


Nomogram Incorporating Contrast-Enhanced Ultrasonography Predicting Time to the Development of Castration-Resistant Prostate Cancer

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ABSTRACT

BACKGROUND: It is valuable to predict the time to the development of castration-resistant prostate cancer (CRPC) in patients with advanced prostate cancer (PCa). This study aimed to build and validate a nomogram incorporating the clinicopathologic characteristics and the parameters of contrast-enhanced ultrasonography (CEUS) to predict the time to CRPC after androgen deprivation therapy (ADT).

METHODS: Patients with PCa were divided into the training (n = 183) and validation cohorts (n = 37) for nomogram construction and validation. The clinicopathologic characteristics and CEUS parameters were analyzed to determine the independent prognosis factors and serve as the basis of the nomogram to estimate the risk of 1-, 2-, and 3-year progress to CRPC.

RESULTS: T stage, distant metastasis, Gleason score, area under the curve (AUC), prostate-specific antigen (PSA) nadir, and time to PSA nadir were the independent predictors of CRPC (all $P < 0.05$). Three nomograms were built to predict the time to CRPC. Owing to the inclusion of CEUS parameter, the discrimination of the established nomogram (C-index: 0.825 and 0.797 for training and validation datasets) was improved compared with the traditional prediction model (C-index: 0.825 and 0.797), and when it excluded posttreatment PSA, it still obtained an acceptable discrimination (C-index: 0.825 and 0.797).

CONCLUSIONS: The established nomogram including regular prognostic indicators and CEUS obtained an improved accuracy for the prediction of the time to CRPC. It was also applicable for early prediction of CRPC when it excluded posttreatment PSA, which might be helpful for individualized diagnosis and treatment.

KEYWORDS: Castration-resistant prostate cancer, androgen deprivation therapy, nomogram, contrast-enhanced ultrasonography, prostate-specific antigen

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Introduction

In China, many patients were diagnosed with locally advanced or metastatic prostate cancer (PCa).¹ Androgen deprivation therapy (ADT) is an initial therapy for the palliation of advanced PCa.² Although most patients are initially responsive, they will inevitably progress to castration-resistant prostate cancer (CRPC) within about 3 years.^{3–6} However, the time for different individuals to develop CRPC varies greatly. Some patients respond to ADT for several years, whereas others progress to CRPC within months.⁷ Hussain et al⁸ proposed that if the CRPC stage occurred in the first 7 months of ADT, the risk of death would increase by 4 times. Sweeney et al⁹ and James et al¹⁰ reported that ADT plus docetaxel in the early hormone-sensitive phase would result in longer overall survival. Therefore, there is a need for a reliable and simple means to predict the time to development of CRPC

for the decision-making of individualized diagnosis and treatment.¹¹ Some prognostic factors for CRPC such as prostate-specific antigen (PSA) and Gleason score have been investigated.^{7,12,13} However, no reliable clinical model is feasible for predicting (especially early predicting) the time to the development of CRPC currently.

There is increasing evidence surrounding angiogenesis, which has been reported to be associated with the PCa progress.¹⁴ Contrast-enhanced ultrasonography (CEUS) permits characterizing the microvascular perfusion of PCa, and its role in the prediction of the time to CRPC deserved to be explored. Thus, the present study aimed to investigate the potential predictors from clinical characteristics, PCa status, and CEUS parameters for the development of CRPC and build a nomogram predicting the risk of progression to CRPC in patients with PCa at 1, 2, and 3 years after ADT.



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Patients and Methods

This prospective cohort study was conducted following the Declaration of Helsinki. All procedures were approved by the ethics committee of Shanghai Pudan Hospital of Pudong New District. Written informed consent was obtained from all participants.

Patients

A total of 183 patients with PCa admitted to Shanghai Pudan Hospital of Pudong New District from April 2010 to April 2017 were recruited as the training cohorts, and 37 patients with PCa from May 2017 to April 2018 were recruited as the validation cohort. All patients were diagnosed by histopathological biopsy and underwent clinically indicated ADT as the initial and only therapy prior to progression. Patients received radical treatment (radical prostatectomy or radical radiotherapy), cryotherapy, or internal radiation before progress to CRPC, with cardiovascular diseases, autoimmune diseases, other malignancies, and died of causes unrelated to PCa were excluded. Androgen deprivation therapy was administered according to the guidelines of European association of urology,² and the applied ADT included castration (leuprorelin, 3.6 mg every 28 days) combined with antiandrogen therapy (bicalutamide, 50.0 mg/d).

Data collection

Medical data regarding clinical characteristics (age and body mass index [BMI]), PCa status (Tumor, Nodes, Metastases [TNM] staging, and Gleason score; classification following standard local practice), and CEUS parameters were collected prior to ADT initiation. Serum PSA level and serum testosterone level were measured before, during, and after ADT initiation.

