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DYNAMIC ANDROGEN RESPONSE INDEX AND ITS ASSOCIATION WITH BIOCHEMICAL RECURRENCE AFTER RADICAL PROSTATECTOMY FOLLOWING NEOADJUVANT ANDROGEN DEPRIVATION THERAPY

Background. Neoadjuvant androgen deprivation therapy (NADT) before radical prostatectomy (RP) remains controversial in the management of localized and locally advanced prostate cancer. A major limitation of this strategy is the lack of biomarkers capable of identifying tumors biologically sensitive to androgen deprivation. This study **aimed** to evaluate the prognostic value of a dynamic androgen response index (IAR) and develop a predictive model for biochemical recurrence (BCR) after RP. **Materials and Methods.** The retrospective single-center study included 84 patients with prostate cancer treated with NADT followed by RP. The IAR was defined as the ratio between logarithmic slopes of PSA and testosterone decline during neoadjuvant therapy. Cox regression analysis was performed to identify predictors of BCR. A predictive model and nomogram were constructed based on independent predictors. Model performance was evaluated using ROC analysis, calibration plots, and decision curve analysis. **Results.** During a median follow-up of 56 months, BCR occurred in 62 patients. Clinical stage ≥ cT3a (HR 2.34; $p = 0.003$) and IAR (HR 1.48; $p = 0.024$) were independent predictors of BCR. The model demonstrated moderate discrimination (AUC 0.68) and satisfactory calibration. **Conclusions.** The IAR may reflect the biological responsiveness of prostate cancer to androgen deprivation. These findings should be considered hypothesis-generating and require further validation in the context of risk stratification for BCR following RP after NADT.

Keywords: prostate cancer, neoadjuvant androgen deprivation therapy, biochemical recurrence, predictive model, nomogram, androgen response.

Prostate cancer (PCa) remains one of the most commonly diagnosed malignancies among men worldwide [1]. While radical prostatectomy (RP) represents an established treatment option for patients with low and intermediate risk [2], oncological outcomes remain suboptimal in men with high

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and very high risk features, frequently necessitating multimodal treatment strategies [3, 4].

Neoadjuvant androgen deprivation therapy (NADT) before RP has been investigated for several decades as a strategy to improve oncological outcomes in patients with localized and locally advanced PCa. Randomized studies have demonstrated that NADT may reduce tumor volume and the rate of positive surgical margins; however, its effect on long-term oncological outcomes such as biochemical recurrence (BCR) and overall survival (OS) remains uncertain [5—7]. One of the major limitations of this therapeutic approach is the lack of reliable biomarkers capable of identifying patients who are biologically sensitive to androgen deprivation and therefore most likely to benefit from NADT.

Traditionally, the response to androgen deprivation therapy (ADT) has been evaluated using absolute prostate-specific antigen (PSA) values, including baseline PSA, post-treatment PSA, and PSA nadir [8, 9]. While these parameters are widely used in clinical practice, they represent static measurements that may be strongly influenced by initial tumor burden and inter-individual variability. Consequently, absolute PSA values alone may provide limited insight into the biological dynamics of tumor response to ADT and may not accurately reflect intrinsic sensitivity of PCa to androgen deprivation.

To overcome this limitation, increasing attention has been directed toward the evaluation of PSA kinetics during hormonal therapy. Parameters such as the rate of PSA decline, PSA half-life, or logarithmic slopes of PSA change have been proposed as more informative indicators of treatment response [10—12]. These dynamic measures reflect the rate of biomarker changes compared to static PSA measurements. Nevertheless, PSA kinetics alone cannot fully distinguish whether PSA decline results from effective androgen suppression or from intrinsic tumor sensitivity to androgen deprivation.

Since the principal mechanism of NADT is the suppression of testosterone production, the relationship between PSA dynamics and testosterone decline may more accurately reflect the biological responsiveness of PCa to androgen deprivation. Integrating the dynamics of these two biomarkers may therefore provide a more comprehensive assessment of treatment response. Based on this concept, we hypothesized that integrating the dynamics of PSA and testosterone decline may provide a more accurate representation of tumor sensitivity to androgen deprivation. Therefore, we set forward a dynamic androgen response index (IAR), defined as the ratio between the slopes of PSA and testosterone decline during NADT.

The aim of the present study was to evaluate the prognostic significance of IAR and to develop a predictive model for biochemical recurrence in patients undergoing NADT before RP.

Materials and Methods

Study population. This retrospective single-center study was conducted in the O.F. Vozianov Institute of Urology, the National Academy of Medical Sciences of Ukraine (IU NAMS) and included patients with clinically localized and locally advanced PCa who underwent NADT followed by RP at a tertiary referral center. Clinical and pathological data were obtained from institutional medical records between January 2015 and December 2021.

