Testosterone recovery after androgen deprivation therapy in prostate cancer: building a predictive model

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Research Article

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Abstract

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

Methods: A longitudinal study was performed on 208 patients in 2003-2019 period. The castrate and normogonadic levels were defined as testosterone, 0.50 and 3.50 ng/ml respectively. Cumulative incidence curve describes testosterone recovery. A univariate and multivariate analysis was performed to predict testosterone recovery with the candidate prognostic factors: PSA at diagnosis, Clinical stage, biopsy Gleason score, age at cessation of ADT, duration of ADT, primary therapy for patients, and LHRH agonist.

Results: The median followup of the study was 80 months, interquartile range (49,99). The 25% and 81% of patients did not recover the castrate and normogonadic level, respectively. Months of ADT and age at ADT withdrawal were significant predictors for testosterone recovery. We built two nomograms of testosterone estimation recovery at 12, 24, 36 and 60 months. The castration recovery model shows good calibration. The c-index was 0.677, with areas under the ROCcurve (AUC) of 0.74, 0.78, 0.78 and 0.78, at 12, 24, 36 and 60 months, respectively. The normogonadic recovery model had an overestimation of high probabilities. The cindex was 0.683, with AUC values of 0.81, 0.71, 0.71 and 0.70 at 12, 24, 36 and 60 months, respectively.

Conclusion: Depending on the age of patients and time of treatment, clinicians can discontinue ADT to maintain castrate levels without treatment with enough confidence, or even recover testosterone to normogonadic levels in short courses of treatment with high probabilities.

Introduction

Androgen deprivation therapy (ADT) neoadjuvant, concomitant or adjuvant to radiotherapy between 6 months and 2-3 years is the most common treatment in high risk and locally-advanced prostate cancer (PCa), and it is the cornerstone in the management of advanced/metastatic PCa as continuous ADT [1].

However, two recent studies question the need to maintain ADT in the setting of metastatic castration-resistant prostate cancer (mCRPC). The combination of abiraterone with prednisone without ADT could be comparable in terms of efficacy with standard treatment with all three drugs together [2-3].

Two main forms let us to obtain this ADT in PCa, the infrequent surgical orchiectomy, or the use LHRH agonists for rising chemical castration (Total testosterone, [T]<0.50 ng/ml). LHRH antagonist, degarelix, it is another possible option but really uncommon till now. For decades, continuous ADT by LHRH agonists have been the standard of care in this context.

Temporal chemical castration exposes the patient to the common symptoms of hypogonadism (sexual dysfunction, infertility, decreased libido, decrease in beard and body hair growth and muscle mass, weight gain, gynecomastia, reduced testicle size, osteoporosis, mental and emotional changes, anemia, fatigue, and hot flashes) during the time interval of treatment, and it is a real limitation on his quality of life.

On the other hand, there is mounting evidence that ADT is linked to significant adverse effects, such as 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 for obtaining the chemical castration [4,6].

After ADT withdrawal by protocol of adjuvancy or in an intermittent/continuous practice, we assume variability and delay until recovery over castration and/or normogonadic level ([T]>3.5 ng/ml). Some patients will never recover their normal levels of [T] nor above the limits of castration, even.

In this situation, we analyse variability, associated factors, and the design of nomograms for individualized [T] recovery after ADT withdrawal. Those nomograms could be extremely useful in the two previous scenarios showed: for counselling patients about the improvement in their quality of life after cessation of ADT when finishing adjuvants protocols, or for avoiding dangerous side effects and unnecessary costs of continuous ADT when the predicted possibility of [T] recovery over castration levels is not expected, leading us to propose ADT withdrawal in these cases.

Material And Methods

A retrospective observational longitudinal study was performed on 208 patients after cessation of ADT in the Miguel Servet University Hospital, Spain. Data recruitment includes patients with ADT withdrawal between 2003 and 2013. The follow-up period begins after cessation of ADT and concludes with death or censure at December 2019. We evaluated the recovery of testosterone levels above the castrate and normogonadic threshold and its associated factors. The castrate and normogonadic thresholds were defined as Total testosterone, [T] = 0.50 and 3.50 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 could be fully anonymized, and 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 through cumulative incidence curves. For both testosterone levels of 0.5 and 3.5 the rate of recovery was analyzed until 120 months after cessation of ADT. In addition, with the purpose to identify factors associated with recovery, a univariate and multivariate stepwise model was built using the Cox proportional hazards model with the candidate prognostic factors: PSA at diagnosis, Clinical stage, biopsy specimen Gleason score in case, age at ADT withdrawal, duration of ADT, primary therapy for patients, and LHRH agonist. Non linear dependences were analyzed using restricted cubic splines. Anova test was used to establish statistical significance for categorical variables in the univariate analysis.

The calibration and the discrimination ability of the multivariate model were established using the calibration curves at 1, 2, 3 and 5 years, and the area under the ROC curve, respectively. The probability density functions provide a graphical perspective of the probabilities provides by the model and, the performance of the model for different threshold probability points was assessed through clinical utility curves. In addition, two nomograms were built in order to predict individualized testosterone recovery (0.50 and 3.50 ng/ml) after ADT withdrawal at 1, 2, 3 and 5 years.

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

Results

The median follow up for patients enrolled in the study was 80 months, interquartile range (49,99), with 80 (38.5%) patients died in the follow-up period. We found high individualised variability in testosterone recovery after ADT withdrawal. Of the 208 patients enrolled in the study, 156 of them recovered castration level, and a 25% of patients

did not recover the 0.5 ng/ml testosterone level in our interval study. The first quartile (p25), median (p50) and third quartile (p75) time until castrate threshold recovery were 7, 11, 13 months in our cohort.

