

Clinical and Ultrasonographic Predictors of Empirical Treatment Outcomes in Women With Urethral and Lower Urinary Tract Symptoms: A Prospective Cohort Study

Hamdan Siddig Sirag Ahmad¹, Dr Mahmood Ahmed², Ehsan ul Haque³, Huma Sardar⁴, Anum Awais^{5*}, Dr Sehrish Fayyaz⁶, Maha Mohammed Bilal⁷, Fahmida Khatoon⁸

¹ Assistant Professor of Obstetrics and Gynecology, Faculty of Medicine, Najran University, Najran, Saudi Arabia

² Assistant Professor, Department of Urology, Hamdard University Hospital, Karachi, Pakistan

³ Assistant Professor, Department of Urology, Polyclinic Hospital, NUST School of Health Sciences, Pakistan

⁴ Senior Registrar, Department of Paediatric Surgery, Farooq Hospital, Islamabad Branch, Pakistan

⁵ Senior Registrar, Radiology, Services Institute of Medical Sciences, Lahore, Pakistan

⁶ Senior Registrar, Gynecology and Obstetrics, Rai Foundation Teaching Hospital, Sargodha, Pakistan

⁷ Assistant Professor of Family Medicine and Consultant Family Medicine, Najran University, Najran, Saudi Arabia

⁸ Professor, Department of Biochemistry, College of Medicine, University of Ha'il, Saudi Arabia; United Medical College, Pakistan

Corresponding Author: Anum Awais
Anumawais0094@gmail.com

ABSTRACT

Background: Women presenting with urethral and lower urinary tract symptoms (LUTS) often receive empirical treatment, yet predictors of short-term response remain incompletely defined. This study evaluated clinical and ultrasonographic factors associated with treatment outcomes.

Methods: This prospective multicenter cohort included 150 women presenting to Hamdard University Hospital, Karachi, and Rai Foundation Teaching Hospital, Sargodha, Pakistan, between January 2025 and January 2026. Baseline assessment included demographic characteristics, symptom duration, recurrent LUTS, urine culture, International Consultation on Incontinence Questionnaire–Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) score, post-void residual (PVR) urine volume, and bladder wall thickness (BWT). Participants received phenotype-directed empirical therapy and were reassessed after four weeks. Clinical response was defined as a $\geq 50\%$ reduction in ICIQ-FLUTS score without treatment escalation.

Results: Overall, 104 women (69.3%) responded to treatment, whereas 46 (30.7%) were non-responders. Non-responders had higher baseline ICIQ-FLUTS scores, greater PVR, and increased BWT. Independent predictors of non-response were PVR ≥ 50 mL (adjusted OR 4.21, 95% CI 1.84–9.63), symptom duration > 4 weeks (adjusted OR 3.32, 95% CI 1.46–7.55), recurrent LUTS (adjusted OR 2.66, 95% CI 1.16–6.11), BWT ≥ 3.0 mm (adjusted OR 2.48, 95% CI 1.08–5.70), and higher baseline ICIQ-FLUTS score. The final model showed good discrimination (AUC 0.85).

Conclusion: Elevated PVR, prolonged and recurrent symptoms, greater baseline symptom burden, and increased BWT predicted empirical treatment failure. PVR may help identify women requiring earlier diagnostic reassessment and more comprehensive lower urinary tract evaluation.

Keywords: Lower urinary tract symptoms; urethral symptoms; post-void residual; bladder wall thickness; ultrasonography; treatment response

How to cite this article: Hamdan Siddig Sirag Ahmad. Clinical and Ultrasonographic Predictors of Empirical Treatment Outcomes in Women With Urethral and Lower Urinary Tract Symptoms: A Prospective Cohort Study. *Int J Drug Deliv Technol.* 2026;16(85s):1086-1096. DOI: 10.25258/ijddt.16.85s.113.

INTRODUCTION

Lower urinary tract symptoms (LUTS) constitute a broad spectrum of storage, voiding, and post-micturition complaints and are among the most frequently encountered urological problems in women[1]. Storage symptoms have been defined as urinary urgency, urinary incontinence, nocturia, urinary frequency, and voiding/post-micturition symptoms, which have been defined

as hesitancy, reduced urinary stream, straining, incomplete emptying, and post-micturition dribbling[2]. Epidemiological studies show that LUTSs are very common in all age groups and that the prevalence of LUTSs generally increases with age and with metabolic, obstetric and pelvic floor-related risk factors[3].

LUTS can have a significant impact on physical function, sleep, psychological well-being, sexual function, social functioning, and quality of life in addition to urinary symptoms[4]. Women can change their fluid intake, avoid going out or meeting people, limit their job duties, and feel anxious about incontinence or the need to get to the bathroom quickly[5]. Yet, many women who have these symptoms do not seek health care due to embarrassment, normalization of symptoms, fear of invasive investigations, and an expectation that urinary symptoms are a normal part of ageing and childbirth[6].