Patients were eligible for inclusion if they had histologically confirmed PCa with a clinical stage ≤ cT4 and no evidence of pelvic wall or urethral sphincter invasion on pretreatment magnetic resonance imaging performed before the initiation of any systemic or local therapy. Availability of baseline clinical data, including measurements of PSA and serum testosterone levels both before initiation of NADT and completion of neoadjuvant treatment, biopsy ISUP, as well as long-term oncological outcomes (date of BCR), was required.

Patients with oligometastatic disease at diagnosis, prior intermittent ADT, previous radiation therapy, and/or systemic chemotherapy before RP, treatment with antiandrogens (AA) monotherapy, or insufficient clinical data precluding reliable oncological assessment were excluded. A total of 84 patients met the inclusion criteria and were included in the final study cohort. The decision to administer NADT before surgery was made on an individual basis, primarily in patients with high- or very high-risk disease features.

All patients subsequently underwent RP with standard pathological evaluation. Postoperative follow-up included serial PSA measurements performed according to the institutional protocols.

The study protocol was approved by the ethics committee of the IU NAMS. The study was conducted in accordance with the principles of the Declaration of Helsinki. The median follow-up duration was 56 months (IQR 38—82).

Neoadjuvant androgen-deprivation therapy. NADT consisted of luteinizing hormone-releasing hormone (LHRH) agonists administered as monotherapy or in combination with nonsteroidal AA. A combined androgen blockade was preferentially used in patients with high-risk disease characteristics. The duration of NADT ranged from 1 to 12 months and was determined by clinical considerations, tumor burden, and treatment planning factors.

Calculations of biomarker dynamics. To quantify the rate of biomarker change during NADT, logarithmic slopes of PSA and testosterone decline were calculated. For each patient, the slope of PSA decline (kPSA) was estimated using the following equation:

$$kPSA = \frac{\ln\left(PSA_{baseline}\right) - \ln\left(PSA_{NADT}\right)}{t}$$

where $PSA_{baseline}$ represents the PSA level before initiation of NADT, PSA_{NADT} is the PSA level measured after therapy, and t is the duration of NADT in months.

Similarly, the slope of testosterone decline (kT) was calculated as:

$$kT = \frac{\ln\left(T_{baseline}\right) - \ln\left(T_{NADT}\right)}{t}$$

where $T_{baseline}$ and T_{NADT} correspond to the serum testosterone levels before and after NADT.

Based on these parameters, a dynamic IAR was defined as the ratio between the slopes of PSA and testosterone decline:

$$IAR = \frac{kPSA}{kT}$$

This index reflects the relationship between tumor PSA response and the degree of androgen suppression.

Study endpoint. The primary endpoint of the study was BCR after RP. BCR was defined as a postoperative PSA level ≥ 0.2 ng/mL confirmed by a second measurement. Biochemical recurrence-free survival (BCRFS) was calculated from the date of RP to the date of BCR or the last follow-up.

Statistical analysis. Descriptive statistics were used to summarize baseline clinical and pathological characteristics of the study cohort. The continuous variables were reported as medians with interquartile ranges (IQRs), whereas the categorical variables were reported as frequencies and percentages.

Comparisons between patients with and without biochemical recurrence (BCR) were performed using the Mann—Whitney U-test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate.

The BCRFS was estimated using the Kaplan—Meier method, and differences between groups were assessed using the log-rank test.

To identify factors associated with BCR, an initial univariable Cox proportional hazards regression analysis was performed. Variables demonstrating potential prognostic significance in the univariable Cox regression were included in an initial multivariable Cox regression model. Variables that retained statistical significance in the initial multivariable analysis were subsequently included in the final reduced prognostic model used for nomogram construction. Therefore, the initial multivariable Cox regression model and the final reduced predictive model were presented separately.

Based on the independent predictors identified in the multivariable analysis, a predictive model for BCR was constructed and presented as a nomogram. The discriminatory performance of the model was evaluated using the receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) and corresponding 95% confidence intervals reported.

The model calibration was assessed using calibration plots comparing the predicted probabilities with the observed outcomes. An internal validation of the model was performed using bootstrap resampling (1,000 iterations) to estimate model optimism and stability.

The potential clinical utility of the predictive model was further evaluated using a decision curve analysis, which quantified the net benefit of the model across a range of threshold probabilities.

All statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA), GraphPad Prism version 10.4.1

Table 1. **Baseline clinical and laboratory characteristics of the study population**

Parameter	Overall (n = 84)
Clinical parameters	
Age, years, median (IQR)	64.5 (60.0—68.7)
BMI, kg/m^2, median (IQR)	27.8 (25.3—30.0)
Baseline PSA (PSA_0), ng/mL, median (IQR)	20.9 (11.5—38.3)
Post-NADT PSA (PSA_1), ng/mL, median (IQR)	1.1 (0.4—3.9)
Baseline testosterone (T_0), nmol/L, median (IQR)	14.3 (11.5—16.7)
Post-NADT testosterone (T_1), nmol/L, median (IQR)	0.7 (0.5—1.1)
Initial prostate volume, cm^3, median (IQR)	55.0 (42.7—75.8)
NADT prostate volume, cm^3, median (IQR)	36.1 (24.7—53.1)
NLR, median (IQR)	3.0 (2.3—4.2)
PLR, median (IQR)	156.8 (121.7—216.3)
CCI, median (IQR)	2.0 (2—3)
Biopsy ISUP grade	
ISUP <4	64 (76.2%)
ISUP ≥4	20 (23.8%)
Clinical stage	
≤ T2c	54 (64.3%)
≥ T3a	30 (35.7%)
NCCN Risk Group	
≤ Intermediate risk	27 (32.1%)
≥ High risk	57 (67.9%)
Duration of NADT	
1—2 months	28 (33.3%)
3 months	29 (34.5%)
>3 months	27 (32.1%)
Type of NADT	
LHRH agonists	54 (64.3%)
LHRH agonists + AA	30 (35.7%)

Notes: IQR — interquartile range; NADT — neoadjuvant androgen deprivation therapy; BMI — body mass index; PSA_0 — initial PSA level; PSA_1 — post-NADT PSA level; T_0 — initial testosterone level; T_1 — post-NADT testosterone level; NLR — neutrophil-to-lymphocyte ratio; PLR — platelet-to-lymphocyte ratio; CCI — Charlson's comorbidity index; ISUP — International Society of Urological Pathology; NCCN — National Comprehensive Cancer Network; LHRH — luteinizing hormone-releasing hormone; AA — antiandrogens.

(GraphPad Software, Boston, MA, USA), and R statistical software version 4.5.2. A two-sided p-value < 0.05 was considered statistically significant.

Results

Patient characteristics. A total of 84 patients were included in the study. Detailed baseline characteristics are summarized in Table 1.

The baseline characteristics in patients with and without BCR are compared in Table 2. Patients who developed BCR had significantly higher baseline PSA levels compared to patients without recurrence (26.1 vs 12.2 ng/mL, p = 0.007). Baseline testosterone levels were significantly lower in patients who experienced BCR (11.1 vs 15.1 nmol/L, p < 0.001), while testosterone levels after neoadjuvant therapy were significantly higher (1.4 vs 0.6 nmol/L, p < 0.001). Clinical stage ≥ cT3a was significantly more frequent among patients with recurrence (p = 0.002). Similarly, patients classified as high-risk according to NCCN criteria demonstrated a higher likelihood of BCR (p = 0.01). The other clinical parameters, including body mass index, prostate volume, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and Charlson comorbidity index, were not significantly associated with recurrence.

Cox regression analysis. Univariable Cox regression analysis identified several predictors associated with BCR, including clinical stage ≥ cT3a (HR 2.52, 95% CI: 1.49—4.28, p = 0.001), testosterone level after neoadjuvant therapy (HR 2.48, 95% CI: 1.42—4.35, p = 0.001), log-transformed PSA (HR 1.52, 95% CI: 1.13—2.06, p = 0.006), and the IAR (HR 1.60, 95% CI: 1.18—2.17, p = 0.003).

In the multivariable model, clinical stage ≥ cT3a (HR 2.34, 95% CI: 1.34—4.07, p = 0.003) and IAR (HR 1.48, 95% CI: 1.05—2.09, p = 0.024) remained independent predictors of BCR. Although log-transformed PSA was significant in the univariable analysis, its significance was lost in the multivariable model. The results of the Cox regression analysis are summarized in Table 3. In the initial multivariable model including the clinical stage ≥ cT3a, IAR, and log-transformed PSA, clinical stage ≥ cT3a and IAR remained independently associated with BCR, whereas log-transformed PSA was not statistically significant. Therefore, log-transformed PSA was not retained in the final reduced predictive model.

Development of the predictive model. Based on the independent predictors identified in the multivariable analysis, a predictive model incorporating clinical stage ≥ cT3a and the IAR was developed (Table 4). A nomogram was plotted to estimate the probability of BCR within 36 months following RP (Fig. 1).

