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Association Between Lower Urinary Tract Symptoms and Frailty in Older Men Presenting for Urologic Care

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Abstract

Objectives—To evaluate the association between non-neurogenic lower urinary tract symptoms (LUTS) and frailty among treatment-seeking older men.

Methods—This is a cross-sectional study of male patients age 65 years and older presenting to an academic urology practice between December 2015 and March 2019. Men with cancer, neurologic disease, indwelling catheter, or continuous leakage were excluded. Participants completed a Timed-Up-and-Go-Test (TUGT) which was used to categorize men as fast (≤10s), intermediate (11-14s), or slow (≥15s). Participants with the following diagnoses were identified using billing codes extracted from the electronic medical record: overactive bladder (OAB), benign prostatic hyperplasia (BPH), mixed OAB/BPH, or non-LUTS urologic condition. Multivariable associations were evaluated using multinomial logistic regression models adjusted for age, race, and BMI.

Results—Among 2206 men included in our sample, 64% were fast (mean TUGT time: 8.3±1.2 seconds), 25% were intermediate (mean TUGT time: 12.0±1.0 seconds), and 11% were slow (mean TUGT time: 18.5±4.7 seconds). Subjects with slow TUGT times were more likely to be older, non-White, and have LUTS. Compared to non-LUTS conditions, OAB (odds ratio (OR)=2.62, 95% CI 1.74, 3.93), BPH (OR=1.70, 95% 1.14, 2.55), and mixed OAB/BPH (OR=1.82, 95% 1.14, 2.92) were all associated with increased odds of slow TUGT time. LUTS diagnosis was not significantly associated with intermediate TUGT time.

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Conflict of Interest: None

Summary for twitter: Male lower urinary tract symptoms are associated with greater frailty defined by slower Timed-Up-And-Go times

Conclusions—LUTS diagnosis, particularly OAB, is associated with increased odds of slow TUGT time, a surrogate of frailty, compared to non-LUTS conditions. Frailty is common among older men with LUTS and should be considered during the initial urological evaluation.

Keywords

overactive bladder; benign prostatic hyperplasia; lower urinary tract symptoms; gait speed; Timed Up and GoTest (TUGT)

INTRODUCTION

Lower urinary tract symptoms (LUTS) affect more than half of men over age 65[1], leading to reduced health-related quality of life[2] and increased risk of falls[3] and mortality[4]. LUTS in older men are multifactorial with overlapping urologic and non-urologic causes and both physical and psychological manifestations.[5] The difficulty of accurately diagnosing and precisely treating this complex urologic syndrome has motivated investigations of novel age-related LUTS risk factors, such as frailty. The phenotype of frailty is defined as "a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, causing vulnerability to adverse outcomes."[6,7] Two clinical hallmarks of frailty are weakness and slowness, which our group has previously demonstrated are both associated with storage LUTS (with and without urinary incontinence) among older women.[8,9] However, it remains unknown if LUTS, overall or specific subtypes, are similarly associated with frailty among older men.

Increasing age is one of the strongest LUTS risk factors.[1] Several neural and genitourinary changes that contribute to LUTS occur with increasing age and possibly increasing frailty, such as reduced bladder capacity, increased bladder sensation and heightened activation of the anterior cingulate cortex, changes in neurotransmitters and related mediators and receptors, and elevated inflammatory markers.[10] LUTS also interfere with exercise routines among older adults and low physical activity increases risk of both frailty and LUTS.[11,12] A better understanding of how frailty is related to LUTS will inform whether these two age-related conditions are likely to co-occur independent of age, however, few studies have examined this relationship in men.[13–15]

To address this knowledge gap, we evaluated the association between LUTS diagnosis and frailty, using the Timed-Up-and-Go Test (TUGT) as a surrogate for frailty. Data from the University of California, San Francisco Geriatric Urology Database (UCSF-GUD) among male patients age 65 years and older presenting to a single academic urology clinical practice was used for this analysis. We hypothesized that older men seeking treatment for LUTS, and particularly OAB, would have slower TUGT times compared those with other benign urologic diagnoses.

METHODS

Study Participants

We used data from the UCSF-GUD collected from December 2015 to March 2019. The UCSF-GUD is an IRB approved, prospective database of subjects age 65 years and older

who present to our adult non-oncologic urology clinical practice, the details of which are previously described.[9] Briefly, data are regularly extracted from the electronic medical record (EPIC, Verona, WI) using extract, transform, and load (ETL) routines via a clinical data reporting database and datamart.