Diagnosis of women with urethral and lower urinary tract symptoms remains difficult as individual symptoms are not specific and can be caused by a number of different or overlapping pathological processes[7]. UTI, overactive bladder, dysfunctional voiding, bladder outlet obstruction, detrusor underactivity, PFD, GUMM and urethral pain syndromes are all associated with dysuria, frequency, urgency, urethral discomfort, suprapubic discomfort, and micturition incontinence. Thus, clinical symptoms are not a reliable indicator of the underlying functional abnormality, especially in women with persistent or recurrent complaints[9]. Initial evaluation thus depends on thorough history taking, targeted physical examination, urinalysis, past urinary infections and treatments, and systematic characterization of symptom severity[10]. Validated patient-reported measures can enhance the repeatability of this evaluation, by quantifying the effect and frequency of individual symptoms, and not relying solely on a subjective clinical judgment. The International Consultation on Incontinence Questionnaire–Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) was used to assess the filling, voiding, and incontinence symptoms in a standardized way, and has been shown to have good validity and reliability in various populations[12]. It is also validated and available in Urdu language to be used for clinical assessment and research on women with LUTS in Pakistan[13].

In the routine outpatient setting, treatment is often started without invasive studies, based on the clinical signs and symptoms of the patient, when the patient lacks signs and symptoms that requires urgent intervention or immediate invasive investigation. This may include antimicrobial therapy in those who have an uncomplicated presentation; behaviour change and bladder training for storage symptoms; and drug therapy in the right patients with urgency and frequency symptoms. But, there is heterogeneity in

treatment response with the presence of persistent symptoms after initial treatment suggesting the possibility of the wrong initial clinical phenotype, resistant infection, poor bladder emptying, underlying functional disorder, or structural abnormality which need more detailed investigation[16].

Ultrasonography is an important, noninvasive adjunct to clinical examination that can be used to evaluate bladder emptying and to detect selected abnormalities without discomfort and morbidity from catheter-based examinations[17]. Urine PVR is especially important in women with voiding/post micturition symptoms because high PVRs imply that the bladder is emptied inadequately, which can be due to detrusor underactivity, increased outlet resistance or dysfunctional voiding[18].

Current recommendations include PVR measurement as part of the evaluation of female LUTS, and the ultrasonographic measurement is non-invasive and readily repeatable, but there is no single cut-off value that defines clinically significant incomplete emptying in all women[19].

Bladder wall thickness (BWT) by ultrasound measurement has also been studied as a potential non-invasive measure of chronic dysfunction of the LUT[20]. The bladder-wall morphology changes may be interpreted as a bladder remodeling following persistent abnormal bladder activity or increased outlet resistance; however, the measurements depend on the site of the imaging and the degree of bladder filling[17]. Although previous studies have shown differences in BWT between different groups of women with and without uro-dynamic abnormalities, differences in the methodology and diagnostic criteria of BWT have prevented its routine clinical use[18]. Formal urodynamic evaluation is also not reliably replaced by BWT alone, as evidenced by large prospective evaluations of the same; in which the presence of detrusor overactivity is suspected[20].

Although there have been significant progressions in the diagnostic assessment of femal LUTS, relatively few efforts have been made to identify baseline factors that predict for success with initial empirical treatment[9]. Previous studies have focused on prevalence, categorization of symptoms, urinary incontinence or association of symptoms with urodynamic results and not specifically predicted treatment outcome early on[16]. If clinical and ultrasound features could be identified that are associated with non-response, these women might reasonably be considered for urine culture directed therapy,

uroflowmetry, urodynamic testing, cystoscopy, pelvic floor assessment or specialist assessment rather than repeat courses of empirical treatment[19].

Therefore, the present prospective cohort study aimed to evaluate the clinical and ultrasonographic predictors of empirical treatment outcomes in women presenting with urethral and lower urinary tract symptoms[20]. Special attention was given to symptom duration, recurrent LUTS, baseline symptom severity, relevant comorbidities, post-void residual urine volume and bladder wall thickness[19]. We hypothesized that prolonged or recurrent symptoms, greater baseline symptom burden, increased PVR, and ultrasonographic evidence of bladder-wall alteration would be associated with a lower probability of clinical response to initial empirical treatment[20].

Materials and Methods

Study Design and Setting

The study was a prospective multicenter cohort study that was conducted in the Department of Urology, Hamdard University Hospital, Karachi, Pakistan and Department of Gynecology and Obstetrics, Rai Foundation Teaching Hospital, Sargodha, Pakistan between January 2025 and January 2026. The women who presented with urethral or LUTS were consecutively screened and followed prospectively from the time of beginning with standardized symptom-directed empirical management. All participated in the study after giving written informed consent and the study was performed in accordance with the principles of the Declaration of Helsinki.

Sample Size

The sample size was determined assuming about 30% empirical-treatment non-response rate, 95% confidence level and an absolute precision of 7.5%. The minimum calculated sample size was about 143 participants. Considering incomplete follow up and missing data, the target sample was further expanded to 150 women who all underwent baseline clinical and ultrasonographic assessment and were included in the final sample.

Participant Selection

All women ≥ 18 years of age attending either center for one or more urethral or LUTS were eligible. Symptoms presented were dysuria, urinary frequency, urinary urgency, nocturia, suprapubic discomfort, urethral pain/burning, urinary hesitancy, weak urinary stream, urinary straining, sensation of incomplete bladder emptying and post-micturition symptoms. All women who presented with new LUTS, and those with past similar episodes, were eligible, to assess

if recurrent LUTS could be a predictor of treatment response.

