

The predictor analysis of response to routine treatment in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia

Yoo Hyun UM¹, Jun Sung KOH², Hyo Jung KO³, Kang Joon CHO²,
Joon Chul KIM², Soo-Jung LEE¹, Chi-Un PAE^{1,4}

¹ Department of Psychiatry, The Catholic University of Korea College of Medicine, Seoul, Korea

² Department of Urology, The Catholic University of Korea College of Medicine, Seoul, Korea

³ Department of Psychiatry, Seoul Metropolitan Eunpyeong Hospital, Seoul, Korea

⁴ Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

Correspondence to: Chi-Un Pae, MD.
Department of Psychiatry
Bucheon St. Mary's Hospital, The Catholic University of Korea College of Medicine
2 Sosa-Dong, Wonmi-Gu, Bucheon 420717, Kyeonggi-Do, Republic of Korea.
TEL: +82-32-340-7067; FAX: +82-32-340-2255; E-MAIL: pae@catholic.ac.kr

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Abstract

OBJECTIVE: This study tried to test predictors of response to routine treatment in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH).

METHODS: Subjects were evaluated at baseline and at week 12 following routine treatment for LUTS/BPH using the Korean version of the International Prostate Symptom Score (IPSS) to measure the severity of LUTS/BPH. Demographics and various clinical variables were analyzed by regression analysis.

RESULTS: Ninety three patients received routine treatment for LUTS/BPH for 12 weeks in a naturalistic treatment setting. None of demographics and clinical variables was different between responders and non-responders. According to multivariate regression analysis, the presence of anxiety (OR=0.203), lower improvement in the GAD-7 total score (OR=0.755) and lower improvement in the PHQ-15 total score (OR=0.811) were independent predictors of treatment response after 12 weeks routine treatment.

CONCLUSIONS: We found the positive association of improvement in anxiety and somatization with treatment response, while presence of anxiety was negatively associated with treatment response, in patients with LUTS/BPH. However, additional studies with adequate power and improved designs are necessary to support the present findings.

INTRODUCTION

The male patients with lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH) suffers from diverse and uncomfortable urinary symptoms including storage, voiding and post-micturition (Madersbacher *et al.* 2004). The underlying pathophysiologies of LUTS/BPH are currently uncertain but it has been considered a subjective indicator of disease, not a confirmative formal diagnosis (de la Rosette Jan 2012).

According to a recent huge cross-sectional population-based study, the negative effects of LUTS/BPH were prominent across several domains of quality of Life (QoL) and on overall perceptions of general health status and mental health (Coyne *et al.* 2009b). Moderate LUTS has a similar impact on physical health-related QoL to that of diabetes, high blood pressure, and cancer, whereas the impact of severe LUTS is similar to the effect of a heart attack or stroke (Robertson *et al.* 2007). Poor health-related QoL and life dissatisfaction can also have adverse effects on psychological health (Rom *et al.* 2012). According to a 5 year follow-up study, LUTS/BPH persisted approximately half of the population experiencing symptoms at baseline, despite of maintaining medications (Maserejian *et al.* 2014).

Although various biological and behavioral therapeutic options are currently available, the mainstay of the treatment depends on several medications such as α -receptor blockers and 5 α -reductase inhibitors. However, the treatment response with such medications is not satisfactory. A recent treatment guideline also suggests the weak efficacy of such medications, where approximately 20–50% reduction in LUTS/BPH symptoms are common after treatment of monotherapy of α -receptor blockers and 5 α -reductase inhibitors based on results from a number of short-term and long-term clinical trials (Oelke *et al.* 2012; Roehrborn 2008). Likewise, in a recent large controlled clinical trial (Chapple Ch *et al.* 2012), the change from baseline in the International Prostate Symptom Score (IPSS) total score with silodosin and tamsulosin was significantly superior to that with placebo, showing a magnitude of difference -2.3 with silodosin and -2.0 with tamsulosin. In addition, the responder rates according to total IPSS were approximately 60% for each medication, showing a magnitude of difference of approximately 15% from placebo. Based on this trial, the number needed to treat (NNT) would be only 7, which is very similar in treatment of depressed patients (Pae & Patkar 2013). In addition, such response rates substantially decrease in recurrent or chronic LUTS/BPH patients (Oelke *et al.* 2012; Roehrborn 2008). These findings clearly indicates the inadequate efficacy of medication for controlling LUTS/BPH, still 30% of such patients suffer bothering symptoms. These insufficient efficacy and response rates are consistently found and replicated in other clinical trials and meta-analysis (Hao *et al.* 2014; Appell 2007).

