

Urodynamic findings in patients with nocturia and their associations with patient characteristicsGarson Chan^{1*}, Liang G. Qu^{2,3*}, Johan Gani^{2,4}¹Department of Urology, University of Saskatchewan, Saskatoon, SK, Canada; ²Department of Urology, University of Melbourne, Austin Health, Heidelberg, Victoria, Australia; ³Young Urology Researchers Organisation (YURO), Australia; ⁴Department of Urology, University of Melbourne, Western Health, Footscray, Victoria, Australia

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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 referred for urodynamic testing, with nocturia (waking to void ≥ 2 x/night).

Data on baseline characteristics, symptoms, urodynamic 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**Key Messages**

- In adults presenting with nocturia for urodynamic testing, storage and voiding lower urinary tract symptoms may help differentiate underlying lower urinary tract pathology.
- The quantity of lower urinary tract symptoms 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 under-diagnosed condition.

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.

Introduction

Nocturia is complex and can reflect multiple overlapping aetiologies. The causes may be lower urinary tract, nephrological, hormonal, sleep-related, cardiovascular, fluid intake-related, and medication-related causes.¹ Clinicians may often depend on empirically managing 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 may confirm lower urinary tract pathology such as detrusor overactivity (DO), detrusor underactivity (DU) or bladder outlet obstruction (BOO). Urodynamic testing may be considered in selective pre-surgical 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 have examined the relationship between nocturia frequency and its relationship with urodynamic findings. Potential predictors within risk factors or clinical features that are identified may influence and guide treatment decision making.

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

Methods

This retrospective observational study was based in a single tertiary centre in Melbourne, Australia. Consecutive patients referred to our centre for urodynamic testing over a seven year period from 2012 to 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 urodynamic testing with a presenting complaint of nocturia at time of referral. Patients included often concurrently presented with a cluster of multiple lower urinary tract symptoms, but were included if

nocturia was one of the primary complaints mentioned within the indication section of the urodynamic testing 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 ICS definitions, nocturia was quantified through the use of a bladder diary and required patients to pass urine during the main sleep period.⁵ Urodynamic testing 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 urodynamic study testing.

Data collection

Data was collected through hospital electronic medical records. A list of all patients who underwent urodynamic testing 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 lower urinary tract symptoms (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 Detrusor underactivity (DU) was defined as a BCI ($P_{det}Q_{max} + 5*Q_{max}$) 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-square 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 pre-determined 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 analysed as a dichotomous variable, however, an exploratory analysis was also conducted analysing 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 analysed by pre-determined strata of 2-5x/night or >5x/night. These brackets were chosen to 1) optimise 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 utilised.

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

Results

From January 2012 to December 2019, there were 1322 patients who underwent urodynamic testing at our institution. There were 943 exclusions due to not being 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, $p < 0.001$, 4 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, $p = 0.129$, 7 patients missing). There were altogether 32 women and 1 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 was associated with DO (95.2% vs 76.5%, $p < 0.001$). For men with DO, there were associations for 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, yrs: 69 vs 56, $p < 0.001$). For men, 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 proportion 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, yrs: 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 to 1.41), being male (2.809; 1.70 to 4.65), having storage symptoms (5.19; 2.57 to 10.47), and not having voiding symptoms (0.45; 0.28 to 0.74), were associated with DO. For DU, the model analysed: age, gender, neurogenic history, presence of storage symptoms, and presence of voiding symptoms. Increasing age (1.48; 1.26 to 1.75), not being male (0.58; 0.37 to 0.91), and having voiding symptoms (1.92; 1.23 to 3.01), were associated with DU. For BOO, the model analysed: age, gender, diabetic history, pelvic surgery history, storage symptoms, and voiding symptoms. Decreasing age (0.78; 0.63 to 0.96), being male (7.00; 3.44 to 14.21), and having voiding symptoms (2.09; 1.11 to 3.95), were associated with BOO.

Exploratory regression analysis was performed examining symptoms as a count variables, and other included covariates unchanged (Supplementary Table 1). This supported the associations of more storage and fewer voiding symptoms for DO (Figure 1a & b), 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 to 1.39) (Figure 1d).

A secondary analysis was performed, stratified by frequency of nocturia of 2-5x/night or >5x/night (Supplementary Table 2). 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 versus 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 urodynamic testing-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 urodynamic testing may not be readily available, clinical decision making should rely upon 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 ten 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 ten 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 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

In the context of other studies, these results appear to align with prior studies characterising nocturia and its relationship with lower urinary tract pathology. Multiple studies have previously analysed urodynamic findings and diagnoses of DO and BOO.¹² A prevalence for DO of roughly 55% has been reported for women presenting with nocturia undergoing urodynamic testing,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 underactive bladder is an underreported 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 categorisation 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

This study's interpretation is restricted by certain limitations. The retrospective, single-centre design produces an inherent selection bias of patients being referred for urodynamic studies with potentially more severe underlying pathology. The generalisability of the findings are also limited only to those with nocturia severe enough to seek urodynamic testing at a tertiary centre. 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.

Urodynamic testing may not always be available or possible. From this study, it is suggested that clinical presentation itself may guide the workup of a suspected lower urinary tract disorder diagnosis, in resource-limited settings where urodynamic testing 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.