With regards to normogonadic level 3.5 ng/ml, the 81% of patients (168 cases) did not normalise the 3.5 level in our interval study, with a median follow up of 76 months, interquartile range (45, 96). The p25, p50 and p75 values for the time until testosterone 3.5 recovery were 64, 93, 103 months. In figure 1, it can be seen the cumulative incidence curves for the recovery of both testosterone levels, 0.5 and 3.5.

We show in Table 1 the descriptive characteristics of the patients enrolled in the study by groups of final testosterone recovery ($T < 0.5$ / $T \geq 0.5$ and $T < 3.5$ / $T \geq 3.5$). The primary therapy distribution for patients was watchful waiting 7.2% (n=15), laparoscopic radical prostatectomy 2.4% (n=5), retropubic radical prostatectomy 48.6% (n=101), external beam radiotherapy 9.6% (n=20), androgen deprivation therapy 20.4% (n=17) and external beam radiotherapy plus androgen deprivation therapy 8.2% (n=17).

The prognostic factors associated with castrate and normogonadic recovery in the univariate analysis are shown in Table 2. The months of ADT and the age at ADT withdrawal are significant factors in both models, but some LHRH agonists (anova test p-value = 0.001) and primary therapies (anova test p-value = 0.019) are significant factor only in the castrate recovery model.

In the multivariate analysis, also in Table 2, it is shown that for the prognosis of Testosterone 0.5 recovery level, the months of ADT and the age at ADT withdrawal were the unique significant predictors. Moreover, for the 3.5Recovery model, the significant factors were again months of ADT and age at ADT withdrawal. Using these models, we built two nomograms of testosterone estimation recovery at 12, 24, 36 and 60 months that can be seen in Figure 2 and 3.

The testosterone 0.5 recovery model shows a high concordance between probability and actual values in the calibration analysis of Supplementary material Figure 4, at 12 24, 36, and 60 months. Its discrimination capacity (c-index) was 0.677, with areas under the ROCcurve of 0.74, 0.78, 0.78 and 0.78, at 12, 24, 36 and 60 months, respectively. Besides, the normogonadic recovery model had an overestimation of high probabilities showed in Supplementary material Figure 5, but due to the low occurrence of recoveries there is a small set of probabilities in the range that happens, over 0.1 at 12 months, over 0.2 at 24 months, and over 0.3 at 36 and 60 months. Anyway, it seems that recovery model is really useful from 36 months Moreover, the cindex was 0.683, with areas under the ROCcurve of 0.81, 0.71, 0.71 and 0.70 at 12, 24, 36 and 60 months, respectively.

The discrimination ability of models can be seen in more detailed in Supplementary material Figures 6 and 7, there is overlap between the probability density functions for patients that recover/not recover castrate or normogonadic levels, thus it seems difficult to choose a threshold probability point that can clearly discriminate both groups. However, it can be seen that most patients with a probability of recovery over 80% finally recovered the castrate level.

An app is provided for the use of the nomograms:

https://urostatisticalsolutions.shinyapps.io/testosteronerecovery/

Discussion

Time to testosterone recovery after ADT has been investigated in previous studies. Oefelein [7], in 1998, reported on 13 patients with clinically localized prostate cancer who received a single dose of 3 months LHRH agonist. In their

study, the median duration of castration levels of testosterone was 6 months, with a median duration of hypogonadal symptoms such as hot flushing of 13. 6 months.

In 1999, Hall [8] found that, after ADT for a minimum of 24 months (median 38.6, range 25-82 months), median testosterone remained at castrate level at 6 and 9 months. Both of them suggested already the possibility to modify dosing schedule of these drugs based on testosterone levels.

Pedraza et al [9], in a quite limited study because of the number of patients, reported a castrate level of testosterone during the 36 months follow-up in 4 patients over 70 years after a median treatment of 108 months (94-120) probably due to an impairment of the function of the Leydig cell, concluding the major implications of their findings not only in the treatment time schedule but in an economical regard. We must point that the median duration of treatment was much longer in their investigation than in ours and that is probably the reason why all their patients remained castrated.

Previous studies have tried to determine testosterone recovery associated factors after ADT withdrawal too. Some of these studies have shown the relationship between the time to recovery and the duration of ADT, the age of patients, the previous levels of testosterone itself or others.

Oefelein [10], studying 32 patients with a median age of 71 years (54-86) treated during a median time of 7.5 months (3-49) found a statistically significant association between the age of patients and testosterone recovery. Pickles [11] found a significant difficulty to recover for patients older than 75 years. Gulley [12] established the same for patients above 66 years. Others have reported similar differences between patients older or younger than 60 [13], 65 [14], 67 [15], or 70 [16] years or have been able even to delimitate age ranges [16-18]. Planas [19] did not found this association, maybe due to the narrow age range (CI 95% 69.1-73.9 years) of his study, as he recognized. He reported instead of the association with duration of ADT, with a significant difference between patients treated for more or less than 60 months.

This influence of ADT duration had been described before. Nejat et al. [20] reported on 68 heterogenous patients with ADT. He concluded that patients treated for less than 24 months reached normal testosterone in 6 months, while 22 months were needed to recover a normal testosterone level for treatments longer than 24 months (log-rank p 0.0034). Other authors set the limit in more or less than 30 [14] or 36 [21] months, as ourselves.

Recently, Nam [22] has reported the association between testosterone recovery and age, SHBG level, initial testosterone level and ADT duration in patients treated with ADT after radical prostatectomy.