The discriminative ability of the model was evaluated using Harrell's concordance index. The model demonstrated moderate discrimination with a C-index of 0.64. Time-dependent ROC analysis at 36 months yielded an AUC of 0.68 (95% CI 0.56—0.80) (Fig. 2). The Brier score was 0.221 (95% CI: 0.181—0.260), indicating acceptable predictive accuracy. An internal validation using bootstrap resampling (1000 iterations) yielded a Somer's Dxy of 0.27, corresponding to a C-index of 0.64, indicating stable predictive performance.

Table 2. **Comparison of baseline characteristics between patients with and without BCR**

Parameter	BCR (n = 62)	No BCR (n = 22)	p
Clinical parameters			
Age, years, median (IQR)	64.0 (60.0—68.0)	66.5 (60.7—69.2)	0.384*
BMI, kg/m^2, median (IQR)	27.6 (24.8—29.9)	28.1 (26.0—30.6)	0.368*
Baseline PSA (PSA_0), ng/mL, median (IQR)	26.1 (13.9—46.5)	12.2 (8.8—27.1)	0.007*
Post-NADT PSA (PSA_1), ng/mL, median (IQR)	1.25 (0.4—5.0)	0.65 (0.2—3.1)	0.136*
Baseline testosterone (T_0), nmol/L, median (IQR)	11.1 (9.3—13.9)	15.1 (13.5—16.9)	<0.001*
Post-NADT testosterone (T_1), nmol/L, median (IQR)	1.4 (0.7—1.6)	0.6 (0.4—0.9)	<0.001*
Initial prostate volume, cm^3, median (IQR)	54.5 (42.5—73.6)	56.7 (43.6—81.9)	0.522*
NADT prostate volume, cm^3, median (IQR)	36.1 (23.4—47.7)	35.4 (29.2—70.1)	0.242*
NLR, median (IQR)	2.9 (2.3—4.0)	3.0 (2.0—4.5)	0.737*
PLR, median (IQR)	155.9 (123.4—220.7)	165.1 (109.9—201.2)	0.919*
CCI, median, (IQR)	2 (2—3)	2 (2—3)	0.776χ^2
Biopsy ISUP grade			
ISUP <4	45 (72.6%)	19 (86.4%)	0.156χ^2
ISUP ≥4	17 (27.4%)	3 (13.6%)	
Clinical stage			
≤ T2c	34 (54.8%)	20 (90.9%)	0.002χ^2
≥ T3a	28 (45.2%)	2 (9.1%)	
NCCN Risk Group			
≤ Intermediate-risk	15 (24.2%)	12 (54.5%)	0.01χ^2
≥ High-risk	47 (75.8%)	10 (45.5%)	
Duration of NADT			
Duration 1—2 months	21 (33.9%)	7 (31.8%)	0.392χ^2
Duration 3 months	19 (30.6%)	10 (45.5%)	
Duration > 3 months	22 (35.5%)	5 (22.7%)	
Type of NADT			
LHRH agonists	39 (62.9%)	15 (68.2%)	0.431χ^2
LHRH agonists + AA	23 (37.1%)	7 (31.8%)	

Notes: * Comparison of groups by Mann-Whitney test; χ^2 Comparison of categorical variables by chi-square test; BCR — biochemical recurrence; IQR — interquartile range; NADT — neoadjuvant androgen deprivation therapy; BMI — body mass index; PSA_0 — initial PSA level; PSA_1 — post-NADT PSA level; T_0 — initial testosterone level; T_1 — post-NADT testosterone level; NLR — neutrophil-to-lymphocyte ratio; PLR — platelet-to-lymphocyte ratio; CCI — Charlson's comorbidity index; ISUP — International Society of Urological Pathology; NCCN — National Comprehensive Cancer Network; LHRH — luteinizing hormone-releasing hormone; AA — antiandrogens.

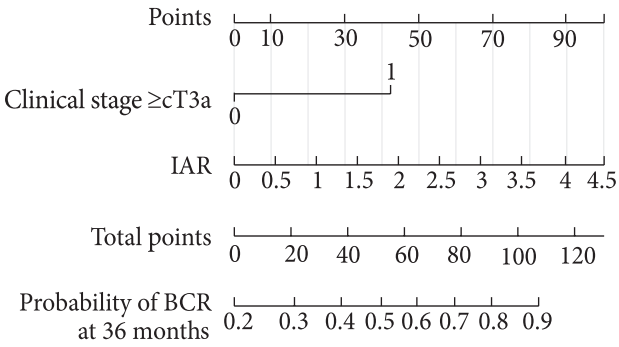


Fig. 1. Nomogram for prediction of biochemical recurrence at 36 months: IAR — androgen response index; BCR — biochemical recurrence

Calibration analysis demonstrated good agreement between predicted and observed probabilities of BCR at 36 months (Fig. 3). The calibration curve indicated satisfactory agreement between predicted and observed event rate across the range of predicted risks.

