

Urologic symptoms and burden of frailty and geriatric conditions in older men: the Aging Study of PyeongChang Rural Area

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Purpose: Frailty is an important consideration in the management of lower urinary tract symptoms and erectile dysfunction in older men; frailty increases vulnerability to treatment-related adverse outcomes, but its burden is not known. The authors aimed to examine the burden of frailty and associated geriatric conditions in community-dwelling older men.

Patients and methods: A cross-sectional study was conducted with 492 community-dwelling older men (mean age, 74.2 years; standard deviation, 5.6 years). All the participants were administered the International Prostate Symptom Score (IPSS) (range: 0–35) and a five-item version of the International Index of Erectile Function (IIEF-5) (range: 5–25). Frailty phenotype was assessed based on exhaustion, inactivity, slowness, weakness, and weight loss. Prevalence of frailty phenotype and geriatric conditions were assessed by the IPSS severity category (mild, 0–7; moderate, 8–19; severe, 20–35 points) and the first IIEF-5 question, which assesses the confidence in erectile function (low, 1–2; moderate, 3; high, 4–5 points).

Results: Older men with severe urologic symptoms had a high prevalence of frailty. According to the IPSS questionnaire, the prevalence of frailty was 7.3% (21/288) in the mild category, 16.3% (26/160) in the moderate category, and 43.2% (19/44) in the severe category. Participants in the severe IPSS category showed high prevalence of disability (45.5%), multimorbidity (43.2%), malnutrition risk (40.9%), sarcopenia (40.9%), and polypharmacy (31.8%). According to erectile confidence based on the first IIEF-5 question, the prevalence of frailty was 18.7% (56/300) for low confidence, 5.3% (6/114) for moderate confidence, and 5.1% (4/78) for high confidence. Participants with low confidence in erectile function showed high prevalence of sarcopenia (39.0%), multimorbidity (37.7%), disability (35.7%), malnutrition risk (33.3%), and polypharmacy (23.0%).

Conclusion: The prevalence of frailty and geriatric conditions was higher in older men with severe urologic symptoms. A frailty screening should be routinely administered in urology practices to identify older men who are vulnerable to treatment-related adverse events.

Keywords: erectile dysfunction, frailty, geriatric assessment, lower urinary tract symptoms, risk management

Introduction

Lower urinary tract symptom (LUTS) and erectile dysfunction (ED) are highly prevalent and negatively associated with the quality of life in older men.¹ The prevalence of moderate to severe LUTS is 46% in the United States, with an increasing prevalence and severity into the 5th decade of life.² Meanwhile, ED affects 30% of men in their 60s³ and over 80% of those in their 80s.⁴ These symptoms can negatively affect the activity level⁵ and increase the risk of falls.⁶ ED is also associated with cardiovascular

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disease, metabolic syndrome, depressive symptoms, and poor quality of life.^{7,8}

While proper treatments of LUTS and ED can improve the well-being of older men,⁹ they are not without risks.^{6,10,11} Medications for LUTS, such as alpha-blockers and antimuscarinics, can worsen orthostatic hypotension and cognitive impairment.¹⁰ Transurethral resection of the prostate (TURP) can increase the risk of bleeding, delirium, and TURP syndrome, which is associated with morbidity, mortality, prolonged hospitalization, and costs.^{12,13} These risks may be particularly elevated in older men with frailty,¹⁴ that is, in individuals who have decreased physiologic reserve and increased vulnerability to acute stressors. Therefore, recognizing frailty and geriatric syndromes in older men with urologic symptoms is crucial for the optimal management and prevention of treatment-related adverse events. However, the burden of frailty and geriatric conditions in community-dwelling older men with urologic symptoms is unknown.

We conducted a cross-sectional study to evaluate the burden of frailty and geriatric conditions according to the severity of LUTS and ED in community-dwelling older men. We administered two widely used questionnaires to assess LUTS and ED, the International Prostate Symptom Score (IPSS) and the five-item version of the International Index of Erectile Function (IIEF-5),^{15,16} respectively. We hypothesized that severe symptoms of LUTS and ED are associated with frailty and geriatric syndromes.

