INTRODUCTION

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic syndrome with unknown etiology that is characterized by urgency, frequency, and bladder pain, with a negative impact on quality of life.[1] Frequent voiding is almost universal in IC/BPS with an average length of diagnosis of seven years.[1] IC/BPS has been divided into subtypes of Hunner (HIC) and non-Hunner (NHIC, or BPS) IC.[2] Generally, inflammatory conditions in IC/BPS are due to regional neuropathy, resulting in suprapubic pain and voiding dysfunction.[2]

Development of objective examinations to evaluate IC/BPS patients with dysfunctional voiding symptoms may be beneficial for earlier diagnosis and treatment.[3] Video urodynamic study (VUDS) consists of a group of tests performed under fluoroscopy to assess the function and morphology of the urinary tract by measuring various aspects of urine storage and evacuation. VUDS has been used widely to aid in understanding the physiologic mechanisms of lower urinary tract dysfunction.[3] However, some studies revealed associations between diagnostic parameters,[4] and a previous study demonstrated that UDS parameters were significantly associated with IC symptom severity, the result of a potassium chloride (KCl) test, maximum bladder capacity (MBC) under cystoscopic hydrodistention, and the degree of glomerulation in IC/BPS patients.[5] According to prior studies, the treatment outcome of patients with IC/BPS has not been satisfactory, which might be attributable to the underlying voiding or storage dysfunction. Sastry et al.[6] reported that certain cystometric parameters were significantly associated with symptom severity in patients with IC/PBS. Assessment of pain, pressure, or discomfort perceived with bladder filling may be an important key during urodynamic testing in patients with IC/PBS.

More advanced disease progression of IC/BPS involving neovascularization and possible neurogenic inflammation of the bladder may lead to more unpleasant sensations during bladder filling and, thus, limit bladder capacity. A recent study revealed that voiding dysfunction is encountered frequently in patients with IC/BPS.[7] Kuo et al.[5] further observed that the severity of glomerulation is negatively correlated with bladder volume measured objectively by UDS parameters. IC/PBS can be diagnosed without cystoscopic hydrodistention in women with increased bladder sensation, storage symptoms, acystometric bladder capacity (CBC) ≤350 mL, a positive KCl test result, and a visual analog score (VAS) ≥ 2.[5]

Few reports have focused on urodynamic studies and treatment outcome of IC/BPS patients. Since bladder outlet dysfunction has been observed to accompany a certain portion of IC/BPS patients,[7,8] it is interesting to know whether these patients with voiding dysfunction have a less favorable treatment outcome. We evaluated the correlation of baseline voiding dysfunctions with long-term treatment outcome in a large cohort of patients with IC/BPS.

MATERIALS AND METHODS

All 455 IC/BPS patients retrospectively enrolled in the study from 1997 until 2019 underwent VUDS examination and cystoscopic hydrodistention at baseline to identify their voiding and storage conditions, and all received subsequent treatments. Among them, 211 cases of non-Hunner's IC (182 women, 29 men) could be traced using chart review or telephone interviews to collect questionnaires at initial enrollment and after they had received many different types of treatment to date. IC/PBS was diagnosed based on the characteristic symptoms and cystoscopic findings of glomerulations, petechia, or mucosal fissures after hydrodistention.[2] The patients were investigated thoroughly upon enrollment and were excluded if they did not meet the inclusion criteria of the National Institute of Diabetes and Digestive and Kidney Diseases.[9]

VUDS was performed using a multichannel urodynamic system (Life-Technique, Inc., Stafford, TX, USA) and a C-arm fluoroscope (Toshiba, Tokyo, Japan). The pressure-flow study was performed using a 6 French double lumen catheter via the standard procedure with the patient sitting. Warmed normal saline containing 20% Urografin was infused at a filling rate of 30 mL/min. The C-arm fluoroscope was positioned 45° from the buttocks so that the urethra could be lengthened and the bladder neck, urethral sphincter, and distal urethra could be identified clearly. The measured parameters included first sensation of filling (FSF), first desire to void, strong desire to void (SD), CBC, maximum flow rate (Qmax), detrusor pressure at Qmax (Pdet), voided volume, and post-void residual volume. The KCl test using 30 mL 0.4 M KCl solution was performed and a positive result was considered if patients felt bladder pain or a strong urge to void.[10]

