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Title of Research Thesis:

A sub-analyses from the Benign Prostatic Hyperplasia (BPH) Registry and Patient survey: Predictive validity of the International Prostate Symptom Score (IPSS) in Ethnic Minority-African Americans with Benign Prostatic Hyperplasia (BPH)

INTRODUCTION

Background

Benign prostatic hyperplasia (BPH) is one of the most common causes of urinary problems in aging men, and it conveys its morbidity through lower urinary tract symptoms (LUTS), urinary complications and reduced quality of life [1]. In the U.S. alone approximately 14 million men suffer from BPH, and at an estimated annual cost for treatment of four (4) billion U.S. dollars [2].

Treatment algorithms for BPH show that patients with mild symptoms or no symptoms need not be treated while those with severe symptoms may need surgery hence, the establishment of a symptom validity scale may be a significant clinical instrument [6]. The International Prostate Symptom Score (IPSS) has been developed and used by various researchers for the measurement of benign prostatic symptoms related outcomes such as assessment of lower urinary tract symptoms. It has been adopted by the American Urological Association (AUA) and originally only seven scores categories were described [7]. Recently, the eighth category, the bother Score (or quality of life outcome) was added to the I-PSS by AUA [8].

The IPSS is a questionnaire that grades the severity of symptoms on a numerical scale in categories. The higher the number score, the more the degree of bother and the more aggressive is the recommended treatment. I-PSS is often considered during the development of treatment algorithms and for measuring the efficacy of individual treatment options [6].

There have been several assessments of the predictive validity of IPSS in BPH patients with lower urinary tract symptoms (LUTS), but most of these studies have been conducted in predominantly white populations. Changes in IPSS have been found to be important predictors of disease progression, and in monitoring the response to therapy [9]. Disease progression is defined as worsening of symptoms (increase of points in the I-PSS from baseline initial score) and other urinary complications, while response to therapy (clinical benefit) is defined as point reduction in the I-PSS from baseline Ruffion, A *el al*.

While the I-PSS can predict symptom severity, and disease progression in men with BPH, studies are scanty at best on the racial/ethnic predictive validity of the I-PSS in minority populations like the African Americans (AA) men with BPH.

OBJECTIVE: The objective of this study is to determine if the use of IPSS has a predictive validity of disease progression in African American men diagnosed with BPH associated with LUTS. The test of this hypothesis is a change of IPSS from baseline score. This project may be clinically significant as the outcome measurements may facilitate better understanding of the effect of treatment variations and responses within the African American population. This may subsequently lead to development of more cost effective treatment approach in the management of BPH among this racial/ethnic group.

METHODOLOGY

Study design:

This is a prospective before-after study sub-analysis of the national BPH Registry and Patient Survey with a six-month follow-up. Our study utilized data collected between 06/2004 to 12/2004 from a single outpatient clinic, Millennium Medical Center located in Metropolitan Detroit, Michigan. This study was approved by Millennium Medical Center (letter attached). This study population is comprised of sub-analysis of 68 from 84 African American men only, aged 45 years or older with complete data at time of this analysis. They consented to the BPH Registry and Patient Survey study sponsored by Sanofi-Synthelabo Inc. Millennium Medical Center was one of 500 national study sites and the national study enrolled patients from 01/23/04 through 02/25/2005. The men had documented diagnoses of benign prostatic hyperplasia (BPH) associated with lower urinary tract infection (LUTS) at baseline, and agreed to be treated with prescription products for symptoms of BPH. BPH was defined by clinical diagnosis, which included LUTS and enlarged prostate as detected by digital rectal exam.

Also, included in the analysis are patients who agreed to complete the study questionnaire.

These questionnaires were administered by a trained study coordinator and medical assistants at the clinic.

IPSS score of 0-7 represents mild symptoms; 8 to 19 represents moderate symptoms and 20 or more represents severe symptoms. Questionnaires and the survey measuring instruments were completed by the subjects at baseline and at a follow-up period six (6) months later. Demographic and socio-economic status including data on monthly

medication cost, insurance type, education, alcohol intake, and smoking were collated from the completed questionnaire.