Our study has demonstrated a statistically significant association between both the duration of ADT and the age at treatment withdrawal with the delay and the probability of testosterone recovery. Moreover, our study has been 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.

Actually, the question is not just to provide a tool to modify dosing schedule to obtain an economical benefit. The question is to be able to discontinue the treatment when the patient will probably remain castrated in order to avoid the adverse effects of ADT with LHRH agonists themselves [6].

It has been reported that surgically castrated men had significantly lower risks to suffer cardiac–related complications, peripheral arterial disease or fractures compared with men treated with GnRHa. Additionally, diabetes mellitus and venous thromboembolism appear to be more frequent when treatment is maintained over 35 months

[4]. In this sense, the 36 months is a clue time in our study: we have shown that most of castrate recovery events happen in this 2 first years with a minimal increase in recovery until 3 years and the recovery to normal levels is improbable after 36 months and moreover, we have proved that more than 25% patients remain castrated at LHRH withdrawal after 36 months of ADT and nearly 80% do not reach normal testosterone levels after this time.

That is why to discontinue ADT with LHRH agonist is crucial. Our study could be relevant to decide when to finish the treatment with LHRH agonists if we want our patient to recover testosterone and improve his quality of life, but also when we desire to maintain castration avoiding the use and the side effects of these drugs, maybe even in progressive, mCRPC treated with other drugs, as abiraterone [23-24]. The SPARE trial, a multicenter, prospective, randomized, exploratory phase II study, and the retrospective, non-randomized study of Jha et al. have evaluated the efficacy of abiraterone plus prednisone alone, without ADT, with excellent results compared to the three drugs together [2-3] and as in the pivotal study COU-AA-302 [25]. In this scenario, mCRPC, we can expect a long time of treatment with ADT before its withdrawal. So withdrawing ADT could be a low-risk decision, as a very low testosterone recovery rate would be expected, the only goal of maintaining ADT. The evaluation of these studies with a prediction tool like the one we propose would be desirable to know the expected recovery of [T] upon withdrawal of ADT, and even an analysis of the differences in progression according to the probability of recovery of [T]. Likewise, an analysis of the control and treatment groups on their overall recovery probabilities of [T] would be desirable to verify the absence of biases.

With our data, a 75 year old male who has been treated with LHRH agonist for 3 years has a very little probability of recovering testosterone levels even over castrate level and might benefit of treatment discontinuation in order to prevent undesirable and potentially severe side effects and costs.

Besides, we cannot compare or confound our findings with intermittent androgen deprivation therapy (IADT). Actually, IADT tries to achieve the non progression of prostate cancer in patients who are supposed to have recovered eugonadal testosterone levels after ADT withdrawal. We try though, if this is necessary, to maintain castrated patients without any treatment or to warrant the recovery of testosterone level if this is the objective.

Our study has a major limitation: we did not know the testosterone level of our patients before the ADT start. So, it is theoretically possible that some patients who did not reach a normal testosterone after ADT withdrawal were in fact in a hypogonadic range even before the treatment.

Declarations

Funding

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Conflicts of interest/Competing interests

Regarding the content of this paper, the authors declare that they have no conflict of interest.

Ethical approval

The research protocol was approved by the Clinical Research Ethics Committee of Aragon (PI 20/307). The research have been performed in accordance with the Declaration of Helsinki.

Consent to participate

Due to the retrospective observational nature of this study, data could be fully anonymized, and informed consent was waived.

Consent for publication

Non applicable

Availability of data and material

Non applicable

Code availability

An app is provided for the use of the nomograms:

https://urostatisticalsolutions.shinyapps.io/testosteronerecovery/

Author's contributions

ABF: protocol and project development, data management, and manuscript writing, FED: data collection, data management and manuscript writing, LME: data management, data analysis, and manuscript writing and editing, GS: data analysis. MJG: protocol and project development.

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Tables

Table 1 Descriptive analysis

		Final subgroup status after ADT withdrawal					
Variable	Total	Testosterone < 0.5	Testosterone ≥ 0.5		Testosterone < 3.5	Testosterone ≥ 3.5	
Continuous	Median (IQR)	Median (IQR)	Median (IQR)		Median (IQR)	Median (IQR)	
Categorical	N(%)	N(%)	N(%)	p-value	N(%)	N(%)	p-value
PSA	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 withdrawal(years)	76 (71-81)	79 (75-82)	75 (69-81)	<.001	78 (72-82)	72 (68-77)	<.001
Months of ADT	56 (29-102)	102 (55-137)	48 (25-81)	<.001	63 (32-106)	40 (23-66)	0.011
Gleason:				0.663			0.972
6	113 (56.5%)	32 (60.7%)	82 (55.0%)		91 (56.1%)	22 (57.9%)	
7	64 (32%)	14 (27.5%)	50 (33.6%)		52 (32.1%)	12 (31.6%)	
8-10	23 (11.5%)	6 (11.8%)	17 (11.4%)		19 (11.8%)	4 (10.5%)	
Clinical Stage:				0.163			0.275
T1	76 (36.7%)	14 (26.9%)	62 (39.8%)		57 (33.9%)	19 (47.5%)	
T2	109 (52.7%)	30 (57.7%)	79 (50.7%)		91 (54.1%)	18 (45.0%)	
T3	22 (10.6%)	8 (15.3%)	14 (9.0%)		19 (11.4%)	3 (7.5%)	
LHRH agonist:				0.387			0.497
Leuprolerin (Procrin®)	55 (26.4%)	10 (19.2%)	45 (28.8%)		41 (24.4%)	14 (36.0%)	
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%9	0 (0%)	1 (0.6%)		1 (0.6%)	0 (0%)	
Primary				0.220			0.117

treatment:						
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 (20.4%)	18 (34.6%)	32 (20.5%)		46 (27.4%)	4 (10.0%)	
Intervals of dosage				0.386			0.985
Every 6 months	34 (18.1%)	6 (11.5%)	28 (17.9%)		28 (16.7%)	6 (15.0%)	
Every 3 months	154 (81.9%)	46 (88.5%)	128 (82.1%)		140 (83.3%)	34 (85.0%)	