CEUS examination

All patients underwent transrectal ultrasound assessments (LOGIQ E9, GE Healthcare, Milwaukee, Wis., USA) to observe the size, location, and blood supply of the tumor. Subsequently, CEUS mode was performed using the SonoVue ultrasound contrast agent (Bracco SpA, Milan, Italy), and the time-intensity curves (TIC) were observed. Time-intensity curve indicators in the region of interest (ROI) include peak intensity (PI), gradient from arrive intensity to peak intensity (Grad), time to peak (TTP), and area under the curve (AUC) (Figure 1).

Follow-up

A 3-year follow-up was assessed for each patient. The patients were followed up once a month for the first 3 months after the initiation of ADT. A regular 3-month follow-up was performed if the PSA was stable. Physical examinations and laboratory

tests were performed at each visit. Radiologic examination was performed and the follow-up interval was shortened if PSA was persistently increased or new pain experienced, which is likely to be related to the PCa. The endpoint was the development of CRPC. Castration-resistant prostate cancer was defined as a castrate serum testosterone level < 50 ng/mL (1.7 nmol/L) plus either of the followings: (1) biochemical progression defined as ≥ 3 consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with PSA > 2 ng/mL, or (2) radiologic progression defined as the appearance of 2 or more bone lesions or enlargement of a soft tissue lesion.^{2,15} Patients who progressed to CRPC during the follow-up were included in the poor prognosis group, and those who were in stable condition without deterioration were included in the good prognosis group.

Statistical analysis

Kaplan-Meier (KM) plots were used to describe the time to CRPC. Independent samples *t* test, chi-square test, Fisher exact test, and Mann-Whitney *U* test were used for the comparison of training and validation cohorts. In the training cohort, associations between CEUS parameters and PCa status including T stage and Gleason score were determined using Spearman correlation. Univariate Cox regression was performed to investigate the predictors associated with CRPC. Those with $P < 0.05$ were entered into a multivariate Cox regression model to determine the independent prognostic factors of CRPC. The hazard ratio (HR) and 95% confidence interval (CI) of each factor were estimated. A nomogram was built based on the independent prognostic factors to estimate the risk of 1-, 2-, and 3-year progress to CRPC. The discrimination of the nomogram was evaluated by the AUC of the receiver operating characteristic (ROC) curve, which is also known as the concordance index (C-index). Bootstrap resampling (1000 times) analysis was applied to address model overfit and obtain a relatively unbiased evaluation (a corrected C-index). The calibration was evaluated by the calibration curve combined with the Hosmer-Lemeshow (HL) test. IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA), R package version 3.6.2., and MedCalc (Version 22.0.1; MedCalc Software, Ostend, Belgium) were used for statistical analyses.

Results

Characteristics and prognosis

A total of 124 (124/183, 67.8%) patients in the training cohort and 25 (25/37, 67.6%) patients in the validation cohort were diagnosed with CRPC during the follow-up. The clinicopathological characteristics in the training and validation cohorts are shown in Table 1. Before ADT initiation, a plurality had Gleason scores of 8 to 10 (52.5% and 56.7% for training and validation cohorts, respectively), advanced stages of T3 to T4 (92.3% and 94.6%), and distant metastasis (bone metastases) (76.5% and 81.1%). The median number of bone lesions