Decision curve analysis demonstrated that the predictive model provided a higher net benefit compared to both the "treat-all" and "treat-none" strategies across a wide range of threshold probabilities (Fig. 4). These findings suggest that the model may provide clinically useful risk stratification for patients undergoing RP after NADT.

Risk stratification analysis. To evaluate the clinical applicability of the proposed predictive model, the patients were stratified into three risk groups (low, intermediate, and high) according to the calculated risk score derived from the multivariable Cox regression model.

Kaplan—Meier analysis demonstrated a clear separation of BCRFS among the three groups (Fig. 5). The median BCRFS was 69 months in the low-risk group, 57 months in the intermediate-risk group, and 26 months in the high-risk group. Similarly, the estimated mean BCRFS was 62.4 months in the low-risk group, 53.9 months in the intermediate-risk group, and 29.6 months in the high-risk group, indicating a progressive reduction in survival with increasing risk. The differences in survival distributions between the groups were significant according to the log-rank test ($\chi^2 = 18.95$, $p < 0.001$). These findings support the proposed model's ability to effectively stratify patients by risk of BCR following RP.

Table 3. **Cox proportional hazard regression analysis for predictors of biochemical recurrence**

Parameter	HR	95% CI	*p*
Univariable analysis			
cT ≥ T3a	2.52	1.49—4.28	0.001
ISUP Grade after biopsy ≥ ISUP 4	1.29	0.74—2.25	0.378
Baseline testosterone (T_0)	0.84	0.77—0.91	< 0.001
Post-NADT testosterone (T_1)	2.48	1.42—4.35	0.001
kPSA	0.94	0.69—1.29	0.716
kT	0.69	0.49—0.96	0.027
Log (PSA)	1.52	1.13—2.06	0.006
IAR	1.60	1.18—2.17	0.003
Multivariable analysis			
cT ≥ T3a	2.34	1.34—4.07	0.003
IAR	1.48	1.05—2.09	0.024
Log (PSA)	1.17	0.84—1.62	0.367

Notes: HR — hazard ratio; CI — confidence interval; cT — clinical stage; ISUP — International Society of Urological Pathology; T_0 — initial testosterone level; T_1 — post-NADT testosterone level; kPSA — logarithmic slope of PSA level decline; kT — logarithmic slope of testosterone level decline; IAR — dynamic androgen response index.

Discussion

The present study evaluated the prognostic significance of a novel IAR and developed a predictive model for BCR in patients undergoing NADT before RP. The main findings of this study are threefold. First, the IAR integrating PSA and testosterone kinetics during NADT was independently associated with BCR. Second, the integration of IAR with the clinical stage enabled the development of a simple predictive model capable of stratifying patients into distinct recurrence-risk groups. Third, the proposed model demonstrated acceptable discrimination, satisfactory calibration, and potential clinical benefit in decision curve analysis.

Neoadjuvant systemic therapy before RP has been investigated for several decades. Early randomized trials demonstrated that NADT could reduce prostate volume, tumor burden, and the rate of positive surgical margins. However, these studies failed to consistently demonstrate improvements in long-term oncologic outcomes such as BCR or OS [6, 7]. For instance, Soloway et al. [6] reported improved pathological findings

following neoadjuvant androgen ablation but no significant reduction in BCR after surgery. Similarly, Schulman et al. [7] observed favorable pathological outcomes without a clear survival advantage in patients receiving neoadjuvant hormonal therapy before RP.

In recent years, interest in neoadjuvant therapy has re-emerged due to the development of intensified androgen receptor signaling inhibitors (ARSI) and combination systemic approaches. Current studies suggest that neoadjuvant treatment with AR-targeted agents such as abiraterone, enzalutamide, or apalutamide can induce significant pathological responses in patients with high-risk localized PCa, including the rates of minimal residual disease and complete pathological response [13—16]. Despite these promising results, patient selection remains a major challenge, as tumors exhibit heterogeneous biological sensitivity to androgen deprivation.

Several recent reviews emphasize that reliable predictive biomarkers capable of selecting patients most likely to benefit from neoadjuvant therapy represent a major unmet clinical need in localized high-risk and locally advanced PCa [17]. In this context, dynamic biomarkers reflecting biological response during treatment may provide clinically valuable information about tumor endocrine sensitivity and treatment responsiveness.

