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Testosterone Recovery after Androgen Deprivation Therapy in Prostate Cancer: Building a Predictive Model

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Purpose: To analyze the variability, associated actors, and the design of nomograms for individualized testosterone recovery after cessation of androgen deprivation therapy (ADT).

Materials and Methods: A longitudinal study was carried out with 208 patients in the period 2003 to 2019. Castrated and normogonadic testosterone levels were defined as 0.5 and 3.5 ng/mL, respectively. The cumulative incidence curve described the recovery of testosterone. Univariate and multivariate analyzes were performed to predict testosterone recovery with candidate prognostic factors prostate-specific antigen at diagnosis, clinical stage, Gleason score from biopsy, age at cessation of ADT, duration of ADT, primary therapy and use of LHRH (luteinizing hormone-releasing hormone) agonists.

Results: The median follow-up duration in the study was 80 months (interquartile range, 49–99 mo). Twenty-five percent and 81% of patients did not recover the castrate and normogonadic levels, respectively. Duration of ADT and age at ADT cessation were significant predictors of testosterone recovery. We built two nomograms for testosterone recovery at 12, 24, 36, and 60 months. The castration recovery model had good calibration. The C-index was 0.677, with area under the receiver operating characteristic curve (AUC-ROC) of 0.736, 0.783, 0.782, and 0.780 at 12, 24, 36, and 60 months, respectively. The normogonadic recovery model overestimated the higher values of probability of recovery. The Cindex was 0.683, with AUC values of 0.812, 0.711, 0.708 and 0.693 at 12, 24, 36, and 60 months, respectively.

Conclusions: Depending on the age of the patient and the length of treatment, clinicians may stop ADT and the castrated testosterone level will be maintained or, if the course of treatment has been short, we can estimate if it will return to normogonadic levels.

Keywords: Castration; Hypogonadism; Nomograms; Prostatic neoplasms

INTRODUCTION

Neoadjuvant o adjuvant androgen deprivation therapy (ADT) is the most common treatment in patients with high-risk and locally advanced prostate cancer (PCa). Also, continuous ADT is the cornerstone in the management of metastatic PCa [1]. Two recent studies questioned the need to maintain ADT in metastatic castration-resistant PCa (mCRPC). The combination of abiraterone with prednisone without ADT could be comparable with standard treatment involving all three drugs [2,3].

There are two main approaches to ADT for PCa: surgical orchiectomy, which is uncommon, or the use of luteinizing hormone-releasing hormone (LHRH) agonists for chemical castration (total testosterone, [T]<0.5 ng/mL). The LHRH antagonist, degarelix, is another less used option. Continuous ADT with LHRH agonists has been the standard of care in this context.

Chemical castration exposes the patient to the symptoms of hypogonadism (sexual dysfunction, infertility, decreased libido, decrease in facial and body hair, decrease in muscle mass, weight gain, gynecomastia, reduced testicle size, osteoporosis, mental and emotional changes, anemia, fatigue, and hot flashes), impairing patient quality of life.

In addition, ADT is linked to cardiovascular events, diabetes, acute kidney injury, and bone loss [4,5], and these dangerous effects could be related not to the absence of testosterone but to the drug used to achieve chemical castration [4,6].

After ADT cessation, whether due to the use of an adjuvant protocol or an intermittent protocol, we assume a variability in the recovery to the normogonadic level ([T]>3.5 ng/mL). Some patients never recover a normal [T] above the limit of castration.

Given this context, we analyzed the variability of, factors associated with, and the design of individualized nomograms for [T] recovery after ADT cessation. These nomograms could be useful in counselling patients about the improvement in their quality of life after the cessation of ADT at the conclusion of adjuvant protocols, or when seeking to avoid dangerous side effects and unnecessary costs of continuous ADT when is not expected the recovery of [T] in case of ADT cessation.

MATERIALS AND METHODS

A retrospective observational longitudinal study was performed with 208 patients after the cessation of ADT in Miguel Servet University Hospital, Spain. Aged at start of ADT was in the range 48 to 91 years (mean, 69.6 y; 95% confidence interval [CI], 68.6–70.0 y; median, 70 y; interquartile range [IQR], 64–75 y). Patients who stopped ADT between 2003 and 2013, regardless of the indications for ADT or the reasons for cessation, were recruited. As this is a retrospective study, the criteria for discontinuation of the ADT were not predetermined. Adjuvant treatment to external beam radiotherapy (EBRT) was mainly maintained for approximately 3 years according to standard clinical practice. The intermittency of the ADT was managed by "phase-on" at least up to a prostate-specific antigen (PSA) lower than 4 ng/mL, allowing the change to "phase-off" according to clinical criteria. The reintroduction of ADT was recommended if the PSA increased above 15 to 20 ng/mL, or with better clinical criteria. All patients were included in the study from the start of ADT to their first cessation of it, either due to the end of adjuvancy to EBRT or to the start of the phase-off in an intermittent ADT approach. The follow-up period began after the cessation of ADT and stopped at the time of patient death or censoring in December 2019. We evaluated the recovery of testosterone levels above the castrate and normogonadic thresholds and the associated factors. The castrate and normogonadic thresholds were defined as a [T] of 0.5 and 3.5 ng/mL, respectively. The research protocol was approved by the Clinical Research Ethics Committee of Aragon (PI 20/307) in accordance with the Declaration of Helsinki. Due to the retrospective observational nature of this study, data were fully anonymized, and the need to obtain informed consent was waived. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.

A survival analysis was performed by cumulative incidence curves. For the testosterone levels of 0.5 and 3.5 ng/mL, the rate of recovery was analyzed until 120 months after the cessation of ADT. Univariate and multivariate stepwise models were built using the Cox proportional hazards model with the following candidate prognostic factors: PSA at diagnosis, clinical stage, biopsy specimen Gleason score, age at ADT cessation, duration of ADT, primary therapy, and use of LHRH

agonists. Nonlinear dependences were analyzed using restricted cubic splines. ANOVA test was used to establish statistical significance for categorical variables in the univariate analysis. To more accurately identify the significant predictors in univariate analyses beyond the results of an extensive search, we estimated the p-values adjusted for multiple comparisons using the Holm method [7].

The calibration and discrimination ability of the multivariate model were established using calibration curves at 1, 2, 3, and 5 years and the area under the receiver operating characteristic curve (AUC-ROC). The probability density functions provided a graphical representation of the probabilities yielded by the model, and the performance of the model for different threshold probability points was assessed with clinical utility curves. In addition, two nomograms were built to predict individualized testosterone recovery (0.5 and 3.5 ng/mL) after ADT cessation at 1, 2, 3, and 5 years.