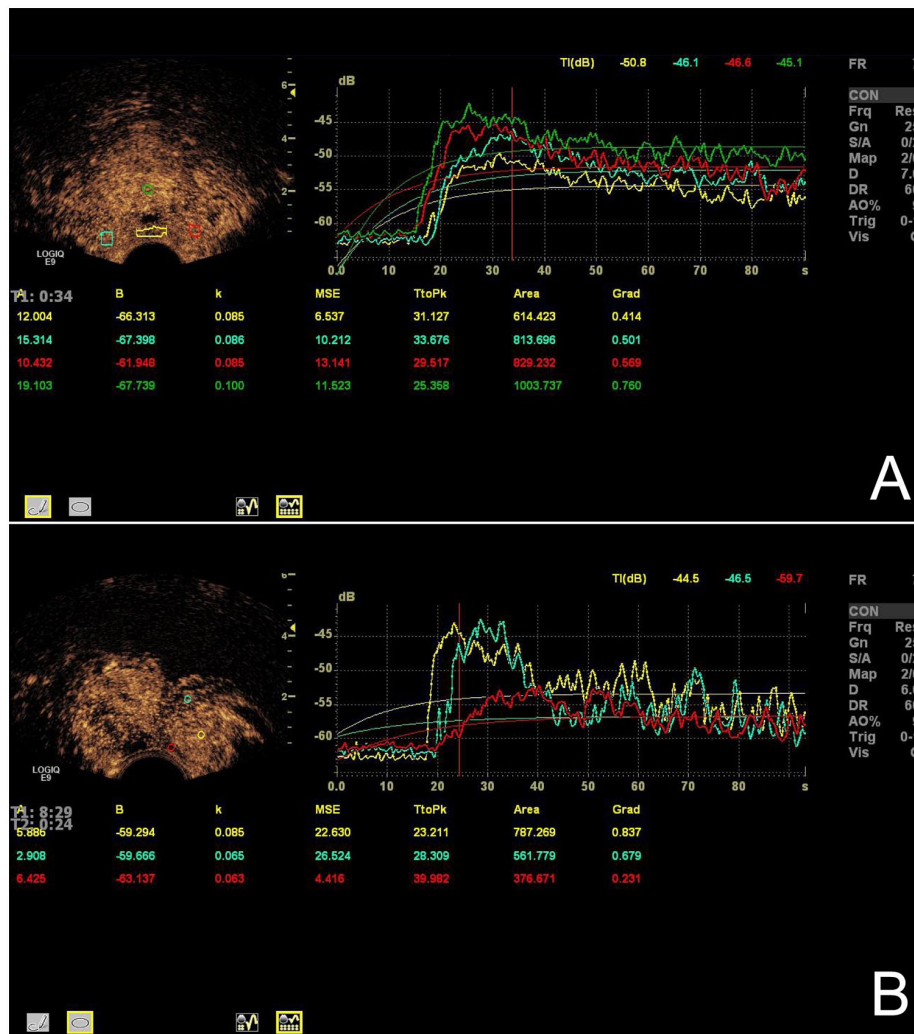


Figure 1. CEUS-TIC in patients with PCa. The extent of tumor enhancement in (A) is lower than that in (B), suggesting a good prognosis. In (A), the yellow, red, blue, and green ROIs represent the hypo-enhanced tumor in the outer gland, normal outer gland tissue, and normal inner gland tissue, respectively. In (B), the yellow, red, and blue ROIs represent the hyper-enhanced tumor in the outer gland, normal outer gland tissue, and normal inner gland tissue, respectively. CEUS indicates contrast-enhanced ultrasonography; PCa, prostate cancer; ROI, region of interest; TIC, time-intensity curves.

was 4 both in the training and validation cohorts. Three patients with bone metastases in the training cohort were accompanied by lung metastases. Most patients initially responded to ADT. The median times to CRPC were 21 and 23 months. No significant difference in the prognosis between the training and validation cohorts was observed (Figure 2). The clinicopathological characteristics between the training and validation cohorts were comparable, which justified their use as training and validation datasets.

Independent prognostic factors in the training cohort

To identify the associations between the potential variables and the time to CRPC in the training cohort, univariate Cox regression analysis was performed and it indicated that PCa status including the proportion of stage T4, distant metastasis, Gleason score (4+3, 4+4, and 9-10), CEUS parameters

including PI and AUC, and posttreatment PSA including PSA nadir and time to PSA nadir were associated with CRPC ($P < 0.05$ for all, Table 2). Spearman correlation analyses revealed that both PI and AUC were positively correlated with T stage ($r = 0.419$ for PI, $r = 0.585$ for AUC) and Gleason score ($r = 0.575$ for PI, $r = 0.679$ for AUC) (Figure 3). Multivariate Cox proportional analysis further revealed that T stage, distant metastasis, Gleason score, AUC, PSA nadir, and time to PSA nadir were the independent predictors of CRPC ($P < 0.05$ for all, Table 2).

Nomogram development

Three nomograms were built to predict the risk of 1-, 2-, and 3-year progress to CRPC, which were a complete nomogram with 6 independent predictors (nomogram A), a nomogram without posttreatment PSA (PSA nadir and time to PSA nadir) (nomogram B), and a nomogram without CEUS (AUC)

Table 1. Comparison of the clinicopathological characteristics between the training and validation cohorts.

CHARACTERISTICS		TRAINING COHORT (N=183)	VALIDATION COHORT (N=37)	P
Age (y)		72.48 ± 6.83	73.16 ± 6.52	.578 ^a
BMI (kg/m ²)		23.72 ± 4.03	23.17 ± 4.37	.456 ^a
T stage, n (%)	1-2	14 (7.7)	2 (5.4)	.848 ^b
	3	70 (38.3)	13 (35.1)	
	4	99 (54.0)	22 (59.5)	
Distant metastasis, n (%)	No	43 (23.5)	7 (18.9)	.544 ^c
	Bone metastases	140 (76.5)	30 (81.1)	
Number of bone lesions		4 (1, 7)	4 (1, 8)	.492 ^d
Gleason score	≤6	23 (12.5%)	3 (5.4%)	.739 ^b
	3 + 4	25 (13.7%)	5 (10.8%)	
	4 + 3	39 (21.3%)	8 (27.0%)	
	4 + 4	73 (39.9%)	15 (43.2%)	
	9-10	23 (12.6%)	6 (13.5%)	
Tumor size (cm)		2.3 (1.9, 2.5)	2.4 (2.0, 2.6)	.167 ^d
CEUS TIC parameters	PI (dB)	9.72 (7.53, 13.35)	10.30 (7.12, 13.74)	.084 ^d
	Grad	0.52 ± 0.10	0.55 ± 0.13	.116 ^a
	TTP (s)	25.35 ± 4.39	25.25 ± 3.36	.896 ^a
	AUC (dB*s)	776.30 ± 114.92	782.82 ± 124.01	.756 ^a
Testosterone (ng/dL)		348.29 ± 61.37	351.26 ± 56.03	.786 ^a
Pre-treatment PSA (µg/L)	<20	13 (7.1%)	4 (10.8%)	.668 ^b
	20-100	69 (37.7%)	14 (37.8%)	
	>100	101 (55.2%)	19 (51.4%)	
PSA nadir (µg/L)		3.32 (1.74, 5.93)	3.62 (1.93, 6.34)	.176 ^d
Time to PSA nadir (mo)		8 (5, 11)	7 (4, 10)	.082 ^d

Abbreviations: AUC, area under the curve; BMI, body mass index; CEUS, contrast-enhanced ultrasonography; Grad, gradient from arrive intensity to peak intensity; PI, peak intensity; PSA, prostate-specific antigen; TIC, time-intensity curves; TTP, time to peak.