Therefore, proper and timely intervention to reduce LUTS/BPH symptoms should be crucial in the treatment of such patients. Before initiating treatment, it should be very helpful and useful for clinicians to determine whether they can presumably expect the likelihood of achieving symptomatic improvement in LUTS/BPH based on known predictors to treatment response, so that they can efficiently decide how they will approach and manage their patients. However, such predictor analysis data are still inadequate and fragmented for patients with LUTS/BPH, especially Asian patients. Hence, the aim of this study was investigate the potential clinical predictors to treatment response after routine treatment with α -blockers, 5- α -reductase inhibitors, or combination for LUTS/BPH in outpatient clinic basis.

METHODS

Study design

The original research was a 12-week prospective observational study in a naturalistic treatment setting in outpatient clinic basis.

Subjects

Male subjects with LUTS/BPH were recruited at an outpatient clinic in the Department of Urology at Bucheon St. Mary's Hospital in Bucheon, Gyeonggi-Do, Korea between March 2011 and February 2012.

Principal inclusion criteria included men aged ≥ 40 years, a clinical diagnosis of LUTS/BPH evaluated by medical history, a careful physical examination (including digital rectal examination), and laboratory tests including PSA levels. Few exclusion criteria were applied because the aims of the study were based on a naturalistic observational research approach. However, patients who exhibited the following symptoms were excluded for diagnostic stability: 1) PSA level >10 ng/ml, 2) a history or evidence of prostate cancer by prostate biopsy, 3) previous prostatic surgery, 4) any causes of LUTS other than BPH (i.e., neurogenic bladder, bladder neck contracture, urethral stricture, bladder malignancy, acute or chronic prostatitis, or acute or chronic urinary tract infections), and 5) speech or language deficits and cognitive dysfunction.

This study utilised the Korean version of the IPSS (range of total scores=0–35; 0–7, none to mild; 8–19, moderate and 20–35, severe) to measure the severity of LUTS/BPH at baseline and the end of treatment (12 weeks) (Choi 1996). The Korean versions of the Patient Health Questionnaire-9 (PHQ-9, range of total scores=0–27; 0–4, none to minimal; 5–9, mild; 10–19, moderate and 20–27, severe) to assess depression, the Patient Health Questionnaire-15 (PHQ-15, range of total scores=0–30; 0–4, none to minimal; 5–9, mild; 10–14, moderate and 15–30, severe) to evaluate somatization, and the Generalized Anxiety Assessment 7 items (GAD-7, range of total scores=0–21; 0–4, none to minimal; 5–9, mild; 10–14, moderate and 15–21,

severe) to measure anxiety, were collected at each visit during the study.

Alpha-blockers, 5- α -reductase inhibitors, or combination were utilised for the treatment of LUTS/BPH during the entire course of the study. Throughout the study period, patients remained on the same medication and the same dosage as was given at the time of enrollment.

The present study followed the Declaration of Helsinki and ethical principles regarding human experimentation and the study protocol was approved by the Institutional Review Board of Bucheon St. Mary's Hospital in Bucheon, Gyeonggi-Do, Korea (HC11OISE0004).

Definition of responders by clinical outcome

The responders were defined as follows: $\geq 30\%$ decrease in IPSS total score from baseline to week 12 (Chapple *et al.* 2011; Barkin 2011). Regarding definition of % improvement of IPSS total score from baseline, 25% or 30% reductions in IPSS total score were mostly utilized (Chapple *et al.* 2011; Barkin 2011). However, none of % improvement in IPSS total score has been validated as established response criterion, they were usually empirically used by different individual research group. Hence, we have also empirically chosen a 30% improvement of IPSS total score as proper response criterion.

Statistical analyses

Demographics and various clinical variables were described and compared between responder and non-responders by the Student's *t*-test, Chi-square test with Yate's correction, or Fisher's test as appropriate.

Baseline demographics and various clinical variables collected during the study were modeled as potential predictors of treatment response. The analysis was adjusted for all variables that showed an association with treatment response in the univariate analysis. A multivariate logistic regression analysis was conducted to examine the factors associated with treatment response. The forward conditional method was used to determine the variables in the final model. Independent variables included age, education level, family history of LUTS/BPH, severity of LUTS/BPH, presence of depression, anxiety and somatization, economic status, duration of disease, medications, comorbidity, alcohol history, smoking history, marriage status, baseline total scores of the IPSS, PHQ-9, PHQ-15 and GAD-7, and the changes of PHQ-9, GAD-7 and PHQ-15 total scores from baseline to week 12. The dependent variable was a response defined according to a $\geq 30\%$ reduction in total scores in IPSS from baseline to week 12. Odds ratios (ORs) with 95% confidence intervals (CIs) were also utilized for the responder analysis. Statistical significance was two-tailed and set at $p < 0.05$.

