Measurement of International Prostate Symptom Score Subscores in Male Lower Urinary Tract Symptoms

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INTRODUCTION

Lower urinary tract symptoms (LUTS) is a global term that includes storage symptoms (increased bladder sensation, daytime urinary frequency, urgency, urge incontinence and nocturia), empty symptoms (slow stream, splitting or spraying, intermittency, hesitancy, straining, terminal dribble), and postmicturition symptoms (sensation of incomplete emptying, postmicturition dribble) [1]. The term LUTS has a clear definition and meaning, and is a non-sex-specific and non-organ-specific group of symptoms. However, the management of LUTS is often confused owing to the failure to appreciate its multifactorial etiology [2].

Male patients commonly suffer from both storage and emptying symptoms [3,4], and the frequent co-morbidity with benign prostatic hyperplasia (BPH) adds complexity to the diagnosis and management of male LUTS. Because LUTS are common among elderly men and patients will develop LUTS when the bladder outlet obstruction (BOO) has developed to a considerable degree, male LUTS are usually attributed to BPH or BOO and are traditionally treated with α-adrenoceptor antagonists [5]. Conversely, similar symptoms in females are predominantly considered to be an overactive bladder (OAB), which is a symptom syndrome characterized by urgency, frequency with or without urge incontinence [1], and are thus treated with antimuscarinic agents [2].

Several investigations suggest that not all male LUTS are associated with prostate pathology or BOO, and that bladder dysfunction plays a role in the development of LUTS. Recently, the focus on LUTS has shifted from the prostate to the bladder as the source of some of the LUTS and also as a therapeutic target [5]. Unfortunately, it is difficult to distinguish the causes of male LUTS merely based on their clinical symptoms, and a subset of men who receive treatment for prostate conditions may have persistent OAB symptoms [6-8]. Detailed urological investigations are mandatory for the exact diagnosis of lower urinary tract dysfunctions (LUTD). However, the equipment needed is not available in most community hospitals or general practices .

RELATIONSHIP BETWEEN OAB, BPH/BOO, AND LUTS

Since OAB symptoms comprise the same symptoms as storage LUTS in BPH and most men with OAB do not experience incontinence, men with storage LUTS are often misdiagnosed as having clinical BPH.

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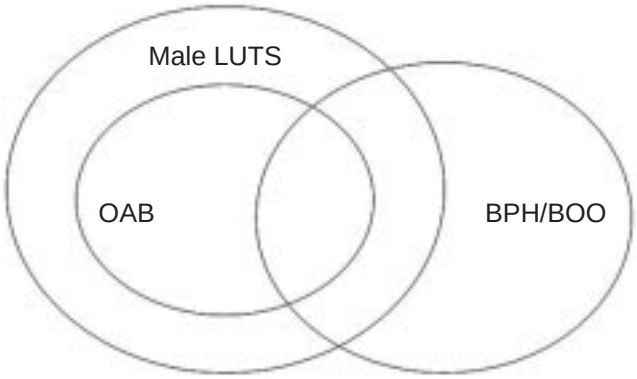

Fig. 1. Association between male LUTS, OAB, and BPH/BOO.

The cause of male OAB symptoms may be due to bladder dysfunction such as detrusor overactivity (DO) or impaired detrusor contractility, or occur in combination with BOO [5].

In fact, the association between OAB, BPH, and male LUTS is really complex (Fig. 1). It has been estimated that only 25%-50% of men with BPH have LUTS, and only 48%-53% of men with LUTS have urodynamically proven BOO due to BPH or other urethral conditions [9]. In addition, approximately 50%-75% with BOO have OAB symptoms [4,10], and 46%-66% with prostate obstruction on urodynamic have DO [11,12]

The pathophysiology of male LUTS could be bladder dysfunction (hypersensitive bladder, HSB; detrusor overactivity, DO), BOO (bladder neck dysfunction, prostatic obstruction, urethral stricture, poor urethral sphincter relaxation, urethral sphincter dyssynergia) or a combination of these etiologies [13-15].

