EJACULATORY FUNCTION

An Internally Validated Nomogram for Predicting the Likelihood of Improvement of Clinical Global Impression in Patients With Lifelong Premature Ejaculation Treated With Dapoxetine

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ABSTRACT

Background: Although the introduction of dapoxetine has ushered in a new era in the treatment of premature ejaculation, many patients with lifelong premature ejaculation (LPE) exhibit an unimproved clinical global impression even after treatment with dapoxetine.

Aim: To investigate independent predictors of the improvement of Clinical Global Impression (iCGI) in patients with LPE treated with dapoxetine and develop a nomogram to predict a patient's likelihood of achieving iCGI.

Methods: Data of 243 patients with LPE diagnosed at Xijing Hospital (Xi'an, China) and Northwest Women's and Children's Hospital (Xi'an, China) from January 2019 to May 2020 were analyzed. Independent predictors of iCGI were identified, and a nomogram was developed using R software based on a multivariate logistic regression model. The predictive accuracy of the nomogram was measured using the area under the receiver operating characteristic curve. The nomogram was calibrated by comparing predictions with observations.

Main Outcome Measures: The primary outcome was the patient-rated Clinical Global Impression of Change scale score after a 4-week course of dapoxetine treatment, which was collected via an online questionnaire. A Clinical Global Impression of Change score of ≥ 1 was defined as iCGI in this study.

Results: Patients with LPE with at least a bachelor's degree, a self-reported intravaginal ejaculation latency time of >1 minute, and an International Index of Erectile Function question 5 score of ≥ 3 were independent factors associated with achieving iCGI, whereas a Premature Ejaculation Diagnostic Tool question 1 score of ≥ 2 was an independent factor negatively associated with achieving iCGI. The predictive accuracy of the nomogram, which was developed by integrating all variables with independent predictive significance, was 0.710 (95% confidence interval: 0.702−0.718). In addition, the calibration plot demonstrated excellent agreement between predictions and observations.

Clinical Implications: If the predictive performance of our nomogram is further proven in multiple external validations, it can be used to select suitable patients for dapoxetine treatment, thereby reducing the number of patients discontinuing treatment.

Strengths & Limitations: This study developed the first nomogram for predicting the likelihood of achieving iCGI in patients with LPE treated with dapoxetine. However, our nomogram was not externally validated using independent cohorts from other institutions.

Conclusion: This study identified several independent predictors of iCGI in patients with LPE treated with dapoxetine. An effective nomogram was developed to predict their likelihood of achieving iCGI. External

INTRODUCTION

Premature ejaculation (PE) is one of the most common male sexual complaints.[1] In clinical practice, approximately 5% of men are affected by PE, which is mainly characterized by decreased ejaculation latency.[2] The International Society for Sexual Medicine (ISSM) proposed the most widely accepted definition of PE in 2014, categorizing PE as lifelong PE (LPE) and acquired PE.[2] The former is characterized by early ejaculation in almost every intercourse; within 1 minute in about 80% of cases, or between 1 and 2 minutes in about 20% of cases, from the first sexual encounters onwards and with every or almost every sexual partner.[3] The latter is characterized by an latency time <3 minutes,[4,5] with previous normal ejaculation experiences.[3] Although not captured by the ISSM definition, 2 additional PE subtypes (namely variable PE and subjective PE) have also been proposed.[4,6] Patients with these 2 subtypes are distressed about their ejaculatory function but do not meet the diagnostic criterion for PE,[2] which may be one of the reasons why these 2 subtypes are considered provisional.[2] PE interferes with sexual satisfaction and can further result in mental health concerns and interpersonal difficulties.[7] Fortunately, dapoxetine, the only on-label oral treatment for PE[8] that is given on demand, has been proven to delay ejaculation by approximately threefold, improve overall sexual satisfaction, and reduce psychological and relationship issues.[9]

However, in clinical practice, nearly 30% of patients with PE discontinue dapoxetine treatment within 1 month, mainly because of unmet expectations and side effects,[10] although the response rate is nearly 75% and the mean intravaginal ejaculation latency time (IELT) was prolonged.[11] IELT remains the most commonly used endpoint to measure the treatment efficacy of dapoxetine and other treatments (such as psychotherapy and behavioral therapy) in clinical trials, but it captures only one element of the PE condition.[12] The Clinical Global Impression scale, a tool for measuring the overall severity of an individual's symptoms or changes in functioning over time, was previously used mainly for mental disorders.[13,14] Recently, the Clinical Global Impression of Change (CGIC) scale, which reflects the overall impact of the treatment on a patient's clinical condition, has been proven as a valid and brief tool to assess conditions in patients with PE[12] and may be used more reasonably than IELT for evaluating the overall function of dapoxetine. However, to the best of our knowledge, few studies have investigated the

association between the pretreatment variables and the posttreatment CGIC score in patients with PE treated with dapoxetine. Moreover, a nomogram for predicting an individual's likelihood of achieving improvement of the Clinical Global Impression (iCGI) has not yet been developed.

