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Lower Urinary Tract Symptoms in Patients with COVID-19: Results of a Cross-sectional Study

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What's known on the subject? and What does the study add?

The most prevalent Coronavirus disease-2019 (COVID-19) symptoms are those of the respiratory, however, lower urinary tract as well as the gastrointestinal, cardiovascular, central nervous, and urinary systems are also affected. To date, there are published articles regarding Lower urinary tract symptoms (LUTS) in COVID-19-infected patients. Some studies reported any association between the severity of symptoms, and LUTS, while the others did not find this link. Among 709 patients, 42.2% of women and 45.6% of men with COVID-19 had nocturia. The frequency of urination per day was higher than normal in 23% of women and 40.4% of men. 15% of women complained of a sense of urinary urgency while urinating, and 13.7% and 20% of men complained of straining and hesitancy in urinating, respectively. People with COVID-19 may acquire or experience de novo LUTS, particularly storage symptoms.

Abstract

Objective: We aimed to investigate the effect of severe acute respiratory syndrome-coronavirus-2 infection on lower urinary tract function using validated questionnaires in patients with patients.

Materials and Methods: This descriptive cross-sectional study was conducted according to the inclusion and exclusion criteria on 709 patients with Coronavirus disease-2019 (COVID-19) on an outpatient basis from September 2020 to May 2021 in Kerman's health centers. After signing the consent form and completing the demographic information, the International Consultation on Incontinence Questionnaire male Lower Urinary Tract Symptoms Modules and International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms questionnaires were completed. Finally, the data were analyzed using the SPSS version 26 software.

Results: Patients with COVID-19 (n=709) (365 questionnaires related to women and 344 questionnaires related to men) were examined on an outpatient basis. In general, 42.2% of women and 45.6% of men with COVID-19 had nocturia. The frequency of urination per day was higher than normal in 23% of women and 40.4% of men. In addition, 15% of women complained of a sense of urinary urgency while urinating, and 13.7% and 20% of men complained of straining and hesitancy in urinating, respectively. Similar to the males, the common symptoms in women were nocturia and increased daily frequency. In addition, with increasing age, lower urinary tract symptoms (LUTS) became common in COVID-19 patients.

Conclusion: The results of our investigation imply that people with COVID-19 may acquire or experience *de novo* LUTS, particularly storage symptoms. All symptoms were more in people over 50 years old than in those younger. COVID-19 infection should be investigated in any patient presenting with LUTS during the current pandemic. Further research is needed to clarify the exact pathophysiology of this correlation.

Keywords: COVID-19, lower urinary tract symptoms, LUTS

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Introduction

The new severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)-caused Coronavirus disease-2019 (COVID-19) was discovered in Wuhan, China. Millions of people have been infected, thousands have died, and the disease became a pandemic in 2020 (1). The severity of a disease's symptoms can range from none to serious (2). The most prevalent COVID-19 symptoms are those of the respiratory system, including coughing, rhinorrhea, and shortness of breath. Many reports indicate that symptoms of the lower urinary tract as well as the gastrointestinal, cardiovascular, central nervous, and urinary systems are also affected (3). A study found that patients with COVID-19 had pyuria and hematuria for unknown reasons. There are some tentative hypotheses concerning urinary tract infections and acute kidney injury (4,5). Lower urinary tract symptoms (LUTS), particularly in elderly people, are one of the early symptoms of COVID-19 (6). The International Continence Society defines LUTS as an all-encompassing term that is used to describe a wide range of symptoms that fall into three categories: voiding, storage, and postmicturition (7). According to a study, both male and female COVID-19 patients frequently report storage and voiding LUTS as their main presenting symptoms (8). Importantly, COVID-19 infection is only occasionally found in the urine of individuals who have the disease; as a result, it is unlikely that COVID-19 can be spread by urine (9). Patients with COVID-19 may experience a new onset or an aggravation of baseline urinary symptoms, most notably overactive bladder (OAB), which is less common but increasingly described (10,11). The term "COVID-19-associated cystitis" has been used to describe this condition (12,13). Although the underlying pathophysiology of urine symptoms in COVID-19 patients is unclear, theories have started to form as a result of smaller, single-center investigations that are currently shedding light on the effects of effects on the genitourinary system. Furthermore, it has not been adequately explored whether patients with post-acute COVID-19 syndrome or extended COVID experience urine symptoms and any related discomfort. To date, there are published articles regarding LUTS in COVID-19-infected patients (5,8,14,15), and some of them reported any association between the severity of symptoms and LUTS, whereas others did not find this link. Herein, we aimed to investigate the effect of SARS-CoV-2 infection on lower urinary tract function using validated questionnaires in patients admitted with patients referred to Kerman healthcenters in southeastern of Iran.