The sensitivity, specificity, accuracy, positive predictive value (PPV), negative predictive value (NPV) and diagnostic odds ratio (DOR) for categorical variables as a predictor of treatment response (or non-

response) was also calculated if any case incurred, as follows: a) sensitivity=the proportion of responder who also experienced such risk factor b) specificity=the proportion of participants not experiencing a treatment response who also did not experience such risk factor; c) accuracy=the number of responder who also experienced such risk factor plus the number of non-responder who not experienced such risk factor/total number of patients d) PPV=the proportion of participants experiencing such risk factor who went on to achieve a treatment response; e) NPV=the proportion of participants not experiencing such risk factor who did not achieve a treatment response; f) DOR=the ratio of the odds of participants experiencing such risk factor if they experienced a treatment response relative to the odds of participants experiencing such risk factor if they did not experience a treatment response.

With these statistical parameters and after adjusting with covariates, the power of the sample to detect a medium effect size ($d=0.5$) was 0.6108, which corresponds to a difference of 2.6 in the mean changes of IPSS total scores between those with high and low neuroticism. All statistical analyses were conducted using the NCSS 2007[®] and PASS 2008[®] software (Kaysville, Utah, USA).

RESULTS

Baseline characteristics

Ninety three completed the study. Descriptive baseline demographics and clinical data of the participants are summarised and compared in Table 1.

The mean age of the whole population was approximately 62 years, and the majority of subjects were married. More than half of patients exhibited comorbid medical diseases. The mean total score on the IPSS among all groups was approximately 17, which indicates moderate severity of LUTS/BPH symptoms. The mean baseline IPSS total score was approximately 17, respectively indicating a moderate severity of LUTS/BPH symptoms. The mean total scores of PHQ-9, PHQ-15 and GAD-7 were each approximately 5, indicating the presence of mild depression, somatization and anxiety. Approximately 38% ($n=35$), 41% ($n=38$) and 50% ($n=46$) of patients accompanied by depression, anxiety and somatization, respectively. The responder ($n=41$) and non-responder ($n=52$) rates were 44.1% and 55.9%, respectively. There were no differences in age, education level, family history of LUTS/BPH, severity of LUTS/BPH, presence of depression, anxiety and somatization, economic status, duration of disease, medications, comorbidity, alcohol history, smoking history, or marriage status, baseline total scores of the IPSS, PHQ-9, PHQ-15 and GAD-7 between responders and nonresponders. However, there were significant differences in the changes of GAD-7 and PHQ-15 from baseline to week 12 between the two groups favoring responders over nonresponders.

Tab. 1. Baseline demographics and clinical variables.

Characteristics	Responder (n=41)	Non-responder (n=52)
Age	61.6 (8.0)	61.8 (7.9)
Duration of illness (months)	16.5 (19.3)	11.5 (1.6)
Marital status	39 (95.1)	46 (88.5)
Education level (college or above)	16 (39.0)	15 (28.8)
Comorbidity	26 (63.4)	38 (73.0)
Alcohol history	22 (53.7)	26 (50.0)
Family history	1 (2.4)	4 (7.7)
Smoking history	9 (31.0)	13 (25.0)
Work status	31 (75.6)	27 (51.9)
Severity of LUTS/BPH		
Mild	2 (4.9)	8(15.4)
Moderate	23 (56.1)	29(55.8)
Severe	16 (39.0)	15(28.8)
Depression	17 (41.5)	18 (34.6)
Anxiety	15 (36.6)	23 (44.2)
Somatization	19 (46.3)	27 (51.9)
Economic status		
Low	12 (29.3)	16 (30.8)
Medium	26 (63.4)	31 (59.6)
High	3 (7.3)	5 (9.6)
Baseline total scores in rating scales		
IPSS	17.1 (6.9)	16.0 (8.3)
PHQ-9	4.7 (3.9)	4.4 (4.6)
GAD-7	4.6 (3.8)	4.4 (4.2)
PHQ-15	5.3 (4.6)	5.0 (4.1)
Changes in total scores in rating scales		
IPSS	-8.6 (2.1)	-0.8 (3.6)*
PHQ-9	-1.5 (3.0)	-0.8 (2.1)
GAD-7	-2.0 (3.4)	-0.7 (2.6)**
PHQ-15	-1.4 (2.6)	-0.3 (2.2)***

Data represent mean(\pm SD) or number (%). International Prostate Symptom Score, IPSS; Patient Health Questionnaire-9, PHQ-9; Patient Health Questionnaire-15, PHQ-15; Generalized Anxiety Assessment 7 items, GAD-7; lower urinary tract symptoms, LUTS; benign prostatic hyperplasia, BPH; * $p=0.0001$, ** $p=0.0394$, *** $p=0.0297$, otherwise non-significant between the two groups.