According to the VUDS finding, bladder dysfunction (hypersensitive bladder, HSB) or bladder outlet dysfunction was diagnosed. Bladder outlet dysfunction was classified into three categories: dysfunctional voiding (DV), poor relaxation of external urethral sphincter (PRES), and bladder neck dysfunction (BND). HSB was

defined as an early FSF (< 100 mL) that occurred at low CBC (<250 mL) and persisted.[11] DV was defined as having a high Pdet and dilation of the proximal urethra combined with a “spinning top” appearance at the middle urethra during voiding cystourethrography in VUDS. PRES was defined as normal Pdet with dilation of the proximal urethra and a narrow distal urethra. BND was defined as a high Pdet and lack of a funnel shape of the bladder neck during voiding.[12] All VUDS procedures and finding were conducted and followed the standardization of the International Continence Society.[13]

The IC symptoms were evaluated by a linguistic validated questionnaire of O'Leary-Sant score (OSS), including IC symptom index and the IC problems index. The degree of bladder pain perceived was measured by a 10-point VAS scale, and self-reported treatment effectiveness was determined by global response assessment (GRA). VUDS parameters, MBC, and glomerulation at cystoscopic hydrodistention, and flare-up rate during follow-up also were recorded, and the parameters were used to compare therapeutic outcome.

The primary endpoint was the changes in self-reported treatment outcome score from the beginning of treatment to the present interview. The score was adapted from GRA with 3 indicating markedly improved, 2 moderately improved, 1 mildly improved, 0 no change, and −1 as getting worse. Secondary endpoints included the changes in OSS and VAS for pain and the symptom flare-up rate.

Statistical comparisons between the groups were tested using the Pearson's χ^2 test or Fisher's exact test for categorical variables, and an independent *t*-test or analysis of variance for continuous variables. All statistical analyses were performed using the statistical package SPSS (Version 22.0, SPSS, Inc., Chicago, IL, USA), with $P < 0.05$ indicating statistical significance.

RESULTS

A total of 211 IC/BPS patients (182 women [86.3%], 29 men [13.7%]; mean age, 56.8 ± 12.8 years; mean duration of IC symptoms, 16.0 ± 9.9 years) were enrolled in this study. According to their baseline VUDS reports, 83 (39.3%) patients had a voiding VUDS diagnosis and 62.7% of them had one to three medical comorbidities. Patients received different treatment modalities for IC/BPS, including cystoscopic hydrodistention, intravesical hyaluronic acid instillation, intravesical botulinum toxin A injection, and any medication for bladder pain. In addition, they also received

antimuscarinics or mirabegron for bladder overactivity or hypersensitivity, and an α-blocker with or without baclofen or urethral sphincter botulinum toxin A injection for VUDS-proven bladder outlet dysfunction. If patients had good satisfaction with the previous treatments, they usually did not receive new treatments during the long follow-up period.

Regarding the baseline voiding condition, patients were divided into four subgroups according to the VUDS, including normal voiding (*n* = 128), PRES (*n* = 54), DV (*n* = 22), and BND (*n* = 7). There was a significant difference in the sex distribution; there were more women than men in the normal, PRES, and DV subgroups (*P* = 0.001). The other characteristics, such as age, mean duration of IC symptoms, comorbidity, type of treatment, OSS, VAS, MBC, glomerulation, treatment outcome, and flare-up rate, all showed no significant difference among the subgroups (Table 1).