LRP: Laparoscopic radical prostatectomy, RRP: Retropubic radical prostatectomy, ADT: Androgen deprivation therapy; EBRT: External beam radiotherapy;

Table 2 Univariate and multivariate analyses

	Testosterone ≥ 0.5 recovery				Testosterone ≥ 3.5 recovery			
	Univariate		Multivariate		Univariate		Multivariate	
Variable	H.R. (95% C.I.)	p-value	H.R. (95% C.I.)	p-value	H.R. (95% C.I.)	p-value	H.R. (95% C.I.)	p-value
PSA	0.99 (0.99-1.00)	0.864		n.s.	0.99 (0.96-1.01)	0.231		n.s.
Age at ADT withdrawal	0.96 (0.94-0.98)	<.001	0.964 (0.944-0.984)	<.001	0.93 (0.89-0.97)	<.001	0.94 (0.90-0.98)	0.002
Months of ADT	0.99 (0.98-0.99)	<.001	0.988 (0.984-0.992)	<.001	0.99 (0.98-0.99)	0.005	0.99 (0.98-0.99)	0.011
Gleason								
6	Ref.			n.s.	Ref.			n.s.
7	1.22 (0.86-1.74)	0.260			0.99 (0.49-2.02)	0.996		
8-10	1.08 (0.64-1.81)	0.785			0.87 (0.29-2.51)	0.792		
Clinical Stage								
T1	Ref.			n.s	Ref.			n.s.
T2	0.82 (0.59-1.14)	0.242			0.62 (0.33-1.19)	0.151		
T3-T4	0-65 (0.36-1.16)	0.144			0.44 (0.13-1.50)	0.191		
LHRH agonist								
Leuprolerin (Procrin®)	Ref.			n.s.	Ref.			
Triptorelin (Decapeptyl®)	0.64 (0.41-0.99)	0.047			0.48 (0.19-1.19)	0.113		n.s.
Leuprolerin (Eligard®)	0.79 (0.48-1.29)	0.341			0.92 (0.37-2.28)	0.857		
Buserelin (Suprefact®)	0.44 (0.21-0.89)	0.024			0.24 (0.03-1.86)	0.174		
Goserelin (Zoladex®)	0.71 (0.46-1.08)	0.107			0.76 (0.34-1.67)	0.491		
Leuprorelin	NA	NA			NA	NA		

(Lutrate®)						
Primary treatment						
Watchful waiting	Ref.		n.s.	Ref.		n.s.
LRP	3.03 (1.08-8.56)	0.036		4.22 (0.59-29.9)	0.150	
RRP	0.78 (0.43-1.40)	0.407		1.90 (0.45-8.02)	0.383	
EBRT	0.71 (0.33-1.51)	0.368		2.13 (0.41-10.9)	0.366	
EBRT+ADT	0.86 (0.40-1.82)	0.688		0.76 (0.11-5.39)	0.784	
ADT	0.50 (0.26-0.95)	0.036		0.58 (0.11-3.19)	0.535	
Intervals of dosage						
Every 3 months	Ref.		n.s.	Ref.		n.s.
Every 6 months	1.38 (0.91-2.08)	0.128		0.98 (0.41-2.33)	0.960	

Ref: Category of reference, NA: non available, n.s.: non significative, LRP: Laparoscopic radical prostatectomy, RRP: Retropubic radical prostatectomy,