Women were excluded from the study if they had fever, known or suspected acute pyelonephritis, clinically significant urinary tract calculi that needed treatment, an indwelling urinary catheter, previous large reconstructive surgery of the urinary tract, advanced pelvic organ prolapse with mechanical bladder outlet obstruction, severe renal impairment or another condition requiring immediate hospitalization, surgery or invasive urological management. Patients who were not able to fill out the symptom questionnaire or four-week follow-up assessment were also excluded.

Baseline Clinical Assessment

A standardised clinical proforma was used to document the demographic details, including age, body mass index, parity, menopausal status, history of diabetes mellitus, hypertension, previous urinary tract infection, history of similar urinary symptoms, previous exposure to antimicrobials, duration of symptoms and predominant presenting symptoms at enrolment. Recurrent LUTS were considered as at least two similar symptomatic episodes in the previous 6 months or at least three in the previous 12 months. Symptoms were categorized by a validated lower urinary tract terminology as storage, voiding and postmicturition. The severity of the symptoms was measured using the International Consultation on Incontinence Questionnaire – Female Lower Urinary Tract Symptoms (ICIQ – FLUTS), which measures filling, voiding and incontinence related symptoms among women[12]. When needed, the validated Urdu version was used to ensure uniformity of understanding among the participants[13].

Laboratory Evaluation

Urinalysis was performed on all participants before starting empirical treatment. The tests done for assessment were the following: Leucocyte esterase, nitrite, microscopic pyuria, microscopic hematuria, proteinuria and glycosuria. Women with an infective clinical phenotype, recurrent symptoms, history of antimicrobial use, diabetes mellitus, or positive urinalysis underwent a clean-catch midstream urine sample for culture and antimicrobial susceptibility testing.

Urine culture results were then compared at follow-up. If there was clinically significant bacterial growth and they became resistant to the first antimicrobial agent prescribed, the therapy was adjusted based on culture and susceptibility results. Culture results were documented as a clinical variable only and not for redefining baseline ultrasonographic predictors.

Ultrasonographic Assessment

A standardized protocol for transabdominal ultrasonography of the urinary tract was performed at baseline at both participating centers. The participants were first tested with a full bladder. Bladder contour, intravesical abnormalities, bladder wall appearance and dilatation of the upper urinary tract were evaluated. When clinically indicated, the kidneys were evaluated for hydronephrosis, calculi and other abnormalities.

For bladder wall thickness (BWT) measurements, the bladder was adequately distended and the wall thickness measured at the anterior wall. Three measurements were taken from the trigone and from regions free of structural abnormalities and the mean value was taken. BWT was analysed continuously and categorically with $BWT \geq 3.0$ mm defined as an increased measurement for exploratory prognostic analysis.

Immediately after spontaneous micturition, post-void residual (PVR) urine volume was measured within 5 min using ultrasonography. Bladder volumes were either automatically calculated by the ultrasound system or by the standard ellipsoid formula if automatic calculation was not possible. A non-invasive method to measure bladder-emptying efficiency in women with LUTS[19] was chosen: ultrasonographic measurement. Analysis was performed continuously and categorically and the prespecified threshold for clinically relevant residual urine was ≥ 50 mL for the primary predictive model.

Empirical Treatment Protocol

No single treatment was used for all the participants, instead initial management was standardized, based on the dominant clinical phenotype. If there were no contraindications women who presented with predominantly dysuria, urinary frequency, urinary urgency and supportive urinalysis results consistent with uncomplicated lower urinary tract infection were prescribed oral nitrofurantoin 100 mg twice daily for 5 days. Subsequent adjustment of the treatment was made based on the results of urine culture and susceptibility.

Behavioral management with fluid optimization, limited excessive caffeine intake, timed voiding and bladder training were provided for women with predominantly storage symptoms (urgency, increase in daytime frequency, nocturia) without bacterial infection. Solifenacin once daily 5 mg was prescribed for four weeks in the presence of moderate to severe symptoms and in the absence of a contraindication.

For women who had predominantly sterile urethral symptoms (discomfort) with few signs of bacteriuria, advice on hydration, avoidance of known bladder irritants and short-term symptomatic treatment, if needed, and behavior modification was provided. Applying appropriate treatment modification and further investigation in patients who developed red-flag features, microbiologically resistant infection, significant worsening of symptoms, and/or evidence of structural urinary tract disease.

Follow-up and Definition of Treatment Outcome

Reassessment was carried out 4 weeks after start of empirical treatment. Presenting symptoms, medication compliance, other treatment needs, adverse events and re-ICIQ-FLUTS scores were obtained at follow-up.

Primary outcome was clinical response on empirical treatment. A responder was defined as a participant with a $\geq 50\%$ decrease in the total ICIQ-FLUTS score from baseline and who did not require rescue treatment, therapeutic class switch due to persistent symptoms, emergency consultation or urological invasive intervention during the four weeks follow-up period. Women who failed to meet the above criteria were considered to be non-responders.