The model was internally validated with a tenfold cross validation analysis. For this analysis, the entire dataset was divided into 10 groups, 9 of which were used to build the prognostic model and 1 of which was used to validate the model. This procedure was repeated, taking into account all possible ways to select the 9 subgroups, ensuring different ways of validating the testosterone recovery models with data not used in the model construction process.

The statistical analysis was performed using R ver. 3.6.1 programming language (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The median follow-up duration for patients was 80 months (IQR, 49–99). Eighty patients (38.5%) died during follow-up. We found high individualized variability in testosterone recovery after ADT cessation. Of the 208 patients enrolled, 156 (75.0%) recovered to the castrate threshold level, 0.5 ng/mL. The first quartile (p25), median (p50) and third quartile (p75) of time until this recovery 7, 11, 13 months.

With regards to the normogonadic level of 3.5 ng/mL, 81% of the patients (168 cases) did not recover to this level, with a median follow-up duration of 76 months (IQR, 45–96). The p25, p50, and p75 values for the time until recovery to the normogonadic level were 64, 93, and 103 months, respectively. Fig. 1 shows the cumulative incidence curves for the recovery of testosterone levels to 0.5 and 3.5 ng/mL.

Table 1 shows the stage of cancer leading to the initiation of ADT, the duration and type of treatment. Table 2 displays the descriptive characteristics of the patients stratified by final testosterone recovery group ([T]<0.5 ng/mL, [T]≥0.5 ng/mL; [T]<3.5 ng/mL, [T]≥3.5 ng/mL). The distribution of primary therapy was as follows: watchful waiting, 7.2% (n=15); laparoscopic radical prostatectomy, 2.4% (n=5); retropubic radical prostatectomy, 48.6% (n=101); EBRT, 9.6% (n=20); ADT, 24.0% (n=50); and EBRT+ADT, 8.2% (n=17).

The prognostic factors associated with recovery to the castrate and normogonadic levels in the univariate analysis are shown in Table 3. The duration of ADT and the age at ADT cessation were significant factors
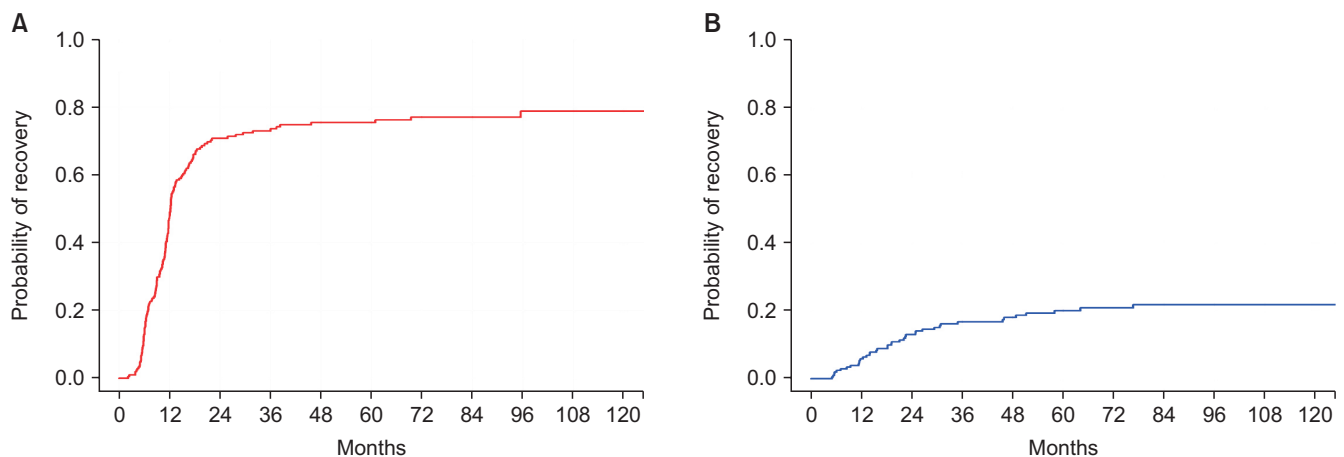

Fig. 1. Cumulative incidence curves for the recovery of the castrate and normogonadic testosterone levels. Cumulative incidence of testosterone (A) 0.5 ng/mL and (B) 3.5 ng/mL recovery.

Table 1. Stage of cancer and ADT characteristics

Cancer stage at the start of ADT	Reason for discontinuation	Number of patients	Duration of treatment (mo)			PSA nadir after the start of ADT PSA (ng/mL)		
			Mean (95% CI)	Median (IQR)	Rank	Mean (95% CI)	Median (IQR)	Rank
Localized								
Unfit for primary treatment	Intermittent ADT	33 (15.9)	71 (53–88)	56 (24–117)	7–170	0.32 (0.00–0.63)	0.07 (0.01–0.19)	0.01–5.10
Progression in watchful waiting	Intermittent ADT	15 (7.2)	40 (22–58)	31 (16–58)	6–125	0.32 (0.09–0.54)	0.09 (0.04–0.62)	0.01–1.28
Locally advanced								
Clinical stage, unfit for primary treatment	Intermittent ADT	12 (5.8)	131 (97–164)	150 (88–177)	27–192	0.23 (0.00–0.65)	0.02 (0.01–0.07)	0.01–2.32
Pathological stage, adjuvant treatment	Intermittent ADT	19 (9.1)	92 (75–109)	98 (69–110)	35–151	0.01 (0.01–0.02)	0.01 (0.01–0.01)	0.00–0.04
EBRT	Adjuvant ADT	18 (8.7)	37 (32–42)	41 (30–44)	16–51	0.02 (0.01–0.02)	0.01 (0.01–0.02)	0.00–0.06
Progression after primary treatment	Intermittent ADT	106 (51.0)	66 (57–749)	62 (29–95)	6–215	0.03 (0.01–0.06)	0.01 (0.01–0.02)	0.00–1.09
Metastatic disease	Intermittent ADT	5 (2.4)	119 (26–212)	125 (67–182)	23–199	0.1 (0.00–0.34)	0.01 (0.01–0.03)	0.01–0.45

ADT: androgen deprivation therapy, PSA: prostate-specific antigen, CI: confidence interval, IQR: interquartile range, EBRT: external beam radiotherapy.

in both models, but some LHRH agonists (ANOVA test p-value=0.001) and primary therapies (ANOVA test p-value=0.019) were significant factors only in the castrate level recovery model. The adjusted p-values for multiple comparisons in univariate analysis remained significant for age at ADT cessation in both models, but duration of ADT was significant only in the model for the recovery of [T] to 0.5 ng/mL, although it was nearly significance in the model for the recovery of [T] to 3.5 ng/mL, with a p-value of 0.084. The rest of variables were not significant according to the adjusted p-values.