For these reasons, this study aimed to find out which factors were independently associated with the likelihood of achieving iCGI after dapoxetine treatment in patients with PE and ascertain whether an effective pretreatment nomogram for predicting their individual chance of achieving iCGI could be developed.

METHODS

Subjects

An observational study was conducted at Xijing Hospital (Xi'an, China) and Northwest Women's and Children's Hospital (Xi'an, China) from January 2019 to May 2020. Data of patients with PE were collected before and after dapoxetine treatment.

The inclusion criteria for the study were as follows: (i) men aged 18–64 years, (ii) those in a stable sexual relationship (ie, a monogamous sexual relationship with the same partner for at least 6 months) and engaging in full sexual intercourse at least twice monthly, (iii) those who practiced heterosexual and vaginal intercourse, and (iv) those diagnosed with LPE. The exclusion criteria were as follows: (i) comorbidity with hypoactive sexual desire disorder, erectile dysfunction (ED), or other sexual dysfunctions as determined by clinical and psychometric examination; (ii) inability to engage in sexual intercourse because of malformed reproductive organs; (iii) inability to engage in intercourse as per our requirement (at least 6 times in 4 weeks and at least once per week) or inability to take dapoxetine because of severe heart disease (eg, valvular disease, *New York Heart Association* II-IV heart failure) or cerebrovascular disease (eg, during stroke rehabilitation); (iv) severe mental disorders such as epilepsy; (v) a long history of substance abuse; and (vi) use of other selective serotonin reuptake inhibitors, tricyclic antidepressants, triazole pyridine antidepressants, tramadol, sedatives, and hormones in the past 2 months.

In our study, LPE was diagnosed by 2 experienced andrologists according to the ISSM diagnostic criteria,[2] in which LPE was defined as ejaculation always or nearly always occurring within approximately 1 minute of vaginal penetration ever since the first sexual experience. Notably, an IELT of 1–2 minutes

Table 1. Comparison of pretreatment variables between iCGI group and non-iCGI group

Variables	iCGI group (N = 92)	Non-iCGI group (N = 151)	P value
Age at visit (years), median (IQR)	29 (26−32)	29 (26−33)	.544
BMI (kg/m²), median (IQR)	24.2 (22.1−26.3)	23.8 (21.9−25.6)	.227
Years of education, n (%)			**.025**
≤9	14 (15.2)	39 (25.8)	
9−16	41 (44.6)	74 (49.0)	
≥16	37 (40.2)	38 (25.2)	
IELT (min), n (%)			**<.001**
IELT = 0	11 (12.0)	44 (29.1)	
0 < IELT ≤ 1	43 (46.7)	75 (49.7)	
1 < IELT ≤ 2	38 (41.3)	32 (21.2)	
IIEF-5 score (Q1), n (%)			.961
≤2	38 (41.3)	63 (41.7)	
3	35 (38.0)	59 (39.1)	
4 & 5	19 (20.7)	29 (19.2)	
IIEF-5 score (Q2), n (%)			.249
≤2	21 (22.8)	48 (31.8)	
3 & 4	34 (37.0)	55 (36.4)	
5	37 (40.2)	48 (31.8)	
IIEF-5 score (Q3), n (%)			.085
≤3	33 (35.9)	67 (44.4)	
4	27 (29.3)	51 (33.8)	
5	32 (34.8)	33 (21.9)	
IIEF-5 score (Q4), n (%)			**.038**
≤2	11 (12.0)	38 (25.2)	
3 & 4	29 (31.5)	45 (29.8)	
5	52 (56.5)	68 (45.0)	
IIEF-5 score (Q5), n (%)			**.001**
1	27 (29.3)	81 (53.6)	
2	32 (34.8)	39 (25.8)	
≥3	33 (35.9)	31 (20.5)	
PEDT score (Q1), n (%)			**.007**
≤1	18 (19.6)	11 (7.3)	
2 & 3	46 (50.0)	74 (49.0)	
4	28 (30.4)	66 (43.7)	
PEDT score (Q2), n (%)			.281
≤2	10 (10.9)	15 (9.9)	
3	32 (34.8)	39 (25.8)	
4	50 (54.3)	97 (64.2)	
PEDT score (Q3), n (%)			.141
≤2	36 (39.1)	69 (45.8)	
3	40 (43.5)	47 (31.1)	
4	16 (17.4)	35 (23.2)	
PEDT score (Q4), n (%)			.810
≤3	30 (32.6)	47 (31.1)	
4	62 (67.4)	104 (68.9)	
PEDT score (Q5), n (%)			.323
≤3	40 (43.5)	56 (37.1)	
4	52 (56.5)	95 (62.9)	
PHQ-9 score, n (%)			.279
0−4	30 (32.6)	35 (23.2)	
5−9	36 (39.1)	59 (39.1)	
10−14	18 (19.6)	35 (23.2)	
≥15	8 (8.7)	22 (14.6)	

