External validation of a prediction model for penile prosthesis implantation for erectile dysfunction management

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ANELE UA, SEGAL RL, LE BV, BURNETT AL. External validation of a prediction model for penile prosthesis implantation for erectile dysfunction management. *Can J Urol* 2014;21(6):7554-7559.

Introduction: *Penile prosthesis implantation (PPI) is the definitive surgical treatment for erectile dysfunction (ED), yet it is often delayed for a variety of reasons. From commercial and Medicare claims data, we previously developed a tool for determining a patient's likelihood of eventually receiving PPI. We validated this instrument's utility by comparing cohorts receiving surgical (PPI) versus non-surgical ED management at a single institution.*

Material and methods: *The prediction model was based on a logistic regression incorporating claims data on demographics, comorbidities and ED therapy. A risk score is calculated from the model as the product of relative risks for the individual variables. The current validation was a retrospective analysis of ED patients seen at this institution from January to December 2012. Inclusion criteria included ED diagnosis and either first-time PPI or non-surgical treatment (controls). Risk scores for patients receiving PPI were compared to those of non-surgical controls.*

Results: *We established a cohort of 60 PPI patients (mean age 54.4 ± 9.5) and compared them with 120 non-PPI patients (mean age 53.4 ± 11.2 years). The median score of the PPI cohort was 5.7 (IQR 2.8-9.9) versus the non-PPI cohort's 1.8 (IQR 0.9-5.5) ($p < 0.0001$). The area under the receiver operator characteristic curve for predicting eventual PPI was 0.72 (95% CI, 0.64-0.79) ($p < 0.0001$).*

Conclusion: *The prediction model risk-stratified men who ultimately underwent PPI compared to non-surgically managed controls. This external validation study suggests that the prediction model may be used on an individual patient basis to support a recommendation of PPI for managing ED.*

Key Words: ED, surgical management, risk factors, medical comorbidities

Introduction

Erectile dysfunction (ED) is an increasingly prevalent condition with a profound impact on quality of life. Worldwide prevalence rates of ED are estimated to increase to over 300 million men by 2025.[1] First-line therapy for organic ED typically includes one or more trials with a phosphodiesterase-5 (PDE5) inhibitor, which typically work well, with success rates on the order of 80%.[2-6] Treatments such as intracavernosal injection (ICI), urethral suppositories (MUSE), and vacuum erection devices (VEDs) offer second-line options for those who fail initial oral therapies, but these are often associated with high dissatisfaction[7-13] and dropout rates, at times over 50%.[14]

Penile prosthesis implantation (PPI) often represents the definitive option for individuals who are dissatisfied

Accepted for publication October 2014

Acknowledgment
We thank Dr. Bruce Trock for his assistance in data analysis and interpretation.

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with or unresponsive to other therapies; however, it can be significantly delayed by trials of available, less-invasive, treatment options. Over the course of this delay, patients may experience worsening declines in both function and quality of life. Due to the high success and patient satisfaction rates associated with PPI, a prediction model was previously developed to assist physicians in determining a patient's likelihood of eventually receiving PPI and thus reduce the potentially lengthy period of time an individual may experience ED symptoms.[15] This prediction model was derived using risk factors identified as being associated with progression to PPI using commercial and Medicare claims databases. The aim of this study was to validate this prediction model using an institutional patient database comparing cohorts receiving surgical versus non-surgical ED management.

Materials and methods

Patients selection

A retrospective database review was performed on ED patients treated at this institution from January-December 2012. Patients undergoing management for ED were eligible for inclusion. All patients who had a diagnosis of ED and underwent first-time PPI were selected. Patients receiving PPI for neophallic reconstructions were excluded. The database was arranged according to clinic visit date whereby patients meeting these criteria were identified and selected for the PPI cohort. For each PPI patient selected, the next two consecutive ED patients who underwent non-surgical ED management were selected for the non-PPI cohort ("controls").

Prediction model

The prediction model for PPI was previously established using a retrospective analysis of claims data from commercial and Medicare databases.[15] The risk factors in the model were derived using patient baseline characteristics, comorbidities, and prior history of ED treatment. In that study, risk factors were analyzed as fixed covariates and 24 different variables, Table 1, were selected using stepwise regression. Relative risks were determined upon quantification of those predictive risk factors associated with future PPI, Table 1. Previously determined risk factors carrying the most weight were Peyronie's disease (4.39), prostate cancer (2.98), priapism (2.66), and use of second-line ED therapies such as intracavernosal injections (ICI) (2.07).[15] In the current study, these factors were identified using individual medical record review of patients in the PPI and non-PPI ED management groups. Scores were determined by calculating the product of relative risks.