In the multivariate analysis, also shown in Table 3, the duration of ADT and the age at ADT cessation were the significant independent predictors of a recovery of [T] to 0.5 ng/mL. Moreover, for the model of the recovery of [T] to 3.5 ng/mL, the significant factors were also duration of ADT and age at ADT cessation. Using these models, we built two nomograms to estimate [T] recovery at 12, 24, 36, and 60 months (Fig. 2, 3).

The model for the recovery of [T] to 0.5 ng/mL had a high concordance between the predicted and actual values in the calibration analysis at 12, 24, 36, and 60 months (Fig. 4). Its discrimination capacity (Cindex) was 0.677, with AUC-ROC of 0.736, 0.783, 0.782, and 0.780 at 12, 24, 36, and 60 months, respectively. In addition, the normogonadic recovery model overestimated the probability of recovery (Fig. 5), although there was a low actual incidence of recovery: greater than 0.1 at

12 months, greater than 0.2 at 24 months, and greater than 0.3 at 36 and 60 months. Regardless, it seems that the recovery model is truly useful starting at 36 months. Moreover, the Cindex was 0.683, with AUC-ROC of 0.812, 0.711, 0.708, and 0.693 at 12, 24, 36, and 60 months, respectively.

The discrimination ability of the models can be seen in more detail in Fig. 6 and 7. There is overlap between the probability density functions for patients who did and did not recover the castrate or normogonadic levels; thus, it seems difficult to choose a threshold probability that clearly discriminates both groups. However, most patients with a probability of recovery greater than 80% recovered the castrate level.

The C-index values for the models of the recovery of [T] to 0.5 and 3.5 ng/mL were internally validated by tenfold cross-validation. Both prognostic models provide robust predictions, as shown by the minimum loss in the C-index (0.666 and 0.678 for the 0.5 and 3.5 ng/mL models, respectively).

An app is provided for the use of the nomograms (https://urostatisticalsolutions.shinyapps.io/testosterone recovery/).

DISCUSSION

Time to testosterone recovery after ADT has been investigated in previous studies. In 1998, Oefelein [8] reported 13 patients with clinically localized PCa who

Table 2. Descriptive characteristics of the patients stratified by final testosterone recovery group

Variable	Total	Testosterone (ng/mL)					
		<0.5	≥0.5	p-value	<3.5	≥3.5	p-value
PSA (ng/mL)	11.9 (7.4–19.9)	14.2 (8.9–24.9)	11.4 (6.9–18.5)	0.039	11.90 (7.18–20.60)	10.6 (6.1–18.3)	0.221
Age at ADT cessation (y)	76 (71–81)	79 (75–82)	75 (69–81)	<0.001	78 (72–82)	72 (68–77)	<0.001
Months of ADT	56 (29–102)	102 (55–137)	48 (25–81)	<0.001	63 (32–106)	40 (23–66)	0.011
Gleason				0.744			0.836
6	116 (55.8)	31 (59.6)	85 (54.5)		92 (54.8)	24 (60.0)	
7	69 (33.2)	15 (28.9)	54 (34.6)		57 (33.9)	12 (30.0)	
8–10	23 (11.1)	6 (11.5)	17 (10.9)		19 (11.3)	4 (10.0)	
T stage				0.168			0.265
T1	76 (36.5)	14 (26.9)	62 (39.7)		57 (33.9)	19 (47.5)	
T2	110 (52.9)	30 (57.7)	80 (51.3)		92 (54.8)	18 (45.0)	
T3	22 (10.6)	8 (15.4)	14 (9.0)		19 (11.3)	3 (7.5)	
N stage				0.698			0.638
Nx	9 (4.3)	2 (3.8)	7 (4.5)		8 (4.8)	1 (2.5)	
N0	197 (94.7)	50 (96.2)	147 (94.2)		158 (94.0)	39 (97.5)	
N1	2 (1.0)	0 (0.0)	2 (1.3)		2 (1.2)	0 (0.0)	
M stage							
Mx	2 (1.0)	0 (0.0)	2 (1.3)		2 (1.2)	0 (0.0)	
M0	201 (96.6)	51 (98.1)	150 (96.2)		161 (95.8)	40 (100)	
M1	5 (2.4)	1 (1.9)	4 (2.5)		5 (3.0)	0 (0.0)	
LHRH agonist				0.387			0.497
Leuprolerin (Procrin®)	55 (26.4)	10 (19.2)	45 (28.8)		41 (24.4)	14 (35.0)	
Triptorelin (Decapeptyl®)	53 (25.5)	18 (34.6)	35 (22.4)		46 (27.4)	7 (17.5)	
Leuprolerin (Eligard®)	33 (15.9)	8 (15.4)	25 (16.0)		26 (15.5)	7 (17.5)	
Buserelin (Suprefact®)	14 (6.7)	5 (9.6)	9 (5.8)		13 (7.7)	1 (2.5)	
Goserelin (Zoladex®)	52 (25.0)	11 (21.2)	41 (26.3)		41 (24.4)	11 (27.5)	
Leuprorelin (Lutrate®)	1 (0.5)	0 (0)	1 (0.6)		1 (0.6)	0 (0)	
Primary treatment				0.220			0.117
Watchful waiting	15 (7.2)	2 (3.8)	13 (8.3)		13 (7.7)	2 (5.0)	
LRP	5 (2.4)	0 (0)	5 (3.2)		3 (1.8)	2 (5.0)	
RRP	101 (48.6)	23 (44.2)	78 (50.0)		76 (45.2)	25 (62.5)	
EBRT	20 (9.6)	6 (11.5)	14 (9.0)		15 (8.9)	5 (12.5)	
EBRT+ADT	17 (8.2)	3 (5.8)	14 (9.0)		15 (8.9)	2 (5.0)	
ADT	50 (24.0)	18 (34.6)	32 (20.5)		46 (27.4)	4 (10.0)	
Intervals of dosage				0.386			0.985
Every 6 months	34 (16.3)	6 (11.5)	28 (17.9)		28 (16.7)	6 (15.0)	
Every 3 months	174 (83.7)	46 (88.5)	128 (82.1)		140 (83.3)	34 (85.0)	

Values are presented as median (interquartile range) for continuous variables and number (%) for categorical variables.
PSA: prostate-specific antigen, ADT: androgen deprivation therapy, LHRH: luteinizing hormone-releasing hormone, LRP: laparoscopic radical prostatectomy, RRP: retropubic radical prostatectomy, EBRT: external beam radiotherapy.

received a single dose of a 3-month LHRH agonist. The median duration to recover the castrate level was 6 months, with a median duration of hypogonadal symptoms, such as hot flashes, of 13.6 months. In 1999, Hall et al [9] found that when ADT was terminated after a minimum of 24 months (median, 38.6 mo; range, 25–82 mo), the median [T] remained at the castrate level at 6

and 9 months. Both of these studies suggested the possibility of modifying the dosing scheduling for these drugs based on the testosterone levels.