The subjects who opted for invasive surgery as an initial treatment or have had surgery in the past for BPH were excluded from the study sample. Also, patients with history of urethral stricture, diabetes, and prostate cancer, patients using anti-hypertensive medications like ACE inhibitors or diuretics were excluded. 16 African Americans with incomplete data at time of analysis were excluded.

Recruitment was done by non-probability sampling of all eligible African American (AA) men attending Millennium Medical Center. Sample size of this study was 84 subjects and minimum of 50 subjects to account for incomplete data as well as patients lost to follow-up to give a statistical power. Normality will be assumed because of sample size greater than 30.

Outcomes: The primary outcomes which were assessed included changes in symptom severity and the degree of bother scores between baseline and at 6 month follow-up as measured with I-PSS. IPSS is considered clinically significant if there is a change from baseline IPSS or bother score compared to the follow-up score. The secondary outcome was the assessment of overall clinical benefit as measured by IPSS from treatment or clinical progression of disease [10, 11] .

Statistical Analysis:

Descriptive statistical indices including frequency mean and standard deviation were utilized. χ^2 –test was used to show the mean differences in IPSS and bother score. All continuous data were expressed as mean ± SD

Paired t –test was used to show the differences between baseline and follow-up IPSS and bother scores respectively. Multivariate analysis was generated to show relationship with baseline IPSS as dependent variable and adjusting for socioeconomic and demographic variables (age, monthly medical cost, and insurance type, level of education, smoking, alcohol intake and weekly exercise). *P* value less than 0.05 ($p < 0.05$) was considered statistically significant. All data statistical analysis was completed by SPSS version 11.0.

RESULTS

The patient characteristics including the baseline demographic of the study population are shown in Table 1. A total of 68 African American (AA) men aged between 45 to 82 years (n = 68) were included in the study with 84 % of men completing the study. The mean age was 59.8 ± 10.5, with mean baseline and follow-up IPSS (9.6 ± 6.8 and 8.7 ± 6.0) respectively. The baseline and follow-up bother score were (2.5 ±1.1 and 2.2 ±1.0). Further, the demographic show that 66.2% of the study population were self pay patients, 35% were high school graduates and 81% were smokers (Table 1).

The Chi- square test of this study showed a statistical difference between baseline IPSS *versus* follow-up IPSS ($p = 0.02$); There was also statistical difference between baseline and follow-up bother score of our study ($p < 0.0001$) (Table 2).

However, with paired sample t-test analysis there was significant difference between the means of baseline and follow-up bother score ($p < 0.003$), but there was no significant statistical difference between the means of baseline *versus* follow-up IPSS in our study population of AA men (see Table 3).

Using a multivariable model, with baseline IPSS as the dependent variable and adjusting for confounder such as age, monthly medical cost, insurance type, level of education, alcohol intake, smoking, and weekly exercise, only patient's age ($p < 0.05$) and insurance type ($p = 0.03$) were statistically significant (Table 4).

DISCUSSION

In United States the current prevalence of BPH is about 14 million and the economic burden is about 4 billion dollars annually. There are multi-factorial causes of BPH, but positive family history, and autosomal dominant patterns have been identified. The actual prevalence of BPH differs greatly depending on the geographic region of the study (Garraway, M epid. Of prostate dis, 1995). From our study, we found that the age distribution for BPH was comparable to the age distribution in other studies (Barry, MJ 1992 J Urol; 148: 1549). BPH increase in frequency in men as they age, and histological evidence from autopsy suggests that the incidence of BPH is over 50% in men older than 50 years (Rubenstein, R *et al*, 2006).

I-PSS is a complex but validated instrument, Barry MJ *et al*, 1992. The predictive validity of IPSS is influenced by demographic factors such as age, and level of education, and other physiologic variables [8, 10]. Our study found that after adjusting for age, monthly medical cost, insurance type, level of education, alcohol intake, smoking, and weekly exercise, only patient's age ($p < 0.05$), insurance type ($p = 0.03$) and monthly medical cost ($p = 0.02$) were statistically significant.