EBRT: External beam radiotherapy; ADT: Androgen deprivation therapy

Figures

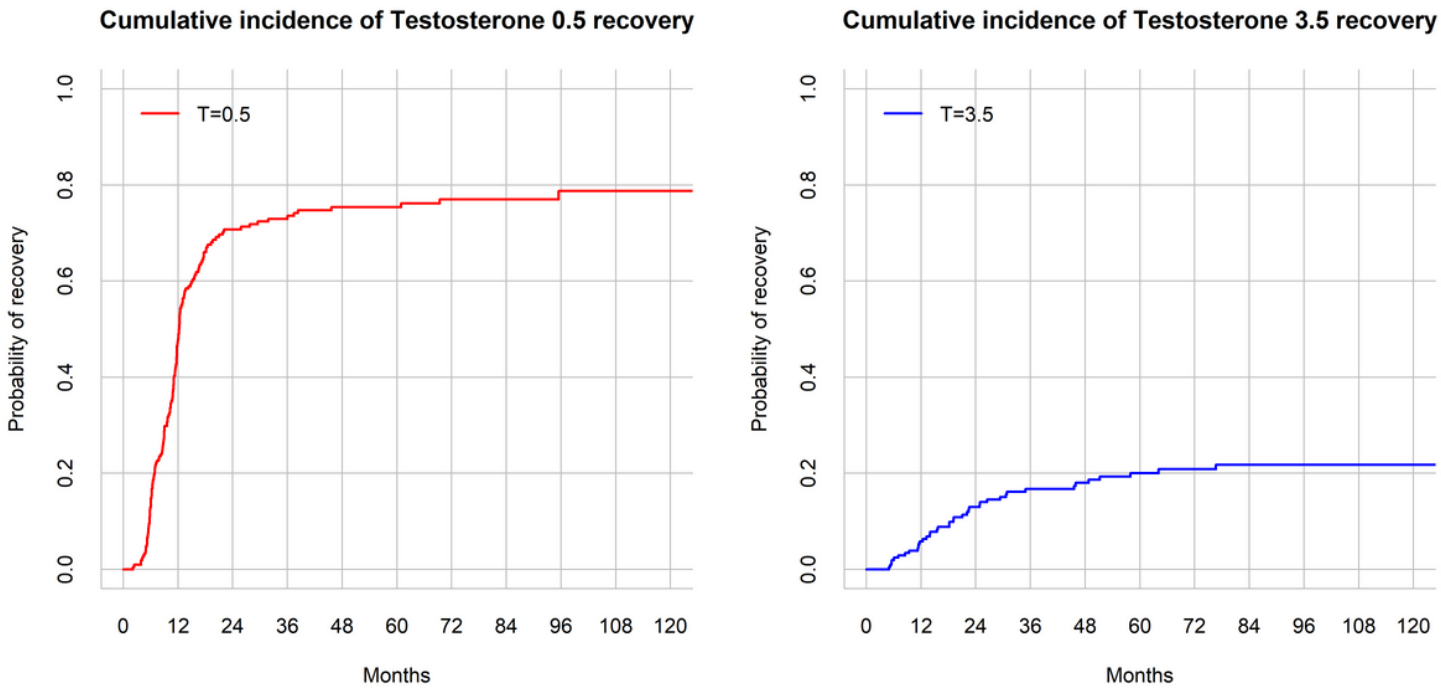

Figure 1

Cumulative incidence curves for the recovery of the castrate and normogonadic testosterone levels