PSA kinetics have long been investigated as a marker of treatment response in PCa. Several studies have demonstrated that dynamic PSA changes during hormonal therapy may provide prognostic information beyond baseline PSA measurements. Foo et al. [10] reported that PSA kinetics during neoadjuvant hormonal treatment was associated with BCR and PCa-mortality. Similarly, Kang et al. [11] demonstrated that PSA half-life during neoadjuvant hormone therapy predicted the risk of developing castration-resistant PCa following RP. McDonald et al. [12] further confirmed that PSA response to NADT may serve as an independent prognostic indicator of oncologic outcomes. Despite these findings, PSA dynamics alone may not fully reflect tumor sensitivity to androgen deprivation. PSA reduction during ADT may reflect both suppression of androgen-dependent PSA production and intrinsic tumor susceptibility to endocrine therapy. Therefore, PSA kinetics evaluated without consideration of the degree of achieved androgen suppression may provide an incomplete representation of biological treatment response.

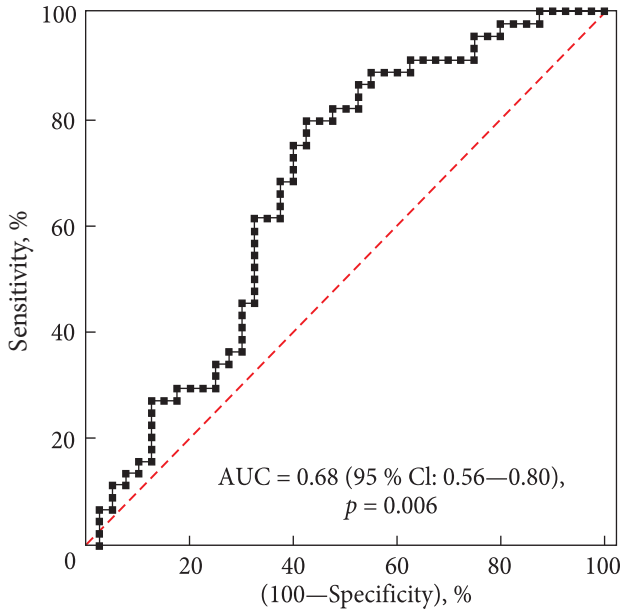


Fig. 2. ROC curve for prediction of biochemical recurrence at 36 months based on the final Cox regression model: AUC — area under the curve

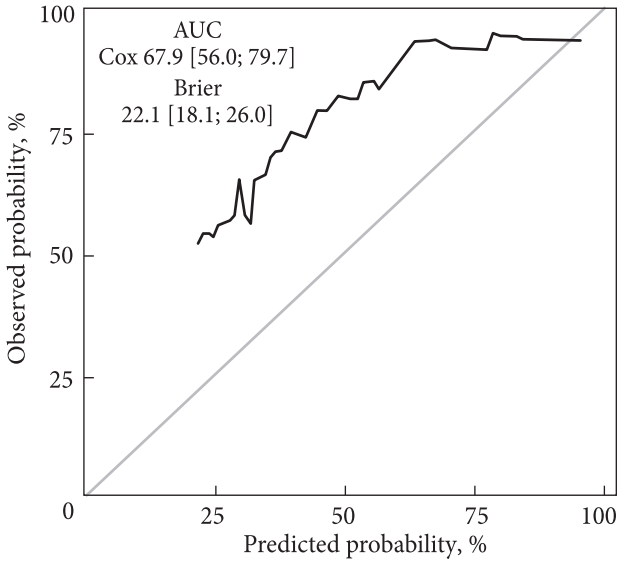


Fig. 3. Calibration plot demonstrating agreement between predicted and observed probabilities of biochemical recurrence at 36 months. AUC and Brier score values shown in the figure are expressed as percentages

The present study addresses this limitation by integrating PSA and testosterone kinetics into a composite biomarker — the IAR. Since the primary mechanism of ADT action involves suppression of circulating testosterone levels, evaluating PSA decline relative to testosterone suppression may