^aFor independent samples *t* test.

^bFor Fisher exact test.

^cFor chi-square test.

^dFor Mann-Whitney *U* test.

(nomogram C), respectively. Nomogram B was a traditional prediction model and nomogram C was suitable for early prediction of CRPC. Each predictor was assigned a number with the weight equal to the hazard ratio of Cox regression to estimate the time to CRPC (Figure 4).

Comparison of the discriminations of the 3 nomograms

A C-index of 0.939 (95% CI: 0.873-0.982) was achieved in nomogram A, and an overfitting-corrected C-index (0.914,

95% CI: 0.849-0.957) was acquired after 1000 bootstrapping, which indicated good discrimination (C-index > 0.75). The ROC curves for evaluating the discriminations of different nomograms are presented in Figure 5. The C-indexes provided by nomogram A (0.914 for the training cohort and 0.885 for the validation cohort) were higher than those of nomogram B (0.813 and 0.766) and nomogram C (0.824 and 0.807). It indicated that the complete nomogram including posttreatment PSA and CEUS showed the best discrimination in predicting the time to CRPC. Besides, it still obtained an acceptable discrimination (>0.75) when posttreatment PSA was excluded,

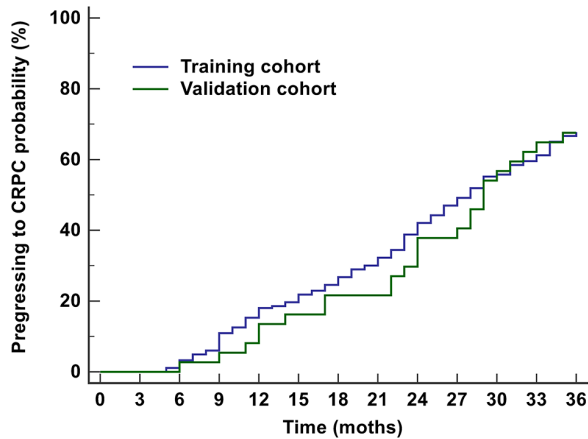


Figure 2. KM curves for the time to the development of CRPC in the training and validation cohorts. No significant difference in the time to CRPC is observed. CRPC indicates castration-resistant prostate cancer; KM, Kaplan-Meier.

indicating its potential to be applicable in early predicting the time to CRPC.

Calibration validation of the 3 nomograms

In the training cohort, the calibration plots graphically showed that the predicted probabilities of 1-, 2-, and 3-year progress to CRPC in the 3 nomograms were almost identical to the actual observations (Figure 6A to C). There is no difference between the predicted prognosis estimated by the 3 nomograms and the actual prognosis throughout the HL tests (Nomogram A: $P=0.536, 0.473, 0.283$; Nomogram B: $P=0.659, 0.535, 0.462$; Nomogram C: $P=0.657, 0.537, 0.439$). In the validation cohort, good calibrations were also demonstrated by the HL tests (Nomogram A: $P=0.573, 0.435, 0.263$; Nomogram B: $P=0.663, 0.552, 0.436$; Nomogram C: $P=0.648, 0.524, 0.455$), as displayed by the calibration plots (Figure 6D to F).

Table 2. Univariate and multivariate Cox regressions for investigating the predictors associated with CRPC.

VARIABLES		UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
		P	HR	95% CI	P	HR	95% CI
Age (y)		.323	1.016	0.985-1.047			
BMI (kg/m ²)		.897	1.004	0.949-1.062			
T stage	1-2	Reference			Reference		
	3	.175	1.890	0.754-4.737	.575	1.310	0.510-3.364
	4	.015	3.294	1.492-11.394	.025	8.272	1.352-68.931
Distant metastasis	No	Reference			Reference		
	Yes	.025	2.683	1.131-6.366	.032	6.824	1.314-47.935
Gleason score	≤6	Reference			Reference		
	3 + 4	.252	1.592	0.825-5.295	.492	1.395	0.802-4.892
	4 + 3	.037	2.757	1.063-7.146	.108	2.482	0.752-6.927
	4 + 4	.007	13.579	1.425-98.990	.026	10.358	1.220-83.246
	9-10	<.001	14.924	1.620-105.294	.003	12.834	1.395-92.394
Tumor size (cm)		.265	1.473	0.746-2.909			
CEUS TIC parameters	PI (dB)	.031	1.075	1.007-1.149	.680	1.014	0.950-1.082
	Grad	.478	0.462	0.055-3.903			
	TTP (s)	.338	1.027	0.972-1.085			
	AUC (dB*s)	<.001	1.018	1.009-1.031	<.001	1.015	1.004-1.025
Testosterone (ng/dL)		.646	1.001	0.997-1.005			
Pretreatment PSA (μg/L)	<20	Reference					
	20-100	.181	1.114	0.618-2.008			
	>100	.720	1.295	0.725-2.352			
PSA nadir (μg/L)		<.001	1.251	1.162-1.347	<.001	1.180	1.083-1.286
Time to PSA nadir (mo)		<.001	0.885	0.829-0.944	.003	0.907	0.834-0.963