Materials and Methods

This study was conducted in accordance with all the guidelines and directives on medical research in Kerman. All participants in this experiment provided written informed consent. The regional ethics committee gave its consent to this work, which followed the ethical code of (approval number: IR.KMU.AH.REC.1400.130, date: 25.09.2021 - Afzalipour Hospital-Kerman University of Medical Sciences Research Ethics Committees).

Inclusion and Exclusion Criteria

Between September 2020 and May 2021, all patients over 18 years of age who were referred to the health centers of Kerman because of symptoms of COVID-19, such as fever and respiratory symptoms, and who tested positive for SARS-CoV-2 by real-time polymerase chain reaction and/or COVID-19 fast antigen were enrolled in our study. Informed consent was obtained from each patient before participation. Patients with pre-existing LUTS were excluded from the study. Additionally, women who had significant pelvic organ prolapse and consequently may experience certain degrees of LUTS were excluded from the study. Moreover, patients with urological malignancies, those who had undergone urological surgery in the past, and those who were taking drugs that changed urine patterns were excluded. The other exclusion criteria were neurogenic bladder, history of untreated BPH and prostatitis, history of recurrent urinary tract infection, diabetes, pregnancy, and Foley catheter use.

These patients did not present with LUTS symptoms that warranted evaluation using sonography, urodynamic testing, or other imaging studies. Instead, they sought medical attention for common COVID-19 symptoms. Our aim was to investigate LUTS symptoms in these patients, and diagnostic methods for evaluating LUTS were not considered in our study. To determine the prevalence of LUTS in COVID-19-confirmed outpatients in Kerman, Iran, a cross-sectional research approach was used in this investigation.

The three main categories of lower urinary tract disorders are storage, voiding, and post-micturition. LUTS in males and females were assessed using the International Consultation on Incontinence Questionnaire male Lower Urinary Tract Symptoms Modules and International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms, respectively.

These questionnaires evaluate the day urinary frequency, nocturia, urgency, urgency urinary incontinence (UUI), bladder pain, stress urinary incontinence (SUI), unexplained urinary incontinence, amount of urinary leakage, hesitancy, straining, intermittency, nocturnal enuresis, strength of urine stream, urinary retention, dysuria, and incomplete emptying. A score of 1 or more (grade 1: low, grade 2: moderate, grade 3: severe, grade 4: very severe) was considered as a sign of severe disease. This questionnaire has been translated and validated in Persian and has high validity and reliability (16).

Statistical Analysis

To determine the effect of COVID-19 infection severity on the incidence of LUTS, a comparison statistical test was performed between the two variables. P-value less than 0.05, was considered statistically significant.

Results

The current study included 709 confirmed confirmed patients, comprising 344 (48.5%) men and 365 (51.5%) women. The participants' average (standard deviation) age was 43.30 (16.30) years. For men, it was 37.95 (12.93) years and for women, 48.22 (17.50) years, respectively. Of the participants who were included, 241 (34.8%) and 452 (65.2%) were under the age of 50 years. The youngest patient was 18 years old, and the oldest was 85 years old. Tables 1 and 2 show LUTS in the studied patients. The common LUTS was nocturia, which was reported in 44.2% of cases. The second was day frequency, which was reported in 220 cases (31.7%), and the next was straining in 12.7%.

