

Urodynamic findings in patients with nocturia and their associations with patient characteristics

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Abstract

Introduction: This study identified associations between lower urinary tract pathology confirmed on urodynamic testing, baseline characteristics, and symptoms for adults with nocturia. Nocturia frequency was examined for predictors.

Methods: This retrospective study from 2012–2019 analyzed adult patients with nocturia (waking to void ≥ 2 x/night) referred for urodynamic testing (UDS). Data on baseline characteristics, symptoms, UDS parameters, and lower urinary tract pathology were recorded. Males and females were analyzed separately, and univariable analyses were conducted, stratified by lower urinary tract pathology. Multivariable regression models were fit. Nocturia frequency was analyzed for associations with clinical parameters.

Results: Altogether, 372 patients were included (159 men and 213 women). More men had detrusor overactivity (DO) ($p < 0.001$) and bladder outlet obstruction (BOO) ($p < 0.001$). DO was associated with storage symptoms (odds ratio [OR] 5.19, $p < 0.001$), in addition to older age ($p = 0.009$) and being male ($p < 0.001$). Detrusor underactivity (DU) was associated with voiding symptoms (OR 1.92, $p = 0.004$), older age ($p < 0.001$), and being female ($p = 0.018$). BOO was associated voiding symptoms (OR 2.09, $p = 0.023$), younger age ($p = 0.018$), and being male ($p < 0.001$). The quantity of lower urinary tract symptoms was associated with DU and DO. Nocturia frequency was not associated with baseline variables or underlying pathologies. A substantial number of patients were diagnosed with DU alone ($n = 69$, 18.7%) or associated with other diagnoses ($n = 108$, 29.3%).

Conclusions: Careful assessment of risk factors and symptoms may help identify underlying lower urinary tract pathology for adults with nocturia. DU is found in a significant proportion of patients with nocturia, a previously under-reported result.

KEY MESSAGES

- In adults presenting with nocturia for urodynamic testing, storage and voiding lower urinary tract symptoms (LUTS) may help differentiate underlying lower urinary tract pathology.
- The quantity of LUTS may increase the likelihood of being diagnosed with certain lower urinary tract pathologies.
- A substantial proportion of adults presenting with nocturia have underlying detrusor underactivity, a known underdiagnosed condition.

Introduction

Nocturia is complex and can reflect multiple overlapping etiologies. The causes may be cardiovascular, nephrological, hormonal, sleep-related, fluid intake-related, medication-related, or linked to lower urinary tract.¹ Clinicians may often depend on empirically managing nocturia with overactive bladder medications with a less-than-ideal success rate.²

To assist with distinguishing between causes of nocturia, the International Continence Society (ICS) has outlined components to diagnose the underlying cause of nocturia.¹ These may include history, examination, bladder diary, and blood tests. The use of urodynamic testing (UDS) may confirm lower urinary tract pathology, such as detrusor overactivity (DO), detrusor underactivity (DU), or bladder outlet obstruction (BOO). UDS may be considered in selective presurgical settings to better counsel patients with treatment options after identifying the root cause of their symptoms.^{3,4}

In addition, nocturia may present with differing severity and frequency. Currently, limited literature has examined the relationship between nocturia frequency and its relationship with UDS findings. Potential predictors within risk factors or

clinical features that are identified may influence and guide treatment decision-making.

Hence, this study aimed to characterize UDS findings in adult males and females with nocturia, and to identify the relationship of nocturia with underlying lower urinary tract pathologies.

Methods

This retrospective, observational study was based in a single tertiary center in Melbourne, Australia. Consecutive patients referred to our center for UDS over a seven-year period from 2012–2019 were assessed for inclusion. This study was approved by the local institutional human research ethics committee.

Study inclusion

Patients were included for analysis if they underwent formal UDS with a presenting complaint of nocturia at time of referral. Patients included often concurrently presented with a cluster of multiple lower urinary tract symptoms (LUTS) but were included if nocturia was one of the primary complaints mentioned within the indication section of the UDS report. Only adult (≥ 18 years) males and females were included. Patients were excluded if they did not have sufficient data for analysis. In this study, nocturia was defined as patients needing to void ≥ 2 times per night. To align with the ICS definitions, nocturia was quantified through the use of a bladder diary and required patients to pass urine during the main sleep period.⁵ UDS was performed in accordance to the outlined ICS standards.⁶ All testing was either supervised or performed by one of two consultant urologists. Patients were not required to withhold pharmacotherapy prior to undergoing UDS.