DISTINGUISHING THE CAUSES OF MALE LUTS

Because the pathophysiology of male LUTS may be multifactorial, an ability to distinguish the causes of male LUTS is very important for its effective treatment. Multichannel urodynamic studies (UDS) or videourodynamic studies (VUDS) are considered the standard for diagnosing BOO and the underlying pathophysiologies of male LUTS. However, it is a relatively complex, invasive method and not cost-effective. So they are not routinely performed by physicians, and can be reserved for when complicated cases are encountered or poor response to first-line treatment occurs.

A variety of non-invasive urodynamic and non-urodynamic methods have been used to evaluate LUTS. Uroflowmetry and post-void

residual (PVR) measurements are simpler than UDS and are recommended as the initial evaluation in the European Association of Urology (EAU) guideline [16] in addition to a complete medical history, physical examination including digital rectal examination (DRE), symptoms assessment with the international prostate symptom score (IPSS) questionnaire, prostate specific antigen (PSA) measurement; creatinine measurement, and urinalysis. However, uroflowmetry and maximum flow rate (Qmax) lack specificity for a reliable urodynamic diagnosis of the cause of LUTS, and elevated PVR is only weakly associated with BOO [5,17]. Ultrasound-derived measurements of the bladder wall thickness and estimated bladder weight offer a potential non-invasive alternative to pressure flow study, but their diagnostic parameters are still under evaluation [18].

A combination of different diagnostic methods may be another way to predict BOO. Porru et al [19] reported BOO could not be accurately predicted by non-invasive methods alone, and a high proportion of patients who were successfully operated on (71.1%) had a combination of IPSS >16 and Qmax <10 mL/s. Kuo [20] also conducted a clinical prostate score established by summing scores on seven prostatic and uroflowmetric items, and male patients with LUTS could be diagnosed with good sensitivity and specificity. Van Venrooij GE et al [21] also postulated a formula composed of three readily available parameters: prostate volume, maximal urinary free flow rate, and mean voided volume to predict BOO. However, these scores are too complicated for first-line use.

In addition, uroflowmetry and transrectal ultrasound are not available in some urologic and non-urological clinics. In a practical guide to the evaluation and treatment of male LUTS in the primary setting, Rosenberg et al [22] make a provisional diagnosis using clinical judgment and the provisional diagnosis favors BPH more than OAB.

IPSS AND SUBSCORES

Both EAU and American Urological Association (AUA) practice guidelines agree that evaluating symptom severity with a symptom score is an important part of the assessment of male LUTS [16,23]. The IPSS has been used for years to evaluate the severity of BPH, and has also been applied to other conditions causing LUTS instead of BPH. It has been translated and linguistically validated in many languages, and thus represents a universal tool allowing researchers from around the world to compare results of epidemiological and treatment outcome studies.

The IPSS was designed to be self-administered by the patient, with speed and ease in mind. Hence, it can be used in both urology clinics as well as the clinics of primary care physicians (i.e. by general practitioners). Additionally, the IPSS can be performed multiple times to compare the progression of symptoms and their severity over months and years. In addition to diagnosis and charting disease progression, the IPSS is effective in helping to determine treatment for patients. The IPSS uses seven questions that relate to associated symptoms, classification ranges from mild (0 to 7) to moderate (8 to 19), or severe (20 to 35). Treatment is usually suggested for patients with moderate or severe symptoms.

Although IPSS is helpful to evaluate the severity of LUTS and determine if treatment is needed, total IPSS fails to differentiate the underlying causes of the disorder or elucidate appropriate treatment. Several studies have reported that total IPSS correlates poorly with BOO or OAB, and are unreliable for the correct diagnosis [24-26]. In addition, storage and emptying symptoms do not necessarily reflect disorders of storage and voiding function, respectively [27].