According to the results, the most prevalent symptom in males was nocturia (one episode) in 32.8%, occasionally incomplete emptying in 16.3%, and occasionally straining to continue urination in 14.2%. The common symptoms of the lower urinary tract in females were nocturia (one episode) in 29.3%, urgency in 12.9%, and UUI in 8.8%.

We compared the symptoms based on the gender of the participants. The results are summarized in Table 3. According to the results, the incidence of UUI, SUI, urgency, and unexplained UI was increased in female patients than in male patients ($p<0.001$). In contrast, the incidence of daytime frequency, straining, and hesitancy was high in male patients ($p<0.05$) (Table 3).

Table 1. The frequency of LUTS in males according to the results of the ICIQ-MLUTS questionnaire

Symptoms	n (%)	Symptoms	n (%)
Hesitancy		**Straining to continue urination**	
Never	297 (86.3)	Never	275 (79.9)
Occasionally	43 (12.5)	Occasionally	49 (14.2)
Sometimes	3 (0.9)	Sometimes	20 (5.8)
Most of the time	1 (0.3)	Most of the time	
Strength of urine stream		**Intermittency**	
Normal	319 (92.7)	Never	295 (85.8)
Occasionally reduced	21 (6.1)	Occasionally	42 (12.2)
Sometimes reduced	3 (0.9)	Sometimes	7 (2.0)
Reduced most of the time	1 (0.3)	Most of the time	
Incomplete emptying		**Stress urinary incontinence**	
Never	284 (82.6)	Never	341 (99.1)
Occasionally	56 (16.3)	Occasionally	3 (0.9)
Sometimes	3 (0.9)	**Frequency**	
Most of the time	1 (0.3)	1 to 6 times	205 (59.6)
Urgency		7 to 8 times	108 (31.4)
Never	327 (95.1)	9 to 10 times	29 (8.4)
Occasionally	15 (4.4)	11 to 12 times	1 (0.3)
Sometimes	2 (0.6)	13 or more times	1 (0.3)
Urge urinary incontinence		**Nocturia**	
Never	341 (99.1)	None	187 (54.4)
Occasionally	3 (0.9)	One	113 (32.8)
Unexplained urinary incontinence		Two	39 (11.3)
Never	344 (100.0)	Three	4 (1.2)
		Four or more	1 (0.3)
Nocturnal enuresis		**Post micturition dribble**	
Never	342 (99.4)	Never	342 (99.4)
Occasionally	2 (0.6)	Occasionally	2 (0.6)

LUTS: Lower urinary tract symptoms, ICIQ-MLUTS: International Consultation on Incontinence Questionnaire male Lower Urinary Tract Symptoms Modules

Table 2. The frequency of LUTS in females according to the results of the ICIQ-FLUTS questionnaire			
Symptoms	**n (%)**	**Symptoms**	**n (%)**
Hesitancy		**Straining**	
Never	3321 (91.0)	Never	345 (94.5)
Occasionally	29 (7.9)	Occasionally	16 (4.4)
Sometimes	2 (0.5)	Sometimes	3 (0.8)
Most of the time	1 (0.3)	All of the time	1 (0.3)
All of the time	1 (0.3)	**Intermittency**	
Bladder pain		Never	328 (89.9)
Never	340 (93.2)	Occasionally	33 (9.0)
Occasionally	17 (4.7)	Sometimes	3 (0.8)
Sometimes	5 (1.4)	All of the time	1 (0.3)
Most of the time	3 (0.8)	**Frequency**	
Urgency		1 to 6 times	281 (77.0)
Never	310 (84.9)	7 to 8 times	66 (18.1)
Occasionally	47 (12.9)	9 to 10 times	12 (3.3)
Sometimes	6 (1.6)	11 to 12 times	2 (0.5)
All of the time	2 (0.5)	13 or more times	4 (1.1)
Urge urinary incontinence		**Nocturia**	
Never	328 (89.9)	None	211 (57.8)
Occasionally	32 (8.8)	One	107 (29.3)
Sometimes	4 (1.1)	Two	36 (9.9)
All of the time	1 (0.3)	Three	3 (0.8)
Urine leakage		Four or more	8 (2.2)
Never	328 (89.9)	**Nocturnal enuresis**	
Once or less per week	23 (6.3)	Never	362 (99.2)
Two to three times per week	8 (2.2)	Occasionally	3 (0.8)
Once per day	1 (0.3)	**Stress urinary incontinence**	
Several times per day	5 (1.4)	Never	321 (87.9)
Unexplained urinary incontinence		Occasionally	27 (7.4)
Never	350 (95.9)	Sometimes	12 (3.3)
Occasionally	14 (3.8)	Most of the time	2 (0.5)
All of the time	1 (0.3)	All of the time	3 (0.8)