Data collection

Data was collected through hospital electronic medical records. A list of all patients who underwent UDS in our institute was obtained and cross-checked with inclusion criteria. Two authors (GC and LQ) extracted the data independently onto a spreadsheet and discrepancies were discussed. Baseline characteristics were collected, including age, gender, and past medical history (neurogenic, stroke, diabetes mellitus, pelvic surgery, and pelvic radiotherapy). The number and quantity of separate voiding and storage LUTS (excluding nocturia) were recorded, while the reported frequency of nocturia was documented. Urodynamic parameters were collected, and bladder contractility index (BCI) and bladder outlet obstruction index (BOOI) were calculated according to previous literature.⁷ In this study, DO was defined as detrusor contractions during the filling cystometry;⁸ DU was defined as a BCI (maximum detrusor pressure [P_{det}] maximum flow

rate [Q_{max}] + 5* Q_{max}) of ≤ 100 . BOO was defined as a bladder outlet obstruction index (BOOI= $P_{det} Q_{max} - 2*Q_{max}$) of ≥ 40 .⁹

Statistical analysis

Descriptive statistics were reported separately for males and females for baseline characteristics and by presence or absence of DO, DU, or BOO. Univariate analysis was performed using Chi-squared test of proportions and Wilcoxon rank-sum testing, stratified by DO, DU, or BOO. Adjusted odds ratios (ORs) were reported to assess the association of the baseline variables and clinical features through multivariable logistic regression modelling. Covariate selection was guided by predetermined relevant variables and the inclusion of significant covariates identified during univariate analyses. Age was reported as per-ten-year change. Patients with missing values were not included in these models. Voiding and storage LUTS were analyzed as a dichotomous variable; however, an exploratory analysis was also conducted analyzing LUTS as continuous variables for quantity of symptoms reported.

A secondary analysis focused on examining the relationship between baseline variables, lower urinary tract pathology, and patient-reported nocturia frequency. Nocturia frequency was analyzed by predetermined strata of 2–5x/night or >5x/night. These brackets were chosen to 1) optimize the relative sample sizes between groups, while 2) also ensuring that the 2–5x/night group was not too narrowly defined. Univariate analyses were performed, and ordinary least squares linear regression modelling was used.

Throughout this study, an alpha of 0.05 was used to deem statistical significance. Data were analyzed using StataIC v15.1 (College Station, TX, U.S.).

Results

From January 2012 to December 2019, there were 1322 patients who underwent UDS at our institution. There were 943 exclusions due to not being an adult patient or not presenting with nocturia. At the analysis stage, a further seven patients were excluded based on insufficient data. In summary, 372 patients were included for analysis (159 men and 213 women). There was a higher proportion of men compared to women with DO (123/158 vs. 125/210, $p < 0.001$, four patients missing) and BOO (57/150 vs. 14/199, $p < 0.001$, 23 patients missing) confirmed on UDS. There was a similar proportion of men and women who had confirmed DU (68/155 vs. 109/210, $p = 0.129$, seven patients missing). There were altogether 32 women and one man with no lower urinary tract disorder diagnosed through UDS (Table 1).

Univariable analyses were performed for each gender (Table 2). For women, a greater proportion of those with storage symptoms were associated with DO (95.2% vs. 76.5%, $p < 0.001$). For men with DO, there were associations for