Secondary outcomes included absolute and percentage changes in ICIQ-FLUTS scores and identification of individual clinical and ultrasonographic variables independently associated with treatment non-response.

Predictor Variables

Clinical candidate predictors were prespecified based on age, BMI, menopausal status, DM, LUTS recurrence, previous UTI, duration of symptoms, predominant symptom category, baseline ICIQ-FLUTS score, and urine culture positivity. The PVR volume and bladder wall thickness were the principal ultrasonographic predictors. In the main, multivariable analysis was given special consideration to those symptoms >4 weeks duration, recurrent LUTS, baseline ICIQ-FLUTS severity, $PVR \geq 50$ mL, and $BWT \geq 3.0$ mm.

Statistical Analysis

IBM SPSS Statistics version 29.0 was used to analyze the data. Normality of distribution was tested for continuous variables and normally distributed data were presented as mean $\pm$ standard deviation and skewed data as median and interquartile range. The data of categorical variables were represented in frequencies and percentages.

The independent-samples t test or Mann–Whitney U test was applied to continuous variables and the chi-square test or Fisher exact test was applied to categorical variables, respectively, to compare the baseline characteristics between the responders and non-responders. Paired statistical testing was used to evaluate changes in symptom scores at baseline and follow-up (BF).

Univariable binary logistic regression was first carried out to define factors associated with treatment non-response. All variables that had $p < 0.10$ in univariable analysis and prespecified clinically relevant variables were included in a multivariable logistic regression model. Results are presented as odds ratios (ORs) and adjusted odds ratios (aORs) with 95% confidence intervals. Multicollinearity was examined prior to model creation and highly correlated variables were not included in the final model.

Discriminative performance of the final prediction model was assessed by receiver operating characteristic analysis and the area under the curve (AUC) and 95% confidence interval (CI) reported. The Youden index was used to determine the best probability threshold, with sensitivity and specificity values calculated from this threshold. Hosmer–Lemeshow goodness-of-fit test is used to evaluate the model calibration. All tests were two-sided and $P < 0.05$ was deemed to be statistically significant.

Ethical Considerations

All procedures were voluntary and written informed consent was received from all women prior to participation. Study identifiers were coded and only the research team had access to the identifiable information in order to maintain confidentiality. The study protocol was in accordance with the institutional ethical requirements and the principles of the Declaration of Helsinki. The actual ethics committee approval numbers of the participating institutions should be provided in the final manuscript to be submitted not created or reattributed an ethics committee number.

Results

Participant Characteristics

A total of 150 women completed baseline clinical assessment, ultrasonographic evaluation, empirical treatment, and four-week follow-up and were included in the final analysis. The mean age was 41.5 ± 12.0 years, and the mean body mass index was 27.5 ± 4.7 kg/m². Forty-one women (27.3%) were postmenopausal, 28 (18.7%) had diabetes mellitus and 30 (20.0%) had hypertension. 53 women (35.3%) reported having

recurrent LUTS while 60 (40.0%) reported having LUTS for more than 4 weeks (Table 1).

The most common presenting symptom was urinary frequency (108; 72.0%), followed by dysuria (102; 68.0%), urgency (91; 60.7%), nocturia (72; 48.0%), suprapubic discomfort (60; 40.0%) and sensation of incomplete bladder emptying (45; 30.0%). The mean baseline International Consultation on Incontinence Questionnaire–Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) score was 19.2 ± 5.7 . Fifty-two women (34.7%) had a positive urine culture. Median P VR was 34 mL and 49 women (32.7%) had P VR of ≥ 50 mL. Mean bladder wall thickness was 2.8 ± 0.8 mm, and 60 women (40.0%) had a thickness ≥ 3.0 mm (Table 1).

Table 1. Baseline clinical, laboratory, and ultrasonographic characteristics of the study population

Variable	Total cohort (n=150)
Age, years	41.5 ± 12.0
Body mass index, kg/m ²	27.5 ± 4.7
Postmenopausal status	41 (27.3%)
Diabetes mellitus	28 (18.7%)
Hypertension	30 (20.0%)
Recurrent lower urinary tract symptoms	53 (35.3%)
Symptom duration >4 weeks	60 (40.0%)
Dysuria	102 (68.0%)
Urinary frequency	108 (72.0%)
Urgency	91 (60.7%)
Nocturia	72 (48.0%)
Suprapubic discomfort	60 (40.0%)
Incomplete bladder emptying	45 (30.0%)
Hesitancy or weak stream	31 (20.7%)
Baseline ICIQ-FLUTS score	19.2 ± 5.7

Positive urine culture	52 (34.7%)
Post-void residual urine, mL	34 (16–69)
Post-void residual urine ≥ 50 mL	49 (32.7%)
Bladder wall thickness, mm	2.8 ± 0.8
Bladder wall thickness ≥ 3.0 mm	60 (40.0%)

Treatment Outcomes

At four weeks, 104 of 150 women (69.3%) fulfilled the predefined criteria for clinical response, whereas 46 women (30.7%) were classified as non-responders. The mean ICIQ-FLUTS score decreased from 19.2 ± 5.7 at baseline to 10.2 ± 7.1 at follow-up, corresponding to an overall mean reduction of 9.0 ± 5.2 points.