Statistical analysis

When qualitative descriptors of ED duration such as "longstanding" and "many" were encountered, the median value between 5 and the longest years of duration among the group was substituted for that individual and used in determining the mean in each group. Risk scores were calculated for each individual in the PPI and control cohorts and presented as medians with interquartile ranges (IQR). Duration of ED was derived using medical record review. The surgical management (PPI) group was compared to the non-surgical (non-PPI) group using the nonparametric Wilcoxon rank-sum test. Normally-distributed data were compared using the Student's t test where appropriate. Categorical data were compared using the Chi Square test.

The ability for this prediction model to distinguish between patients undergoing surgical versus non-surgical management was assessed using a receiver operating characteristic (ROC) curve to plot the sensitivity versus 1-specificity values for each risk score cutoff and determine the area under the curve (AUC). Evaluation with the ROC curve was performed using the non-PPI cohort as a reference group. The area under the curve represents the discriminative power in differentiating patients who underwent surgical vs non-surgical management. An AUC > 0.90 demonstrates high accuracy, 0.70 < AUC ≤ 0.90 demonstrates moderate accuracy, 0.50 < AUC ≤ 0.70 demonstrates low accuracy, and AUC = 0.5 demonstrates chance level accuracy.[16,17] An optimal cutoff point, characterized by both maximal sensitivity and specificity, was determined using the Youden index, which is the maximum vertical distance from the reference line to the ROC curve and calculated as sensitivity+specificity-1.[17] Parameters of the ROC curve were presented with their respective 95% confidence intervals (CI). Data were analyzed using GraphPad Prism 5 (GraphPad Software, Inc, La Jolla, CA, USA). A p value < 0.05 was considered statistically significant.

Results

Table 2 depicts the demographic data of the population. There were no differences in age at presentation, age of ED onset, racial composition, marital status, and mean duration of ED. The mean duration of ED from onset to PPI (PPI cohort) was 6.5 ± 5.0 years (median 5.1 years). The median risk score of the PPI cohort was 5.74 (IQR 2.85-9.89) versus 1.75 (IQR 0.93-5.50) among the non-PPI cohort ($p < 0.0001$), Table 2. The presence of Peyronie's disease ($p > 0.0001$), prostate cancer ($p = 0.0001$), second-line ED therapies use ($p = 0.0001$), and mood disorders (depression, $p = 0.007$; and anxiety, $p = 0.04$)

TABLE 1. **Prediction model relative risks**

	Overall population (n = 384,618)		
Risk factor	**Relative risk**	**95% CI**	**p value**
Peyronie's disease	4.39	(3.71, 5.19)	< .001
Prostate cancer	2.98	(2.72, 3.26)	< .001
Priapism	2.66	(1.87, 3.79)	< .001
Other unspecified disorders of the penis	2.27	(1.88, 2.73)	< .001
Second-line ED therapy	2.07	(1.91, 2.24)	< .001
Multiple sclerosis	1.95	(1.29, 2.94)	< .001
Spinal cord injury	1.87	(1.01, 3.49)	0.04
Diabetes mellitus	1.84	(1.71, 1.97)	< .001
Renal transplant	1.69	(1.09, 2.62)	0.02
Arterial bypass procedure	1.52	(1.41, 1.64)	< .001
First-line ED therapy	1.42	(1.34, 1.52)	< .001
Psychosexual dysfunction, unspecified sexual dysfunction	1.41	(1.24, 1.60)	< .001
Radical prostatectomy	1.40	(1.25, 1.56)	< .001
Depression	1.33	(1.20, 1.48)	< .001
Polyneuropathy	1.26	(1.09, 1.45)	< .001
Cardiovascular disease	1.16	(1.05, 1.27)	< .001
Hypertension	1.12	(1.05, 1.20)	< .001
Anxiety and anxiety-related diagnoses	0.82	(0.70, 0.95)	< .001
Dyslipidemia	0.72	(0.68, 0.77)	< .001
Age group			
18-44	0.28	(0.23, 0.33)	< .001
45-54	0.67	(0.61, 0.73)	< .001
55-64	Reference		
65-74	1.19	(1.10, 1.29)	< .001
75+	0.66	(0.58, 0.75)	< .001

n = number; CI = confidence interval; ED = erectile dysfunction

were significantly increased among the PPI group compared to the non-PPI group, Table 2.