(continued)

Table 1. Continued

Variables	iCGI group (N = 92)	Non-iCGI group (N = 151)	P value
GAD-7 score, n (%)			.184
0–4	43 (46.7)	55 (36.4)	
5–9	35 (38.0)	61 (40.4)	
≥10	14 (15.2)	35 (23.2)	

BMI = body mass index; GAD-7 = Generalized Anxiety Disorder-7; iCGI = improvement of clinical global impression; IELT = Intra-vaginal Ejaculation Latency Time; IIEF-5 = 5-item International Index Erectile Function; IQR = interquartile range; PEDT = Premature Ejaculation Diagnostic Tool; PHQ-9 = Patient Health Questionnaire-9.
P values achieved statistical significance were shown in bold.

represents a small proportion of LPE cases,[3] and these patients were not excluded. All patients included in our study were required to engage in sexual intercourse at least 6 times during the 4-week study period and at least once per week. All patients were required to take dapoxetine 30 mg 1–3 h before each planned sexual intercourse. This study was approved by the Ethics Committee of Xijing Hospital (approval number KY20192108-F-1). Written informed consent was provided by all participants.

Variables Before and After Dapoxetine Treatment

Pretreatment variables included age at visit, body mass index, years of education, self-reported IELT, International Index of Erectile Function-5 (IIEF-5) questionnaire,[15] Premature Ejaculation Diagnostic Tool (PEDT) questionnaire,[16] Patient Health Questionnaire-9,[17] and the Generalized Anxiety Disorder questionnaire.[18]

After the 4-week dapoxetine treatment, we focused solely on the patient-rated CGIC,[19] which was collected from a patient-completed Internet questionnaire after a phone discussion with the same andrologist they saw on their first visit. The CGIC questionnaire asks, "Compared to the beginning of this study, would you describe your PE problem as much worse, worse, slightly worse, no change, slightly better, better, or much better?", and the CGIC score is composed of 7 points (−3, −2, −1, 0, +1, +2, and +3), which correspond to the 7 choices mentioned previously.[19] When patients were filling in the CGIC questionnaire, all of them were instructed to consider all aspects into consideration, including IELT, satisfaction with sexual intercourse, control over ejaculation, personal distress associated with ejaculation, and interpersonal difficulties. In this study, patients with CGIC scores of +1, +2, and +3 were considered to have achieved iCGI, and the 2 groups, labeled as the iCGI group and non-iCGI group, were compared.

Statistical Analysis

Data were analyzed using R for Windows, version 3.6.1 (http://www.r-project.org/). Continuous variables were expressed as medians (ranges) and compared among subgroups using the Mann-Whitney U test. Categorical variables were expressed as frequencies (proportions) and compared using the chi-squared test. Variables that were statistically significant in the univariate logistic regression model were included in the multivariate logistic regression model. The nomogram was developed using R software according to the coefficients in the multivariate logistic regression model, where backward variable selection was performed to identify independent predictors. The discriminatory ability of the nomogram was quantified using the area under the receiver operating characteristic curve,[20] whose values ranged from a minimum of 0.5, indicating no discrimination, to a maximum of 1.0, indicating perfect discrimination.[21] A calibration plot of the nomogram was constructed to test the agreement between predictions and observations, with the calibration curve expected to fall on the diagonal line in a perfectly calibrated nomogram.[22] Bootstrapping with 500 resamples was performed for these evaluations. A two-tailed P value of <.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 286 patients with LPE were included in this study. 6 (2.1%) patients were lost to follow-up, and 4 (1.4%) patients were excluded from the final analysis because they received concomitant treatments (psychotherapy [2 patients] and traditional Chinese medicine [2 patients]) along with dapoxetine. Moreover, 33 (11.7%) patients discontinued dapoxetine treatment because of unmet expectations (8.5%) or side effects (mainly including nausea [1.1%], dizziness [0.7%], and headache [0.4%]). These 43 patients were excluded from our cohort, and the remaining 243 patients were used for analysis.