Tab. 2. The predictive model of responders by the results of multivariate regression analysis.

	B	S.E.	Wald	OR (95% CIs)	p-value
Presence of anxiety	-1.595	0.611	6.817	0.203 (0.61-0.672)	0.009
Lower improvement in GAD-7 total score*	-0.281	0.100	7.942	0.755 (0.622-0.918)	0.005
Lower improvement in PHQ-15 total score*	-0.209	0.106	3.926	0.811 (0.660-0.998)	0.048

Patient Health Questionnaire-15, PHQ-15; Generalized Anxiety Assessment 7 items, GAD-7; odds ratio, OR; confidence intervals, CIs; responder definition is $\geq 30\%$ decrease in total International Prostate Symptom score from baseline to week 12; *from baseline to end of treatment (week 12 point - baseline point).

The multivariate predictors of response are shown in Table 2. According to multivariate regression analysis, the presence of anxiety (OR=0.203), lower improvement in the GAD-7 total score (OR=0.755) and lower improvement in the PHQ-15 total score (OR=0.811) were independent predictors of treatment response after 12 weeks routine treatment (Table 2).

The sensitivity, specificity, accuracy, PPV, NPV, and DOR values for anxiety as a predictor to non-responder were 0.44 (0.345-0.535), 0.63 (0.510-0.752), 0.53 (0.418-0.630), 0.61 (0.471-0.732), 0.47 (0.380-0.560), and 1.38 (0.547-3.469), respectively.

DISCUSSION

The present study found that the positive association of improvement in anxiety and somatization symptoms with treatment response, while presence of anxiety was negatively associated with treatment response, in patients with LUTS/BPH. The current findings suggest that some clinical (psychiatric) factors may influence on the treatment response in patients with LUTS/BPH after 12 weeks of routine treatment. This study employed simple, quick, reliable, well-validated, and self-administered rating scales, which are easy to apply and interpret, even in a busy routine practice. The most strength of the present prediction analysis is that, to the best of our knowledge, this is the first one to detect clinical predictors to routine medical treatment in terms of improvement in total IPSS in patients with LUTS/BPH in outpatient clinic basis. Overall the responder rate defined by 30% reduction in IPSS total score from baseline was 44.1% in the present study, which is slightly lower compared to the results from other studies (approximately 50-65%) used similar response criteria (25% improvement from baseline) (Chapple *et al.* 2011; Barkin 2011; Appell 2007).

Although a handful of research groups have proposed several predictors to treatment outcomes as assessed by different methods based on different outcome measures such as symptom rating scales of IPSS, urodynamic measures, pharmacokinetics, laboratory results, or imaging studies, however, confirmative and consistent predictors to treatment response after pharmacotherapy have not yet been established in patients with LUTS/BPH. In this context, our findings propose the potential positive association of improvements

in anxiety and somatization symptoms with treatment response, while the presence of anxiety could be negatively associated with treatment response, in patients with LUTS/BPH. In this context, there has been a paucity of predictor studies simultaneously investigating depression, anxiety and somatization in patients with LUTS/BPH yet. Hence, clear-cut direct comparisons of our results with other studies are discouraged. However, according to previous studies to identify predictors of disease severity in patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) (Clemens *et al.* 2006), depressive symptoms was independently associated with symptom severity in the both gender, which is in line with the findings from other studies documenting an association between the symptom severity of LUTS/BPH, CP/CPPS and depression. (Clemens *et al.* 2007; Clemens *et al.* 2008; Cortes *et al.* 2012; Coyne *et al.* 2009a; Coyne 2009b; Glover *et al.* 2004; Martin *et al.* 2014; Wong *et al.* 2006; Breyer *et al.* 2014; Rom *et al.* 2012) However, our data shows the presence of depression or improvement of depression was not included in the prediction model as a predictor to treatment response, which may be possibly explained by different severity of depression and different clinical characteristics with different treatment settings compared to previous studies. Another one should be that PHQ-9 for depression measure should not be sensitive to detect a meaningful change of depression in patients with LUTS/BPH. Intriguingly the recent prediction study also failed to separate depression as one of predictor to treatment response (Maserejian *et al.* 2014).