Table 1. Summary table of lower urinary tract disorders by gender in patients with nocturia

| Diagnosis (n, %) | Females (n=213) | Males (n=159) | Total (n=372) |
|------------------|-----------------|---------------|---------------|
| One diagnosis | | | |
| DO | 60 (28.4) | 44 (27.9) | 104 (28.2) |
| DU | 46 (21.8) | 23 (14.6) | 69 (18.7) |
| BOO | 6 (2.8) | 8 (5.1) | 14 (3.8) |
| Two diagnoses | | | |
| DO & DU | 59 (28.0) | 33 (20.9) | 92 (24.9) |
| DO & BOO | 4 (1.9) | 37 (23.4) | 41 (11.1) |
| BOO & DU | 2 (1.0) | 3 (1.9) | 5 (1.4) |
| Three diagnoses | | | |
| DO, DU & BOO | 2 (1.0) | 9 (5.7) | 11 (3.0) |
| No LUTD | 32 (15.2) | 1 (0.6) | 33 (8.9) |

Note two female patients and one male patient are missing diagnoses for this summary table. BOO: bladder outlet obstruction; DO: detrusor overactivity; DU: detrusor underactivity; LUTD: lower urinary tract disease.

both the greater proportion of storage symptoms present (91.9% vs. 77.1%, $p=0.016$) and for lesser proportion of voiding symptoms present (56.1% vs. 85.7%, $p=0.001$). For women with DU, the presence of voiding symptoms was observed with a greater proportion (56.0% vs. 40.6%, $p=0.026$), in addition to neurogenic past history (30.3% vs. 17.8%, $p=0.035$). Older age was also associated with DU

(median, years: 69 vs. 56, $p<0.001$). There was insufficient evidence to suggest a difference in proportion with storage symptoms for men with and without DU (83.8% vs. 93.1%, $p=0.067$). Women with BOO had a greater rate of presence of voiding symptoms (78.6% vs. 47%, $p=0.023$). For men with BOO, there was insufficient evidence for a difference in symptoms; however, men with BOO were younger (median, years: 62 vs. 69, $p=0.012$) and less likely to have previous pelvic surgery (3.5% vs. 21.5%, $p=0.002$).

Multivariable logistic regression modelling was performed (Table 3).

For DO, the model included covariates: age, gender, presence of storage symptoms, and presence of voiding symptoms. Increasing age (adjusted OR 1.191, 95% confidence interval [CI] 1.01–1.41), being male (adjusted OR 2.809, 95% CI 1.70–4.65), having storage symptoms (adjusted OR 5.19, 95% CI 2.57–10.47), and not having voiding symptoms (adjusted OR 0.45, 95% CI 0.28–0.74), were associated with DO.

For DU, the model analyzed: age, gender, neurogenic history, presence of storage symptoms, and presence of voiding symptoms. Increasing age (adjusted OR 1.48; 1.26–1.75), not being male (adjusted OR 0.58, 95% CI 0.37–0.91),

Table 2. Baseline characteristics and clinical features stratified by DO, DU, and BOO in patients with nocturia