Of the 243 patients included in the final analysis, 92 patients (37.9%) achieved iCGI, and the number of patients with a CGIC score of +1, +2, and +3 was 80 (87.0%), 2 (2.2%), and 10 (10.9%), respectively. A total of 151 patients (62.1%) did not achieve iCGI, and the number of patients with a CGIC score of 0, −1, −2, and −3 was 121 (80.1%), 10 (6.6%), 12 (7.9%), and 8 (5.3%), respectively. Notably, 42 patients (17.3%) complained of mild side effects, mainly dizziness (n = 18 [7.4%]), headache (n = 15 [6.2%]), nausea (n = 10 [4.1%]), and fatigue (n = 5 [2.1%]).

The pretreatment characteristics of the patients in our final study cohort are listed in Table 1. There were statistically

Table 2. Univariate logistic regression analysis of achieving iCGI in patients with lifelong premature ejaculation treated with dapoxetine

Variables	OR	95% CI	P value
Age at visit (years)			.529
26−30 vs ≤25	1.332	0.666−2.662	.417
31−35 vs ≤25	0.860	0.402−1.840	.698
>35 vs ≤25	1.410	0.604−3.291	.428
BMI (kg/m²)			.641
24−27 vs <24	1.279	0.718−2.279	.404
>27 vs <24	1.294	0.619−2.707	.493
Years of education			.027
9−16 vs ≤9	1.543	0.751−3.171	.237
≥16 vs ≤9	2.712	1.268−5.801	.010
IELT (min)			.001
0 < IELT ≤ 1 vs IELT = 0	2.293	1.073−4.902	.032
1 < IELT ≤ 2 vs IELT = 0	4.750	2.111−10.688	<.001
IIEF-5 score (Q1)			.961
3 vs ≤2	0.983	0.550−1.757	.955
4 & 5 vs ≤2	1.086	0.537−2.198	.818
IIEF-5 score (Q2)			.252
3 & 4 vs ≤2	1.413	0.725−2.755	.310
5 vs ≤2	1.762	0.903−3.438	.097
IIEF-5 score (Q3)			.081
4 vs ≤3	1.014	0.534−1.926	.966
5 vs ≤3	1.941	0.971−3.881	.061
IIEF-5 score (Q4)			.044
3 & 4 vs ≤2	2.226	0.983−5.042	.055
5 vs ≤2	2.642	1.233−5.660	.012
IIEF-5 score (Q5)			.001
2 vs 1	2.462	1.299−4.663	.006
≥3 vs 1	3.194	1.658−6.153	.001
PEDT score (Q1)			.010
2 & 3 vs ≤1	0.380	0.165−0.876	.023
4 vs ≤1	0.259	0.109−0.619	.002
PEDT score (Q2)			.283
3 vs ≤2	1.231	0.487−3.109	.661
4 vs ≤2	0.773	0.324−1.845	.562
PEDT score (Q3)			.143
3 vs ≤2	1.631	0.910−2.923	.100
4 vs ≤2	0.876	0.428−1.792	.717
PEDT score (Q4)			
4 vs ≤3	0.934	0.536−1.628	.810
PEDT score (Q5)			
4 vs ≤3	0.766	0.452−1.300	.323
PHQ-9 score			.286
5−9 vs 0−4	0.712	0.375−1.350	.298
10−14 vs 0−4	0.600	0.284−1.269	.181
≥15 vs 0−4	0.424	0.165−1.091	.075
GAD-7 score			.188
5−9 vs 0−4	0.734	0.413−1.306	.293
≥10 vs 0−4	0.512	0.245−1.069	.075

BMI = body mass index; CI = confidence interval; GAD-7 = Generalized Anxiety Disorder-7; iCGI = improvement of clinical global impression; IELT = Intravaginal Ejaculation Latency Time; IIEF-5 = 5-item International Index Erectile Function; OR = odd ratio; PEDT = Premature Ejaculation Diagnostic Tool; PHQ-9 = Patient Health Questionnaire-9.
Total P values among/between subgroups were shown in bold.

significant differences in the years of education ($P = .025$), self-reported IELT ($P < .001$), IIEF-5 (Q4) scores ($P = .038$), IIEF-5 (Q5) scores ($P = .001$), and PEDT (Q1) scores ($P = .007$) between the iCGI group and the non-iCGI group.