LUTS: Lower urinary tract symptoms, ICIQ-FLUTS: International Consultation on Incontinence Questionnaire Female Lower Urinary Tract Symptoms

Table 3. Association between LUTS and gender of COVID-19 patients			
	Female (n=365)	**Male (n=344)**	**P-value***
Nocturia			0.198
No	211 (57.8)	187 (54.4)	
Yes	154 (42.2)	157 (45.6)	
Urgency			**<0.001**
No	310 (84.9)	325 (95.0)	
Yes	55 (15.1)	17 (5.0)	
Frequency			**<0.001**
No	281 (77.0)	205 (59.6)	
Yes	84 (23.0)	139 (40.4)	

Table 3. Continued			
	Female (n=365)	**Male (n=344)**	**P-value***
Hesitancy			**0.034**
No	332 (91.0)	297 (86.3)	
Yes	33 (9.0)	47 (13.7)	
Straining			**<0.001**
No	345 (94.5)	275 (79.9)	
Yes	20 (5.5)	69 (20.1)	
Intermittency			0.059
No	328 (89.9)	295 (85.8)	
Yes	37 (10.1)	49 (14.2)	
UUI			**<0.001**
No	328 (89.9)	286 (99.0)	
Yes	37 (10.1)	3 (1.0)	
SUI			**<0.001**
No	321 (87.9)	341 (99.1)	
Yes	44 (12.1)	3 (0.9)	
Unexplained UI			**<0.001**
No	350 (95.9)	344 (100.0)	
Yes	15 (4.1)	0	
Enuresis			>0.999
No	362 (99.2)	342 (99.4)	
Yes	3 (0.8)	2 (0.6)	

*: Chi-square; data are presented as n (%), LUTS: Lower urinary tract symptoms, COVID-19: Coronavirus disease-2019

In terms of the LUTS in different age groups, the results showed that with increasing age, the prevalence of symptoms increased except for those aged >70 years (p<0.001). The results are summarized in Table 4 and Figure 1.

In terms of filling, voiding, and incontinence scores, Table 5 shows the details of different domains of questionnaire scores.

Regarding the age groups (<50 years or ≥50 years old), Figure 2 illustrates the different LUTS in this age category.

Discussion

The current study demonstrated that the common LUTS in outpatient COVID-19 males were nocturia, increased daily urinary frequency, and straining, followed by hesitancy, which was significantly higher in men than in females. On the contrary, urgency, SUI, and UUI were more common in females than in males. Similar to the males, the common symptoms in women were nocturia and increased daily frequency. In addition, with increasing age, LUTS became common in COVID-19 patients.