Pedraza and Kwart [10] reported a castrate level of testosterone during the 36 months of follow-up in 4 patients over the age of 70 years after a median treatment duration of 108 months (range, 94–120 mo), prob-

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Table 3. Univariate and multivariate analyses

| Variable | Testosterone ≥0.5 ng/mL recovery | | | | | Testosterone ≥3.5 ng/mL recovery | | | | |
| | Univariate | | | Multivariate | | Univariate | | | Multivariate | |
	HR (95% CI)	p-value	p-value[a]	HR (95% CI)	p-value	HR (95% CI)	p-value	p-value[a]	HR (95% CI)	p-value
PSA	0.99 (0.99–1.00)	0.864	>0.999		n.s.	0.99 (0.96–1.01)	0.231	>0.999		n.s.
Age at ADT cessation	0.96 (0.94–0.98)	<0.001	0.001	0.964 (0.944–0.984)	<0.001	0.93 (0.89–0.97)	<0.001	0.015	0.94 (0.90–0.98)	0.002
Months of ADT	0.99 (0.98–0.99)	<0.001	<0.001	0.988 (0.984–0.992)	<0.001	0.99 (0.98–0.99)	0.005	0.084	0.99 (0.98–0.99)	0.011
Gleason										
6	Ref.		Ref.		n.s.	Ref.		Ref.		n.s.
7	1.22 (0.86–1.74)	0.260	>0.999			0.99 (0.49–2.02)	0.996	>0.999		
8–10	1.08 (0.64–1.81)	0.785	>0.999			0.87 (0.29–2.51)	0.792	>0.999		
Clinical stage										
T1	Ref.		Ref.		n.s	Ref.		Ref.		n.s.
T2	0.82 (0.59–1.14)	0.242	>0.999			0.62 (0.33–1.19)	0.151	>0.999		
T3–T4	0.65 (0.36–1.16)	0.144	>0.999			0.44 (0.13–1.50)	0.191	>0.999		
LHRH agonist										
Leuprolerin (Procrin®)	Ref.		Ref.		n.s.	Ref.		Ref.		n.s.
Triptorelin (Decapeptyl®)	0.64 (0.41–0.99)	0.047	0.611			0.48 (0.19–1.19)	0.113	>0.999		
Leuprolerin (Eligard®)	0.79 (0.48–1.29)	0.341	>0.999			0.92 (0.37–2.28)	0.857	>0.999		
Buserelin (Suprefact®)	0.44 (0.21–0.89)	0.024	0.384			0.24 (0.03–1.86)	0.174	>0.999		
Goserelin (Zoladex®)	0.71 (0.46–1.08)	0.107	>0.999			0.76 (0.34–1.67)	0.491	>0.999		
Leuprorelin (Lutrate®)	NA	NA	NA			NA	NA	NA		
Primary treatment										
Watchful waiting	Ref.		Ref.		n.s.	Ref.		Ref.		n.s.
LRP	3.03 (1.08–8.56)	0.036	0.540			4.22 (0.59–29.90)	0.150	>0.999		
RRP	0.78 (0.43–1.40)	0.407	>0.999			1.90 (0.45–8.02)	0.383	>0.999		
EBRT	0.71 (0.33–1.51)	0.368	>0.999			2.13 (0.41–10.90)	0.366	>0.999		
EBRT+ADT	0.86 (0.40–1.82)	0.688	>0.999			0.76 (0.11–5.39)	0.784	>0.999		
ADT	0.50 (0.26–0.95)	0.036	0.540			0.58 (0.11–3.19)	0.535	>0.999		
Intervals of dosage										
Every 3 months	Ref.		Ref.		n.s.	Ref.		Ref.		n.s.
Every 6 months	1.38 (0.91–2.08)	0.128	>0.999			0.98 (0.41–2.33)	0.960	>0.999		

HR: hazard ratio, CI: confidence interval, PSA: prostate-specific antigen, ADT: androgen deprivation therapy, LHRH: luteinizing hormone-releasing hormone, LRP: laparoscopic radical prostatectomy, RRP: retropubic radical prostatectomy, EBRT: external beam radiotherapy, Ref.: category of reference, NA: not available, n.s.: non-significant.
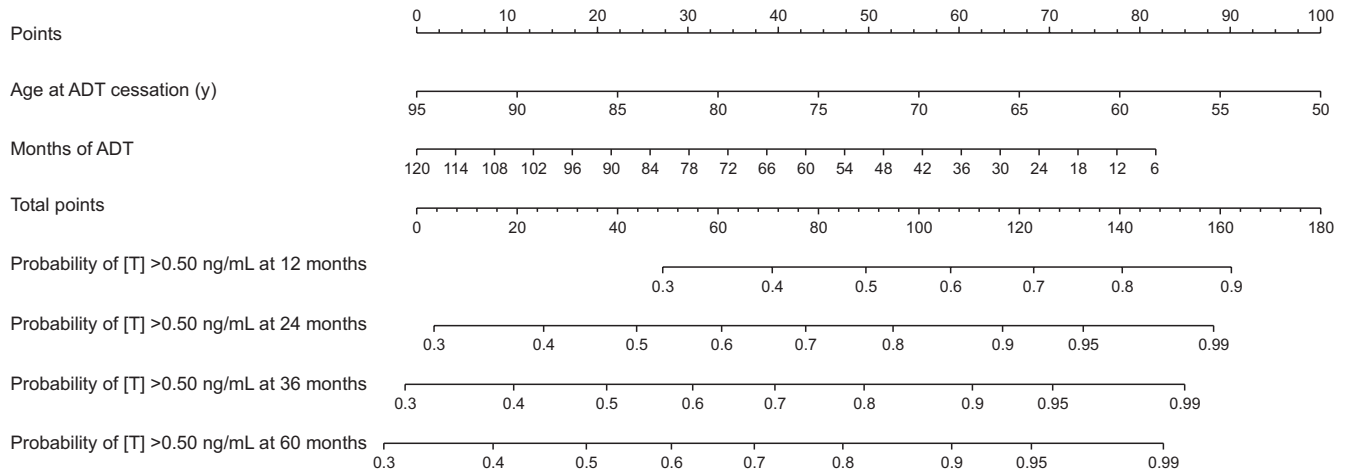[a] Adjust p-values for multiple comparisons in univariate analysis.