Abbreviations: AUC, area under the curve; BMI, body mass index; CEUS, contrast-enhanced ultrasonography; CI, confidence interval; CRPC, castration-resistant prostate cancer; HR, hazard ratio; PI, peak intensity; PSA, prostate-specific antigen; TIC, time-intensity curves; TTP, time to peak.

T stage, distant metastasis, Gleason score, AUC, PSA nadir, and time to PSA nadir were independently associated with the development of CRPC.

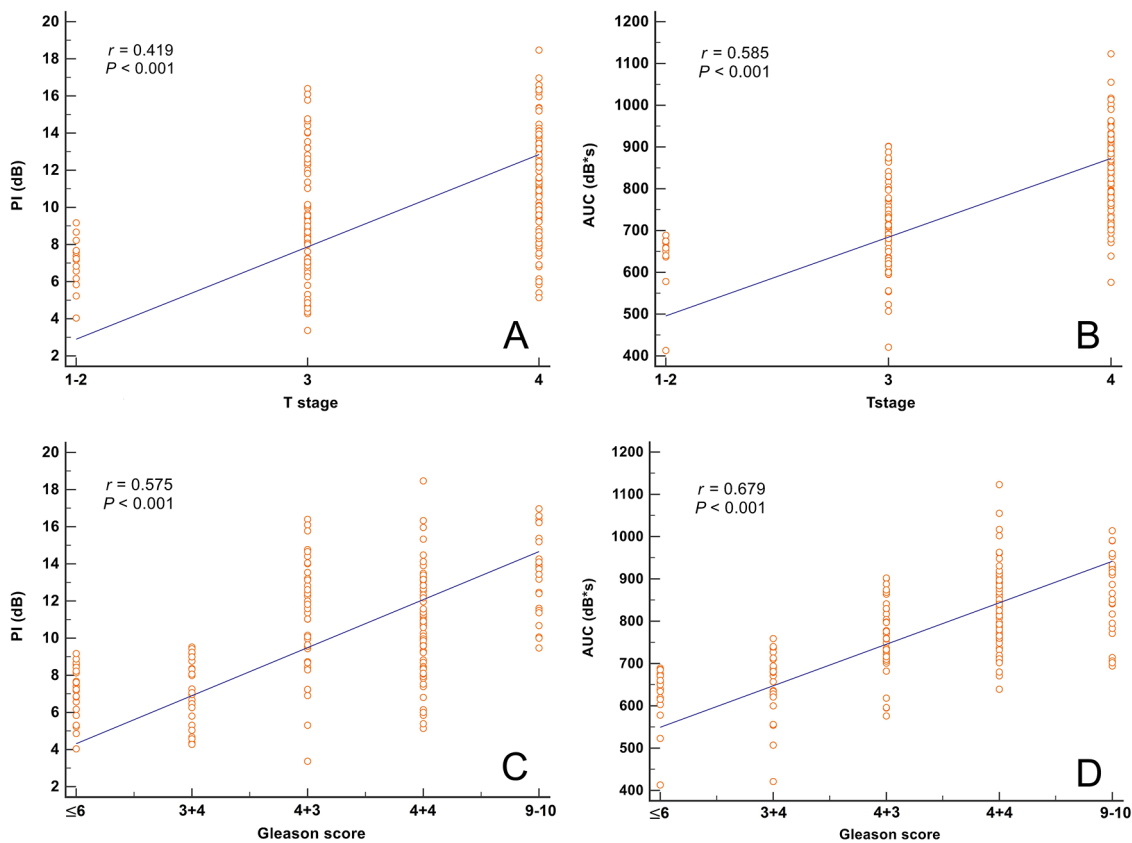


Figure 3. Spearman correlation between CEUS parameters (PI and AUC) and PCa status (T stage and Gleason score). Correlation between T stage and PI and AUC are plotted in (A) and (B). Correlation between Gleason core and PI and AUC are plotted in (C) and (D). AUC indicates area under the curve; CEUS, contrast-enhanced ultrasonography; PCa, prostate cancer; PI, peak intensity.

Discussion

Accurate prediction of the time to CRPC is critical to the decision of the best treatment strategy and improving the survival of patients with PCa. In the present study, T stage, distant metastasis, Gleason score, AUC, PSA nadir, and time to PSA nadir were the independent predictors of the time to CRPC in the multivariate Cox analysis. We developed 3 nomograms (nomograms A, B, and C) to predict the time to CRPC and demonstrated that the predictive value of nomogram A (new model in this study) was higher than nomogram B (traditional model, without CEUS) and nomogram C (for early prediction, without posttreatment PSA). Owing to the inclusion of CEUS, the predictive value of nomogram C was acceptable although it was lower than nomogram A, which might be used for early prediction of the time to CRPC.