Thereafter, we merged the patients with voiding and bladder dysfunctions (HSB) and divided them into three subgroups according to their baseline VUDS findings: normal bladder and voiding (*n* = 32), and HSB with (*n* = 76) and without (*n* = 103) voiding dysfunction. The only significant differences among these three subgroups were noted in sex distribution, MBC (770.3 ± 189.2, 653.7 ± 168.9, and 639.2 ± 187.6 mL, respectively; *P* = 0.002), and glomerulation grade (1.4 ± 0.9, 1.8 ± 0.9, and 1.9 ± 0.8 mL, respectively; *P* = 0.021). Regardless of whether patients were in the HSB with or without voiding dysfunction subgroups, the mean duration of IC symptoms, comorbidity, type of treatment, changes in OSS and VAS, self-reported treatment outcome, and flare-up rate were not significantly different among the different voiding and bladder dysfunction subtypes (Table 2).

Finally, we analyzed and grouped patients by the self-reported treatment outcomes (GRA = −1, *n* = 12; GRA = 0, *n* = 59; GRA = 1, *n* = 37; GRA ≥ 2, *n* = 103). Patients with a GRA ≥ 2 had a significantly shorter duration of IC symptoms. There also were significant associations between GRA and the changes in OSS (*P* < 0.001) and VAS (*P* < 0.001) after treatments. The self-report treatment outcome changed with bladder symptoms and pain improvement. However, the voiding conditions detected by the VUDS did not affect treatment outcome (Table 3).

DISCUSSION

In this large cohort, only 103 of 211 (48.8%) patients with non-Hunner IC had a satisfactory treatment outcome after a mean follow-up of 16 years. Baseline VUDS can differentiate several different subtypes of voiding and storage lower urinary tract conditions in patients with IC symptoms, but cannot predict long-term therapeutic outcomes.

Correlation between IC/BPS subtypes and urodynamic study parameters was found. Perez-Marrero et al.[14] reported that, although urodynamic parameters were not diagnostic for IC/BPS, they were useful in the differential diagnosis of painful voiding disorders and provided a convenient way to quantitate response to therapy. The pathophysiology and the overlap between Hunner and non-Hunner IC remains unclear.[2] However, recent studies have divided these two distinct IC subtypes into two individual diseases that might have different etiologies, clinical characteristics, and treatment modalities.[15] Regarding non-Hunner IC, different subtypes also have been observed to have different combinations of MBC and glomerulation under cystoscopic hydrodistention.[16] A high percentage of IC/BPS patients also had different voiding dysfunctions in VUDS.[15]

Histopathologically, inflammation is a characteristic feature of the IC bladder.[17] Urothelial barrier dysfunction in IC/BPS bladder cases may lead to abnormal migration of urinary solutes, such as potassium, which depolarizes muscle and nerves, and then causes tissue injury and bladder pain.[18,19] Increased cell apoptosis and decreased proliferative cells were noted in IC bladder urothelium compared to control cases.[20] The apoptosis in IC/PBS bladders might be due to upregulation of inflammatory signals. Chronic inflammation in the suburothelium may inhibit normal urothelial basal cell proliferation and affect apical urothelium function.[21] Increased inflammation in the chronic IC bladder might limit bladder distention, resulting in a small functional bladder capacity and frequency/urgency symptoms. Increased sensory afferent activity including pain-associated C-fibers in chronic IC further causes bladder pain with a full bladder.[22]

The pathophysiology underlying voiding dysfunction in patients with IC/BPS has not been completely elucidated. However, from the urinary physiology, increased sympathetic and somatic activity in an inflamed bladder are likely to result in PRES, DV, or BND in women with bladder outlet dysfunction (BOO).[23] One study reported that 48% of IC/PBS patients had BOO, and increasing severity of IC/PBS is associated with higher voiding pressure.[8] Once the bladder inflammation has been solved, these reactive hyperactivities of the bladder neck and urethral sphincter also might

improve.