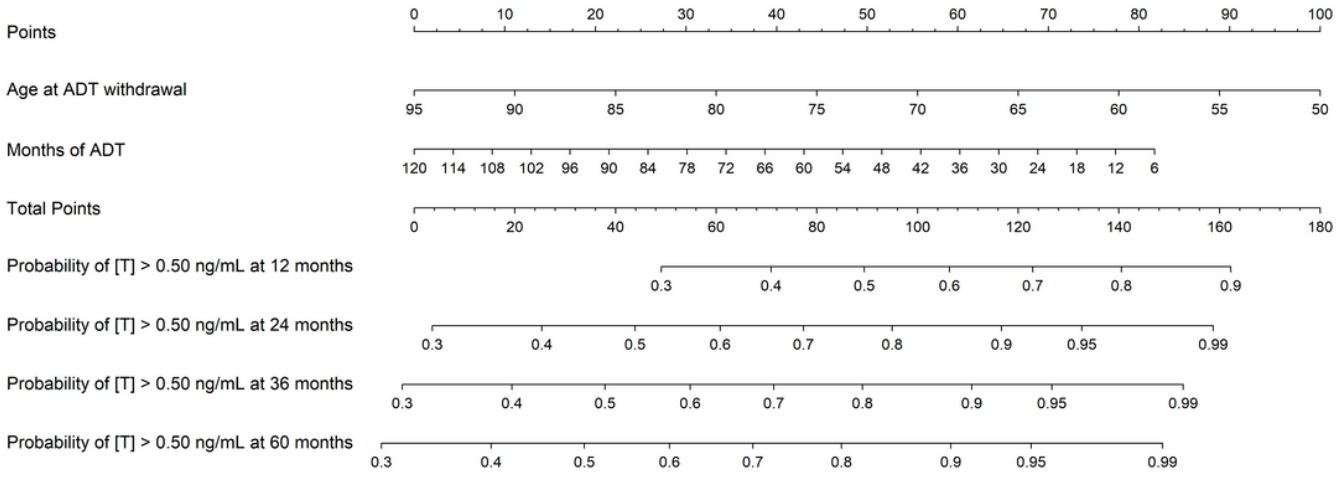

Figure 2

Nomogram for the castrate testosterone recovery model after ADT withdrawal

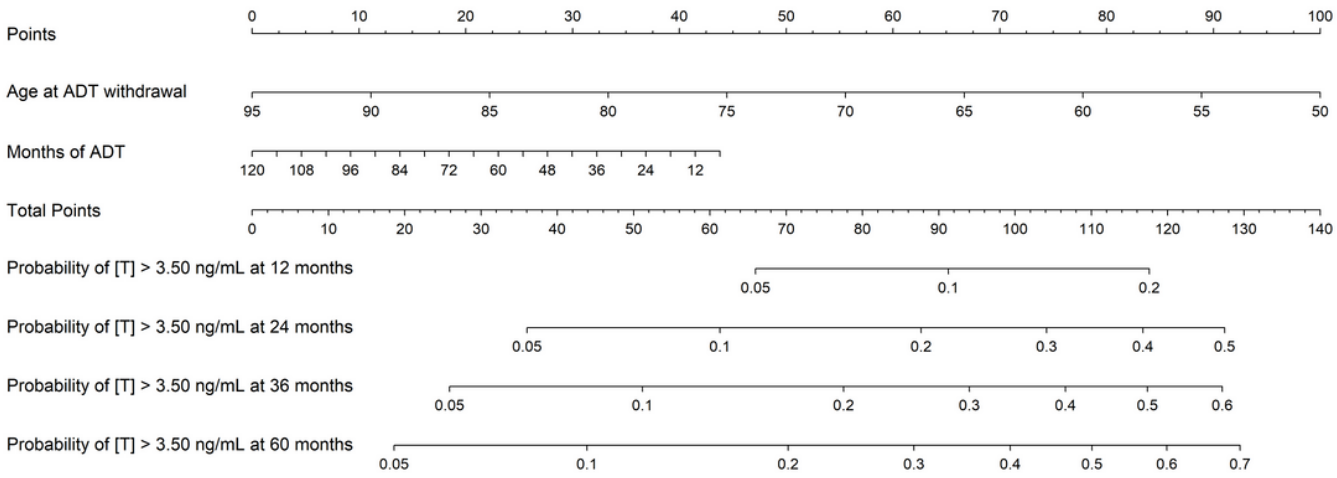

Figure 3

Nomogram for the normogonadic testosterone recovery model after ADT withdrawal

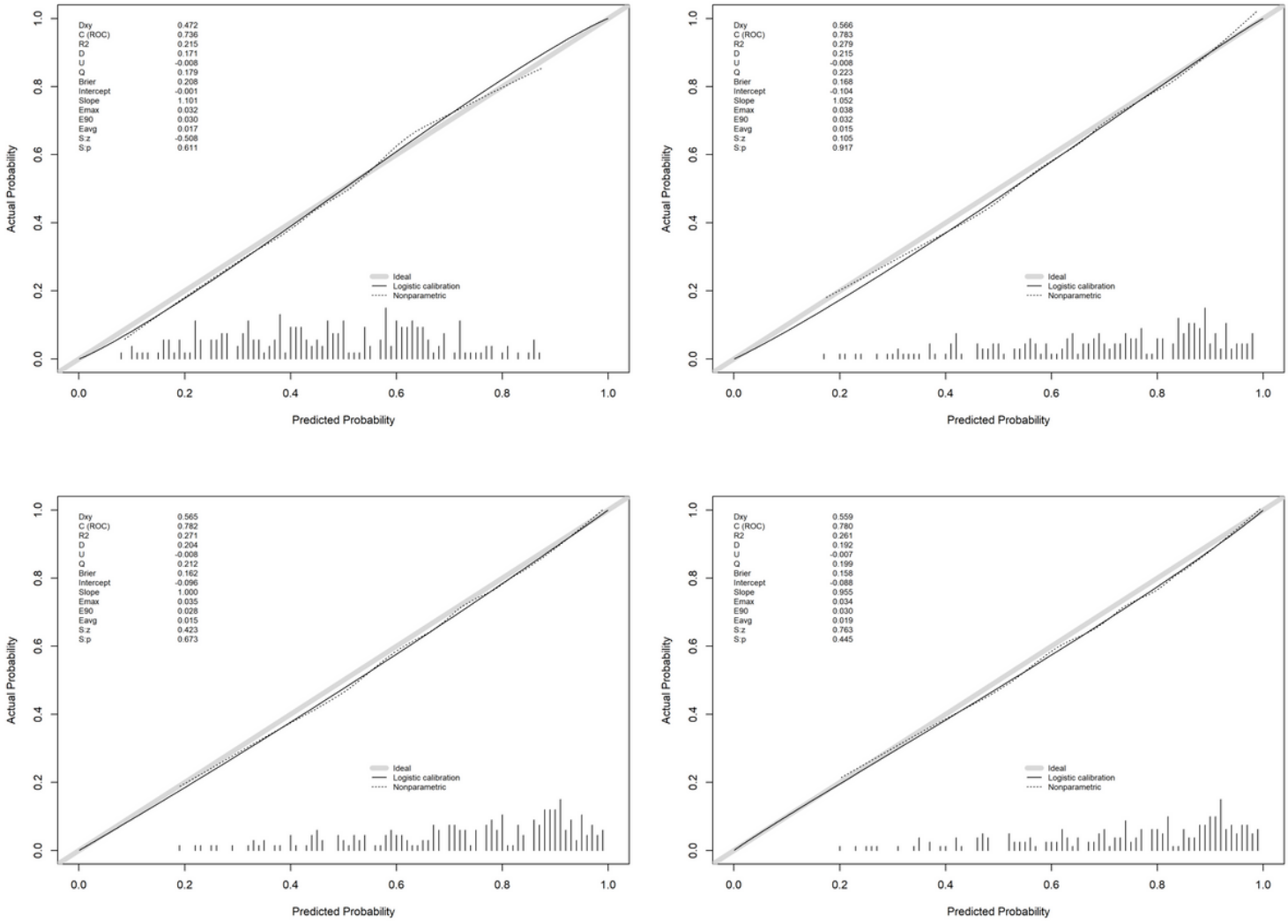

Figure 4

Calibration plot for the castrate testosterone recovery model at 12 months (upper left panel), 24 months (upper right panel), 36 months (lower left panel), and 60 months (lower right panel).