PSA is recognized as a diagnostic biomarker and prognostic predictor in patients with PCa.¹⁶ The prognostic value of the pretreatment PSA remains unclear. Some studies support the prognostic value, while others do not.¹⁷⁻²¹ In our study, the pretreatment PSA was not an independent predictor of CRPC, but the PSA nadir and time to PSA nadir were associated with the development of CRPC. The role of the post-treatment PSA (higher PSA nadir or shorter time to PSA nadir) in predicting the progression to CRPC or the overall

survival has been demonstrated in many reports.^{13,22-26} However, the exact mechanism remains unclear. The possible reason is that the rapid decrease in the PSA level after ADT is due to the suppression of the expression of PSA mediated by the androgen receptor in hormone-sensitive prostate cancer cells. The rapid death of hormone-sensitive prostate cancer cells may induce the growth and proliferation of hormone-resistant prostate cancer cells, thereby progressing to CRPC.^{26,27} Nevertheless, the median time to PSA nadir of patients with PCa who progressed to CRPC in the present study was 7 months. It indicated that the nomogram including posttreatment PSA was meaningless in early prediction of the time to CRPC for most patients with PCa.

We developed 3 nomograms to predict the risk of 1-, 2-, and 3-year progress to CRPC in the present study. Nomogram A was a newly established nomogram that contained 6 independent predictors (including regular prognostic indicators and CEUS parameters). Nomogram B was a traditional model (excluding CEUS parameters), which was used for the comparison with nomogram A to evaluate the utility of CEUS parameters for predicting CRPC. Nomogram C (excluding posttreatment PSA) was constructed to explore its performance in the early prediction of CRPC. The sum of the scores of each predictor in these nomograms was the estimated risks