| Females | DO | | | DU | | | BOO | | |
|--------------------------------|------------|--------------|--------|--------------|---------------|--------|------------|----------------|-------|
| | DO (n=125) | No DO (n=85) | p | DU (n=109) | No DU (n=101) | p | BOO (n=14) | No BOO (n=185) | p |
| Age, median (IQR) | 64 (55–74) | 61 (50–71) | 0.193 | 69 (60–75) | 56 (47–64) | <0.001 | 59 (52–69) | 61 (54–72) | 0.435 |
| Past history, n (%) | | | | | | | | | |
| Neurogenic | 30 (24.0) | 21 (24.7) | 0.907 | 33 (30.3) | 18 (17.8) | 0.035 | 3 (21.4) | 44 (23.8) | 0.841 |
| CVA | 7 (5.6) | 2 (2.4) | 0.254 | 6 (5.5) | 2 (2.0) | 0.183 | 0 (0) | 7 (3.8) | 0.459 |
| Diabetes | 14 (11.2) | 10 (11.8) | 0.900 | 14 (12.8) | 11 (10.9) | 0.662 | 4 (28.6) | 19 (10.3) | 0.039 |
| Pelvic surgery | 67 (53.6) | 41 (48.2) | 0.445 | 60 (55.1) | 50 (49.5) | 0.422 | 7 (50.0) | 97 (52.4) | 0.861 |
| Previous radiotherapy | 0 (0) | 1 (1.2) | 0.224 | 0 (0) | 1 (0.9) | 0.335 | 0 (0) | 1 (0.5) | 0.783 |
| Any symptoms, n (%) | | | | | | | | | |
| Storage | 119 (95.2) | 65 (76.5) | <0.001 | 94 (86.2) | 90 (89.1) | 0.528 | 13 (92.9) | 161 (87.0) | 0.526 |
| Voiding | 54 (43.2) | 47 (55.3) | 0.085 | 61 (56.0) | 41 (40.6) | 0.026 | 11 (78.6) | 87 (47.0) | 0.023 |
| Total # symptoms, median (IQR) | | | | | | | | | |
| Storage | 2 (2–3) | 2 (1–2) | <0.001 | 2 (1–2) | 2 (2–2) | 0.987 | 2 (2–3) | 2 (1–2) | 0.278 |
| Voiding | 0 (0–2) | 1 (0–2) | 0.061 | 1 (0–2) | 0 (0–1) | 0.014 | 2.5 (1–3) | 0 (0–2) | 0.003 |
| Males | n=123 | n=35 | | n=68 | n=87 | | n=57 | n=93 | |
| Age, median (IQR) | 67 (57–73) | 66 (51–72) | 0.314 | 68 (57.5–73) | 66 (54–73) | 0.509 | 62 (50–71) | 69 (61–74) | 0.012 |
| Past history, n (%) | | | | | | | | | |
| Neurogenic | 32 (26.0) | 9 (25.7) | 0.971 | 17 (25.0) | 23 (26.4) | 0.839 | 14 (24.5) | 23 (24.7) | 0.981 |
| CVA | 9 (7.3) | 1 (2.9) | 0.339 | 3 (4.4) | 6 (6.9) | 0.512 | 4 (7.0) | 4 (4.3) | 0.472 |
| Diabetes | 13 (10.6) | 3 (8.6) | 0.730 | 7 (10.3) | 10 (11.5) | 0.812 | 6 (10.5) | 10 (10.8) | 0.965 |
| Pelvic surgery | 17 (13.8) | 5 (14.3) | 0.944 | 13 (19.1) | 9 (10.3) | 0.120 | 2 (3.5) | 20 (21.5) | 0.002 |
| Previous radiotherapy | 9 (7.3) | 2 (5.7) | 0.742 | 6 (8.8) | 5 (5.8) | 0.459 | 2 (3.5) | 9 (9.7) | 0.160 |
| Symptoms Y/N, n (%) | | | | | | | | | |
| Storage | 113 (91.9) | 27 (77.1) | 0.016 | 57 (83.8) | 81 (93.1) | 0.067 | 51 (89.5) | 82 (88.2) | 0.807 |
| Voiding | 69 (56.1) | 30 (85.7) | 0.001 | 49 (72.1) | 51 (58.6) | 0.083 | 41 (71.9) | 55 (59.1) | 0.113 |
| Total # symptoms, median (IQR) | | | | | | | | | |
| Storage | 2 (1–2) | 1 (1–2) | 0.008 | 2 (1–2) | 2 (2–2) | 0.003 | 2 (1–2) | 2 (1–2) | 0.748 |
| Voiding | 1 (0–3) | 3 (1–4) | <0.001 | 3 (0–4) | 1 (0–2) | <0.001 | 1 (0–3) | 1 (0–3) | 0.568 |

BOO: bladder outlet obstruction; CVA: cerebrovascular accident; DO: detrusor overactivity; DU: detrusor underactivity; IQR, interquartile range.

Table 3. Multivariable logistic regression modelling for DO, DU, and BOO in patients with nocturia