The IPSS consists of seven questions and can be divided into emptying symptoms (incomplete empty, intermittency, weak stream, and straining) and storage symptoms (frequency, urgency, and nocturia). If we divide the IPSS into storage (IPSS-S) and empty (IPSS-E) symptom scores, we might be able to differentiate LUTS due to bladder- or urethral-related conditions and medical treatment aiming at these different conditions might be given without urological investigations.

DIAGNOSTIC VALUE OF IPSS-E/S RATIO

We conducted a small study to evaluate the role of IPSS subscores in male LUTS. A total of 87 men with LUTS were enrolled and 15 age-matched men without LUTS served as controls. The patients were then measured with total prostate volume (TPV), transition zone index (TZI), Qmax, PVR, and the causes of LUTS based on these urological investigations then determined.

Patients with a TPV greater than 40 mL, TZI greater than 0.5 and Qmax less than 15 mL/s with obstructive flow pattern was diagnosed to have BPH and BOO. Patients with a TPV less than 30 mL, TZI less than 0.3, and Qmax less than 15 mL/s with an abnormal flow pattern were diagnosed to have non-BPH voiding dysfunction. Patients with TPV less than 30 mL, TZI less than 0.3, and Qmax greater than 15 mL/s with normal flow pattern were diagnosed to be normal. Patients with presence of urgency or urgency urinary incontinence, TPV less than 30 mL, TZI less than 0.3, Qmax greater than 15 mL/s, and with normal flow pattern were diagnosed to have OAB. Patients with no urgency, TPV less than 30 mL, TZI less than 0.3, Qmax greater than 15 mL/s, with normal flow pattern, and voided volume <350 mL were diagnosed to have a hypersensitive bladder (HSB). When a diagnosis was difficult to make when based on these urological investigations, patients underwent VUDS and the final diagnosis was made as bladder- or urethral-related conditions [8].

The diagnosis of OAB/HSB, BPH, and non-BPH VD were made in 41, 25, and 21 patients, respectively. The IPSS-E and IPSS-S of each patient were then plotted in a LUTS symptom score plot (Fig. 2).If we draw a line as IPSS-E/S=1, it seems that more patients with BPH or non-BPH VD were above the line, and more patients with OAB below the line. So we tried to calculate IPSS-E to IPSS-S ratio in each patient and compared the mean IPSS-E/S ratio among subgroups (Fig. 3). The mean IPSS-E/S ratio was ≤1.0 (0.71±0.71, n=41) in patients with OAB or HSB, whereas patients with BPH-BOO (1.99±1.32, n=25) and non-BPH voiding dysfunction (2.92±2.55, n=21) had an IPSS-E/S ratio >1.0 (p=0.000).

Correlation between IPSS (empty, storage, total, and E/S ratio) and different variables including Qmax, PVR, TPV, TZI, and prostate specific antigen (PSA) were also made. Although the total and empty IPSS correlated with Qmax, the storage IPSS and IPSS-E/S ratio did not associate with Qmax, PVR, TPV, TZI, or PSA.

We then constructed receiver operating characteristics (ROC) curves using different methods for predicting BPH/non-BPH VD and OAB/HSB in our patients. An ROC curve is a graphical plot of the sensitivity vs. (1-specificity) for a binary classifier system as its discrimination threshold is varied. ROC analysis provides tools to select possibly