LUTS Diagnosis

LUTS diagnosis was extracted in the form of International Classification of Diseases 10th Revision (ICD-10) codes listed in the Supplemental Table 1. After an initial screen of 2206 men, we identified 206 with ICD-10 codes that indicated a LUTS diagnosis that could not be clearly separated into BPH or OAB (e.g. R39.9 Unspecified symptoms and sings involving the genitourinary system). In order to obtain more information regarding the types of subjects within this subgroup, we conducted a chart review for 20 men with these codes and found that 85% (17 out of 20) had mixed BPH/OAB, 10% (2 out of 20) had cancer that was not listed in their problem list, and 5% (1 out of 20) had another benign urologic condition (nephrolithiasis). Based on this chart review, we determined a final list of ICD-10 codes used to classify men as being diagnosed with BPH, OAB, mixed BPH/OAB, or non-LUTS condition (includes all other benign urologic conditions), which were treated as mutually exclusive categories.

Other Covariates

Additional covariates were extracted from the electronic medical record using direct queries for exclusion criteria or to adjust for confounding. Age, race, and body mass index were all extracted based on the same encounter date as the exposure and outcome assessment.

Frailty Assessment

Frailty was assessed using the surrogate measure of TUGT time, which requires assimilation of several elements including understanding and following directions, transferring from a seated to a standing position (and vice versa), walking speed, strength, and balance. TUGT is single item measure that predicts post-operative complications and 1-year mortality across surgical sub-specialities[16,17], has high sensitivity and specificity for frailty[18], and has been used in several prior studies of various urologic conditions[9,19]. To complete the TUGT, patients were instructed to stand up from a chair, walk 10 feet at their usual pace (premeasured and indicated with a mark on the floor, assistive devices such as canes or walkers are permitted), turn around, walk back to their chair, and sit down. TUGT is completed as a standard assessment in our urology practice, along with vital signs, for all visits with patients age 65 years and older. TUGT times are recorded by medical assistants in the patients' electronic medical record. Patients who are non-ambulatory at the time of their visit or refused to participate were excluded. Based on measured TUGT times and previously validated thresholds[17], participants were classified as fast (≤10 seconds), intermediate (11 to 14 seconds), and slow (≥15 seconds), with slower times corresponding to greater frailty.

Data Analysis

For this study, 2947 men with complete data met inclusion criteria. We then excluded men who had a documented history of cancer (n = 500) or neurologic disease (n = 143) on their electronic medical record problem list. We also excluded men with a chronic indwelling catheter or continuous urine leakage (n = 98) due to these conditions masking OAB or BPH symptoms.

We first compared distributions of demographic and clinical factors across categories of TUGT time using Chi-square tests for categorical variables and Kruskal Wallis test for continuous variables. We then used multivariable multinomial regression model to estimate odds ratios and 95% confidence intervals (CI) for the association between the 4-level primary independent variable – primary urologic diagnosis (BPH, OAB, mixed BPH/OAB, non-LUTS condition) – and the 3-level categorical outcome – TUGT time (fast, intermediate, slow). To adjust for confounding, we included age (continuous, per 5 years), race (White, Asian, Black, or Other), and body mass index (BMI; <25, 25 to <30, and ≥30 kg/m^2) in the final multivariable models. We did not adjust for comorbidities because frailty is the consequence of many different disease processes and we were interested in evaluating associations that encompass all possible reasons for co-occurrence, rather than independent from individual comorbidities. $P<0.05$ was considered statistically significant. All analyses were performed using STATA version 15.1 (StataCorp LLC, College Station, TX).

RESULTS

Baseline demographic and health-related characteristics of the 2206 men in the analytic sample are reported in Table 1. Based on TUGT times, 64% of participants were categorized as fast (≤10 seconds; mean 8.3 ±1.2), 25% were categorized as intermediate (11 to 14 seconds; mean 12.0 ±1.0), and 11 % were categorized as slow (≥15 seconds; mean 18.5 ±4.7). Compared to men with faster TUGT times, men with slower TUGT times were more likely to be older (mean age 79 ± 7 compared to 71 ± 5 years; $P<0.001$) and non-White (25% compared to 55%; $P<0.001$). The percentage of subjects with fast TUGT times who had a diagnosis of BPH, OAB, and mixed BPH/OAB was 14%, 11%, and 12% compared to 22%, 25%, and 16% among men with slow TUGT times frail men.

In multivariable adjusted models, each LUTS diagnosis (OAB, BPH, and mixed OAB/BPH) was independently associated with slower TUGT times. Compared with other non-LUTS urologic diagnoses, men with BPH were 1.7 times more likely to have slow TUGT times (OR = 1.70, 95% 1.14, 2.55), men with OAB were 2.62 times more likely to have slow TUGT times (OR = 2.62, 95% CI 1.74, 3.93), and men with mixed OAB/BPH were 1.82 times more likely to have slow TUGT times (OR = 1.82, 95% 1.14, 2.92), compared to men with fast TUGT times. OAB, BPH, and mixed OAB/BPH diagnosis were not significantly associated with intermediate TUGT times. Older age, non-White race, and higher BMI were positively associated with higher odds of intermediate and slow TUGT times.