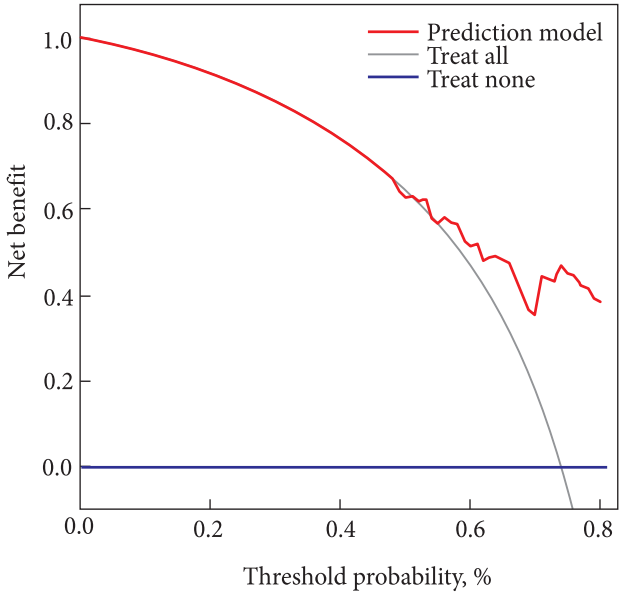
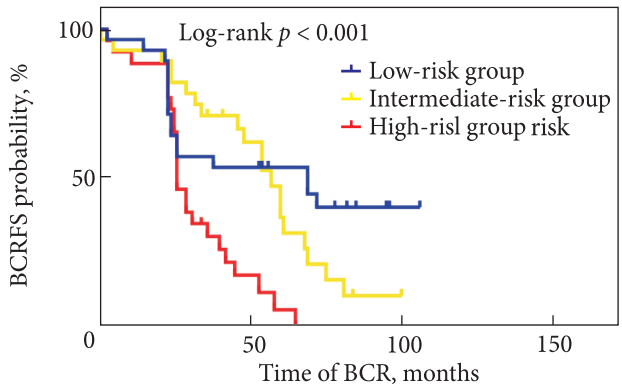


Fig. 4. Decision curve analysis evaluating the clinical utility of the predictive model



Number at risk

Risk group	Months							
	0	15	30	45	60	75	90	105
Low risk	28	27	18	16	13	10	5	3
Intermediate risk	28	27	22	17	9	4	2	1
High risk	28	24	12	5	2	1	1	1

Fig. 5. Kaplan–Meier curves for biochemical recurrence-free survival according to the risk groups derived from the predictive model. BCR — biochemical recurrence; BCRFS — biochemical recurrence-free survival

better reflect the biological responsiveness of PCa to endocrine treatment. However, this interpretation should be considered hypothesis-generating. The present study did not directly evaluate molecular, genetic, or pathological markers of androgen sensitivity. Therefore, IAR should be interpreted as a potential surrogate dynamic marker of response to androgen deprivation rather than as a definitive marker of biological sensitivity. In our analysis, IAR remained independently associated with BCR in multivariable Cox regression analysis, while PSA-related parameters lost statistical significance after adjustment. These findings suggest that composite biomarker dynamics may capture clinically relevant biological information beyond conventional PSA measures alone.

Based on the results, a predictive model incorporating clinical stage and IAR was developed and presented as a nomogram. The model demonstrated moderate discrimination with a concordance index of approximately 0.64 and a time-dependent AUC of approximately 0.67 for prediction of BCR in 36 months. Although these values indicate moderate predictive accuracy, similar levels of discrimination have been reported in several widely used clinical prediction models for PCa. Classic predictive tools such as the Partin tables, CAPRA score, and Kattan nomograms rely primarily on baseline clinicopathological parameters, including PSA level, biopsy Gleason grade, and clinical stage [18—20]. While these models remain useful in clinical practice, they primarily reflect tumor burden and disease extent rather than biological response to therapy. In contrast, the model proposed in the present study incorporates dynamic treatment-response biomarkers obtained during neoadjuvant therapy. By combining tumor biomarker kinetics with endocrine suppression parameters, the IAR may represent a more biologically informative measure of treatment sensitivity. Another important feature of the present model is its simplicity. The final model includes only two variables — clinical stage ≥cT3a and the IAR, which facilitates straightforward clinical implementation in routine practice. Compared with more complex models, requiring multiple clinicopathological variables of postoperative pathological data, such parsimony may enhance reproducibility and applicability in routine clinical practice. The integration of biomarker kinetics and endocrine suppression parameters may therefore represent a promising strategy for identifying patients with biologically sensitive tumors, who are more likely to benefit from NADT.

Importantly, the proposed model demonstrated the ability to stratify patients into low-, intermediate-, and high-risk groups with significantly different BCRFS. This risk stratification may have po-

tential clinical implications, particularly in the context of neoadjuvant therapy. Patients demonstrating poor biological response to NADT may represent a subgroup at increased risk of early recurrence despite surgery and may therefore benefit from closer postoperative monitoring or consideration of multimodal treatment strategies. From a clinical perspective, early identification of patients demonstrating poor biological response to NADT may be particularly relevant. Such patients could potentially benefit from intensified postoperative surveillance, earlier initiation of adjuvant therapies, or enrollment in clinical trials evaluating multimodal treatment strategies.