| Regression model | Adjusted OR | Standard error | p | 95% CI |
|-----------------------------------|-------------|----------------|--------|--------------|
| Detrusor overactivity | | | | |
| Age | 1.191 | 0.009 | 0.038 | 1.010–1.405 |
| Male | 2.809 | 0.723 | <0.001 | 1.697–4.651 |
| Storage symptoms | 5.190 | 1.857 | <0.001 | 2.574–10.466 |
| Voiding symptoms | 0.454 | 0.113 | 0.002 | 0.279–0.741 |
| constant | 0.175 | 0.118 | 0.010 | 0.047–0.655 |
| Detrusor underactivity | | | | |
| Age | 1.484 | 0.125 | <0.001 | 1.257–1.751 |
| Male | 0.582 | 0.134 | 0.018 | 0.371–0.913 |
| Neurogenic history | 1.310 | 0.337 | 0.295 | 0.791–2.169 |
| Storage symptoms | 0.634 | 0.219 | 0.188 | 0.322–1.249 |
| Voiding symptoms | 1.919 | 0.439 | 0.004 | 1.225–3.006 |
| constant | 0.096 | 0.062 | <0.001 | 0.027–0.343 |
| Bladder outlet obstruction | | | | |
| Age | 0.775 | 0.011 | 0.018 | 0.628–0.958 |
| Male | 6.991 | 2.531 | <0.001 | 3.439–14.214 |
| Diabetes history | 1.858 | 0.857 | 0.179 | 0.753–4.587 |
| Pelvic surgery history | 0.519 | 0.220 | 0.122 | 0.227–1.191 |
| Storage symptoms | 1.318 | 0.643 | 0.571 | 0.507–3.429 |
| Voiding symptoms | 2.091 | 0.679 | 0.023 | 1.107–3.951 |
| constant | 0.216 | 0.182 | 0.068 | 0.042–1.121 |

Logistic regression models for each lower urinary tract pathology were created with covariates selected and shown below. BOO: bladder outlet obstruction; CI: confidence interval; DO: detrusor overactivity; DU: detrusor underactivity; OR: odds ratio.

and having voiding symptoms (adjusted OR 1.92, 95% CI 1.23–3.01) were associated with DU.

For BOO, the model analyzed: age, gender, diabetic history, pelvic surgery history, storage symptoms, and voiding symptoms. Decreasing age (adjusted OR 0.78, 95% CI 0.63–0.96), being male (adjusted OR 7.00, 95% CI 3.44–14.21), and having voiding symptoms (adjusted OR 2.09, 95% CI 1.11–3.95), were associated with BOO.

Exploratory regression analysis was performed examining symptoms as count variables, and other included covariates unchanged (Supplementary Table 1; available at cuaj.ca). This supported the associations of more storage and fewer voiding symptoms for DO (Figures 1A, 1B), and more voiding symptoms for DU (Figure 1C); however, an association with BOO for increasing number of voiding symptoms was no longer observed (adjusted OR 1.15, 95% CI 0.95–1.39) (Figure 1D).

A secondary analysis was performed, stratified by frequency of nocturia of 2–5x/night or >5x/night (Supplementary Table 2; available at cuaj.ca). Altogether, there were 31 females and 26 males with nocturia >5x/night (14.55 vs. 16.55%, respectively, $p=0.634$). Upon univariable analysis of baseline variables and lower urinary tract pathology, there were no differences between those with less frequent vs. more frequent nocturia, for men or women. There was a higher proportion of men with nocturia >5x/night with early sensation at filling phase compared to those with nocturia 2–5x/night (72.0% vs. 36.8%, $p=0.001$). Multivariable linear regression modelling poorly fit the observed data due to the limited number of significantly associated covariates.

Discussion

This study aimed to investigate the relationship between nocturia and UDS-defined lower urinary tract pathology. Despite the substantial overlap in symptomology, there are certain features and risk factors that may guide the diagnostic process.¹⁰ Where formal UDS may not be readily available, clinical decision-making should rely on a patient's clinical presentation. In this study, older males with nocturia and accompanying storage LUTS were more likely to have DO. Older females with nocturia and voiding LUTS were more likely to have DU, while younger males with these symptoms were more likely to have BOO. An increase of 10 years in age led to 1.19 and 1.48 times the odds of developing DO and DU, respectively. Meanwhile, the odds of BOO decreased by 22.5% with an increase in 10 years of age.