Patient and methods

Study population

The Aging Study of PyeongChang Rural Area (ASPRA) is a population-based, prospective cohort study of frailty and geriatric syndromes in 1,350 community-dwelling older adults residing in PyeongChang, Gangwon, Korea.¹⁷ The design and conduct of ASPRA cohort are described elsewhere.¹⁷ Briefly, since the cohort was established in October 2014, participants have undergone annual assessments of medical, physical, and psychosocial status. The inclusion criteria for participation in ASPRA were 1) age ≥ 65 years; 2) registered in the National Healthcare Service; 3) ambulatory with or without an assistive device; 4) living at home; and 5) able to provide informed consent. Those who were living in a nursing home, hospitalized, or bed-ridden and receiving nursing-home-level care at the time of enrollment were excluded. The study enrolled 95% of eligible people in the study regions. The characteristics of ASPRA participants were overall similar to those of the Korean rural population represented in the Korea National Health and Nutrition Examination Survey.¹⁷ Of the total of 498 men who completed

the comprehensive geriatric assessment between January 1, 2016 and December 31, 2016, 492 (98.8%) were assessed for LUTS and ED. The protocol of this study was approved by the Institutional Review Board of the Asan Medical Center. All the participants provided written informed consent.

Urologic questionnaires

The IPSS and IIEF-5 questionnaires were administered to the participants by male physicians in a privacy-protected area.

IPSS urologic questionnaires

The IPSS is a widely used questionnaire for screening, diagnosis, and monitoring of the symptoms of benign prostatic hyperplasia and LUTS.¹⁵ It consists of seven questions regarding voiding symptoms and one question on quality of life, with a scoring range of 0–35. We classified the participants into mild (0–7 points), moderate (8–19 points), and severe (20–35 points) categories.¹

IIEF-5

We evaluated sexual desire (ie, libido) and ED using a five-item version of the IIEF (also known as the Sexual Health Inventory for Men)¹⁶ with a scoring range of 5–25. However, since many participants were not sexually active, we focused on the first IIEF-5 question – “How do you rate your confidence that you could get and keep an erection?” – that assesses the confidence in the erectile function, regardless of their sexual activity. Based on the first IIEF-5 question, we classified the participants as low (1–2 points), moderate (3 points), or high confidence (4–5 points).

Frailty assessment

Frailty was assessed according to the Cardiovascular Health Study frailty criteria, a widely validated definition for frailty.¹⁸ The frailty phenotype scale is calculated by assigning 1 point to the following five components that are relevant to a given individual:¹⁸ 1) exhaustion: moderate or most of the time during the last week, to either of the following: “I felt that everything I did was an effort” or “I could not get going”; 2) low activity: lowest quintile in physical activity level measured using International Physical Activity Questionnaires Short Form (below the 20th percentile cutoff point in a representative sample of older Koreans in the Korea National Health and Nutrition Examination Survey [KNHANES]); 3) slowness: usual gait speed < 0.8 m/s from 4-m walk test; 4) weakness: dominant handgrip strength < 26 kg for men, < 17 kg for women; and 5) weight loss: unintentional weight loss > 3 kg during previous 6 months.^{19,20,33} On the basis of the total score, individuals were classified as robust (0 points), prefrail (1–2 points), or frail (3–5 points).

Other measurements

Trained nurses performed a comprehensive geriatric assessment to evaluate the common geriatric conditions and use of benign prostatic hyperplasia (BPH) medications (alpha-blockers, 5-alpha-reductase inhibitors, or anticholinergics). Multimorbidity was defined as having five or more of the 11 diagnoses (angina, arthritis, asthma, cancer excluding minor skin cancer, chronic lung disease, congestive heart failure, diabetes, heart attack, hypertension, kidney disease, and stroke). Sarcopenia was defined according to the Asian Working Group for Sarcopenia using a bioimpedance analysis.¹⁷ Polypharmacy was defined as taking five or more prescription medications. Low cognition was defined as a Korean version of Mini-Mental-State Examination score <24.²¹ Depressive mood was defined as a Korean version of the Center for Epidemiological Studies Depression scale score >20.²² Slow gait was defined as a usual gait speed <0.6 m/s from a timed 4-m walk.²³ Malnutrition risk was defined as a score of ≤ 11 according to the Mini-Nutritional Assessment-Short Form.²⁴ Disability was defined as requiring assistance in performing any of the seven activities of daily living (ADL; bathing, continence, dressing, eating, toileting, transferring, and washing face and hands) or 10 instrumental activities of daily living (IADL; food preparation, household chores, going out a short distance, grooming, handling finances, laundry, managing own medications, shopping, transportation, and using a telephone).²⁵