Various studies conducted in patients with BPH associated with LUTS suggested that the severity of the urinary symptoms and the degree of bother experienced by the patients determines the health outcome [3] and their quality of life [4-6]. Our study showed a similar pattern.

This study focused in part on the socioeconomic risk factors for BPH and validity of IPSS in AA. We found as in previously published studies that age, insurance type and cost of treatment affected the patient's ability to be treated and therefore, the prevention of BPH progression as measured by IPSS.

Our study showed like the findings of Roehrborn, CG *et al*, that alcohol consumption was not associated with difference in BPH progression or IPSS validity. Alcohol consumption may be protective against BPH development (Tujan, T *et al.* 2006). Although, not statistically significant in our study 81 % of the men were smokers. While some studies show that smoking promote BPH probably as in our study (Elizabeth, A.P.

et al, 1999) various other studies have implicated smoking to have an inhibitory role on the development of BPH (Tujan, T *et al.* 2006 and Haim, M et al 1995). In the first population based study of African-American (Flint Men's Health Study), risk factors such as demographic, lifestyle and medical history were clearly found to play important role in the natural history of BPH and LUTS. These factors were found to affect the predictive validity of the I-PSS.

Limitation of this study: After the questionnaire was administered to the subjects, trained staff did not assist patients in completing the questionnaire. Some questions in the IPSS items need to be modified to sixth grader level for clarification and good description for better validity of a self-administered tool and instrument. We had only one follow up before analyses; other studies have utilized a higher number of follow up visits, and repeated application of the questionnaire to increase instrument reliability and validity. Also, a small sample and single population of AA was utilized.

In conclusion, the IPSS symptom score may be dependent on the bother score (quality of life). The test reliability of IPSS is the same and valid in African American males with BPH as it is for the general male population with BPH. More studies are still needed in this area.

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Table I: Baseline Characteristic Distribution of African American men with BPH

VARIABLES	Patient
Males Age Years (Mean ±SD)	59.8 ± 10.5
Baseline IPSS (Mean ±SD)	9.6 ± 6.8
Follow UP IPSS (Mean ±SD)	8.7 ± 6.0
Baseline bother score (Mean ±SD)	2.5 ± 1.1
Follow Up BS (Mean ±SD)	2.2 ± 1.0
Monthly med cost (%) < $20 $20-50 >$ 50	 27.9 52.9 19.1
Insurance type (%) Self pay Self pay & Medicare Medicare	 66.2 14.7 19.1
Level of education completed high school (%)	35
Alcohol intake (%)	49
Smoking (%)	81
Weekly exercise (%)	30

Table 2: Chi Square Test of IPSS in AA Men

VARIABLES	Pearson *chi* square	*p-value*
IPSS	417.28	**0.020**
Bother score	162.03	**0.000**

* ***P*** < 0.05 is significant

ϕ Regression coefficients show the estimated change in **IPSS** per unit change in each predictor

SD-standard deviation

Table 3: Paired t-test of IPSS and bother score at baseline with 6 months follow-up

VARIABLES	Mean ± SD	t-test	p-value

Baseline (follow-up) IPSS	0.94 ± 5.5	1.4	0.163
Baseline (follow-up)Bother Score	0.29 ± 0.8	3.1	**0.003**

* ***P*** < 0.05 is significant

ϕ Regression coefficients show the estimated change in **IPSS** per unit change in each predictor

Table 4: Multivariate Logistic Regression Model with IPSS as Dependent Variable (n=68)

Independent Variables	Baseline IPSS	
	Coefficient(SEM)	P-value
Males Age in yrs (Mean ±SD)	2.2(1.2)	**0.05**
Bother Score	1.8(1.6)	0.08
Monthly med cost (%)	0.8(0.1)	**0.02**
Insurance type (%)	25.1(4.7)	**0.03**
Level of education (%)	-3.6(2.1)	0.44
Alcohol intake (%)	2.4(1.6)	0.27
Smoking (%)	4.5(2.2)	0.61
Weekly exercise (%)	-7.1(5.3)	0.26

* ***P*** < 0.05 is significant

ϕ Regression coefficients show the estimated change in **IPSS** per unit change in each predictor