Table 4. LUTS in different age groups of COVID-19 patients								
***Age groups**	**Nocturia (n=693)**	**Urgency (n=691)**	**Frequency (n=693)**	**Hesitancy (n=693)**	**Straining (n=693)**	**Intermittency (n=693)**	**UUI (n=638)**	**SUI (n=693)**
18-29	51 (34.0)	7 (4.7)	31 (20.7)	2 (1.3)	6 (4.0)	2 (1.3)	1 (0.8)	2 (1.3)
30-39	80 (37.4)	9 (4.2)	57 (26.6)	13 (6.1)	20 (9.3)	14 (6.5)	4 (2.1)	4 (1.9)
40-49	37 (42.5)	8 (9.2)	31 (35.6)	11 (12.6)	14 (16.1)	9 (10.3)	4 (4.7)	6 (6.9)
50-59	57 (61.3)	17 (18.3)	33 (35.5)	19 (20.4)	21 (22.6)	28 (30.1)	10 (10.9)	12 (12.9)
60-69	36 (43.4)	18 (22.2)	40 (48.2)	20 (24.1)	18 (21.7)	17 (20.5)	9 (12.7)	10 (12.0)
70<	45 (68.2)	13 (19.7)	28 (42.4)	13 (19.7)	9 (13.6)	13 (19.7)	12 (19.0)	13 (19.7)
Total	306 (44.2)	72 (10.4)	220 (31.7)	78 (11.3)	88 (12.7)	83 (12.0)	40 (6.3)	47 (6.8)

*: Chi-square; data are presented as n (%). P-value for all symptoms was <0.001, UUI: Urgency urinary incontinence, SUI: Stress urinary incontinence

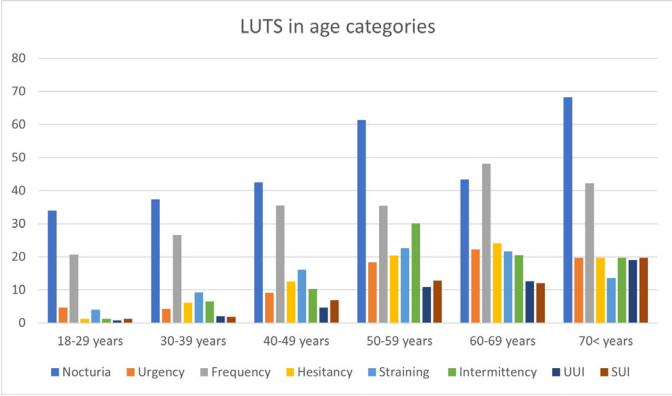

Figure 1. Lower urinary tract symptoms in different age groups of COVID-19 patients

COVID-19: Coronavirus disease-2019

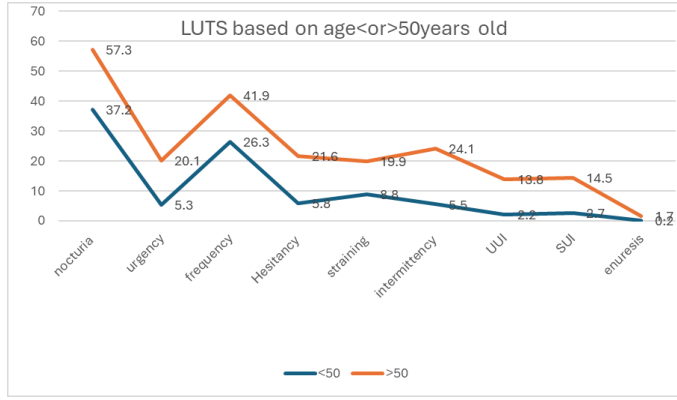

Figure 2. Lower urinary tract symptoms in COVID-19 patients older or younger than 50 years old

COVID-19: Coronavirus disease-2019

Table 5. Filling, voiding and incontinence score of questionnaire

Questionnaires score	Females	Males
Filling score	1.0 (0.0, 14.0)	-
Voiding score	0.0 (0.0, 12.0)	0.0 (0.0, 8.0)
Incontinence score	0.0 (0.0, 16.0)	0.0 (0.0, 2.0)