Among responders, the mean ICIQ-FLUTS score decreased from 17.6 ± 4.8 to 6.7 ± 3.3 , representing a mean reduction of 10.9 ± 4.2 points. In contrast, non-responders demonstrated a smaller reduction from 22.7 ± 5.9 to 18.1 ± 6.2 , corresponding to a mean improvement of 4.6 ± 3.9 points. The difference in symptom-score improvement between the two groups was statistically significant ($p < 0.001$).

Clinical and Ultrasonographic Factors Associated With Treatment Response

Non-responders were significantly older than responders (45.3 ± 12.6 vs 39.8 ± 11.4 years; $p = 0.009$). Diabetes mellitus was also more common among non-responders (28.3% vs 14.4%; $p = 0.043$). Recurrent lower urinary tract symptoms were observed in 60.9% of non-responders compared with 24.0% of responders ($p < 0.001$). Similarly, symptoms persisting for more than four weeks were present in 69.6% versus 26.9%, respectively ($p < 0.001$) (Table 2).

Baseline symptom severity was substantially greater among women who subsequently failed empirical treatment. The mean baseline ICIQ-FLUTS score was 22.7 ± 5.9 among non-responders compared with 17.6 ± 4.8 among responders ($p < 0.001$). Positive urine culture rates, however, were comparable between groups (34.8% vs 34.6%; $p = 0.985$) (Table 2).

Marked differences were observed in ultrasonographic parameters. Median post-void residual urine volume was 76 mL among non-responders compared with 24 mL among responders ($p < 0.001$). A post-void residual volume ≥ 50 mL was identified in 63.0% of non-

responders compared with 19.2% of responders ($p < 0.001$). Mean bladder wall thickness was also greater in non-responders (3.3 ± 0.8 mm vs 2.6 ± 0.6 mm; $p < 0.001$), while bladder wall thickness ≥ 3.0 mm was present in 65.2% and 28.8%, respectively (Table 2).

Table 2. Comparison of clinical and ultrasonographic characteristics between responders and non-responders

Variable	Responders (n=104)	Non-responders (n=46)	p-value
Age, years	39.8 ± 11.4	45.3 ± 12.6	0.009
Body mass index, kg/m ²	27.2 ± 4.5	28.2 ± 5.0	0.226
Postmenopausal status	24 (23.1%)	17 (37.0%)	0.077
Diabetes mellitus	15 (14.4%)	13 (28.3%)	0.043
Hypertension	18 (17.3%)	12 (26.1%)	0.210
Recurrent lower urinary tract symptoms	25 (24.0%)	28 (60.9%)	<0.001
Symptom duration >4 weeks	28 (26.9%)	32 (69.6%)	<0.001
Baseline ICIQ-FLUTS score	17.6 ± 4.8	22.7 ± 5.9	<0.001
Positive urine culture	36 (34.6%)	16 (34.8%)	0.985
Post-void residual urine, mL	24 (12–43)	76 (48–110)	<0.001

Post-void residual urine ≥ 50 mL	20 (19.2%)	29 (63.0%)	<0.001
Bladder wall thickness, mm	2.6 $\pm$ 0.6	3.3 $\pm$ 0.8	<0.001
Bladder wall thickness ≥ 3.0 mm	30 (28.8%)	30 (65.2%)	<0.001

Predictors of Empirical Treatment Non-response

On univariable logistic regression, increasing age, diabetes mellitus, recurrent lower urinary tract symptoms, symptom duration >4 weeks, greater baseline ICIQ-FLUTS score, post-void residual urine ≥ 50 mL, and bladder wall thickness ≥ 3.0 mm were associated with increased odds of treatment non-response. Post-void residual urine ≥ 50 mL demonstrated the strongest unadjusted association with treatment failure, with an odds ratio of 7.16 (95% CI 3.36–15.25; $p < 0.001$) (Table 3).

After multivariable adjustment, post-void residual urine ≥ 50 mL remained the strongest independent predictor of treatment non-response, with an adjusted odds ratio of 4.21 (95% CI 1.84–9.63; $p < 0.001$). Symptom duration >4 weeks was associated with more than threefold higher odds of treatment failure (adjusted OR 3.32, 95% CI 1.46–7.55; $p = 0.004$). Recurrent lower urinary tract symptoms (adjusted OR 2.66, 95% CI 1.16–6.11; $p = 0.021$) and bladder wall thickness ≥ 3.0 mm (adjusted OR 2.48, 95% CI 1.08–5.70; $p = 0.032$) also remained independently associated with non-response (Table 3).

Each five-point increase in baseline ICIQ-FLUTS score was associated with a 51% increase in the adjusted odds of treatment non-response (adjusted OR 1.51, 95% CI 1.08–2.11; $p = 0.016$). Age and diabetes mellitus were no longer statistically significant after adjustment, suggesting that their univariable associations were partly explained by differences in symptom severity, recurrence, and bladder-emptying characteristics (Table 3).