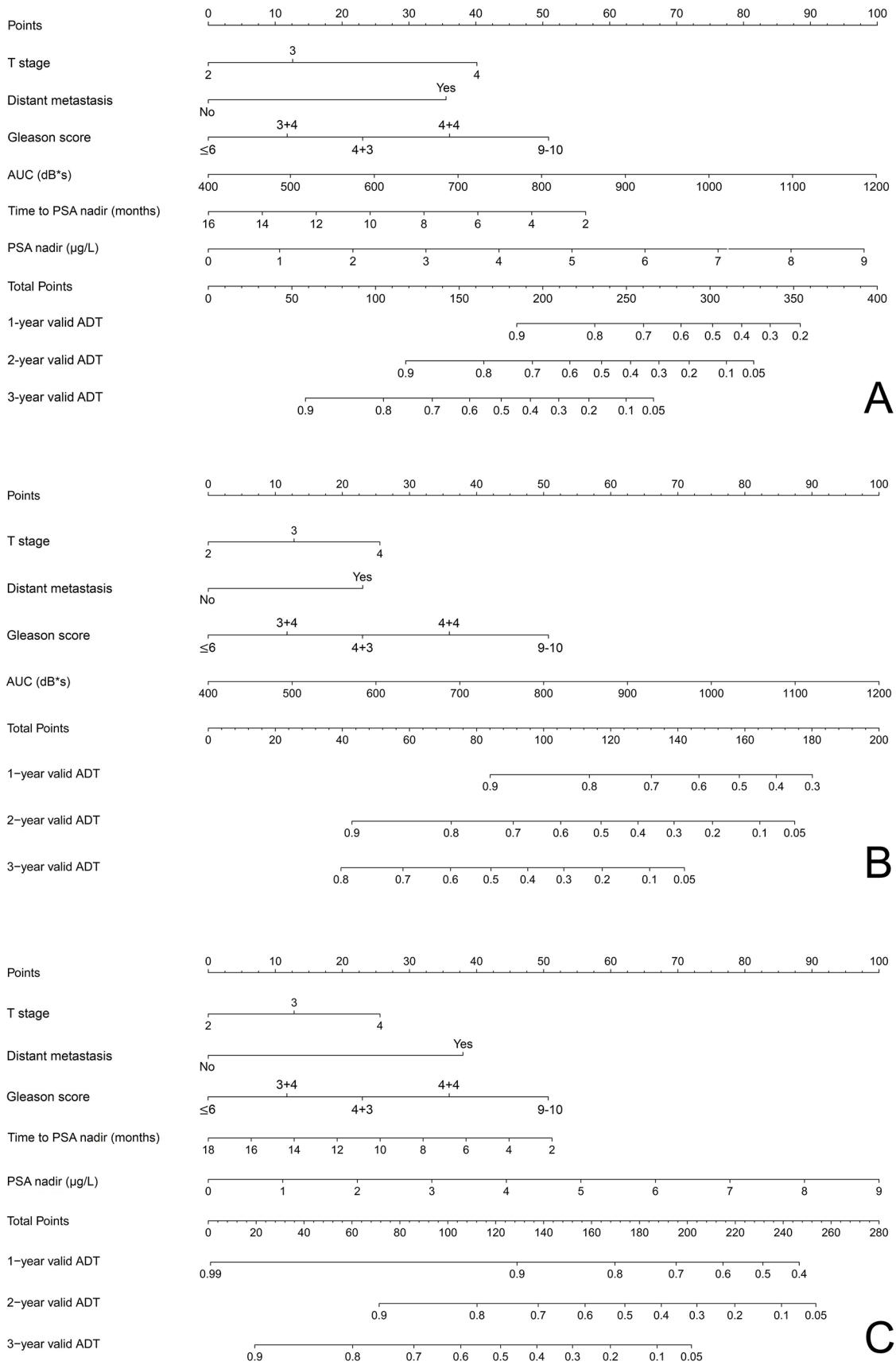


Figure 4. Three nomograms predicting the risk of 1-, 2-, and 3-year progress to CRPC in patients with PCa. Nomogram A: complete nomogram with the 6 independent predictors (A); Nomogram B: nomogram without posttreatment PSA (PSA nadir and time to PSA nadir) (B); Nomogram C: nomogram without CEUS (AUC) (C). ADT indicates androgen deprivation therapy; AUC, area under the curve; CRPC, castration-resistant prostate cancer; PCa, prostate cancer; PSA, prostate-specific antigen.

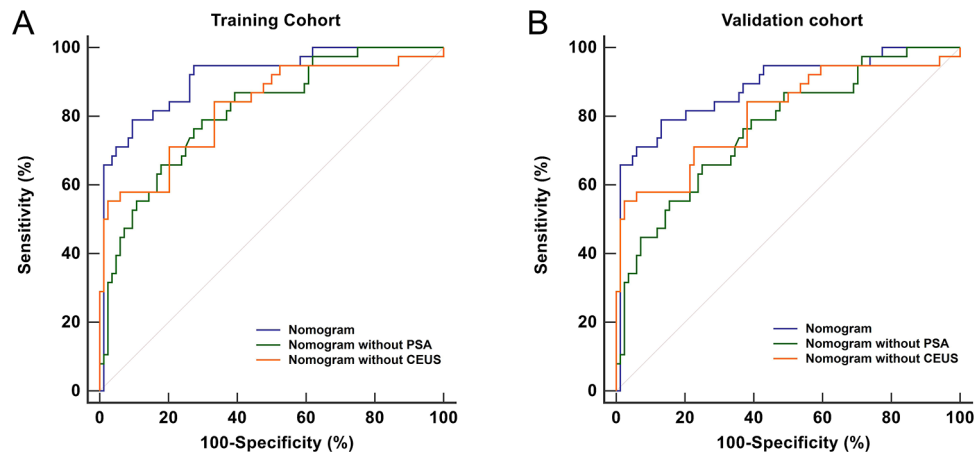


Figure 5. ROC curves to evaluate the discriminations of different nomograms. The discriminations are evaluated in the training cohort (A) and in the validation cohort (B). Both indicate that the nomogram A shows the highest discrimination compared with nomogram B and C. Nomogram A: complete nomogram with the 6 independent predictors, Nomogram B: nomogram without posttreatment PSA (PSA nadir and time to PSA nadir), and Nomogram C: nomogram without CEUS (AUC). AUC indicates area under the curve; CEUS, contrast-enhanced ultrasonography; PSA, prostate-specific antigen; ROC, receiver operating characteristic.