One of the biggest global health issues currently facing the world is the COVID-19 outbreak, which has historically been the most significant disease worldwide. The strongest national health systems experienced a serious crisis because of this epidemic. Regardless of their specialties, almost all physicians have collaborated to deal with this issue. Most clinical researchers have concentrated on the consequences of the disease on these systems because of the nature of COVID-19 disease, which frequently affects the pulmonary and digestive systems. There is still a substantial gap in the thorough research of this clinical field, despite the studies that have been conducted in the field of urology and the impact of COVID-19 on it. In this context, it has been noted that certain COVID-19 patients experience uncomfortable urine symptoms and heartburn (6). Angiotensin-converting enzyme-2 (ACE2) receptors are highly affine to COVID-19. Therefore, COVID-19 infection is more likely to affect organs with high ACE2 receptor expression. Zou et al. (17) showed that there is a cut-off value for the ratio of ACE2 expression in organs. An expression level of more than 1% was considered to indicate a high risk of COVID-19. The bladder urothelium, which expresses ACE2 at a rate of 2.4%, is at high risk of viral invasion.

This study discovered that over 50% of the participants experienced nocturia. In addition, all symptoms were more common in people over 50 than in people under 50 years old. The results of this study were consistent with those of Daryanto et al. (18). According to their findings, the most common symptoms of the lower urinary tract were frequency, urgency, and nocturia. Complaints about the frequency of urination in the present study were much more than those in the study of Mumm and colleagues, where 7 out of 57 male patients (12%) had this symptom (10). In the study of Kaya et al. (8), on 46 out of 96 patients with COVID-19, all patients completed the LUTS-ICIQ questionnaire. The authors concluded that in male patients, there was no significant difference in the score of the questionnaire in the 3 periods (based on their condition pre-COVID-19, during hospitalization, and post-hospitalized time). In female patients, urinary incontinence and OAB scores were significantly different between the three periods. The presence of reports of intermittent urination in approximately one-eighth of the subjects in the current research is consistent with the study of Kaya et al. (8), who reported that male patients did not have significant voiding symptoms during the illness or after treatment, and these symptoms did not affect their quality of life. In addition, in Chen et al. (19), 5.5% of patients had intermittent urination. The data obtained from the sense of urgency were inconsistent with the results of Chen et al. (6), who stated that only 1.6% of the respondents had a sense of urgency. According to Can et al. (6), elderly patients' lutses dramatically increased with COVID-19 infection. The younger patients did not exhibit this increase. In addition, they stated that the distribution of ACE2 receptors and the various patient age groups are associated with these outcomes. This serves as a reminder of the importance of being aware of the various pathogenic strains of the COVID-19 virus, individual genetic variations, and potential triggers including drug use and urinary system function in patients. The individuals' average age was also lower in this study than in prior investigations. Urinary incontinence, nocturia, daytime urgency, and voiding issues are all common symptoms of LUTS. According to several studies, COVID-19 has been associated with an increased prevalence of LUTS in addition to reducing immunity in patients. Urinary

frequency (97.56%) and nocturia were the two most prevalent LUTSs among COVID-19 patients in Jain et al. (20). Similar conclusions were reached by Dhar et al. (12) in a case study conducted at a tertiary care COVID-19 unit, which found that the most common urological complaints were nocturia (87%) and a urine frequency of 13 episodes/24 hours (85%). They could establish a connection between cystitis and COVID-19 infection because of these findings. Another analysis (21) found a link between COVID-19 and the onset of acute renal damage, infection, and mortality (5.3%). This study discovered that patients' signs of renal dysfunction, such as a 59% rise in proteinuria, a 44% rise in haematuria a 14% rise in blood urea nitrogen, and a 10% rise in serum creatinine levels, increased considerably after contracting COVID-19. Along with a fever or cough, storage symptoms could be one of the first symptoms of COVID-19 because they might have developed after the patient became infected with the virus. The OAB symptoms that the female patients encountered at the outset of the disease and while they were in the hospital were similar to those that the male patients experienced, although these symptoms were managed while they were recovering at home.