Statistical analysis

We summarized the characteristics of our study participants according to the mean and standard deviation (SD) for continuous variables and proportions for categorical variables. We evaluated the prevalence of the frailty phenotype and its components according to the severity categories of the IPSS and the first IIEF-5 question. The proportion of frailty and its component was compared across the severity category using a logistic regression to adjust for age. The odds ratio (OR) and 95% confidence interval (CI) of frailty across the severity category were also estimated. Statistical analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY, USA). A two-sided p -value <0.05 was considered statistically significant.

Results

Characteristics of study participants

The mean age of the 492 men was 74.2 years (standard deviation: 5.6) (Table 1). Most men were prefrail (73.2%) or frail (13.4%), and multimorbidity (32.5%), low cognition

Table 1 Characteristics of male participants in the Aging Study of PyeongChang Rural Area

Characteristics	N (%) or mean \pm SD
Sample size	492
IPSS (range: 0–35 points)	
Mild (IPSS 0–7 points)	288 (58.5)
Moderate (IPSS 8–19 points)	160 (32.5)
Severe (IPSS 20–35 points)	44 (8.9)
On BPH medication	117 (23.8)
IIEF-5 (range: 5–25 points)	
Normal to mild (IIEF 17–25 points)	103 (20.9)
Mild to moderate (IIEF 12–16 points)	83 (16.9)
Moderate to severe (IIEF 5–11 points)	68 (13.8)
No sex partner or sexual behavior (IIEF 1–4 points)	238 (48.4)
First IIEF-5 question (range: 1–5 points)	
Low erectile confidence (1 or 2 points)	300 (61)
Moderate erectile confidence (3 points)	114 (23.2)
High erectile confidence (4 or 5 points)	78 (15.9)
Age, years	74.2 \pm 5.6
CHS frailty phenotype	
Robust	66 (13.4)
Prefrail	360 (73.2)
Frail	66 (13.4)
Multimorbidity	160 (32.5)
Hypertension	240 (48.8)
Arthritis	111 (22.6)
Diabetes	85 (17.3)
Heart disease	55 (11.2)
Chronic lung disease	37 (7.5)
Sarcopenia	164 (33.3)
Polypharmacy	91 (18.5)
MMSE <24	82 (16.7)
Depression	12 (2.4)
SPPB score	8.7 \pm 2.2
Dismobility	160 (32.5)
Fall in past year	64 (13)
At risk of malnutrition	135 (27.4)
ADL disability	41 (8.3)
IADL disability	77 (15.7)

Abbreviations: ADL, activities of daily living; BPH, benign prostatic hyperplasia; CHS, Cardiovascular Health Study; IADL, instrumental activities of daily living; IIEF-5, five-item version of International Index of Erectile Function; IPSS, International Prostate Symptom Score; MMSE, mini-mental-state examination; SPPB, short physical performance battery.

(16.7%), IADL disability (15.7%), and fall history (13.0%) were common. The most prevalent underlying diseases diagnosed by physicians were hypertension (48.8%), arthritis (22.6%), diabetes (17.3%), heart disease (11.2%) and chronic lung disease (7.5%). Alpha-blockers, 5-alpha-reductase inhibitors, or anticholinergics were used by 117 men (23.8%). The IPSS questionnaire classified 288 men (58.5%) as mild, 160 (32.5%) as moderate, and 44 (8.9%) as severe for LUTS symptoms. According to the first IIEF-5 question, which assesses the confidence in erectile function, 300 men (61.0%) had low confidence.