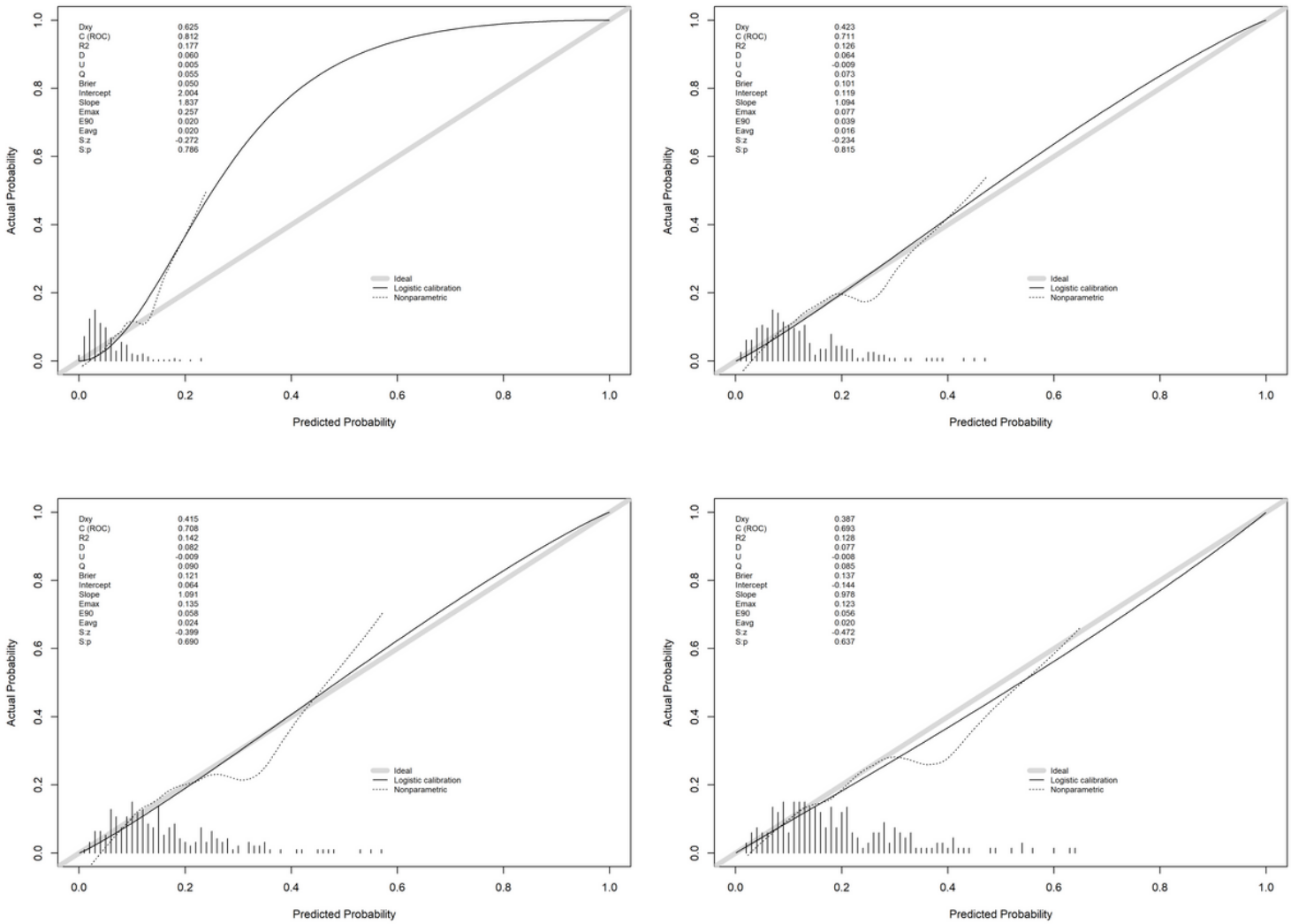

Figure 5

Calibration plot for the normogonadic testosterone recovery model at 12 months (upper left panel), 24 months (upper right panel), 36 months (lower left panel), and 60 months (lower right panel).