The bladder outlet dysfunction might be secondary to the bladder-centered disease, such as in IC/BPS or detrusor overactivity. Patients with increased urethral sphincter tone and pelvic floor muscle hyperactivity not only have increased urethral resistance, but also increased bladder sensation or developing detrusor overactivity through neuromodulation, resulting in different types of sensory dysfunction.[24] Urothelial dysfunction in IC/BPS bladder cases also might be exaggerated by the presence of bladder outlet dysfunction. However, no significant difference in age, duration of IC symptoms, comorbidity, changes in OSS or pain VAS, MBC, glomerulation, and treatment outcome was noted among the normal, PRES, DV, and BND subgroups (Table 1), suggesting that the voiding condition does not influence clinical presentation and treatment results of IC/BPS patients.

Lower urinary tract symptoms are very common in women. Previous studies reported 2.7% to 8% prevalence rates among women referred for evaluation of lower urinary tract symptoms.[25] In this study, 39.3% of women with IC/BPS had voiding dysfunction according to VUDS. Among our 211 patients, 84.3% (*n* = 179) had HSB, but only 36.0% (*n* = 76) had voiding dysfunction. We found no difference between patients with HSB with and without voiding dysfunction, further suggesting that the voiding condition was not a predictive factor for the unfavorable treatment outcome of IC/BPS. It is reasonable to consider that voiding dysfunction occurring in IC/BPS might be secondary to the bladder dysfunction and not the cause of bladder disease.

The pressure-flow study is an objective urodynamic examination that was considered the best investigating tool to assess the voiding phase of the micturition cycle. However, accurate diagnosis of voiding dysfunction still must depend on VUDS.[7] A video urodynamic study can provide accurate diagnostic evidence not only for dysfunction in the storage phase (such as HSB, low bladder compliance, detrusor overactivity), but also in the voiding phase (such as detrusor underactivity, bladder outlet dysfunction). Treatment targeting these bladder or bladder outlet dysfunctions can be given concomitantly in association with treatment for IC/BPS. All of our patients underwent VUDS at baseline, and patients also received specific treatment for the bladder or bladder outlet dysfunction, which might have an impact on the treatment outcome at final analysis.

We noted that IC/BPS patients had small MBC and high grade glomerulation when they had HSB with or without voiding dysfunction. However, this classification did not affect the treatment outcome after a long follow-up. The overall satisfactory rate as reported by GRA was similar among the subgroups, but patients with HSB and voiding dysfunction had a relatively lower satisfactory rate (normal 53.1%, HSB with voiding dysfunction 44.7%, HSB without voiding dysfunction 50.5%). Because the bladder inflammation in IC/BPS affects the symptoms and bladder capacity, and might result in increased bladder outlet resistance through the guarding reflex mechanism, it is reasonable to conclude that IC/BPS patients with storage and voiding symptoms might have less favorable treatment outcomes and require active management.

Although VUDS cannot predict the outcome of treatment, VUDS still can be used to understand voiding or storage dysfunction in patients with IC/BPS before further treatment can be provided. That is why the treatment outcomes look the same as those of IC/BPS patients without voiding or storage dysfunction. Therefore, VUDS is clinically important to understand the IC/BPS patient’s voiding or storage condition.

The limitations of this study are that there were no uniformed treatment modalities during the long follow-up and that it also was impossible to determine how long the patient had been symptomatic. Not only do these patients have an "endurance period" before they are diagnosed, but also because many new treatment modalities have been consecutively developed and patients without a satisfactory outcome will receive new treatment, it is not possible to analyze the treatment outcome based on the same treatment. Nevertheless, the long-term follow-up treatment outcome can reflect the real-world practice outcome of the non-Hunner IC patients.

CONCLUSION

Voiding dysfunctions in patients with non-Hunner IC do not affect long-term treatment outcome. Active treatment for IC patients with voiding dysfunction is important.

Disclosure

None.

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Author Contributions

HCK conceived the study, made critical comments, and provided supervision. WRY designed the study workflow; and acquired, analyzed, in addition to drafting the article and making critical revisions, WCC interoperated the data. All the authors reviewed the manuscript.

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