Independent Predictors of iCGI

Results of the univariate logistic regression revealed that years of education ($P = .027$); self-reported IELT ($P = .001$); Q4 and Q5 scores of IIEF-5 ($P = .044$ and $P = .001$, respectively), which explored the satisfaction from sexual intercourse; and Q1 score of PEDT ($P = .010$), which explored the ability to control ejaculation, were significantly associated with iCGI (Table 2). The multivariate logistic regression results showed that patients with LPE with at least a bachelor's degree (years of education ≥ 16), self-reported IELT >1 minute, and Q5 score of IIEF-5 of ≥ 3 were independent factors positively associated with achieving iCGI. Conversely, a Q1 score of PEDT of ≥ 2 was an independent, negatively associated factor (Table 3).

Construction and Evaluation of the Nomogram

The nomogram was developed using R software by integrating the 4 pretreatment variables that demonstrated independent predictive significance for achieving iCGI. As shown in Figure 1, self-reported IELT >1 minute, closely followed by strong control over ejaculation (Q1 score of PEDT [≤ 1]) and at least a bachelor's degree, were the largest contributors to increasing the likelihood of achieving iCGI. Pretreatment satisfaction with sexual intercourse (Q5 score of IIEF-5) also had a moderate influence on the predictive outcome.

Each subtype of the 4 predictors corresponded to a point on the "Points" scale, and each score on the "total points" scale corresponds to a probability value on the "possibility of achieving iCGI" scale. To determine the likelihood that a randomly selected patient with LPE will achieve iCGI, we only need to perform the following 2 steps. First, we calculate his total points by summing each score corresponding to his subtype of each predictor. Second, we draw a vertical line downward from the location of his total points on the "total points" scale. For example, if the 4 variables of an LPE patient are (i) 10 years of education, (ii) self-reported IELT of 90 s, (iii) IIEF-5 (Q5) score of 2, and (iv) PEDT (Q1) score of 1, his total points are calculated to be 284.4 (42.5 + 100 + 51.4 + 90.5 = 284.4). Then, his possibility of achieving iCGI (74%) will be shown, as in Figure 2.

The discriminatory ability of the nomogram was 0.710 (95% confidence interval: 0.702−0.718), which indicated a moderate accuracy (Figure 3A). The predictive accuracy of the nomogram was higher than that in models constructed by integrating any one, 2, or 3 of the variables among years of education, self-reported IELT, IIEF-5 (Q5) score, and PEDT (Q1) score, as shown in Table 4. Moreover, the calibration plot demonstrates excellent agreement between predictions and observations

Table 3. Multivariate logistic regression analyses of achieving iCGI in patients with lifelong premature ejaculation treated with dapoxetine

| Characteristic	Coefficient	OR (95% CI)	P value
Years of education			
9–16 vs ≤9	0.477	1.611 (0.738–3.518)	.231
≥16 vs ≤9	0.959	2.608 (1.153–5.898)	**.021**
IELT (min)			
0 < IELT ≤ 1 vs IELT = 0	0.548	1.729 (0.776–3.851)	.180
1 < IELT ≤ 2 vs IELT = 0	1.125	3.081 (1.277–7.434)	**.012**
IIEF-5 score (Q5)			
2 vs 1	0.581	1.788 (0.882–3.627)	.107
≥3 vs 1	0.774	2.169 (1.041–4.517)	**.039**
PEDT score (Q1)			
2 & 3 vs ≤1	−1.022	0.360 (0.147–0.879)	**.025**
4 vs ≤1	−1.012	0.364 (0.142–0.928)	**.034**

CI = confidence interval; iCGI = improvement of clinical global impression; IELT = Intravaginal Ejaculation Latency Time; IIEF-5 = 5-item International Index Erectile Function; OR = odd ratio; PEDT = Premature Ejaculation Diagnostic Tool.
P values achieved statistical significance were shown in bold.

(Figure 3B). These findings indicate that our nomogram possesses good discrimination and excellent calibration.