The ability of the prediction model to distinguish between PPI and non-PPI patients was plotted using an ROC curve. The AUC was 0.72 (95% CI, 0.64-0.79) ($p < 0.0001$), Figure 1. Using the Youden index, the optimal cutoff for predicting patients progressing to PPI was a relative risk score > 4.17 (0.67 [95% CI, 0.53-0.78] sensitivity and 0.68 [95% CI, 0.58-0.76] specificity), Table 3.

Discussion

The duration of ED symptoms can be quite prolonged, and definitive treatment with PPI can be delayed. As such, a prediction model offers a tool to estimate the risk of progression to PPI with the prospect of decreasing these lengthy periods of time. The purpose of this study was to externally validate the previously developed model for predicting eventual receipt of a PPI using a single-center, ED population.

The prediction model revealed a significantly increased relative risk score in the PPI cohort compared to the non-PPI cohort, demonstrating the utility of this instrument in confirming the distinct risk profiles of patients proceeding to PPI. Our findings that Peyronie's disease, prostate cancer, and the use of second-line ED therapies are significant factors in the progression to PPI are consistent with the previous study, which established this model.[15] The calculated AUC indicates a moderate level of predictive accuracy[16] and as such this model performs adequately in distinguishing risk scores between those managed with surgical and

TABLE 2. **Demographic information and prediction model risk scores and factors**

	PPI group (n = 60)	Non-PPI group (n = 120)	p value
Age at presentation (years), mean (SD)	59.87 (9.32)	57.69 (10.65)	0.18
Race, n (%)			0.91
Caucasian	32 (53.33)	59 (49.17)	
African American	24 (40)	47 (39.17)	
Other†	4 (6.67)	6 (5)	
Marital status, n (%)			0.49
Married	44 (73.33)	82 (68.33)	
Unmarried‡	16 (6.67)	38 (18.33)	
Age of ED onset (years), mean (SD)	54.43 (9.55)	53.36 (11.16)	0.52
Duration of ED (years), mean (SD)	4.88 (4.73)	5.55 (5.70)	0.44
Duration of ED to PP, mean (SD)	6.53 (4.99)	N/A	
Prediction model risk score			< 0.0001
Mean (95% CI)	8.46 (5.33-11.59)	3.95 (3.12-4.79)	
Median (IQR)	5.74 (2.85-9.89)	1.75 (0.93-5.50)	
Risk factors			
Peyronie's disease	12 (20)	1 (0.83)	0.0001
Prostate cancer	32 (53.33)	41 (34.17)	0.01
Priapism	2 (3.33)	2 (1.67)	0.47
Other unspecified disorders of the penis	0 (0)	0 (0)	
Second-line ED therapy	35 (58.33)	33 (27.5)	0.0001
Multiple sclerosis	2 (3.33)	1 (0.83)	0.21
Spinal cord injury	0 (0)	0 (0)	
Diabetes mellitus	11 (36.67)	29 (24.17)	0.37
Renal transplant	0 (0)	3 (2.5)	0.22
First-line ED therapy	48 (80)	88 (73.33)	0.33
Arterial bypass procedure	3 (5)	2 (1.67)	0.20
Radical prostatectomy	28 (46.67)	37 (30.83)	0.04
Psychosexual dysfunction, unspecified sexual dysfunction	1 (1.67)	0 (0)	0.16
Depression	15 (25)	12 (10)	0.007
Polyneuropathy	0 (0)	3 (2.5)	0.22
Hypertension	39 (65)	72 (60)	0.52
Cardiovascular disease	11 (36.67)	14 (11.67)	0.22
Hyperlipidemia	31 (51.67)	54 (45)	0.40
Anxiety/anxiety-related diagnoses	2 (3.33)	0 (0)	0.04
Age group			
18-44	7 (11.67)	20 (16.67)	0.38
45-54	24 (40)	42 (35)	0.51
55-64	16 (26.67)	43 (35.83)	0.22
65-74	13 (21.67)	14 (11.67)	0.08
75+	0 (0)	1 (0.83)	0.48

PP = penile prosthesis; ED = erectile dysfunction; SD = standard deviation; n = number;
N/A = not applicable; CI = confidence interval,
IQR = interquartile range
†Hispanic, Asian, unknown; ‡single, divorced/separated, widowed, unknown