Frailty and its components by IPSS and the first IIEF-5 question scores

The prevalence of frail and prefrail states increased with greater IPSS severity (Figure 1A). Frailty was present in 21 of the 288 men (7.3%) with mild symptoms, 26 of the 160 men (16.3%) with moderate symptoms (OR: 2.47; 95% CI: 1.34–4.55; $p=0.004$), and 19 of the 44 men (43.2%) with severe symptoms (OR: 9.66; 95% CI: 4.59–20.33; $p<0.001$). Similarly, the prevalence of frailty was higher in the lower erectile confidence categories according to the first IIEF-5 question (Figure 1B). Frailty was identified in four of 78 men with high confidence (5.1%), six of 114 men (5.3%) with moderate confidence (OR: 1.03; 95% CI: 0.28–3.77; $p=0.967$), and 56 of 300 men (18.7%) with low confidence (OR: 4.25; 95% CI: 1.49–12.10; $p=0.007$). Each component of frailty increased in prevalence with higher severity according to IPSS (Figure 2A) or the first IIEF-5 question (Figure 2B).

Common geriatric conditions according to IPSS and the first IIEF-5 question scores

We also investigated the common geriatric conditions according to the severity as determined by each urologic questionnaire (Table 2). The prevalence of most geriatric conditions was higher as the severity of LUTS increased.

Close to a half of the individuals with severe IPSS symptoms had disability (45.5%), multimorbidity (43.2%), malnutrition risk (40.9%), or sarcopenia (40.9%). The severe LUTS group showed significantly high prevalence of multimorbidity (43.2% of severe LUTS group; 43.1% of moderate group; 25.0% of mild group; $p<0.001$), polypharmacy (31.8% of severe LUTS group; 21.3% of moderate group; 14.9% in mild group; $p=0.015$), and the mean number of regular medications taken regularly (3.6 tablets [SD 3.5] in severe LUTS group; 2.7 tablets [SD 2.7] in moderate group; 2.0 tablets [SD 2.4] in mild group, $p<0.001$) than low LUTS group.

Similarly, geriatric conditions were more prevalent in those with low erectile confidence: sarcopenia (39.0%), multimorbidity (37.7%), disability (35.7%), and malnutrition risk (33.3%) were common. Compared to the group of high confidence of erectile function, the group of low confidence of erectile function showed significantly high prevalence of multimorbidity (37.7% in the group of low confidence of erectile function; 24.6% in the group of moderate confidence; 24.4% in the group of high confidence; $p=0.010$), polypharmacy (23.0% in the group of low confidence of erectile function; 11.4% in the group of moderate confidence; 11.5% in the group of high confidence; $p=0.006$), and the mean number of medications taken regularly (2.8 tablets [SD 2.9] in the group of low confidence of erectile function; 1.8 tablets [SD 2.2]

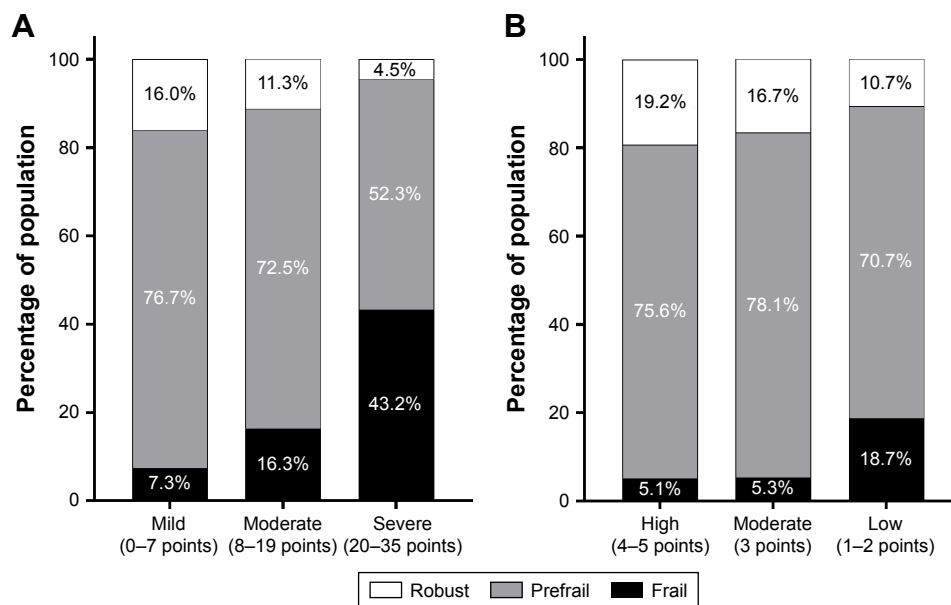


Figure 1 Frailty status according to IPSS category (A) and the first IIEF-5 question (B).