Fig. 2. Nomogram for the castrate testosterone level recovery model after ADT cessation. ADT: androgen deprivation therapy, [T]: total testosterone.
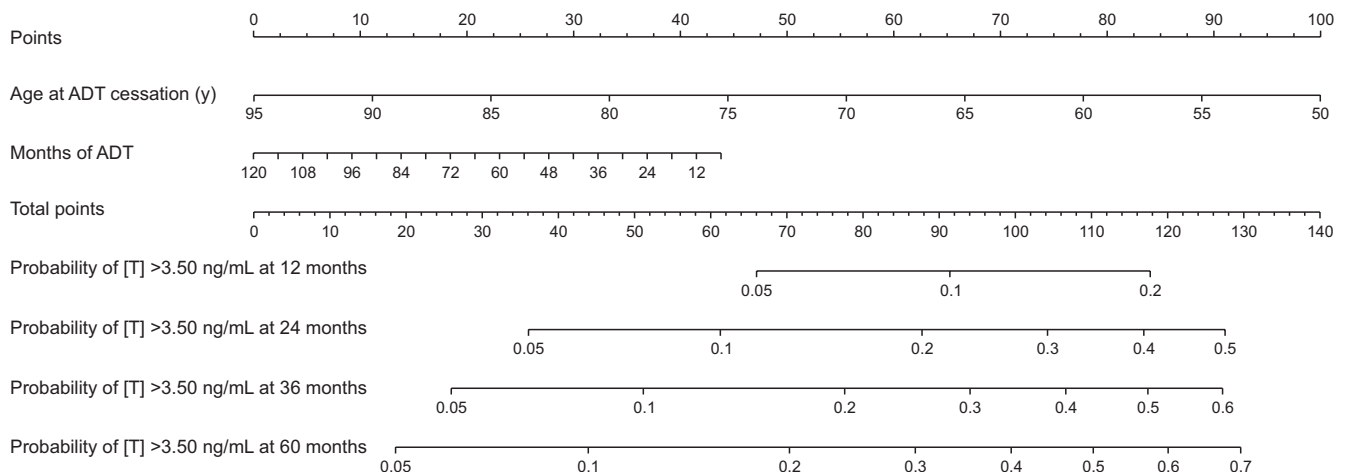

Fig. 3. Nomogram for the normogonadic testosterone level recovery model after ADT cessation. ADT: androgen deprivation therapy, [T]: total testosterone.

ably due to the impairment of the function of Leydig cells. This was a major implication of their findings, not only with regard to the treatment schedule but also economics. The median duration of treatment was much longer in their study than in ours, which is probably the reason all their patients remained castrated.

Oefelein [11] studied 32 patients with a median age of 71 years (range, 54–86 y) who were treated for a median of 7.5 months (range, 3–49 mo) and found a significant association between patient age and testosterone level recovery. Pickles et al [12] found that patients older than 75 years had significant difficulty recovering. Gulley et al [13] found the same result in patients older than 66 years. Others have reported similar differences between patients older or younger than 60 [14], 65 [15], 67 [16], or 70 [17] years, and some have been able even to delineate age ranges [17-19]. Planas et al [20]

did not find this association, perhaps due to the narrow age range (95% CI, 69.1–73.9 y) of the patients in their study, as they acknowledged. Instead of an association with duration of ADT, they reported a significant difference between patients treated for more or less than 60 months.

This influence of ADT duration has been described before. Nejat et al [21] reported 68 heterogeneous patients who received ADT. They concluded that patients treated for less than 24 months achieved normal testosterone levels in 6 months, while 22 months were needed to recover a normal testosterone level among those who were treated for longer than 24 months (log-rank p-value=0.0034). Other authors set the limit as more or less than 30 [15] or 36 [22] months, as in the present study.

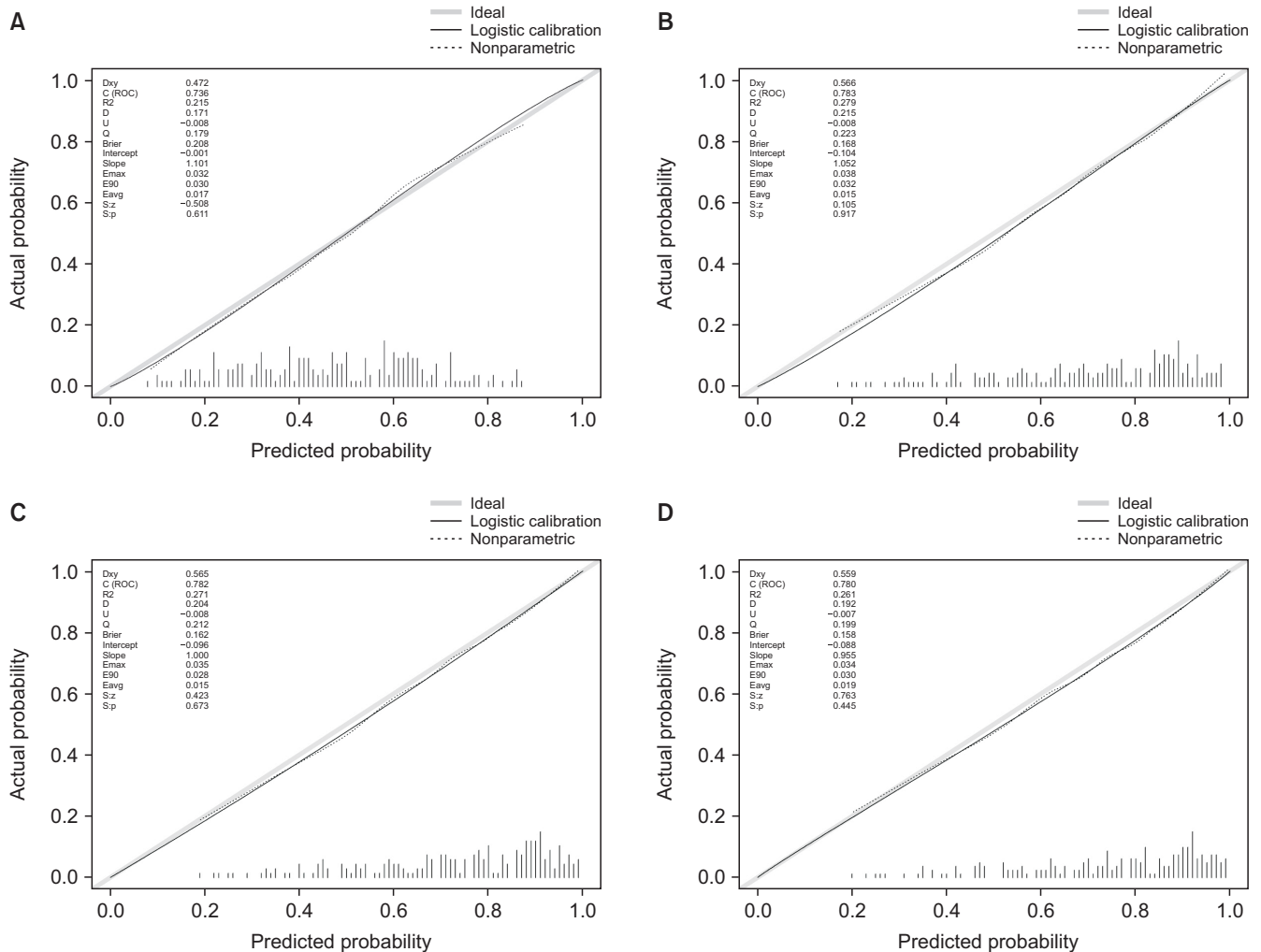Recently, Nam et al [23] reported the associations be-

