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Original Research

De Novo or Increasing Lower Urinary Tract Symptoms during COVID-19 Infection: Long-term Results

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Abstract

Background: How COVID-19 affects lower urinary tract symptoms (LUTS) in men has not been demonstrated by published research. This study examined the *de novo* development of LUTS and the change in the severity of pre-existing LUTS in men hospitalized with COVID-19. A follow-up period of 12 months after COVID-19 infection provided data on the long-term effect of COVID-19 vs. LUTS. **Methods**: Data were collected from 70 male patients diagnosed with COVID-19 via nasopharyngeal swab RT-PCR technology between June 2020 and April 2021. The patient's age, comorbidities, date of COVID-19 diagnosis, date of LUTS, International Prostate Symptom Score (IPSS), prostate-specific antigen (PSA), creatinine, and D-dimer levels, urinalysis, urine culture and duration of hospital stay were recorded. Statistical analyses were conducted to compare between pre-COVID and post-COVID IPSS and other data. **Results**: 42 patients were included in this study with a, mean age of patients were 54.76 $\pm$ 11.95 years. In 8 patients there was no change in IPSS pre- vs. post-COVID. In the remaining 34 patients (80.9%), the median IPSS increased from a pre-COVID value of 2 to 10 during COVID ($p < 0.001$). In the subgroup analysis based on age $<$50 years vs. $\geq$50 years, statistically significant increase in IPSS were found in both age groups pre- and post-COVID. **Conclusions**: In male patients of all ages, COVID-19 results in the *de novo* occurrence of LUTS and an increase in pre-existing LUTS in approximately 80% of patients. These symptoms were found to persist at a 12-months follow-up.

Keywords: cohort; COVID-19; IPSS; LUTS; observational study; urinary tract

1. Introduction

After its first discovery in Wuhan, China, the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread worldwide; the World Health Organization soon declared a pandemic for coronavirus 2019 disease (COVID-19) [1]. Since the World Health Organization declared the disease to be a global pandemic on July 29, 2020, a total of 396,558,014 SARS-CoV-2 cases have been confirmed, and 5,745,032 patients have died of COVID-19 [2]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 2019 (COVID-19), which causes coronavirus disease, is a multisystem disease affecting the respiratory, cardiovascular, gastrointestinal, neurological, and urogenital systems. It can primarily cause acute respiratory distress syndrome and lead to a relatively high risk of death that increases for patients with multiple comorbidities or compromised immune systems [3,4]. For example, COVID-19-related mortality ranged from 0.9% in patients without comorbidities to 10.5% in patients with comorbid diseases. In general, diagnosing COVID-19 can be difficult because patients often present with mixed or even subclinical symptoms [5]. Therefore, the symptomatology of the disease is still not fully defined, even two years into the pandemic [3].

Viral infections of the lower urinary tract can be detected in immunocompromised patients, especially recipients of stem cells and organ transplants. Hemorrhagic cystitis is the most common presentation of lower urinary tract infections in this immunocompromised patients. Angiotensin-converting enzyme (ACE) receptors and transmembrane serine protease 2 (TMPRSS2) enzyme groups have shown to be effective in adhering to and spreading SARS-CoV-2 virus cells to human cells [6]. Despite the presence of ACE 2 receptors in the bladder, there is no consensus on the isolation of SARS-C0V-2 in urine. In publications that reported the isolation of SARS-CoV-2 had in urine, the rate of isolated patients was very low [7–9]. The lower urinary tract (LUT) is a highly vascularized functional system with a unique muscular structure innervated by the somatic nervous system and the autonomic nervous system.

Determining the impact of COVID-19 on lower urinary tract symptoms (LUTS) is important for understanding of inflammation in the bladder. COVID-19 may play a role in the pathogenesis of LUTS. The possible pathophysiology of COVID-19 related lower urinary tract dysfunction may be cytokine cystitis. Lamb *et al.* [10] hypothesized that increased inflammatory cytokines, secondary to COVID-19 infection, may be released into the urine and/or involve the bladder and lead to *de novo* LUTS.

We observed that patients without a history of LUTS

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applied to our clinic with *de novo* LUTS after COVID-19 infection. We designed our study by generating hypotheses informed by our clinical observations. Few published studies have evaluated the short-term effects of COVID-19 on LUTS [11,12]. However, there has been no detailed follow-up relating to long-term LUTS in patients with COVID-19.

This study presents the *de novo* occurrence as well as an increase in previously existing LUTS in patients hospitalized for COVID-19 and its effect on disease prognosis.