Notes: IIEF-5 first question asks participants, “How do you rate your confidence that you could get and keep an erection?” (A) LUTS from IPSS category; (B) Erectile confidence from the first IIEF-5 question; Frailty status was defined by Cardiovascular Health Study frailty criteria. We defined 0–7 points of IPSS score as “mild”, 8–19 points as “moderate”, and 20–35 points as “severe” LUTS. We also defined 4 or 5 points of the first IIEF-5 question as “high”, 3 points as “moderate”, and 1 or 2 as “low” erectile confidence.

Abbreviations: IPSS, International Prostate Symptom Score; IIEF-5, five-item version of International Index of Erectile Function; LUTS, lower urinary tract symptom.

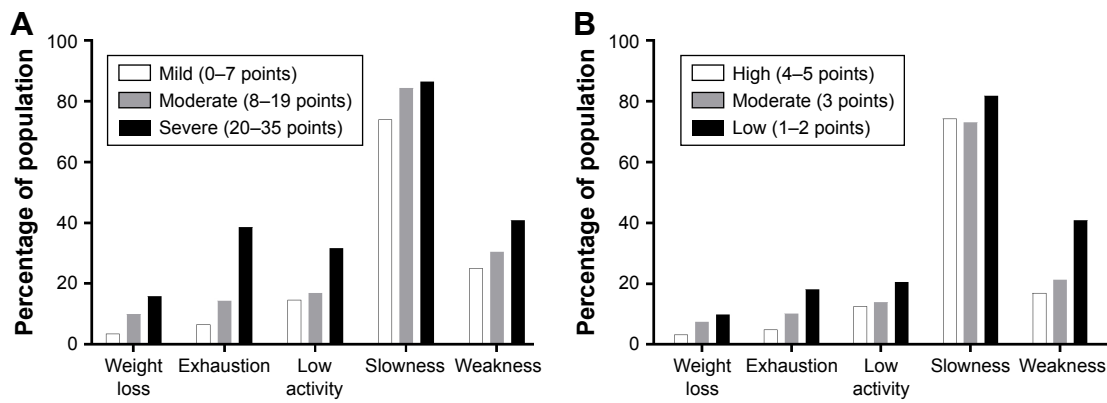


Figure 2 Frailty components according to IPSS category (A) and the first IIEF-5 question (B).

Notes: The first IIEF-5 question asks participants, “How do you rate your confidence that you could get and keep an erection?” (A) LUTS from IPSS category; (B) Erectile confidence from the first IIEF-5 question; Frailty components originated from Cardiovascular Health Study frailty criteria. We defined 0–7 points of IPSS score as “mild”, 8–19 points as “moderate”, and 20–35 points as “severe” LUTS. We also defined 4 or 5 points of the first IIEF-5 question as “high”, 3 points as “moderate”, and 1 or 2 as “low” erectile confidence.

Abbreviations: IPSS, International Prostate Symptom Score; IIEF-5, five-item version of International Index of Erectile Function; LUTS, lower urinary tract symptom.

in the group of moderate confidence; 2.7 tablets [SD 2.1] in the group of high confidence; $p < 0.001$).

Discussion

A majority of patients seeking medical or surgical treatment for moderate or severe LUTS are older men, and our study indicates that almost a half of these patients satisfy the criteria for frailty. Given that frail older adults may have increased vulnerability to treatment-related adverse events, our findings

suggest the importance of recognizing frailty in older men with severe LUTS symptoms through a validated frailty assessment in the management of urological symptoms in these patients.