This study suggests that importance should be drawn to the role of clinical history for guiding the diagnosis of lower urinary tract pathology. Although patients with DO in this study tended to report more storage LUTS, the presence of voiding symptoms may detract from a diagnosis of DO. The clinical presentations of DU and BOO both appear to be associated with voiding symptoms, but these may be distinguished by baseline characteristics. The exploratory regression modelling analysis conducted on the number of separately reported voiding and storage LUTS demonstrated that although DU was associated with a greater number of voiding symptoms, this was not observed for patients with BOO. This may be due to the complex pathophysiology underlying BOO, where features of DU and DO may occur at different phases of its natural history.¹¹

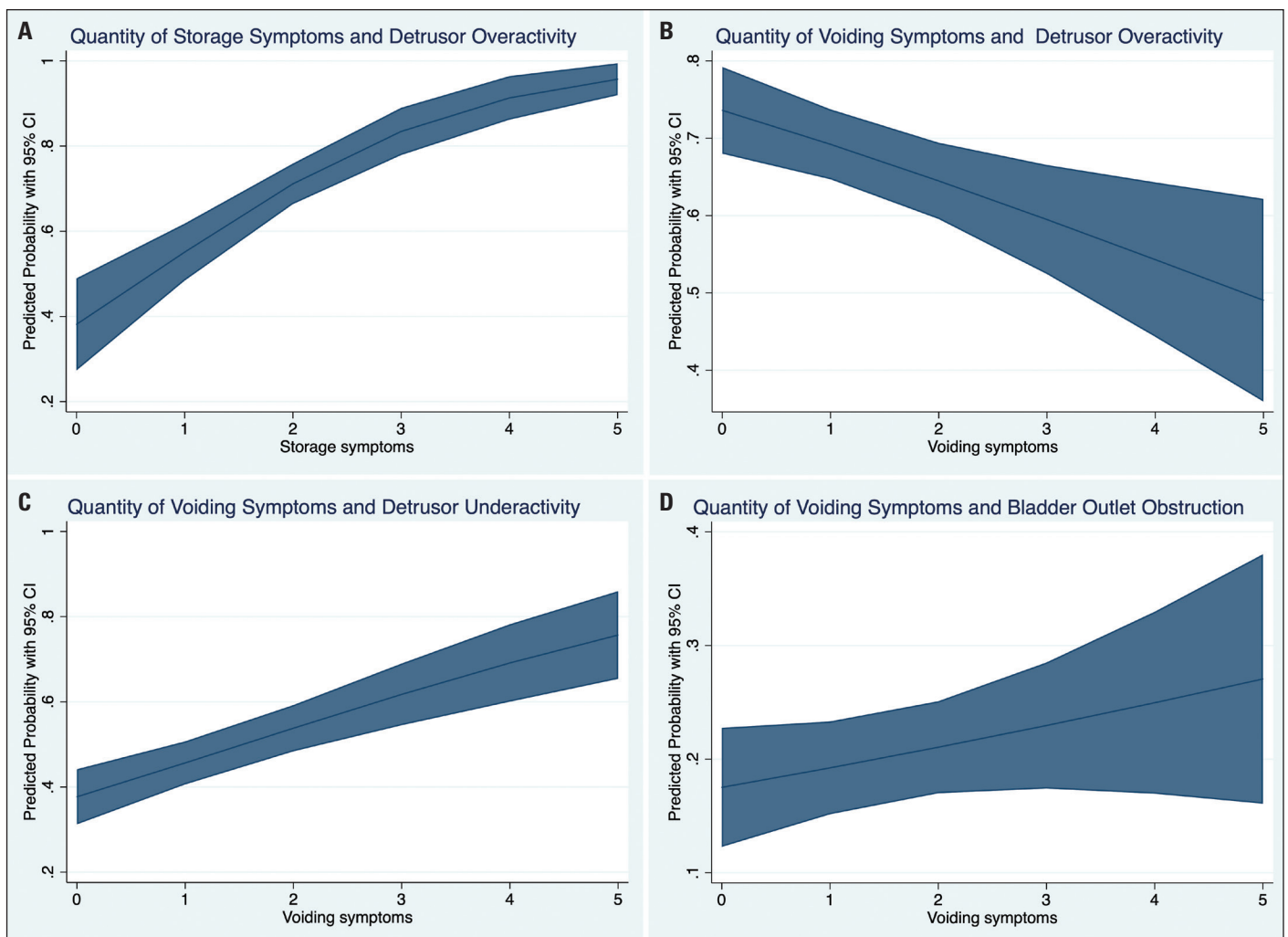


Figure 1. Modelling number of symptoms for predicting detrusor overactivity, underactivity, and bladder outlet obstruction in patients with nocturia. Exploratory regression modelling using quantity of symptoms reported were fit, with predictive plots demonstrated below for detrusor overactivity (**A**, **B**), detrusor underactivity (**C**), and bladder outlet obstruction (**D**). CI: confidence interval.