The presence of anxiety and improvement of anxiety was significantly associated with the non-response in the present study, indicating that clinicians may benefit in expectation of future response in clinical practice if they know the level or improvement of anxiety. Our results are in line with the previous findings that anxiety may be involved as a risk factor in the severity and progression of LUTS/BPH (Cortes *et al.* 2012; Coyne *et al.* 2009a; Coyne 2009b; Glover *et al.* 2004). However, the PPV of the presence of anxiety for non-response were modest level of 61%, potentially indicating that patients who demonstrate anxiety at baseline are unlikely to meet response criteria later in the course of treatment. Although the validity and utility of GAD-7 has been widely investigated in a numerous chronic diseases (i.e., seizure (Hamilton *et al.* 2013), heart failure (Fischer *et al.* 2013), myocardial infarction (Liang *et al.* 2014), diabetes mellitus (Dixon *et al.* 2013), hepatitis (Schramm *et al.* 2013), erectile dysfunction (Shim *et al.* 2011) and pulmonary disorders) as well as in elderly population (Wild *et al.* 2013) for diagnosis of anxiety, it has not been widely used for urologic patient population; this point should be further tested in future studies.

Interestingly, the improvement of somatization was also included in the prediction model in the present study, indicating a potential usefulness of somatization changes as a prediction to responder or non-responder

to treatment in clinical practice. An increasing evidence suggests the possibility that for some patients with LUTS/BPH (Seyfried *et al.* 2009; Cortes *et al.* 2012), CP/CPPS (Anderson *et al.* 2008; Lai *et al.* 2012) and urinary incontinence (Walters *et al.* 1990), urinary symptoms could be part of a somatizing process and requires further consideration (Cortes *et al.* 2012). In fact, previous studies have consistently reported that the worse physical health ratings are significantly associated with more bother in patients with LUTS/BPH, indicating that measures of urinary bother capture somatic distress should be necessary and that treating LUTS/BPH alone may not completely ameliorate urinary bother if underlying such somatic concerns are not addressed (Cortes *et al.* 2012). In our previous study, somatization symptoms were also involved in the development and improvement of erectile dysfunction (Shim *et al.* 2013; Shim *et al.* 2011).

Although the present findings propose that presence of anxiety and lower improvement of anxiety and somatisation symptoms may be potential predictors to treatment response in patients with LUTS/BPH, there are a number of limitations to this study. First, the small sample size was insufficient to make any definite conclusions regarding treatment response and symptom severity in patients with LUTS/BPH. Our patients were treated by different medications without uniform protocol since the study was based on routine practice. Recent data analysis suggests that optimal management of BPH progression in men with very small prostates at baseline can be achieved with α -blocker therapy alone, whereas combination therapy is more effective in patients with larger prostates (Kaplan 2005; Marberger 2013; Filson *et al.* 2013). Hence more homogenous treatment group would provide more valuable information in terms of response prediction to treatment outcomes. It has been frequently proposed that baseline prostate volume and symptom severity of LUTS/BPH can be a principal predictive factor to progression of LUTS/BPH (Kaplan 2005; Marberger 2013), however, in our study the severity of LUTS/BPH was not included in the prediction model; possibly due to different outcome measures, sample characteristics and treatment settings. Interestingly in one study (Quek *et al.* 2000), transurethral resection of the prostate (TURP) was a better treatment than medication for minimizing anxiety, depression and psychiatric morbidity after treatment of patients with LUTS, potentially indicating a possible existence of differential clinical factors to surgical and medical treatments. Currently, there are no large and unselected population-based studies that have utilised the GAD-7 and PHQ-15 on patients with LUTS/BPH, and thus, the current results should be considered entirely exploratory. The observation period in the current study was only 3 months in duration, which may not be sufficient to fully evaluate the clinical response, in fact, a consensus on an adequate duration of treatment for LUTS/BPH has been still lacking.

Although, PHQ-9, PHQ-15 and GAD are significantly and highly correlated with objective psychiatric rating scales for such symptoms, objective rating scales may complement the weakness of self-rating scales as well for research purpose. Active and/or control groups were not used as a comparison group. Finally, the sample was only recruited in one teaching hospital and may not represent the general LUTS/BPH population.

In conclusion, the present study found the positive association of improvement in anxiety and somatization with treatment response, while presence of anxiety was negatively associated with treatment response, in patients with LUTS/BPH. However, additional studies with adequate power and improved designs are necessary to support the present findings.

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