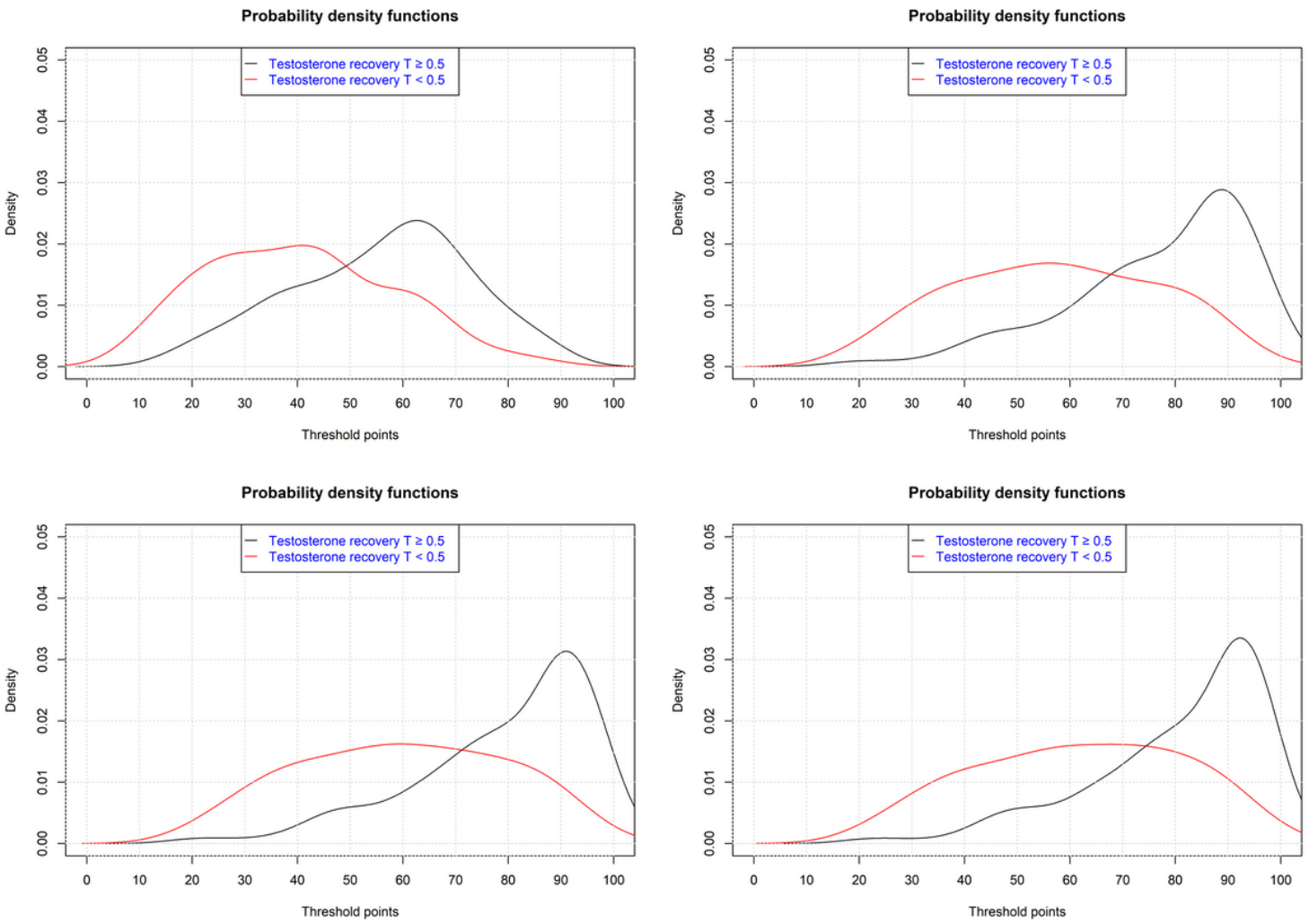

Figure 6

Probability density functions for the castrate testosterone recovery model at 12 months (upper left panel), 24 months (upper right panel), 36 months (lower left panel), and 60 months (lower right panel).

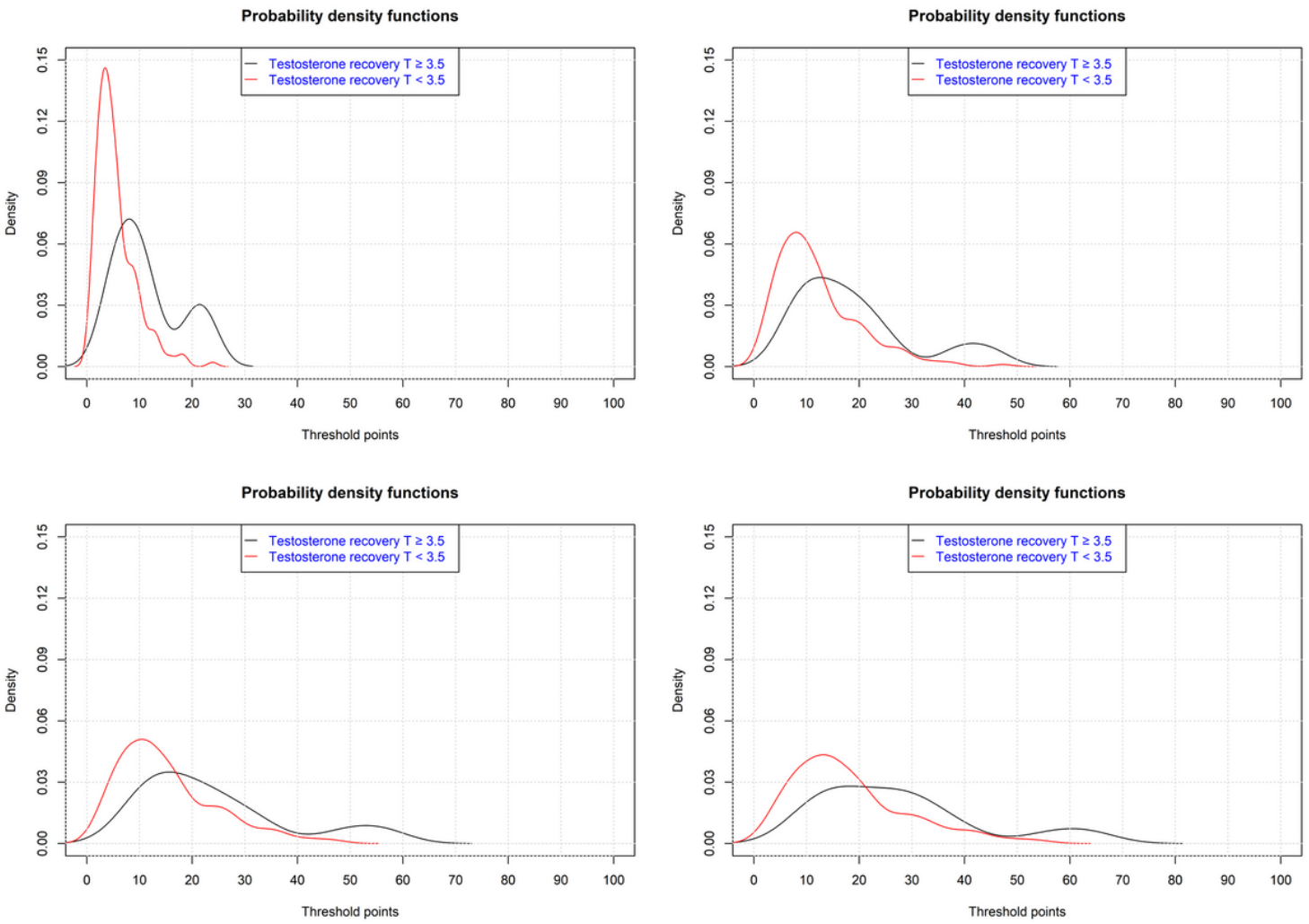

Figure 7

Probability density functions for the normogonadic testosterone recovery model at 12 months (upper left panel), 24 months (upper right panel), 36 months (lower left panel), and 60 months (lower right panel).