Fig. 4. Calibration plot for the castrate testosterone level recovery model at 12 months (A), 24 months (B), 36 months (C), and 60 months (D).

tween testosterone level recovery and age, sex hormone binding globulin level, initial testosterone level, and ADT duration in patients treated with ADT after radical prostatectomy.

Our study has demonstrated statistically significant associations between both the duration of ADT and the age at treatment cessation with the delay in and the probability of testosterone recovery. Moreover, our study was able to determine the individual probability of testosterone recovery and its delay based on the duration of treatment and the age of the patient through the use of nomograms. Our model, based on age at ADT cessation and duration of ADT treatment, is particularly useful in young men with an indication for short periods of neoadjuvant ADT. In them we can make a useful estimate of the recovery of testosterone that ends with the limitation in the quality of life associated with castration.

It is know that the recovery of testosterone levels after cessation of ADT depends on the age of the patient and the duration of treatment. But so far there is no predictive model that combines both aspects and gives an individualized prediction of recovery in each isolated patient.

It is important to not only provide tool that can be used to modify the dosing scheduling to obtain a financial benefit but also to provide one that can be used to determine when a patient can discontinue the treatment yet remain castrated to avoid the adverse effects of ADT with LHRH agonists [6].

Despite the number of variables analyzed, only two had significant associations with testosterone level recovery. This apparent simplicity contributes to the applicability of the model.

Our model has two clinical scenarios in which it is applicable. The first is in the counselling session to dis-
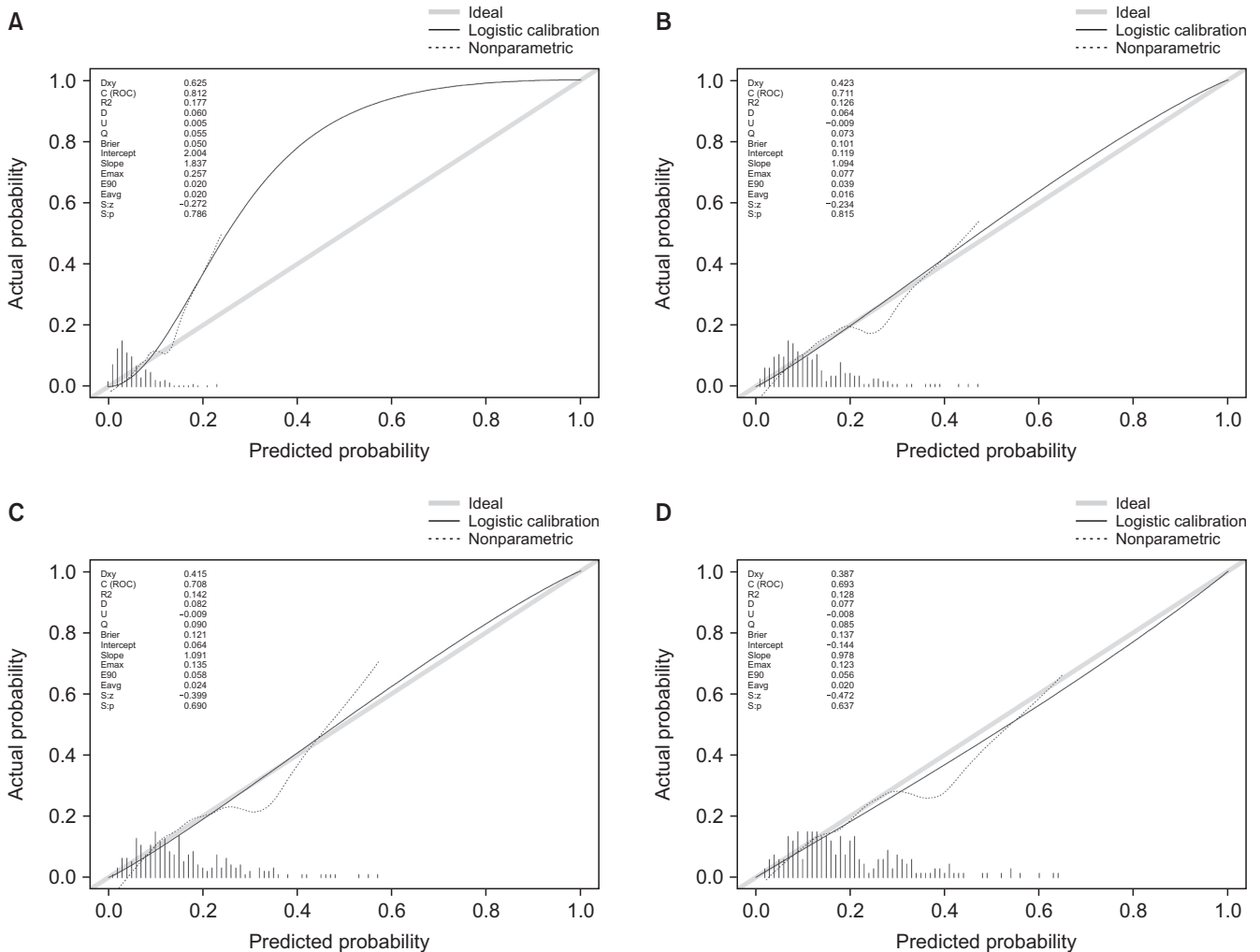
Fig. 5. Calibration plot for the normogonadic testosterone level recovery model at 12 months (A), 24 months (B), 36 months (C), and 60 months (D).

cuss the indications for neoadjuvant/adjuvant/concurrent treatment of PCa with a NCCN stage indicating unfavorable intermediate risk, high risk or very high risk. In addition to advising the patients of the possible side effects of ADT, we can offer an individualized estimate of their disappearance after the cessation of ADT. The second is for patients with advanced/metastatic PCa, who do not intend to avoid the protocol for the measurement of serum testosterone levels during chemical castration. For these patients, the nomogram can help make the decision to terminate ADT based on the assumption that castration will continue even without treatment.