The findings of this study should be interpreted in light of several limitations. First, the retrospective and single-center design may introduce potential selection bias. Second, the relatively modest sample size may limit statistical power and the generalizability of the results. Third, although internal validation was performed, external validation in independent cohorts is required before the proposed model can be implemented in routine clinical practice. In addition, the incremental prognostic value of IAR compared with models based solely on conventional static biomarkers or individual components of the index was not directly assessed. Future studies should evaluate whether the addition of IAR improves the model discrimination, calibration, and clinical utility beyond established clinical and laboratory predictors. Another limitation relates to the treatment regimens used in this cohort. The study population primarily received conventional ADT with LHRH agonists and AA rather than modern intensified androgen receptor signaling inhibitors. Therefore, the predictive performance of the proposed model in patients treated with contemporary intensified neoadjuvant regimens remains to be determined. Future studies, including larger multicenter cohorts and patients treated with modern intensified ARSI, will be necessary to validate and further refine the proposed model.

Despite these limitations, the study has several strengths. It proposes a biologically plausible composite biomarker reflecting endocrine treatment response, applies a comprehensive predictive modeling workflow including Cox regression, nomogram development, calibration analysis, and decision curve analysis, and demonstrates clinically meaningful survival-based risk stratification. In a field where the main challenge is identifying patients who may truly benefit from neoadjuvant therapy, biomarker-oriented approaches such as the one proposed in this study may contribute to more individualized treatment strategies. Importantly, the present findings should be interpreted in an exploratory context. The proposed index may reflect biological tumor responsiveness to androgen deprivation; however, it should not be considered a definitive predictive tool without external validation.

In sum, the present study introduces a novel dynamic androgen response index integrating PSA and testosterone kinetics during NADT. The proposed index was independently associated with BCR and enabled the development of a simple predictive model capable of stratifying patients according to their risk of recurrence following RP. IAR may serve as a surrogate dynamic marker of response to androgen deprivation. However, this interpretation remains hypothesis-generating and requires further validation. Further prospective studies with external validation are warranted to confirm the clinical applicability of this approach and to explore its potential role in guiding personalized neoadjuvant treatment strategies in PCa.

Conflict of interests

The authors declare no conflict of interest.

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Ethics approval and informed consent

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the IU NAMS (Protocol #6, 14 December 2023). Given the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

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ДИНАМІЧНИЙ ІНДЕКС АНДРОГЕННОЇ ВІДПОВІДІ ТА ЙОГО АСОЦІАЦІЯ З БІОХІМІЧНИМ РЕЦИДИВОМ ПІСЛЯ РАДИКАЛЬНОЇ ПРОСТАТЕКТОМІЇ НА ТЛІ НЕОАД'ЮВАНТНОЇ АНДРОГЕН-ДЕПРИВАЦІЙНОЇ ТЕРАПІЇ

Стан питання. Неоад'ювантна андроген-депривaційна терапія (НАДТ) перед радикальною простатектомією (РПЕ) залишається дискусійним підходом у лікуванні локалізованого та місцево розповсюдженого раку передміхурової залози (РПЗ). Одним з основних обмежень цієї стратегії є відсутність біомаркерів, які могли б ідентифікувати пухлини, біологічно чутливі до андрогенної депривації. **Метою** цього дослідження було оцінити прогностичне значення динамічного індексу андрогенної відповіді (IAB) та розробити прогностичну модель біохімічного рецидиву (БР) після РПЕ. **Матеріали та методи.** У ретроспективне одноцентрове дослідження було включено 84 пацієнти з РПЗ, які отримували НАДТ із подальшим виконанням РПЕ. IAB визначали як співвідношення логарифмічних нахилів зниження концентрацій простат-специфічного антигену (ПСА) та тестостерону під час неоад'ювантної терапії. Для визначення предикторів БР проведено регресійний аналіз Кокса. На основі незалежних предикторів побудовано прогностичну модель та номограму. Ефективність цієї моделі оцінювали за допомогою ROC-аналізу, калібрувальних графіків та аналізу кривих клінічної доцільності. **Результати.** Протягом спостереження (медіана 56 місяців) БР виник у 62 пацієнтів. Клінічна стадія ≥ cT3a (ВР 2,34; $p = 0{,}003$) та IAB (ВР 1,48; $p = 0{,}024$) були незалежними предикторами БР. Модель продемонструвала помірну дискримінаційну здатність (AUC 0,68) та задовільне калібрування. **Висновки.** IAB може відображати біологічну відповідь РПЗ на андрогенну депривацію. Отримані результати слід розглядати як такі, що генерують гіпотезу, і вони потребують подальшої валідації в контексті стратифікації ризику БР після РПЕ на тлі НАДТ.

Ключові слова: рак передміхурової залози, неоад'ювантна андроген-депривaційна терапія, біохімічний рецидив, прогностична модель, номограма, андрогенна відповідь.