DISCUSSION

In this study, we found that older men presenting to an academic non-oncologic urology clinic with non-neurogenic LUTS were more likely to be frail, based on slow TUGT times, compared to older men with non-LUTS urologic diagnoses. This positive association was independent of age, race, and BMI and strongest for older men with OAB, but was also observed for men with BPH and mixed OAB/BPH. These results suggest that there is a high co-occurrence of non-neurogenic LUTS and frailty among older men seeking care from academic urologists. Therefore, screening older men with LUTS for frailty using a single item surrogates, such as the TUGT, is appropriate when the presence of frailty would alter work-up or treatment recommendations.

Our findings are consistent with the few prior studies examining the association between LUTS and frailty, but few studies have focused on older men and male LUTS subtypes. Among 492 community-dwelling older men enrolled in the Aging Study of PyeongChang Rural Area, the prevalence of frailty (defined by a frailty phenotype that includes slow gait speed, exhaustion, low physical activity, weakness, and weight loss) was 7% among men with none/mild LUTS, 16% among men with moderate LUTS, and 43% among men with severe LUTS.[13] LUTS subtypes were not evaluated separately in this study. Among 710 Japanese adults age 60 years or older enrolled in the Iwaki Health Promotion Project, three frailty measures were examined in relation to overall LUTS (defined as IPSS ≥8), OAB (defined as OAB Symptom Score ≥6), and nocturia (defined as >1 void/night) in a cross-sectional analysis. The frailty discriminant score was positively associated with LUTS (adjusted OR = 2.13, 95% Cl 1.48, 3.06) and OAB (adjusted OR = 2.07, 95% Cl 1.31,3.29) and all frailty measures were associated with higher odds of nocturia.[15] Among 350 community-dwelling Japanese adults age 75 years or older enrolled in the Sukagama Study, each standard deviation of slower gait speed was associated with higher odds of overactive bladder (adjusted OR = 1.47, 95% CI 1.11, 1.95), urinary urgency (adjusted OR = 1.35, 95% CI 1.04, 1.74), and urgency urinary incontinence (adjusted OR = 1.40, 95% CI 1.06, 1.84).[14] Our group also published one the first studies to demonstrate a strong association between slower TUGT times and OAB among older adults (adjusted OR for = 3.0, 95% 2.0, 4.8)[9], however this study examined both men and women which precludes comparisons across male LUTS subtypes. Our current study contributes to the existing evidence by specifically focusing on older men seeking treatment at an academic non-oncologic urology clinic and evaluating male LUTS subtypes, including both OAB and BPH.

Although there is growing evidence that these conditions commonly co-occur, it remains unknown if LUTS precedes frailty or frailty precedes LUTS and there are proposed mechanisms for both temporal directions. As humans age and in some cases become frail, multiple age-related changes occur in the genitourinary tract, nervous system, and immune system that could cause LUTS, particularly OAB.[10] Frailty could also contribute to LUTS by limiting behaviors that are known to reduce the risk of LUTS or LUTS progression, such as regular physical activity.[20,21] Conversely, LUTS interfere with employment, willingness to leave the house or travel, social connections, and hobbies which promote physical activity and are protective against developing frailty.[2223] Lastly, LUTS and frailty may be caused by a shared mechanism. Insulin resistance[24] and inflammatory markers[25] that increase with age

are associated with risk of both frailty and LUTS or LUTS progression. Additional studies are needed to determine if LUTS and frailty co-occur because they contribute to each other or they are caused by a shared mechanism.

The effect of LUTS interventions on frailty and frailty interventions on LUTS remains unknown and is an important area of future research.[26] In the meantime, frailty may be important to consider during LUTS evaluations since frail older men are more likely to suffer from adverse drug reactions[27] and new LUTS medications will inherently contribute to polypharmacy. Preliminary data from our group and others among predominantly older frail women have demonstrated acceptable efficacy and safety of b3-adrenoceptor agonists[28] and onabotulinumtoximA and sacral neuromodulation[19]. However, given the higher burden of LUTS among older frail men, their lack of representation in LUTS intervention trials remains problematic.

We recognize several limitations to our study. TUGT time is one of several markers of frailty, however TUGT is a highly feasible measure for clinical settings and is consistently associated with adverse surgical outcomes among older adults.[16,17] LUTS diagnosis and subtype was defined using ICD-10 codes which are designed for billing purposes but have been widely used in clinical urology research.[29,30] The study population was recruited from a single academic non-oncologic urology clinic and therefore may not be generalizable to the general population, however the population seeking care at other academic centers is likely similar. Lastly, unmeasured confounding is always possible with observational data and could lead to falsely positive associations if an unmeasured variable, such as physical activity, is positively associated with both the LUTS and frailty.