It has been reported that surgically castrated men have significantly lower risks of cardiac–related complications, peripheral arterial disease and fractures than men treated with GnRHa. Additionally, diabetes mellitus and venous thromboembolism appear to be

more common when treatment is maintained for longer than 35 months [4]. In this sense, 36 months is a crucial time in our study. We have shown that most recoveries to the castrate level happen in the first 2 years, with a minimal increase in recovery at 3 years, and almost no additional increase recovery after 36 months. Moreover, we have shown that more than 25% of patients remain castrated after LHRH cessation after 36 months of ADT and nearly 80% do not reach normal testosterone levels after this time.

Therefore, discontinuing ADT with an LHRH agonist is important. Our study could help clinicians decide when to conclude treatment with LHRH agonists not only if we want the patient to recover his testosterone level, thereby improving his quality of life, but also when we want the patient to maintain the castrate level while avoiding the side effects of the chemical castration drugs; this may also be feasible in
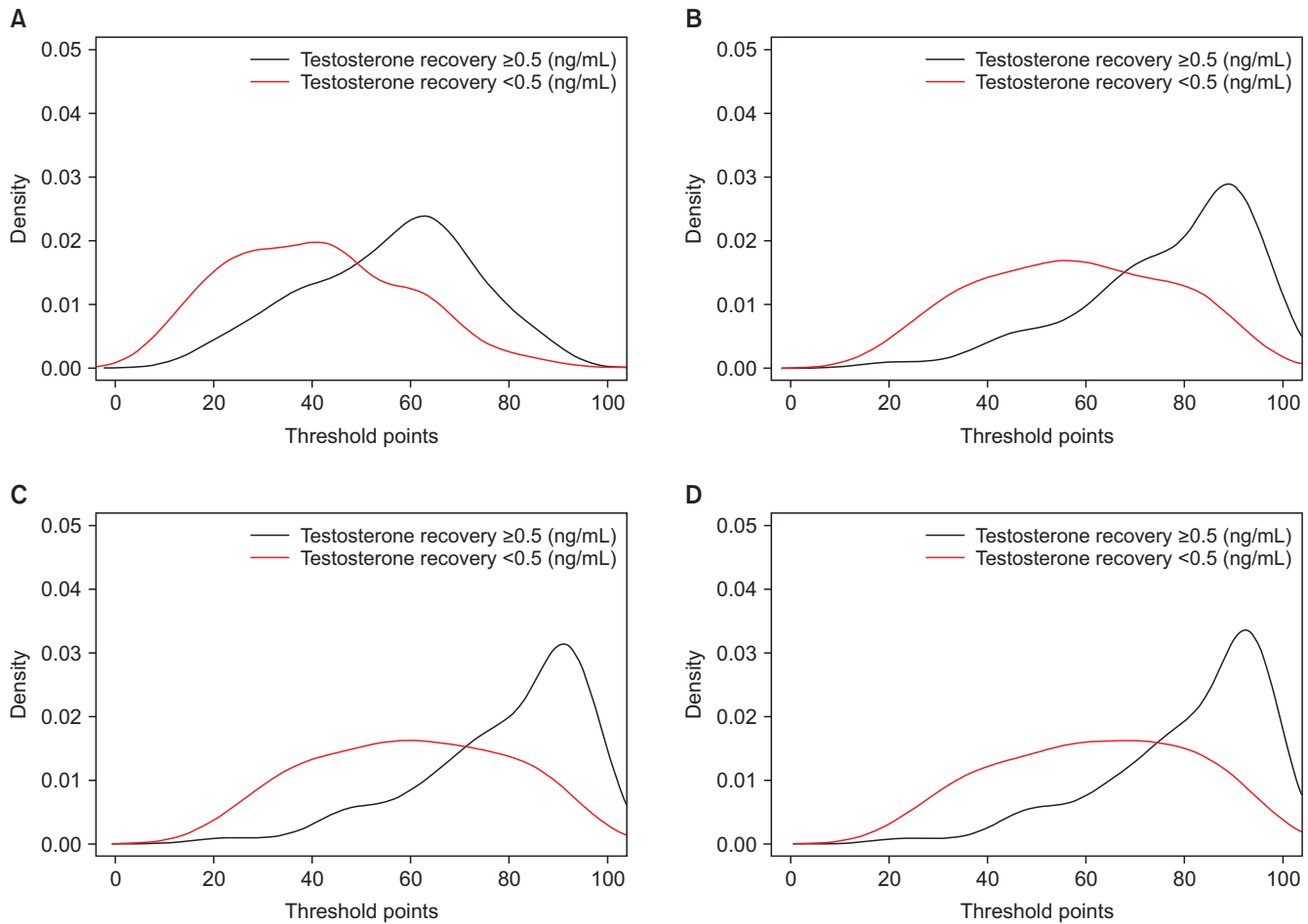
Fig. 6. Probability density functions for the castrate testosterone level recovery model at 12 months (A), 24 months (B), 36 months (C), and 60 months (D).

patients with progressive mCRPC treated with other drugs, such as abiraterone [24,25]. The SPARE trial, a multicenter, prospective, randomized, exploratory phase II study, and the retrospective, nonrandomized study performed by Jha and Jeff [3] evaluated the efficacy of abiraterone plus prednisone alone, without ADT, and achieved excellent results compared to those of the three drugs together [2,3], as in the pivotal study COU-AA-302 [26]. In the case of mCRPC, we can expect a long duration of treatment with ADT before its cessation. Therefore, withdrawing ADT could be a low-risk decision, as a very low testosterone level recovery rate would be expected; in these cases, the only goal is maintaining ADT. The evaluation of the patients in these studies with a prediction tool such as the one we propose would be desirable because it would enable us to know the expected recovery of [T] upon the cessation of ADT and even analyze the differences in progression according to the probability of recovery of

[T]. Likewise, an analysis of the control and treatment groups with regard to their overall probabilities of recovering [T] would be desirable to verify the absence of biases. However, any initiative in this regard must be undertaken with caution, with close monitoring to guarantee the persistence of castrate levels.

According to our data, a 75-year-old male who has been treated with an LHRH agonist for 3 years has a very low probability of recovering testosterone levels above the castrate threshold and might benefit from treatment discontinuation to prevent undesirable and potentially severe side effects and costs.