Table 3. Univariable and multivariable predictors of empirical treatment non-response

Predictor	Univariable OR (95% CI)	p -value	Adjusted OR (95% CI)	p -value
Age, per 10-year increase	1.47 (1.10–1.96)	0.009	1.20 (0.86–1.68)	0.285
Diabetes mellitus	2.34 (1.01–5.41)	0.047	1.62 (0.61–4.31)	0.334
Recurrent lower urinary tract symptoms	4.92 (2.35–10.29)	<0.001	2.66 (1.16–6.11)	0.021
Symptom duration >4 weeks	6.20 (2.89–13.29)	<0.001	3.32 (1.46–7.55)	0.004
ICIQ-FLUTS score, per 5-point increase	2.08 (1.50–2.88)	<0.001	1.51 (1.08–2.11)	0.016
Post-void residual urine ≥ 50 mL	7.16 (3.36–15.25)	<0.001	4.21 (1.84–9.63)	<0.001
Bladder wall thickness ≥ 3.0 mm	4.63 (2.22–9.64)	<0.001	2.48 (1.08–5.70)	0.032

The final multivariable model showed good discrimination for empirical treatment non-response with an area under the ROC curve of 0.85 (95% CI 0.79-0.91). The sensitivity was 80.4% and the specificity was 76.0% at the optimal probability threshold. Model fit was acceptable, with no indication that the fit was poor using the Hosmer–Lemeshow test ($p=0.62$).

In overall, high PVR, long duration of symptoms, recurrent LUTS, higher baseline symptom scores, and higher bladder wall thickness were all independently correlated with the failure of empirical treatment. Of all these parameters, the strongest prognostic relationship to non-response was found for $\text{POUR} \geq 50$ mL.

DISCUSSION

The present prospective multicenter cohort study evaluated clinical and ultrasonographic factors associated with short-term response to empirical treatment among women presenting with urethral and lower urinary tract symptoms [1]. Approximately two-thirds of participants achieved the predefined clinical response at four weeks, whereas nearly one-third remained symptomatic or required modification of treatment. Increased post-void residual (PVR) urine volume, longer duration of symptoms, recurrent lower urinary tract symptoms (LUTS), higher baseline ICIQ-FLUTS score, and greater bladder wall thickness (BWT) were independently associated with non-response to treatment. Of these variables, $\text{PVR} \geq 50$ mL showed the highest independent association, with the adjusted odds of non-response being more than four times greater. These findings confirm the heterogeneity of female LUTS, and suggest that relatively simple clinical and ultrasound measurements can be used to identify those women who are unlikely to benefit from initial empirical management [2,3].

The overall response rate of 69.3% confirms the usefulness of symptom guided empirical therapy in a significant number of women with uncomplicated urethral and lower urinary tract symptoms. However, a high non-response rate (30.7%) is clinically significant as repeated empirical treatment without retesting may lead to the failure to diagnose underlying dysfunctional voiding, detrusor abnormalities, recurrent infection, bladder outlet dysfunction and other conditions that need specific investigations. The symptoms of LUTS in women are not mutually exclusive but include all of the following – storage symptoms, voiding symptoms, and post-micturition symptoms – and epidemiological evidence shows significant variation in

prevalence and clinical presentation of LUTS between populations [2]. Therefore, the results of the present study advocate for a non-uniform approach to women with persistent symptoms [3,4].

PVR was the most powerful ultrasonographic predictor identified in this cohort. The adjusted odds ratio (aOR) of $\text{PVR} \geq 50$ mL for treatment non-response was 4.21 when compared with lower PVR [5]. An increase in PVR indicates inefficient bladder emptying and can occur due to decreased detrusor contractility, increased outlet resistance, or dysfunctional pelvic floor relaxation or due to a combination of these mechanisms. According to the current EAE recommendation, PVR should be measured as part of the initial evaluation of women with LUTS, and ultrasonography should be performed due to its favorable risk-benefit ratio [6]. However, there is no universally accepted PVR threshold that defines abnormal emptying in women and thus the threshold of 50 mL in the present study should be considered more as a prognostic cutoff within this population than as a definitive diagnostic threshold [7].

It was also remarkable that there was a correlation between the duration of symptoms and failure to respond to treatment. Women with symptoms for over four weeks were about 3 times more likely to be non responsive [8]. If symptoms continue, this may mean that what appeared to be an uncomplicated primary presentation is a more chronic functional or structural disorder and not a transient event. Prior studies have focused on the importance of the combination of clinical history and symptom characterization to differentiate the various causes of female LUTS, which may overlap, including detrusor underactivity, bladder outlet dysfunction, and overactive bladder [9]. For this reason, prolonged persistence after the expected response to initial treatment should lead to rethinking of the initial clinical phenotype as opposed to empirical retreatment [10].

Favorable treatment outcome was also independently predicted by recurrent LUTS. When other clinical and ultrasonographic factors were taken into account, women with recurrent symptoms were about 2.7 times more likely to be non-responsive. Recurrent presentations may be due to repeated bacterial infection or due to incomplete bladder emptying, pelvic floor dysfunction, genitourinary changes due to menopause, or metabolic disorders or chronic bladder hypersensitivity. It is important to get a detailed prior urinary history at baseline and not just the history of the current symptomatic

episode, as recurrent symptoms were found to be independently associated with non-response [10,11].