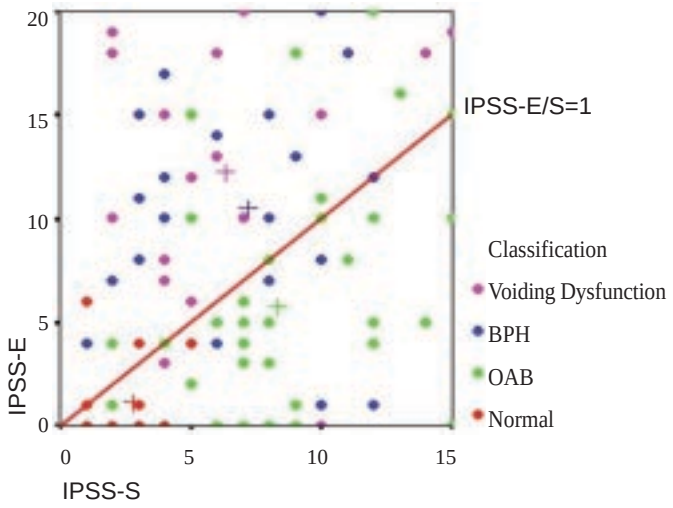

Fig. 2. The IPSS-E and IPSS-S of each patient were plotted in a LUTS symptom score plot.

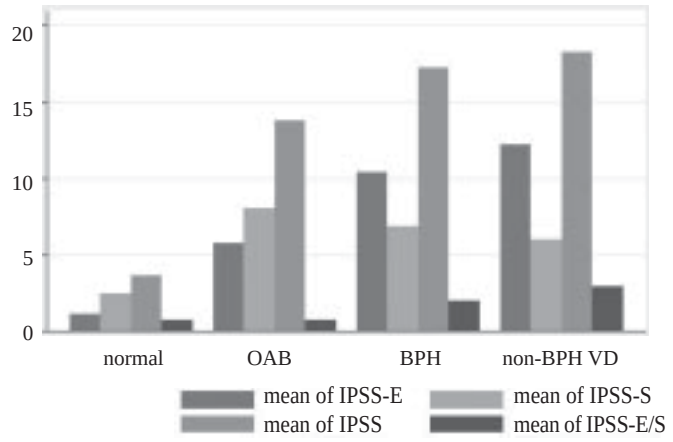

Fig. 3. IPSS, IPSS-E, IPSS-S, and IPSS-E/S ratios in different patient groups.

optimal models and to discard suboptimal ones independently from (and prior to specifying) the cost context or the class distribution. ROC analysis is related in a direct and natural way to cost/benefit analysis of diagnostic decision making.

The area under the ROC curve was greatest when IPSS-E/S was used and compared with the total IPSS, empty IPSS, storage IPSS, Qmax, PVR, TPV, TZI or PSA (Table 1). IPSS-E/S might be a better method to predict urethral-related LUTD and bladder-related LUTD when compared with other noninvasive methods. Although this diagnostic method can not replace UDS or VUDS, it may be considered an easy method in first-line use for general practitioners to treat men with LUTS.

If we chose IPSS-E/S=1 as a cut-off point to predict whether or not urethra-related LUTD (BPH-BOO or non-BPH voiding dysfunction) was present, the sensitivity and specificity was 80.4% and 71.4%, respectively. The sensitivity and specificity was 67.2% and 70.7% for predicting bladder-related LUTD (OAB or HSB). If we excluded patients with an IPSS <7, the sensitivity and specificity was 83.3% and 65.6% for the prediction of urethra-related LUTD, and the sensitivity and specificity was 81.4% and 64.5% for bladder-related LUTD.

Table 1. Comparisons between Areas in ROC Curves Using Different Methods to Predict BOO/non-BPH VD and OAB

Area under ROC curve	BOO/non-BPH VD	OAB/HSB
	N=102	
IPSS-E/S	0.84	0.72
IPSS-E	0.80	0.37
IPSS-S	0.50	0.69
IPSS	0.73	0.51
Qmax	0.69	0.57
PVR	0.71	0.31
TPV	0.74	0.28
TZI	0.63	0.34
PSA	0.56	0.36

THE ROLE OF IPSS-E/S RATIO IN TREATMENT

The α-adrenoceptor antagonists and 5α-reductase inhibitors are effective treatments for men with BOO due to BPH or non-BPH VD. Although patients with BPH may also have their OAB symptoms relieved after initial treatment for BPH-BOO, these agents may not be the most effective treatments for storage symptoms. Studies have suggested that α-adrenoceptor antagonists [6] and transurethral resection of the prostate (TURP) [7,8] fail to improve storage symptoms in some men with BOO.