Medications are a primary treatment option in older men with moderate to severe LUTS. However, several medications used to treat LUTS can increase the risks of confusion, falls, and possibly mortality.^{10,14} Alpha-1 blockers, especially doxazosin, terazosin, and prazosin, should be avoided in older

Table 2 Common geriatric syndromes according to IPSS category and first IIEF-5 question in the Aging Study of PyeongChang Rural Area

Geriatric syndrome	LUTS from IPSS category			p-value	Erectile confidence from first IIEF-5 question			p-value
	Mild (0–7 points)	Moderate (8–19 points)	Severe (20–35 points)		High (4–5 points)	Moderate (3 points)	Low (1–2 points)	
	N (%) or mean \pm SD (N=288)	N (%) or mean \pm SD (N=160)	N (%) or mean \pm SD (N=44)		N (%) or mean \pm SD (N=44)	N (%) or mean \pm SD (N=114)	N (%) or mean \pm SD (N=300)	
Multimorbidity	72 (25.0)	69 (43.1)	19 (43.2)	<0.001	19 (24.4)	28 (24.6)	113 (37.7)	0.010
Sarcopenia	88 (30.6)	58 (36.3)	18 (40.9)	0.254	11 (14.1)	36 (31.6)	117 (39.0)	<0.001
Polypharmacy	43 (14.9)	34 (21.3)	14 (31.8)	0.015	9 (11.5)	13 (11.4)	69 (23.0)	0.006
Number of medications taken regularly	2.0 \pm 2.4	2.7 \pm 2.7	3.6 \pm 3.5	<0.001	1.7 \pm 2.1	1.8 \pm 2.2	2.8 \pm 2.9	<0.001
MMSE <24	40 (13.9)	30 (18.8)	12 (27.3)	0.059	9 (11.5)	15 (13.2)	58 (19.3)	0.134
Depression	2 (0.7)	6 (3.8)	4 (9.1)	0.001	0 (0)	1 (0.9)	11 (3.7)	0.082
SPPB score	9.0 \pm 2.0	8.1 \pm 2.3	7.8 \pm 2.7	<0.001	9.3 \pm 1.6	9.2 \pm 2.0	8.3 \pm 2.4	<0.001
Disability	79 (27.4)	61 (38.1)	20 (45.5)	0.011	19 (24.4)	34 (29.8)	107 (35.7)	0.129
Fall in past year	33 (11.5)	23 (14.4)	8 (18.2)	0.385	13 (16.7)	9 (7.9)	42 (14.0)	0.149
At risk of malnutrition	84 (29.2)	56 (35.0)	18 (40.9)	0.191	28 (35.9)	30 (26.3)	100 (33.3)	0.291
ADL disability	8 (2.8)	23 (14.4)	10 (22.7)	<0.001	3 (3.8)	3 (2.6)	35 (11.7)	0.003
IADL disability	32 (11.1)	35 (21.9)	10 (22.7)	0.004	8 (10.3)	8 (7.0)	61 (20.3)	0.001

Note: The first IIEF-5 question asks participants, “How do you rate your confidence that you could get and keep an erection?”

Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living; IIEF-5, five-item version of International Index of Erectile Function; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptom; MMSE, mini-mental-state examination; SPPB, short physical performance battery.

men with syncope, due to the risk of orthostatic hypotension. Antimuscarinics such as oxybutynin should be avoided in older patients with delirium, cognitive impairment, dementia, and Parkinson disease, due to their strong anticholinergic effects. Desmopressin, often used to treat nocturia or nocturnal polyuria, can increase the risk of hyponatremia. Based on these facts, the 2015 American Geriatric Society Beers Criteria recommended these medications be avoided or used with caution.²⁶ Oelke et al also warned of the potential harm of LUTS medication based on efficacy, safety, and tolerability.¹⁰ In treating ED, discontinuation of certain culprit medications, such as antidepressants, diuretics, and beta-blockers, can help ED, but it might also exacerbate the comorbidity conditions.²⁷ Phosphodiesterase-5 inhibitors should be prescribed with caution in men with angina or coronary artery disease, which, it should be noted, are often undiagnosed in older patients. Dyspepsia, headache, flushing, visual disturbance, and drug–food interactions, meanwhile, are other potentially important issues.²⁷ According to several reports and experts, the risk of these adverse events may be higher in frail older adults.^{28–30}