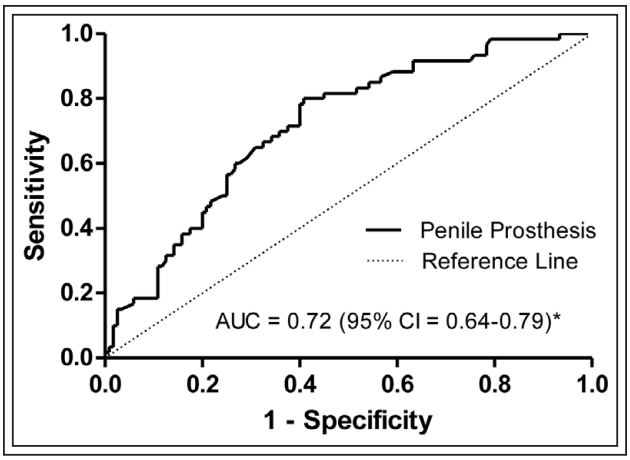

Figure 1. Receiver operating characteristic (ROC) curve and area under curve (AUC) of prediction model risk scores in identifying progression to PP. *= $p < 0.0001$.

non-surgical therapy. Although the sensitivity and specificity combination at the optimal cutoff value of > 4.17 is not remarkably high, we must note that ultimately, the cutoff point can be chosen based on the sensitivity and/or specificity required for the setting in which this model may be utilized (eg clinical versus epidemiological).[17] As such, given the risks inherent to surgical intervention, a higher specificity and thus higher cutoff point is preferred. The likelihood ratio at the optimal cutoff value indicates that a relative risk score > 4.17 is obtained over two times more often from a patient who underwent PPI than from a patient who received non-surgical management.

PPI is often the last offered and hence delayed option in the management of ED due to multiple factors ranging from patient concerns regarding invasiveness and irreversibility to clinician unfamiliarity.[15] Subsequently, the effects of deferring PPI are not always entirely considered. Issues such as advancing age, progression of comorbidities, and even potential adverse effects of certain treatments such as ICI (corporal scarring) may make later PPI more difficult.[15] As such, this prediction model serves to provide specific and definable parameters, that when considered together, may assist care providers and patients regarding consequences of treatment decisions at the time of ED diagnosis. Ultimately, this tool may serve as a complementary aid in assessing predictability of progressing to PPI. Thus, it may offer an advantage to a patient with this predictability in that he is better informed and may achieve successful resumption of sexual activity sooner with PPI while avoiding further challenges associated with alternative ED management.

We acknowledge potential limitations of this study. This model fails to account for reasons for PPI that may extend beyond the influence of a patient's comorbidities. Specifically, influences such as insurance coverage status and interpersonal relationships, as well as cultural issues may additionally influence this decision.[15] We also acknowledge that the precision of our findings may be limited by the small, retrospective, and single-center nature of this investigation. Additionally, medical records may not always be entirely complete or accurate in regards to characteristics of patient history such as onset/duration of ED or even comorbidity profiles. Moreover, we only identified patients within a relatively brief period of time (1 year) which may have contributed to an overestimation of the mean risk within the control group as several of those patients

TABLE 3. **Accuracy of prediction model in identifying progression to penile prosthesis**

Risk score	Sensitivity, %	(95% CI)	Specificity, %	(95% CI)	Likelihood ratio
> 3.90	70	(56.79-81.16)	64.17	(54.90-72.71)	1.95
> 4.01	68.33	(55.04-79.74)	64.17	(54.90-72.71)	1.91
> 4.11	68.33	(55.04-79.74)	65	(55.76-73.48)	1.95
> 4.12	68.33	(55.04-79.74)	65.83	(56.62-74.24)	2
> 4.15	66.67	(53.31-78.31)	65.83	(56.62-74.24)	1.95
> 4.17	66.67	(53.31-78.31)	67.5	(58.35-75.77)	2.05
> 4.22	65	(51.60-76.87)	67.5	(58.35-75.77)	2
> 4.31	65	(51.60-76.87)	68.33	(59.22-76.52)	2.05
> 4.40	65	(51.60-76.87)	69.17	(60.09-77.27)	2.11
> 4.61	61.67	(48.21-73.93)	70.83	(61.84-78.77)	2.11
> 4.84	60	(46.54-72.44)	72.5	(63.60-80.25)	2.18

progressed to undergoing PPI following the period of study. Therefore, the AUC and, consequently, the discriminatory ability, as well as sensitivity and specificity of this model in identifying such patients are likely underestimated and thus potentially greater than that which we determined.

In this external validation study, men receiving penile prostheses scored significantly higher using this instrument than the control group. Those that ultimately underwent penile prosthesis implantation were risk-stratified by this prediction model compared to those managed with non-surgical therapies. This model is a useful tool for estimating likelihood of PPI in men with ED and may support clinicians in the recommendation of PPI for managing ED on an individual patient basis. □

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