Each 5 point increase in baseline ICIQ-FLUTS score was independently associated with increased adjusted odds of non-response by 51%. Structured symptom instruments may then be useful for providing prognostic information as well as the baseline level of symptom burden. ICIQ-FLUTS assesses filling, voiding symptoms and captures incontinence symptoms, and provides a standardized assessment across patients [12]. It has been validated for Urdu, and has shown high internal consistency as well as test-retest reliability among Pakistani women, making it suitable for the population assessed in the current study [13].

There was also an independent association between BWT and empirical treatment failure, but this finding should be interpreted with some caution. The adjusted odds of non-response were around 2.5 times higher among women with BWT ≥ 3.0 mm [14]. Theoretically, these chronic changes in detrusor workload and bladder remodeling can lead to increased wall thickness, but the measurement of BWT by ultrasound is highly dependent on the bladder volume, the measurement site, the ultrasound technique and the operator [15]. Previous studies have shown only limited diagnostic value of BWT for the diagnosis of detrusor overactivity in women and recent evidence also showed that BWT had no role in the substitution of formal urodynamic assessment [10].

Thus, the BWT finding should be regarded as a prognostic exploratory association, but not as a new diagnostic cut-off [16]. Current guidance reports that no consistent correlation has been found between an increase in BWT or DWT and OAB or FBOO and there is also a lack of standardization of bladder volume requirements for these measurements [17]. With this in mind, BWT ≥ 3.0 mm can provide information in conjunction with clinical variables and PVR, but should not be used alone. Before this parameter can be used in routine prediction strategies, external validation with standardized bladder filling and imaging protocols will be necessary [18].

Interestingly, there was no relationship between a positive urine culture at baseline and response to treatment. There was a very similar culture positivity rates between responders and non-responders [19]. An explanation is that microbiological results allowed for subsequent antimicrobial modification if necessary and thus,

lessened the impact of the baseline culture status on four week outcome. Further, infectious and non-infectious mechanisms can lead to dysuria, urgency, frequency and urethral discomfort. For this reason, symptoms that persist after appropriate antimicrobial therapy should be a clue to consider another cause of lower urinary tract pathology before re-exposing to antimicrobial therapy for the same symptoms [14].

In univariable analysis, age and diabetes mellitus were correlated with non-response, but were not statistically significant following multivariable adjustment. This indicates that their apparent effects may have been mediated in part because of an increased symptom burden, recurrence, longer symptom duration or impaired bladder emptying [17]. An association with increasing age and metabolic comorbidities has been found with female LUTS in the past, however this association does not necessarily indicate the underlying mechanism of treatment failure [3]. The current findings are therefore in favour of direct assessment of urinary characteristics, especially symptom history and PVR, instead of only taking into account demographic risk factors [18].

The combined multivariable model had good discrimination, with an ROC AUC of 0.85, sensitivity of 80.4%, and specificity of 76.0% for discriminating women who did or did not respond to empirical therapy. Importantly, the model included variables that can be largely acquired with routine outpatient assessment without invasive testing. This approach may result in the identification of women who should be offered earlier uroflowmetry, culture-directed management, pelvic examination, urodynamic evaluation, cystoscopy, or specialist reassessment. The relevance of urodynamic testing is especially high when there is diagnostic uncertainty or when there is anticipation that the urodynamic results will influence further invasive management [19].

The study features a number of strengths. It was designed to be a prospective multicenter study that included patients from both urology and gynecology departments from two geographically different cities in Pakistan to achieve better clinical representation. Independent prognostic factors were further assessed by standardized symptom assessment, objective PVR measurement, predefined treatment-response criteria, and multivariate analysis. Additionally, employing a locally validated symptom questionnaire boosted the suitability of outcome evaluation in the study population [13].

There are also several drawbacks to be taken into account. The number of samples was moderate, and no external validation was done, so the performance of the predictive model might be lower in independent populations [15-18]. Empirical therapy was not identical for all participants and was based on phenotype. The filling of the bladder and the technical skills of the operator might have affected BWT measurement, and the cut-off value of 3.0 mm is still experimental and has not been confirmed in all situations. There was no systematic use of uroflowmetry and invasive urodynamic testing for the mechanistic classification of elevated PVR. Lastly, follow-up was limited to 4 weeks, so the study could not address whether any of the identified predictors are related to long-term recurrence of symptoms or long-term lack of treatment success [20].

In larger populations, the present model should be externally validated in future multicenter investigations and continuous measurements of PVR and BWT should be evaluated in addition to only dichotomized measurements. Selective urodynamic phenotyping, bladder voiding efficiency, uroflowmetry and standardized bladder-volume protocols could also help to better understand the mechanisms of treatment failure. Prospective evaluations should also assess if the implementation of a risk-based pathway to prompt earlier evaluation leads to a decrease in repeated empirical therapy, persistence of symptoms, healthcare utilization or time to definitive diagnosis [19,20].

CONCLUSION

Approximately 30% of women presenting with urethral and lower urinary tract symptoms did not achieve a satisfactory response to initial empirical treatment. Among the non-independent factors, the strongest predictor of treatment non-response was post-void residual urine (PVR) ≥ 50 mL followed by symptom duration >4 weeks, recurrent LUTS, greater baseline ICIQ-FLUTS severity and bladder wall thickness (BWT) ≥ 3.0 mm. These results indicate that a structured clinical assessment plus non-invasive PVR measurement could help with earlier identification of women who need more detailed diagnostic assessment. BWT can be an exploratory parameter, although BWT may give additional information of prognosis.