Nevertheless, this study served to comprehensively analyse a large cohort of patients and their urodynamic findings. This study identified a substantial crossover in symptoms across lower urinary tract pathologies, whilst also further characterising 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 urodynamic testing or when patients may be too frail to undergo testing. Detrusor underactivity is found in a significant proportion of patients with nocturia, and this

has been underreported in previous literature. Severity of nocturia demonstrated insufficient evidence for differences across gender and subgroups, suggesting the need to choose subsequent treatment based on objective urodynamic findings rather than reported symptomology.

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Figures and Tables

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.

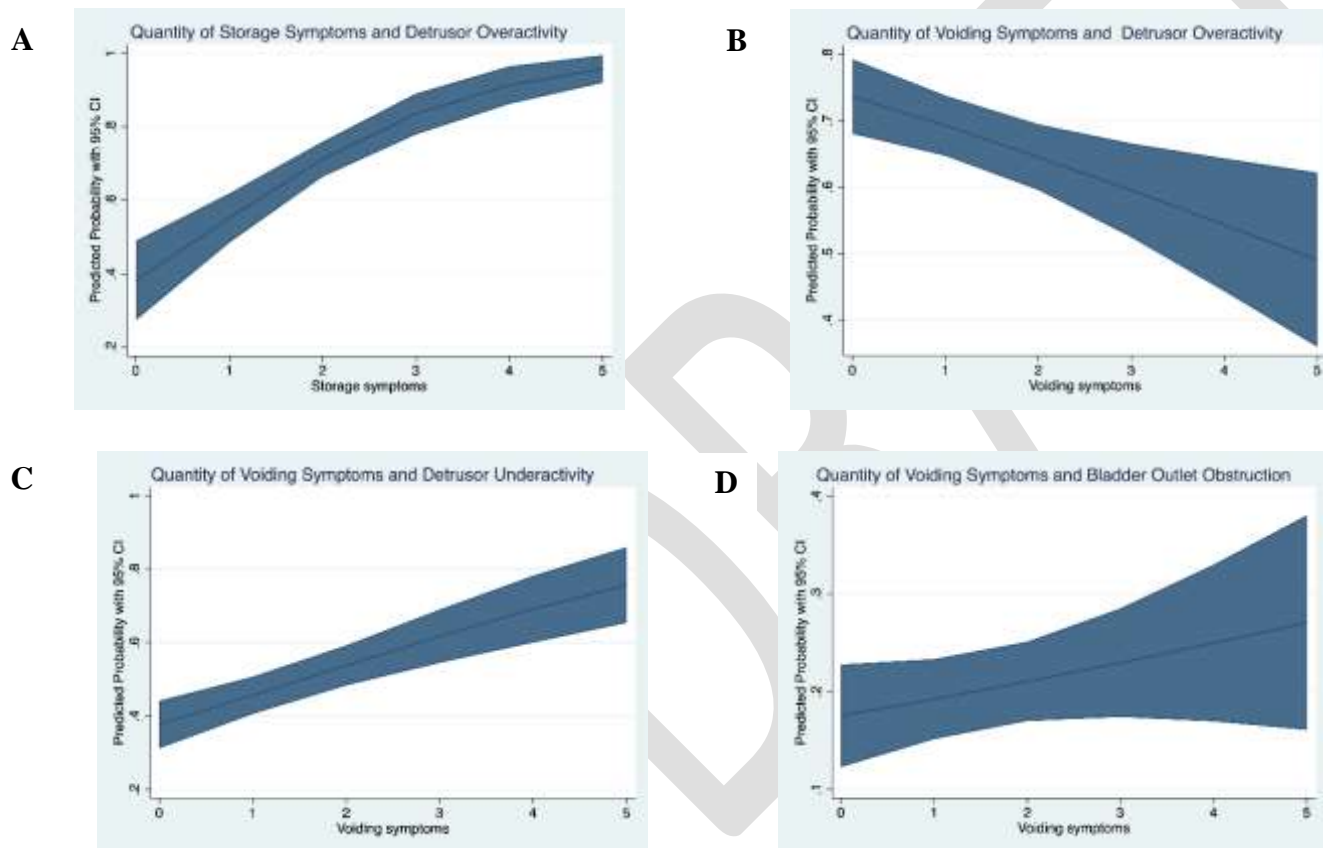


Table 1. Summary table of lower urinary tract disorders by gender, in patients with nocturia			
Diagnosis (n, %)	Females (n=213)	Males (n=159)	Total (n=372)
One diagnosis			
DO	60 (28.4)	44 (27.9)	104 (28.2)
DU	46 (21.8)	23 (14.6)	69 (18.7)
BOO	6 (2.8)	8 (5.1)	14 (3.8)
Two diagnoses			
DO & DU	59 (28.0)	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)

Lower urinary tract disorders are shown, stratified by gender. *Note two female patients missing diagnosis, and one male patient missing diagnosis for this summary table. BOO: bladder outlet obstruction; DO: detrusor overactivity; DU: detrusor underactivity; LUTD: lower urinary tract disease.

Table 2. Baseline characteristics and clinical features, stratified by detrusor overactivity, underactivity, and bladder outlet obstruction in patients with nocturia									
	Detrusor overactivity (DO)			Detrusor underactivity (DU)			Bladder outlet obstruction (BOO)		
Females	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

Baseline characteristics and lower urinary tract symptoms are shown, stratified by those with and without detrusor overactivity, detrusor underactivity, and bladder outlet obstruction. CVA: cerebrovascular accident; IQR, interquartile range.

Table 3. Multivariable logistic regression modelling for detrusor overactivity, underactivity, and bladder outlet obstruction 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.
CI: confidence interval; OR: odds-ratio.

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