In conclusion, the prevalence of frailty based on slow TUGT times is higher among older men seeking treatment at an academic non-oncologic urology clinic for non-neurogenic LUTS, particularly OAB, compared to other diagnoses. Older men with frailty may suffer from a higher burden of LUTS despite their lack of representation in most LUTS intervention trials. Given their high co-occurrence among men seeking urological specialty care, additional research is needed to determine which LUTS treatments are most effective among older men with frailty.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline characteristics of 2206 men in an academic non-oncologic urology clinic registry, stratified by Timed-Up-and-Go Test time.

	TUGT Category (time in seconds)			
Characteristic	**Fast (≤10s)**	**Intermediate (11-14s)**	**Slow (≥15s)**	**P-value***
Total, N (%)	1408 (64)	549 (25)	249 (11)	
Age, mean ± SD	71 ± 5	75 ± 7	79 ± 7	0.0001
Age group, N (%)				<0.001
65-69	617 (44)	144 (26)	33 (13)	
70-74	439 (31)	154 (28)	39 (16)	
75-79	228 (16)	121 (22)	69 (28)	
≥80	124 (9)	130 (24)	108 (43)	
Race, N (%)				<0.001
White	1051 (75)	334 (61)	111 (45)	
Asian	125 (9)	85 (15)	71 (29)	
Black	45 (3)	25 (5)	16 (6)	
Other	187 (13)	105 (19)	51 (20)	
BMI, mean ± SD	27 ± 4	27 ± 5	27 ± 5	0.16
BMI category, N (%)				0.16
<25 kg/m^2	516 (34)	182 (33)	100 (40)	
25 to <30 kg/m^2	612 (43)	246 (45)	92 (37)	
≥30 kg/m^2	280 (20)	121 (22)	57 (23)	
Primary Urologic Diagnosis, N (%)				<0.001
Benign Prostatic Hyperplasia (BPH)	201 (14)	94 (17)	56 (22)	
Overactive Bladder (OAB)	150 (11)	82 (15)	61 (25)	
Mixed OAB/BPH	166 (12)	66 (12)	39 (16)	
Non-LUTS condition	891 (63)	307 (56)	93 (37)	
TUGT, mean ± SD	8.3 ± 1.2	12.0 ± 1.0	18.5 ± 4.7	

TUGT Timed Up and Go Test; s seconds; N sample size; SD standard deviation; BMI body mass index; kg kilogram; m meter

*P values calculated using Chi-square tests for categorical variables and Kruskal Wallis test for continuous variables.

Table 2.

Association of lower urinary tract symptom diagnosis with Timed-Up-and-Go Test time among 2206 men in an academic non-oncologic urology clinic registry.

		Multinomial Odds Ratio (95% Confidence Interval)*			
Characteristic	**Total, N (%)**	**Intermediate (11-14s) vs Fast (≤10s)**	***P*-value**	**Slow (≥15s) vs Fast (≤10s)**	***P*-value**
Age, per 5 years	2206 (100)	1.59 (1.46, 1.74)	<0.001	2.36 (2.10, 2.66)	<0.001
Race					
White (Ref.)	1496 (68)	1.00		1.00	
Asian	281 (13)	2.27 (1.65, 3.13)	<0.001	5.34 (3.58, 7.99)	<0.001
Black	86 (4)	2.06 (1.24, 3.42)	0.005	4.18 (2.16, 8.09)	<0.001
Other	343 (16)	1.91 (1.44, 2.53)	<0.001	2.99 (1.97, 4.55)	<0.001
BMI category					
<25 kg/m^2 (Ref.)	798 (36)	1.00		1.00	
25 to <30 kg/m^2	950 (43)	1.36 (1.07, 1.72)	0.12	1.24 (0.87, 1.75)	0.24
≥30 kg/m^2	458 (21)	1.73 (1.29, 2.32)	<0.001	2.67 (1.75, 4.08)	<0.001
Primary Urologic Diagnosis					
Non-LUTS condition (Ref.)	1291 (59)	1.00		1.00	
BPH	351 (16)	1.08 (0.81, 1.44)	0.60	1.70 (1.14, 2.55)	0.01
OAB	293 (13)	1.30 (0.95, 1.78)	0.10	2.62 (1.74, 3.93)	<0.001
Mixed OAB/BPH	271 (12)	1.03 (0.74, 1.43)	0.87	1.82 (1.14, 2.92)	0.01

N sample size; s seconds; BMI body mass index; BPH benign prostatic hyperplasia; kg kilogram; m meter; OAB overactive bladder

*Odds ratios and p-values calculated via multivariable multinomial regression models adjusted for all other covariates listed in table.