Antimuscarinic or anticholibergic drugs are the first line treatment for patients with OAB or HSB [28]. Blake-James et al [29] performed a systemic review of 5 randomized controlled trials (RCT) and 15 investigational studies to assess the role of anticholinergic drugs in men with LUTS and OAB. Although there was no significant difference in the Qmax of men who received anticholinergic therapy as compared with those in control groups, PVRs increased slightly with antimuscarinic administration. In addition, only one RCT reported a significant reduction in the storage symptom score while no significant improvement in IPSS was found in the others. Pooled data showed that 24 patients (4.9%) experienced increased difficulty when voiding or substantially raised PVRs. AUR was an uncommon event, with a comparable incidence in intervention (0.8%), and control groups (0.6%).

Which medication should be used first in male LUTS seems to be a problem for many first-line physicians, especially for those non-urologists without urological diagnostic equipment for uroflowmetry or transrectal ultrasound. Combination therapy with both α1-adrenoceptor antagonist and antimuscarinic medication may be a choice [30]. Kaplan et al reported that men who received tolterodine ER plus tamsulosin experienced significantly greater improvement in LUTS than men who received a placebo or either active treatment alone [31]. It may be speculated that the study population consisted of a combination of responders to tamsulosin and resistance to toltedodine, and responders to tolterodine and resistance to tamsulosine. However, it seems unreasonable and not cost-effective if we use two medications for every patient with both empty and storage LUTS if one medication may be effective enough. The result of treatment also offers important information for confirming our preliminary diagnosis, but the satisfactory result of the combination therapy also leads to less understanding or misunderstanding of the underlying pathophysiology of male LUTS.

In addition, some physicians may be concerned that the inhibi-

tory effect of antimuscarinic agents could aggravate the voiding difficulties or cause urinary retention. Therefore, clear differentiation of urethral-related and bladder related LUTD will help us decide which medication should be used first. We also examined the safety and efficacy of initial treatment using IPSS-E/S as a treatment guide in our study. Doxazosin 4 mg and tolterodine 4 mg QD were given to patients based on the initial diagnosis of urethral- (IPSS-E/S >1) and bladder-(IPSS-E/S ≤1) related conditions, respectively. After medical treatment for 1 month, 34/44 (77%) patients with bladder-related conditions and 33/43(77%) patients with urethral-related conditions reported an improved outcome. No patients treated with tolterodine developed adverse events such as difficult urination or urinary retention.

Gravas et al [32] also suggested that the weighing of storage versus emptying symptoms is a decisive factor for the selection of medical treatment, and postulated a scheme on the initial medical treatment of male LUTS. Anticholinergics therapy was suggested if there were more storage symptoms than emptying symptoms. However, combination therapy with alpha-blocker was suggested for prostate volume >29 mL, Qmax <10 mL/s, and/or PVR >40 mL.

CONCLUSIONS

Dividing the IPSS into storage and empty subscores and recording them separately may have clinical significance,not only in the differentiation between bladder- and urethra-related LUTD but also as an initial treatment guide. IPSS-E/S ratio is a simple and good method for predicting BOO/non-BPH VD or OAB/HSB in male LUTS with a higher area of ROC curve than other non-invasive methods or parameters in our preliminary results.

We understand IPSS-E/S ratio is not a perfect method to diagnosis BOO or OAB, and many of these patients have both conditions. However, it is a simple and useful method for the first-line physicians, especially those who have no urological diagnostic equipment. In our preliminary study results, using IPSS-E/S ratio to guide initial treatment for male LUTS is safe and results in a satisfactory outcome. However, larger and longer placebo-controlled studies are still needed to confirm the role of IPSS-E/S in male LUTS.

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