DISCUSSION

Although dapoxetine doses of 30 mg and 60 mg are proven to result in more than threefold increases in IELT in various clinical trials,[23] many patients discontinue dapoxetine treatment in clinical practice because the medication does not meet their expectation.[10,11] At present, IELT is the most commonly used endpoint for measuring the efficacy of dapoxetine treatment in clinical trials, but its performance is likely to be inferior to CGIC,[19] which represents the overall impact of the treatment on a patient's clinical condition.[12] Few studies have explored the
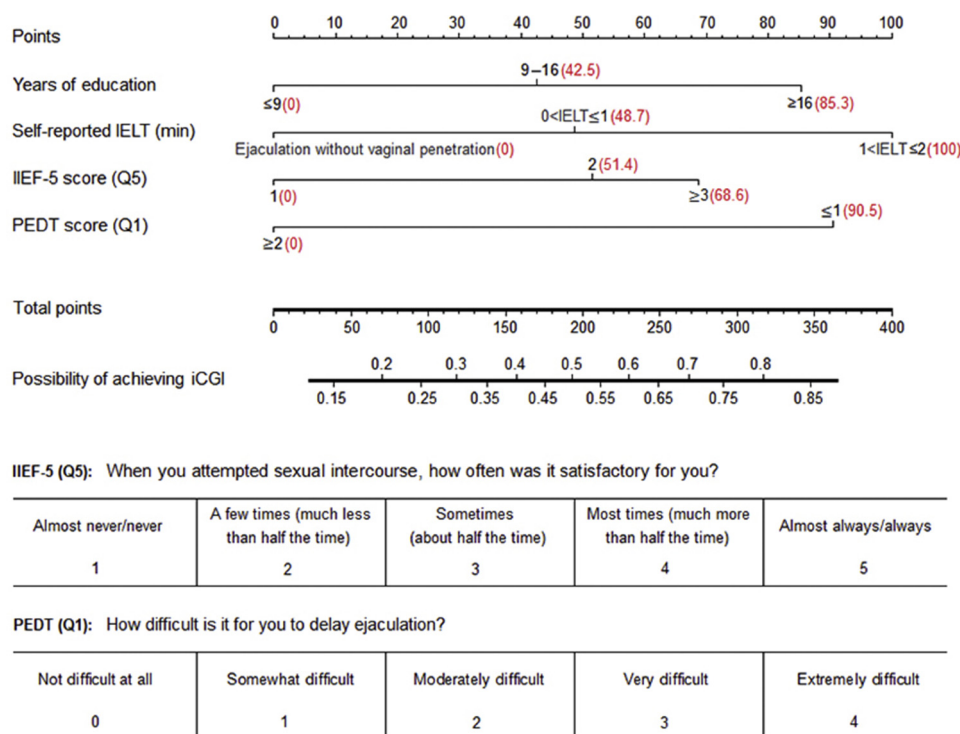
Figure 1. Nomogram for predicting the possibility of iCGI in patients with LPE treated with dapoxetine. Self-reported IELT > 1 min, closely followed by a strong control over ejaculation and a bachelor's degree or above, was the largest contributor to a large possibility of achieving iCGI. iCGI = improvement of clinical global impression; IELT = Intravaginal Ejaculation Latency Time; IIEF-5 (Q5) = International Index of Erectile Function-5 (Question 5); LPE = lifelong premature ejaculation; PEDT (Q1) = Premature Ejaculation Diagnostic Tool (Question 1). Figure 1 is available in color online at www.jsm.jsexmed.org.
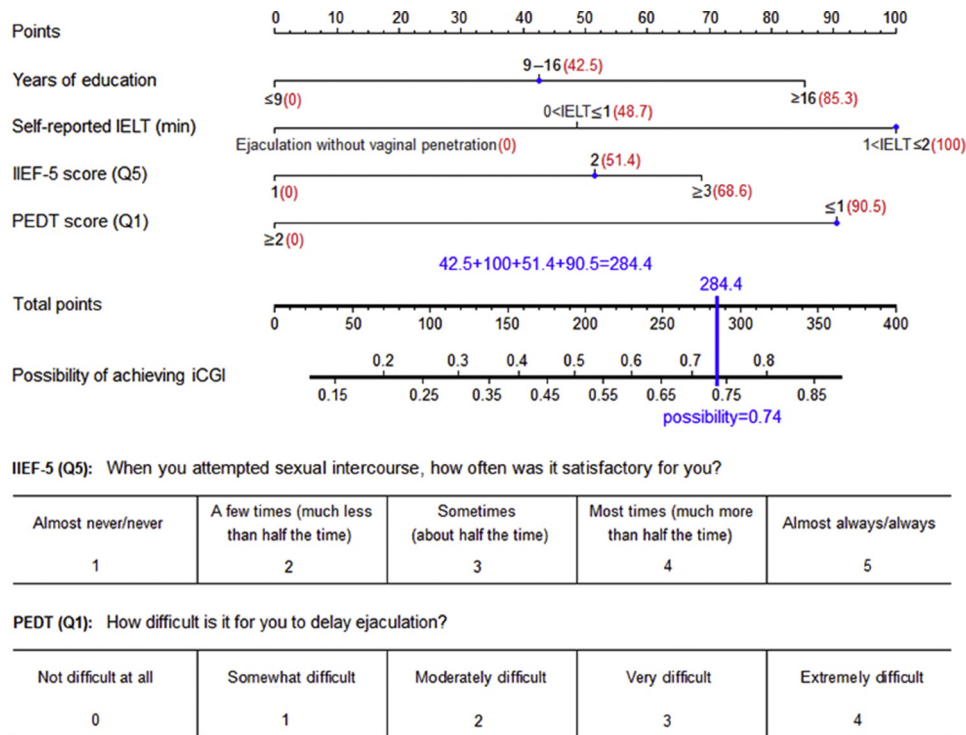
Figure 2. Example estimation of the possibility of iCGI in a patient with LPE treated with dapoxetine whose years of education was 10, self-reported IELT was 90 sec, IIEF-5 (Q5) score was 2, and PEDT (Q1) score was 1. His total points of the 4 predictors add up to a sum of 284.4 points, which indicates that his possibility of achieving iCGI is about 0.74. iCGI = improvement of clinical global impression; IELT = Intravaginal Ejaculation Latency Time; IIEF-5 (Q5) = International Index of Erectile Function-5 (Question 5); LPE = lifelong premature ejaculation; PEDT (Q1) = Premature Ejaculation Diagnostic Tool (Question 1). Figure 2 is available in color online at www.jsm.jsexmed.org.