A study of the patients' medical records revealed that no patients received either intravenous fluid supply or oral hydration therapy that could increase frequency. The results of our investigation, which excluded hospitalized cases, showed that in addition to nocturia, urine frequency was a typical complaint. According to Sakakibara et al. (22), psychogenic LUTS or an OAB were the other likely causes of storage symptoms. Patients with depression problems were hospitalized and infected with COVID-19, and their sad moods were all explained by a dread of dying once it was discovered that they would have voiding symptoms. Stress incontinence was more common during active infection than before and after, which is a first finding in the literature. The fact that cough is one of the main symptoms of COVID-19 may help explain this finding. An intensified cough may lead to incontinence. As COVID-19 recovers, the cough will lessen, decreasing the likelihood of detecting stress incontinence (8).

Our study's conclusions imply that people with COVID-19 may have or acquire de novo LUTS, particularly storage symptoms. However, only outpatient cases are included, which makes it difficult for us to find any links between LUTS and COVID-19 severity. Because patients were referred to health centers at various phases of COVID-19 disease, the primary study limitation was the inconsistent timing of questionnaire completion by patients. The lack of a control group against which the occurrence of symptoms could be compared was the second issue. We tried to use approved techniques to illustrate the urinary symptoms in large COVID-19 individuals. This research was conducted by referring patients with common COVID-19 symptoms (such as fever and respiratory symptoms) to the first referral level, the health center of Kerman University of Medical Sciences, at the city level. In these centers, a general practitioner was present and provided initial assessment and treatment for COVID-19, explaining COVID-19 warning signs (such as decreased oxygen saturation) to the patient. The patient would be referred to hospitals and higher specialized levels if these symptoms occurred. Therefore, diagnostic methods such as uroflowmetry, PVR measurement, and ultrasonography were not performed at this level, and if patients visited a urologist at higher levels, these tests would be conducted. Regarding the use of the MLUTS questionnaire, it is true that the use of the IPSS questionnaire for symptoms in male patients is more common, but the MLUTS questionnaire is also completely valid and usable. Because the patients were both male and female, a questionnaire was used that had more common aspects between them and could be compared. Our research indicates that storage symptoms, in particular, may be one of the first signs of signs and that physicians should evaluate storage symptoms together with other recognized viral symptoms if a patient is suspected of having the disease. Taken together, the study findings demonstrated that the effects of COVID-19 can impact organs other than the lungs and are not restricted to the lungs. Regardless of the severity of is, urinary symptoms can still develop. Therefore, when the cause of LUTS is unknown, individuals presenting with LUTS should also be assessed for COVID-19. To validate our findings, substantial prospective investigations are required. In particular, the detected mutations and various strains of COVID-19 have varying pathogenicities, and their effects on the operation of various bodily organs, including the urinary system, can vary.

Conclusion

The findings of our study suggest that individuals with COVID-19 may develop or go through de novo LUTS, particularly storage symptoms. The common symptoms in outpatient COVID-19 males were nocturia, urinary frequency, and straining, followed by hesitancy, which were significantly higher than those in females. In contrast, urgency, SUI, and UUI were more common in females than in males. Similar to the males, the common symptoms in women were nocturia and frequency. In addition, with increasing age, LUTS became common in COVID-19 patients.

Ethics

Ethics Committee Approval: The regional ethics committee gave its consent to this work, which followed the ethical code of (approval number: IR.KMU.AH.REC.1400.130, date: 25.09.2021 – Afzalipour Hospital-Kerman University of Medical Sciences Research Ethics Committees).

Informed Consent: All participants in this experiment provided written informed consent.

Authorship Contributions

Concept: A.D., Design: A.D., R.S., M.M., Data Collection or Processing: A.D., R.S., M.M., H.S.-P., Analysis or Interpretation: H.S.-P., Literature Search: R.S., M.M., H.S.-P., Writing: R.S., M.M., H.S.-P.

Conflict of Interest: The authors declare no conflict of interest.

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