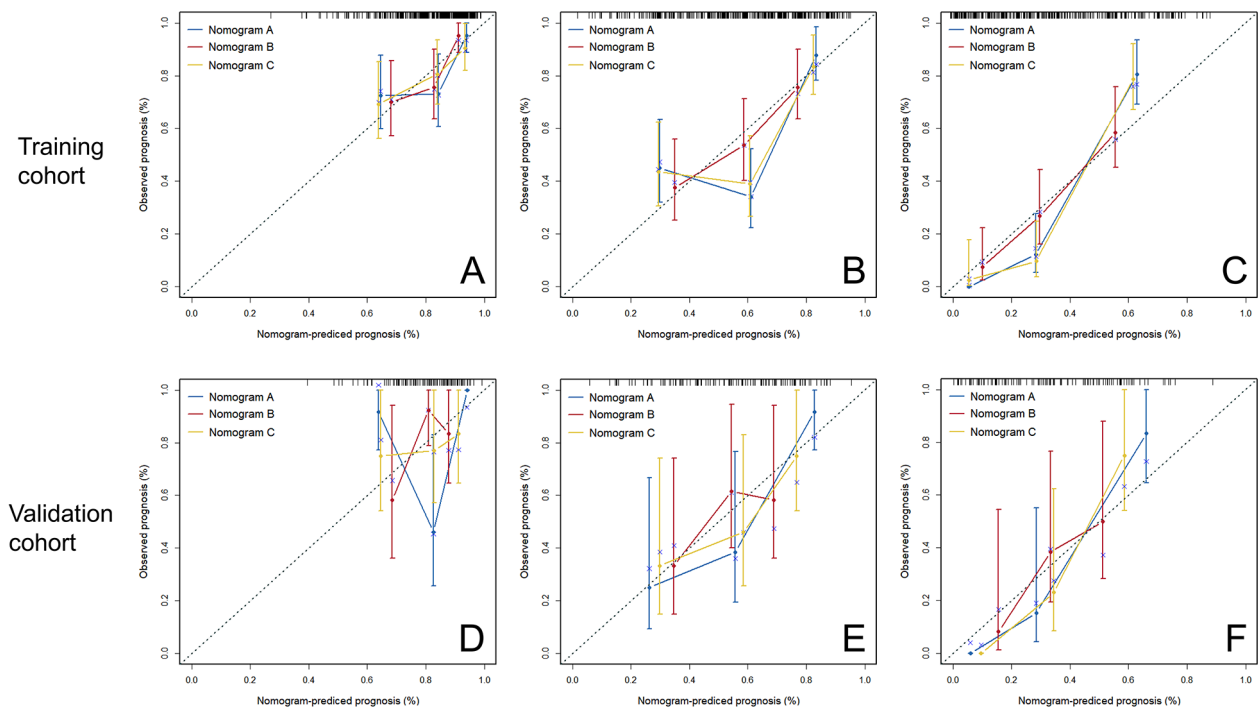


Figure 6. Calibration plots of the 3 nomograms. The calibration plots in the training datasets predicting 1-, 2-, and 3-year valid ADT are shown in (A to C) and those in the validation datasets are shown in (D to F). All plots indicate that the predicted probabilities are almost identical to the actual observations. Nomogram A: complete nomogram with the 6 independent predictors, Nomogram B: nomogram without posttreatment PSA (PSA nadir and time to PSA nadir), and Nomogram C: nomogram without CEUS (AUC). ADT indicates androgen deprivation therapy; AUC, area under the curve; CEUS, contrast-enhanced ultrasonography; PSA, prostate-specific antigen.

of 1-, 2-, and 3-year progress to CRPC. For example, a patient with PCa was diagnosed with clinical stage T4, distant metastasis, and Gleason score 4 + 4. The AUC of TIC was about 800. After ADT initiation, the time to PSA nadir and PSA nadir was 8 months and 3 $\mu\text{g}/\text{L}$. The total score of nomogram A was about 230, which indicated that the risk of 1-, 2-, and 3-year progress to CRPC were about 20%, 50%, and 80%,

respectively. If predicted by the nomograms B and C, they were about 30%, 60%, and 90%, respectively; and about 20%, 50%, and 80%, respectively.

Three nomograms showed good calibrations through calibration plots and HL tests in the present study. The discrimination of nomogram A was higher than that of nomogram B, while the discrimination of nomogram C was acceptable

although it was lower than nomogram A. We think it may owe to the inclusion of the CEUS parameter (AUC) in the nomogram. The CEUS of the poor prognosis group showed rapid hyperenhancement in the arterial wash-in phase and increased blood perfusion compared with the good prognosis group. The possible mechanism is that the increased blood supply demand of malignant tumor tissues induces more neovascularization, which will stimulate them to form a large number of arteriovenous fistulas, thereby significantly increasing the perfusion of the contrast agent.²⁸ Erbersdobler et al²⁹ and Zhu et al³⁰ proved that the microvessel density in prostate cancer, which was closely related to the parameters of CEUS, was associated with the T stage and Gleason score contributing to tumor aggressiveness. Therefore, the AUC had the potential to increase the accuracy of the nomogram in predicting the time to CRPC.

A few limitations were inevitable in this study. First, the established nomograms were only validated in our own hospital. Further external validations in different hospitals are needed in the future. Second, due to the limitation of the detection of PSA, we cannot obtain the specific value when "PSA > 100," which may affect the prognostic value of pre-treatment PSA. Third, we only reported the outcomes of ADT but did not report the results of second-line treatment, because different therapies after CRPC were chosen.

Conclusions

In conclusion, our study provided a novel nomogram incorporating regular prognostic indicators and CEUS parameters for the prediction of the time to CRPC. The performance of the prediction model was improved owing to the inclusion of CEUS parameters, and when it excluded posttreatment PSA, it was applicable for early prediction of CRPC, which might be helpful for individualized diagnosis and treatment.

Author Contributions

YZ, GY, JM, and YJ contributed to study design. YZ, GY, JS, XW, YW, QC, HK, LG, JY, WL, BZ, and JW contributed to data collection and analysis. YZ, GY, JM, and YJ contributed to supervision. JS, XW, YW, QC, HK, LG, JY, WL, BZ, and JW contributed to statistics. YZ, GY, JS, XW, JM, and YJ contributed to manuscript writing. YZ, GY, JM, and YJ contributed to manuscript revision. All authors approved the final manuscript.

Ethical Approval

Ethical approval for the study was obtained from the ethics committee of Shanghai Pudan Hospital of Pudong New District.

Informed Consent

Written informed consent was obtained from all patients.

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