The association of higher body mass index (BMI) levels and hypertension with slower testosterone recovery after cessation of ADT has recently been described by Kato et al [27]. High BMI values are associated with low testosterone levels and in this sense could be important in our prediction. It would be possible to hypothesize whether a high baseline BMI could be as-
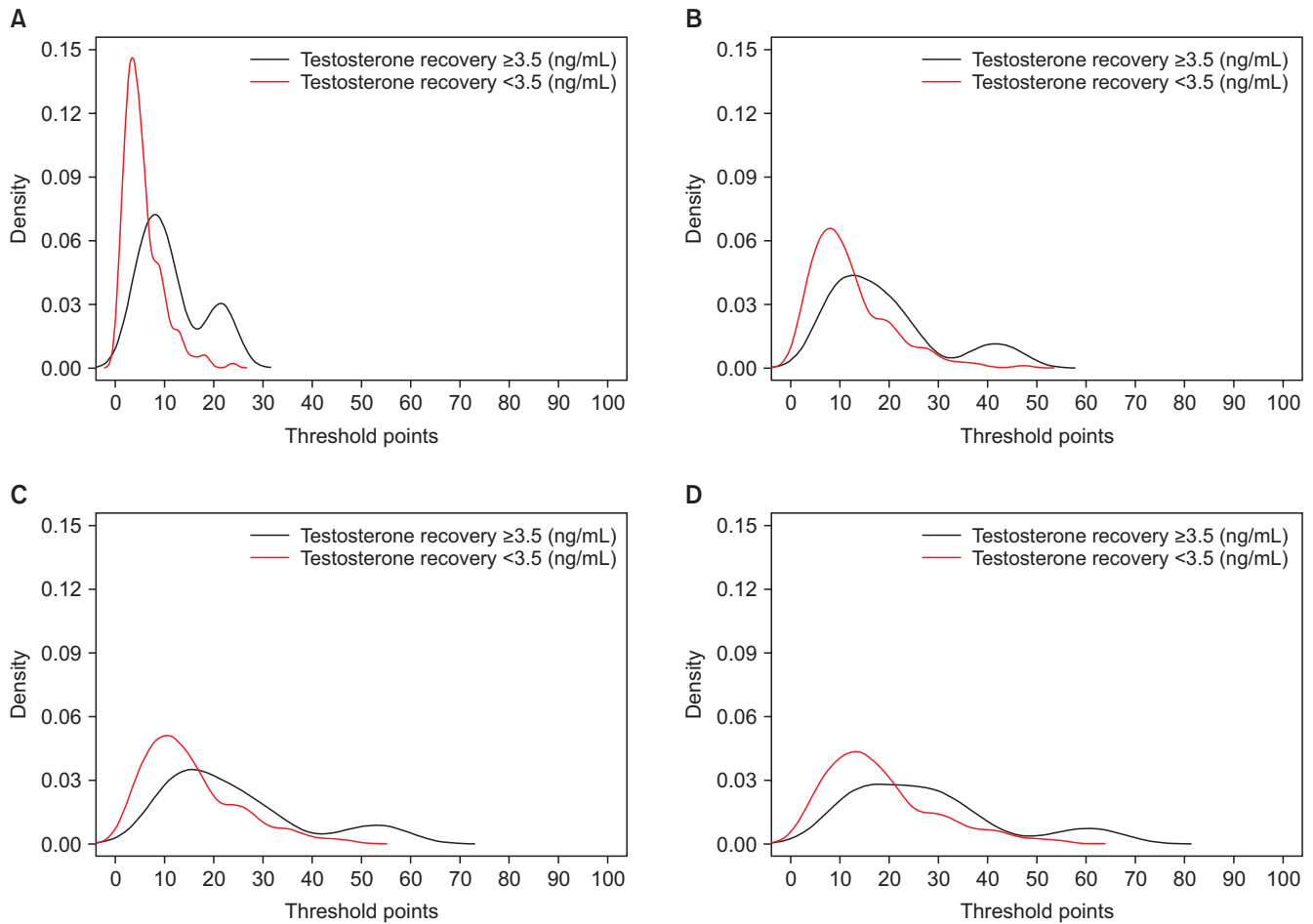
Fig. 7. Probability density functions for the normogonadic testosterone level recovery model at 12 months (A), 24 months (B), 36 months (C), and 60 months (D).

sociated with a higher incidence of hypogonadism prior to ADT and, therefore, a greater probability of hypogonadism when cessation of ADT. Or even if the evolution to higher levels of BMI during the ADT could be associated with a poor recovery of testosterone after its cessation. Likewise, the association of low testosterone levels and hypertension due to the cardioregulatory effect of testosterone is known. As in the previous case, it would be interesting to know if there is a higher incidence of hypogonadism in hypertensive patients at the beginning of the ADT and, therefore, a lower capacity for recovery at the end of the ADT. Or, if the development of hypertension during ADT will normalize after testosterone recovery.

Undoubtedly, these are very interesting analysis scenarios not contemplated in the retrospective nature of our analysis and which should be evaluated in future studies in this regard.

Our findings may contribute to the better manage-

ment of intermittent ADT. In this scenario, our model would allow us to estimate when the recovery of testosterone levels would occur, enabling us to prevent metabolic syndrome associated with continuous ADT while avoiding an increased risk of progression.

Our study has two limitations: we did not know the testosterone levels in our patients before the start of ADT. However, the determination of baseline testosterone is not a common practice before the onset of ADT, as it is assumed to be normal. However, our purpose has been to create a tool for clinical use, and the determination of basal testosterone is not a routine clinical practice nor is it currently included in clinical practice guidelines. Having built a model with this parameter would have limited its applicability in clinical practice, and on the other hand, findings of pre-treatment hypogonadism are not frequent. Additionally, our internal validation of the nomograms showed that they were robust, but external validation of the nomograms is

necessary prior to their extensive use.

CONCLUSIONS

The age of the patient and the duration of ADT are substantial in the evolution of testosterone levels, when chemical castration is suspended. Our predictive model allows us to estimate individually with high reliability whether, when treatment is suspended, castration levels will be maintained. We can also individually predict the time to normalization of testosterone levels if the course of treatment is short.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: ÁBF, FED, LME. Data curation: ÁBF, FED, LME. Formal analysis: LME, GS. Funding acquisition: GS. Investigation: ÁBF, FED, MJG. Methodology: ÁBF, LME, GS. Project administration: ÁBF, MJG. Resources: ÁBF, GS. Software: LME, GS. Supervision: ÁBF, MJG, GS. Validation: ÁBF, FED, LME. Visualization: LME. Writing – original draft: ÁBF, FED, LME. Writing – review & editing: ÁBF, FED, LME, MJG, GS.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at https://doi.org/10.7910/DVN/9Y2LN7.

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