These results appear to align with prior studies characterizing nocturia and its relationship with lower urinary tract pathology. Multiple studies have previously analyzed UDS findings and diagnoses of DO and BOO.¹² A prevalence for DO of roughly 55% has been reported for women presenting with nocturia undergoing UDS,¹³ similar to our findings (125/210=59.5%). Some differences were observed, in relation to baseline variables. In this study, neurogenic history, such as from multiple sclerosis, did not result in an increased proportion of patients with DO, while this has been previously reported in other studies.¹⁴ Other baseline characteristics were also not captured, such as obesity, cardiovascular disease, and history of childhood enuresis.¹⁵

This study also examined the prevalence of DU in patients presenting with nocturia. In this study, DU relied on the calculation of BCI. Although primarily used for men, this definition has also been applied to women.¹⁶ It is interesting

to note the substantial number of patients in this study with DU alone ($n=69$, 18.7%) or associated with other diagnoses ($n=108$, 29.3%). It should be noted that underactive bladder is an under-reported condition that may present with nocturia.¹⁰ In addition, there was a substantial number of females with no lower urinary tract disorder diagnosed ($n=32$, 15.2%). Though selection and referral criteria may have influenced this figure, this result highlights the need to consider causes of nocturia beyond the lower urinary tract.¹

Upon analysis of nocturia frequency, only an isolated association for early first sensation during UDS in males was identified between patients with less frequent nocturia (2–5x/night) and more frequent nocturia (>5x/night). The interpretation of this is impacted by inaccuracy and recall bias, and the categorization of nocturia frequency as a dichotomous variable, which may reduce the ability to identify an effect; however, the lack of association may also be due to a true

null effect. Many other factors may cause nocturia and, referring to previous studies, nocturia frequency could indicate underlying nocturnal polyuria or a hormone-related cause.¹⁷

Limitations

This study's interpretation is restricted by certain limitations. The retrospective, single-center design produces an inherent selection bias of patients being referred for UDS with potentially more severe underlying pathology. The generalizability of the findings are also limited only to those with nocturia severe enough to seek UDS at a tertiary center. These patients with nocturia likely reflect a subpopulation who are more likely to have complex medical history or are referred after being refractory to primary therapy. The reliance of patient-reported LUTS also limits the accuracy of the findings. Although nocturia definition is often easier using severity thresholds, some patients may be bothered more by fewer symptoms, and novel indices that assess bothersome symptoms may be more reflective of underlying pathology rather than the quantification of nocturia.^{18,19} This study's retrospective data collection through medical records is also subject to limited accuracy, especially pertaining to medical history.

Finally, UDS may not always be available or possible. From this study, it is suggested that clinical presentation alone may guide the workup of a suspected lower urinary tract disorder diagnosis in resource-limited settings, where UDS is not readily available. Furthermore, this study highlights the need to consider alternate diagnoses beyond the lower urinary tract for those presenting with nocturia, especially for women.

Conclusions

Despite its limitations, this study comprehensively analyzed a large cohort of patients and their UDS findings. This study identified a substantial crossover in symptoms across lower urinary tract pathologies, while also further characterizing the relationship between symptoms and lower urinary tract pathology. In addition, age and select medical history may also be useful in identifying underlying pathology. This is helpful when there is limited access to UDS or when patients may be too frail to undergo testing. DU is found in a significant proportion of patients with nocturia, and this has been under-reported in previous literature. The severity of nocturia demonstrated insufficient evidence for differences across gender and subgroups, suggesting the need to choose subsequent treatment based on objective UDS findings rather than reported symptomatology.

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