2. Materials and Methods

Data were collected prospectively from 70 male patients diagnosed with COVID-19 via a nasopharyngeal swab RT-PCR test between June 2020 and April 2021. Local institutional review board (Sakarya University) approval (study no. 71522473-317) was obtained before study initiation. The study followed the ethical principles of the Declaration of Helsinki.

Chest computed tomography showed consolidated areas that suggest the presence of pneumonia in all patients. Because LUTS might be aggravated after COVID-19 infection in benign prostatic hyperplasia (BPH) patients, BPH patients undergoing treatment were excluded. From the initial 70 patients, 28 patients were excluded for the following reasons: patients under treatment for BPH or overactive bladder; history of urinary tract cancer and/or infection; received surgery of the urinary system; and presence of a foley catheter. The remaining 42 patients were invited to participate in the study; all 42 patients agreed and written informed consent was obtained from all patients.

Patients' age, body mass index (BMI), smoking, comorbidities, date of LUTS, diagnosis date of COVID-19, International Prostate Symptom Score (IPSS), creatinine levels, prostate-spesific antigen (PSA) levels, D-dimer levels, urinalysis, urine culture and length of hospital stay were recorded. Due to the prohibition of patients leaving their rooms in the early period of the pandemic to prevent exposure to non-COVID-19 patients, prostate volume, uroflowmetry and residual urine volume could not be performed. A subgroup analysis was done according to the patients' ages. Group 1 consisted of patients aged $\leq$50 years, and Group 2 consisted of patients $>$50. A 3- and 12-month follow-ups was conducted for all patients where they were called and questioned about LUTS.

2.1 Nucleic Acid Isolation and RT-PCR Study

Samples were brought to a microbiology laboratory where samples were isolated in a class 2-a biosafety cabinet. RNA isolation from Oro-nasopharyngeal samples was performed with EZ1 Virus Mini Kit v2.0 (Qiagen, Hilden, Germany, Lot number: 172013610) on the EZ1 instrument. Cycle threshold (Ct) was used as an indirect method of quantifying viral load in each sample; Ct is inversely related to viral load. A Ct value of less than 45 was interpreted as positive for SARS-CoV-2 RNA [13].

2.2 Statistical Analysis

Continuous variables were presented using descriptive statistics in the form of mean, median, standard deviation (SD), and minimum-maximum (min-max). Categorical variables were shown as the number of cases (n) and percentage (%). The Mann-Whitney U test was used to compare continuous data, and the Spearman correlation test was used to compare hospitalization time and IPSS values (pre-COVID, post-COVID, and IPSS change). LUTS was classified according to IPSS scores (0–7 mild, 8–19 moderate, 20–35 severe), and the hospitalization time was compared between groups using the Kruskal–Wallis test. Friedman's test was used to analyze IPSS values (total IPSS, plus storage and voiding symptom scores) before, during, and after COVID-19 diagnosis. Further, we investigated independent predictors for LUTS patients over 50 years of age using multivariate linear and logistic regression analyses. We included age, BMI, hypertension, diabetes mellitus, smoking, and PSA as potential variates. The sample size was estimated to detect an adequate number of patients to be included in the study to reveal a significant difference between pre-COVID-19, during COVID-19, and IPSS results at 3- and 12- months follow-ups. According to a pilot study of 46 patients, the adequate sample size for this study was calculated (none of the data from the pilot study were included in the analysis). The standard effect size was set at 0.25 with an 80% effect (1-b) and 5% standard error (a) margin. Based on the calculation, a total of 35 cases were found to provide sufficient data to perform statistical analyses with adequate power. Statistical significance was considered at $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics for Windows (version 21.0, IBM Corp., Armonk, NY, USA) and G*Power for Windows (version 3.1.9.7, Heinrich-Heine-Universität, Düsseldorf, Germany).

3. Results

A total of 42 patients were included in the study. Characteristics of the patients are shown in Table 1.

Table 1. Descriptive analysis of study variables.

	Mean $\pm$ SD	Median (min–max)
Age (year)	54.76 $\pm$ 11.95	54 (36–80)
BMI (kg/m^2)	28.84 $\pm$ 3.45	28.94 (22.09–41.52)
Creatinine (mg/dL)	1.01 $\pm$ 0.46	0.96 (0.68–3.80)
PSA (μg/L)	1.19 $\pm$ 1.40	0.92 (0.27–9.33)
D-dimer (ugFEU/L)	454.21 $\pm$ 328.37	422.50 (110–1570)
Hospitalization time (day)	7.92 $\pm$ 3.95	8 (1–21)

BMI, body mass index; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; SD, tandard deviation.