In cases where medications are not effective, surgical procedures are considered. Surgical procedures in older men, however, can be associated with adverse events. Approximately 15%–20% of patients undergoing TURP experience significant complications such as bleeding, clot retention, perforation of the prostate capsule, urinary tract infection, and post prostatectomy syndrome, and 0.2%–2.5% die.¹³ In a Veterans Administration study, 9% of subjects had perioperative complications, including the need for placement of another urinary catheter, perforation of the prostate capsule, hemorrhage requiring transfusion, urinary tract infections, and thrombophlebitis.³¹ Other studies have revealed that older men were more likely than younger men to develop TURP syndrome and delirium.¹² These complications negatively affect the quality of life and increase medical costs.¹³ Frailty was strongly associated with the risk of postoperative complications after nearly all urologic surgery or procedures (adjusted OR 1.74; 95% CI: 1.64–1.85).^{14,32}

Because frail older men may be at high risk of adverse events from LUTS or ED treatment, our results indicate the importance of recognizing frailty in the management of common urological symptoms in older men. In geriatrics, a number of frailty instruments have been developed and validated. Some of the widely validated instruments include the frailty phenotype, a deficit accumulation of frailty index, and the FRAIL (Fatigue, Resistance, Ambulation, Illnesses, Loss of weight) scale. The frailty phenotype that we used

was developed from a large community-based cohort of older adults in the United States^{18,32} and subsequently validated in several other populations.^{33–35} It is based on the assessment of five specific components that require certain skills and administration time (in our experience, 10–15 minutes). The frailty index developed by Rockwood and Mitnitski originated from a large population-based Canadian cohort.³⁶ It calculates the proportion of deficits from a total of 30–90 health deficit variables. Rather than these extensive evaluations, we recommend that urologists and primary care physicians adopt the FRAIL scale, which is a brief screening tool based on five self-reported items.³⁷ This has been validated for the US,³⁷ European,³⁸ and Asian populations.³⁹ It classifies participants as robust (0 points), prefrail (1–2 points), or frail (3–5 points). This questionnaire does not require a physical examination and can be administered within 3 minutes.³⁹ Frailty screening improves prediction of older adults at high risk for poor surgical outcomes,^{40–43} but few studies examined this in older men undergoing urological procedures.^{14,32} Further studies are warranted to define the role of frailty screening in determining the risk–benefit of the urological procedures in older men.

There are several strengths and limitations to our study. The ASPRA is a population-based prospective cohort study that administered standardized measurements for frailty and an extensive list of geriatric syndromes in addition to the IPSS and IIEF-5 questionnaires.¹⁷ Because our study population had a high participation rate of eligible men residing in the study regions, selection bias due to non-participation is unlikely. Although the ASPRA cohort was based on a rural community in Korea, we previously showed that their demographic characteristics are similar to a nationally representative sample.¹⁷ However, the results from this study may not be generalized to nursing homes or populations of other ethnic origins. As a cross-sectional study, we were not able to determine whether the IPSS scores and the response to the first IIEF-5 question can predict the future development of frailty in older men and whether frailty can predict the worsening of urological symptoms in the future. The long-term follow-up data from the ASPRA cohort will be valuable to answer these clinically important questions.

Conclusion

Our study underscores the high prevalence of frailty and geriatric syndromes in older men with severe LUTS or ED. Considering the high prevalence of frailty and its clinical implications, urologists and primary care physicians should consider adopting a simple frailty screening tool for

identifying frail older patients who may require careful assessment of benefits and risks of medical and surgical management options for their urological symptoms. Future research on whether a frailty screening and subsequent management based on frailty assessment improve patient-centered care and clinical outcomes in these patients is needed.

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Author contributions

All the authors participated in design and study conception, performed statistical analysis, data analysis and interpretation, and drafted the manuscript. All the authors read and revised this manuscript. This manuscript is the final approved version by all authors. All the authors have reviewed and agreed to be responsible for the process, accuracy, and integrity of all the parts of this manuscript.

Disclosure

Dr Dae Hyun Kim is a consultant to Alosa Health, a nonprofit educational organization with no relationship to any drug or

device manufacturer. The other authors report no conflicts of interest in this work.

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