independent predictors of CGIC in patients with PE treated with dapoxetine, and a model for predicting a patient's likelihood of achieving iCGI has not yet been developed.

Althof et al[12] (2010) reported that higher CGIC scores were related to greater improvements in control over ejaculation (r = 0.73) and satisfaction with sexual intercourse (r = 0.62). However, to the best of our knowledge, no study has revealed the relationship between pretreatment control and satisfaction and iCGI. This study found that patients reporting pretreatment satisfaction for more than 50% of experiences were more likely to
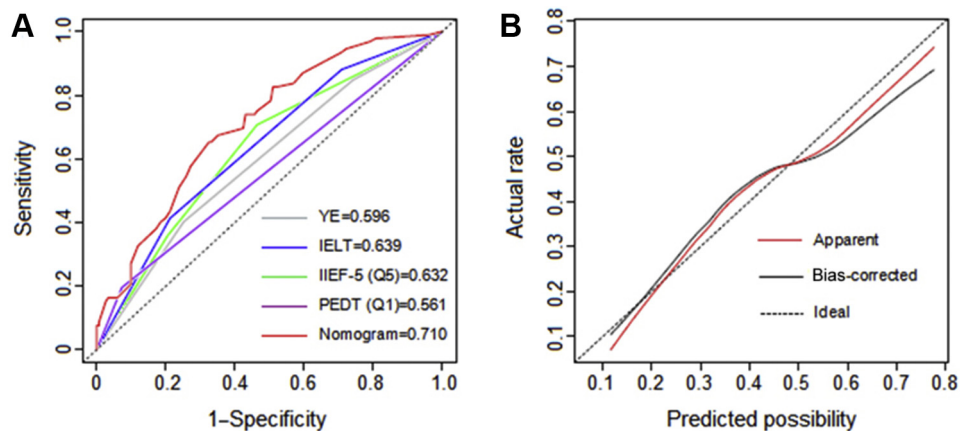
Figure 3. Panel A shows the ROC curves of the nomogram and its constituted variables. Panel B shows the calibration plot of the nomogram. The dotted line represents the performance of an ideal nomogram (the prediction perfectly corresponds to the observation). The red solid line indicates the apparent accuracy of the nomogram without correction for overfitting. The black solid line represents the bootstrap-corrected nomogram. IELT = Intravaginal Ejaculation Latency Time; IIEF-5 (Q5) = International Index of Erectile Function-5 (Question 5); PEDT (Q1) = Premature Ejaculation Diagnostic Tool (Question 1); ROC = receiver operating characteristic; YE = years of education. Figure 3 is available in color online at www.jsm.jsexmed.org.

