model in gray zone PCa detection.

Conclusion

Based on our data, it suggests that in most cases, the prostate TZ morphological parameters offer similar diagnostic usefulness in PHI-based predictive models compared with the total prostate volume adjusted model PHID. However, they demonstrate a notable advantage in the early detection and risk stratification of gray zone csPCa when the sensitivity is fixed at 90%.

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Author Contributions

Y-JY contributed to the conception and design of the manuscript. Y-HQ, Y-TS, and H-HL contributed to the acquisition of data. H-JC contributed to the manuscript writing. B-WS contributed to the data management and analysis. H-JC and X-JS contributed to the manuscript editing. All the authors have read and approved the final version.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics

The Ethics Committee of Xin Hua Hospital affiliated to Shanghai Jiao Tong University School of Medicine approved this study (XHEC-C-2019-113-2). Written informed consents were provided by all study participants before enrollment.

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