REFERENCES:

1. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn.* 2002;21(2):167-178. doi:10.1002/nau.10052.
2. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association/International Continence Society joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn.* 2010;29(1):4-20. doi:10.1002/nau.20798.
3. Tahra A, Bayrak O, Dmochowski R. The epidemiology and population-based studies of women with lower urinary tract symptoms: a systematic review. *Turk J Urol.* 2022;48(2):155-165. doi:10.5152/tud.2022.21325.
4. Milsom I, Kaplan SA, Coyne KS, et al. Effect of bothersome overactive bladder symptoms on health-related quality of life, anxiety, depression, and treatment seeking in the United States: results from EpiLUTS. *Urology.* 2012;80(1):90-96. doi:10.1016/j.urology.2012.04.004.
5. Bilgic D, Beji NK. Lower urinary tract symptoms in women and quality of life. *Int J Urol Nurs.* 2010;4(3):97-105. doi:10.1111/j.1749-771X.2010.01100.x.
6. Liang S, Li J, Chen Z, et al. Prevalence and influencing factors of help-seeking behavior among women with urinary incontinence: a systematic review and meta-analysis. *J Womens Health (Larchmt).* 2023;32(12):1363-1379. doi:10.1089/jwh.2022.0482.
7. Nambiar AK, Arlandis S, Bø K, et al. European Association of Urology guidelines on the diagnosis and management of female non-neurogenic lower urinary tract symptoms. Part 1: diagnostics, overactive bladder, stress urinary incontinence, and mixed urinary incontinence. *Eur Urol.* 2022;82(1):49-59. doi:10.1016/j.eururo.2022.01.045.
8. Meier K, Padmanabhan P. Female bladder outlet obstruction: an update on diagnosis and management. *Curr Opin Urol.* 2016;26(4):334-341. doi:10.1097/MOU.0000000000000303.
9. Kuo HC. Clinical symptoms are not reliable in the diagnosis of lower urinary tract dysfunction in women. *J Formos Med Assoc.* 2012;111(7):386-391. doi:10.1016/j.jfma.2011.05.014.
10. El-Tholoth HS, Alsulihem A. Bladder outflow obstruction in women: clinical and

- basic evaluation. *Neurourol Urodyn.* 2025;44(1):69-75. doi:10.1002/nau.25386.
11. Uren AD, Cotterill N, Pardoe M, et al. The International Consultation on Incontinence Questionnaires (ICIQ): an update on status and direction. *Neurourol Urodyn.* 2020;39(6):1889-1896. doi:10.1002/nau.24437.
12. Angelo PH, Queiroz NA, Leitão ACR, et al. Validation of the International Consultation on Incontinence Modular Questionnaire–Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) into Brazilian Portuguese. *Int Braz J Urol.* 2020;46(1):53-59. doi:10.1590/S1677-5538.IBJU.2019.0234.
13. Habiba U, Ikram M, Noor R, et al. Urdu translation and validation of the International Consultation on Incontinence Questionnaire–Female Lower Urinary Tract Symptoms (ICIQ-FLUTS). *Int Urogynecol J.* 2023;34(7):1423-1428. doi:10.1007/s00192-022-05373-5.
14. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis.* 2011;52(5):e103-e120. doi:10.1093/cid/ciq257.
15. Cameron AP, Chung DE, Dielubanza EJ, et al. The AUA/SUFU guideline on the diagnosis and treatment of idiopathic overactive bladder. *Neurourol Urodyn.* 2024;43(8):1742-1752. doi:10.1002/nau.25532.
16. Bodmer NS, Wirth C, Birkhäuser V, et al. Randomised controlled trials assessing the clinical value of urodynamic studies: a systematic review and meta-analysis. *Eur Urol Open Sci.* 2022;44:131-141. doi:10.1016/j.euros.2022.08.013.
17. Latthe P, Middleton L, Rachaneni S, et al. Ultrasound bladder wall thickness and detrusor overactivity: a multicentre test accuracy study. *BJOG.* 2017;124(9):1422-1429. doi:10.1111/1471-0528.14503.
18. Ruggeri G, Hoehn D, Villiger AS, et al. Clinical relevance and symptom burden associated with elevated post-void residual urine in women: a cohort study. *Int Urogynecol J.* 2026. doi:10.1007/s00192-026-06712-6.
19. Arlandis S, Bø K, Cobussen-Boekhorst H, et al. European Association of Urology guidelines on the management of female non-neurogenic lower urinary tract symptoms. Part 2: underactive bladder, bladder outlet obstruction, and nocturia. *Eur Urol.* 2022;82(1):60-70. doi:10.1016/j.eururo.2022.01.044.
20. Lemmon B, Patel M, Fernando R, et al. Systematic review and meta-analysis of bladder wall thickness for the diagnosis of detrusor overactivity in women. *Int Urogynecol J.* 2026. doi:10.1007/s00192-026-06634-3.