Table 4. Discriminatory ability of predictive models based on our study cohort

Constituted variables	AUC	Constituted variables	AUC
A	0.596	B + D	0.665
B	0.639	C + D	0.658
C	0.632	A + B + C	0.694
D	0.561	A + B + D	0.696
A + B	0.679	A + C + D	0.679
A + C	0.656	B + C + D	0.690
A + D	0.636	A + B + C + D (our nomogram)	**0.710**
B + C	0.677		

A = Years of education; AUC = area under the receiver operating characteristic curve; B = IELT (Intra-vaginal Ejaculation Latency Time); C = IIEF-5 (Q5) [5-item International Index Erectile Function (question 5)]; D = PEDT (Q1) [Premature Ejaculation Diagnostic Tool (question 1)].

achieve iCGI than those reporting satisfaction for less than 50% of experiences. Patients who reported delayed ejaculation with moderate or more than moderate difficulties (Q1 score of PEDT ≥ 2) had a nearly 0.36-fold chance of achieving iCGI compared with those who reported slight or no difficulties in delayed ejaculation (Q1 score of PEDT ≤ 1). This finding was in agreement with that in a study by Peng et al,[8] in which patients with PE with milder symptoms before treatment were more likely to demonstrate improvement with dapoxetine. In addition, pretreatment IELT, as the variable with the highest predictive accuracy, had a significantly lower accuracy than our nomogram (0.639 vs 0.710, $P < .001$), and using pretreatment IELT alone, an individual's iCGI likelihood of less than 30% can persist even if his IELT is up to 2 minutes according to our nomogram. These findings indicate that it is not enough to assess the efficacy of dapoxetine using only pretreatment IELT, and it is necessary to develop a novel predictive tool.

Although IIEF-5 is used for evaluating erectile function in clinical practice, it does reflect ejaculatory function to a certain extent.[24] In clinical practice, ED and PE are frequently comorbid.[24] In previous studies, PE was diagnosed in approximately one-third of patients with ED, and more than 30% of patients with PE reported concomitant ED.[25,26] This has been explained by hypothesizing that ED and PE share a vicious cycle, in which a man trying to control his ejaculation instinctively reduces his level of excitation (which can result in ED) and a man trying to achieve an erection attempts to increase his level of excitation (which can result in PE).[27] In the present study, more frequent satisfaction from sexual intercourse (ie, higher IIEF-5 [Q5] score) before dapoxetine treatment was associated with a higher chance of achieving iCGI, and this phenomenon may be attributed to the following reasons: (i) patients with more frequent satisfaction were more likely to have better erectile function, which represents better ejaculation function, thereby supporting the aforementioned hypothesis,[27] and (ii) patients with PE with better pretreatment ejaculatory function were more likely to benefit from dapoxetine treatment.[8]

Interestingly, years of education was found to be associated with iCGI in our study. According to multivariate logistic regression results, a 2.61-fold chance of achieving iCGI was noted in patients with LPE with at least a bachelor's degree (years of education ≥ 16) compared with those with a middle-school education or below (years of education ≤ 9); this may be because patients with lower education levels have inadequate sexual knowledge[28] and are more likely to have unrealistic expectations of dapoxetine and any other PE treatment, such as achieving a longer IELT. This finding stresses the need for in-depth counseling when prescribing PE treatments.

Nomograms, which are graphical representations of multivariable models that integrate several predictors,[29] have been proven to be useful in clinical settings and to perform well at predicting the individual likelihood of experiencing certain events, such as erectile function recovery after radical prostatectomy,[30] testicle salvage in patients with testicular torsion,[31] and natural conception at various time points for couples diagnosed with unexplained subfertility.[32] The present study is the first to develop an effective nomogram to assess the likelihood of achieving iCGI in patients with LPE treated with dapoxetine. Although the sampling centers were both located in Xi'an, Shaanxi, China, only 72 cases (29.6%) were from Shaanxi province, and the remaining 171 cases (70.4%) were from other regions of China. Therefore, the study sample is largely representative of the general population of Chinese patients with LPE. The 4 predictors used in our nomogram were variables that can be easily recorded in clinical practice, which ensures the convenience of using the nomogram and the feasibility of promoting its use. However, this study has some limitations that should be considered. First, no placebo-treated control group was compared with our cohort. Second, this study was performed with only one follow-up visit after a 4-week dapoxetine treatment. Third, although we communicated with all patients to explain the online questionnaire before they completed it, limitations associated with the online questionnaire can still exist. Fourth, the nomogram was not externally validated using independent cohorts from other institutions, which may limit the broad application of the nomogram. Fifth, the IELT used in our study was self-reported IELT, which may be overestimated[33] and susceptible to subjectivity.

CONCLUSION

This study identified factors that were independently associated with iCGI in patients with LPE treated with dapoxetine. Furthermore, the first nomogram for predicting the likelihood of an individual achieving iCGI was developed. If the good predictive performance of our nomogram is further proven in future studies, it can be used to select suitable patients for dapoxetine treatment, thereby reducing the number of patients discontinuing dapoxetine treatment because of unmet expectations. External validations using data from Western patients are

required to test the broader applicability of this Chinese patient-based tool.

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