No macroscopic hematuria was detected in any patient from a urinalysis. Urine culture results were positive in 3 (7.1% of 42) patients. 2 patients had Staphylococcus aureus and one patient had a positive urine culture for Streptococcus agalactiae (all of them were >100,000 CFU/mL). IPSS scores and LUTS severity of 42 patients before and during COVID-19 were compared. No change was observed in symptom scores in 8 patients. İn addition, 34 patients (80.9%) had a median IPSS score of 2 before COVID-19, which increased to 10 during COVID-19 ($p < 0.05$). Median IPSS scores before COVID-19, during COVID-19, and at 3- and 12-month follow-ups are shown in Table 2.

Table 2. IPSS scores before COVID-19, during COVID-19, and follow-up of patients.

	Median (min–max)
Pre-COVID IPSS	2.5 (0–23)
Pre-COVID storage symptom score	2 (0–11)
Pre-COVID voiding symptom score	1 (0–18)
During-COVID IPSS	10 (0–29)
During-COVID storage symptom score	4 (0–13)
During-COVID voiding symptom score	5 (0–18)
3-month IPSS	5 (0–21)
3-month storage symptom score	2.5 (0–12)
3-month voiding symptom score	2 (0–13)
12-month IPSS	4.5 (0–20)
12-month storage symptom score	2 (0–12)
12-month voiding symptom score	2.5 (0–14)

At the 3- and 12-month follow-ups of 34 patients whose IPSS scores increased during COVID-19, LUTS developed due to COVID-19 persisted in five (14.7%). The mean age of these 5 patients was 48.6 $\pm$ 13.9 years compared to 54.76 $\pm$ 11.95 years for the full sample. Comparison between IPSS pre-COVID, during COVID, and at 3- and 12-months follow-ups are shown in Fig. 1.

7 patients (16.6%) with an IPSS score below 20 in the pre-COVID-19 period reported an increase in LUTS during COVID-19 with IPSS scores of 20 and above. It was observed that LUTS severity in all patients decreased and returned to the pre-COVID-19 period at the 3-month follow-up.

In the subgroup analysis according to age, there was no statistical difference in BMI, D-dimer, creatinine, and hospitalization time between Group 1 and Group 2. IPSS, voiding, and storage median symptom scores pre-and during COVID-19 in the under 50 age group were lower than the over 50 age group. This result was statistically significant ($p < 0.05$).

For the over 50 years groups, total IPSS and, voiding and storage symptom scores during COVID-19 were found to be greater than the scores at the 3- and 12-month follow-ups. Additionally, in the group under 50 years of age, the total IPSS and voiding subscore during COVID-19 were greater than at the 3- and 12-month follow-ups. These results were statistically significant with a p-value of 0.05. The changes in IPSS of patient groups before, during and after COVID-19 infection are shown in Table 3.

A statistically significant increase was seen in both groups when comparing the pre-COVID with the post-COVID period (Fig. 1).

Patients were divided into three groups, according to COVID-19 Reporting and Data System (CO-RADS) assessment of their involvement in the lung with computed tomography (CT) thorax images taken during COVID-19 infection. For these three groups, no statistically significant difference was found between IPSS, and voiding and storage symptom scores.

In patients over 50 years of age, LUTS may be affected by many factors such as age, smoking, hypertension, BMI, and diabetes mellitus. We investigated these parameters using a multivariate analysis of COVID-19 patients whose elevated IPSS persisted at the 3-and 12-month follow-ups. No variables were found to be associated with LUTS in the multivariant analysis shown in Table 4.

4. Discussion

The etiology of LUTS may include inflammation of the lower urinary tract, detrusor overactivity, sphincter weakness, sensory bladder disorders and BPH. LUTS are classically characterized as related to storage (e.g., frequency, urgency, and nocturia) or flow (e.g., weak stream, intermittency, straining, and incomplete emptying).

Developed and validated for LUTS evaluation, the International Prostate Symptom Score (IPSS) is accepted as the gold standard for patient-reported outcomes. IPSS includes seven questions investigating frequency, nocturia, weak urine flow, hesitancy, intermittency, incomplete emptying, and urgency. Each question is attributed between 0 and 5 points, producing a total symptom score ranging from 0 and 35. Based on the total symptom score, symptoms can be classified as mild (0 to 7), moderate (8 to 19), or severe (20 to 35). The set of seven IPSS questions is internally consistent and reliable; it correlates strongly with the global ratings of urinary difficulties in patients and is sensitive to treatment response.

Measuring symptom severity is essential for understanding disease severity, treatment response, and disease progression risk. The detection of symptoms such as storage and voiding provides valuable information for diagnosis. Storage symptoms are mainly seen in conditions such as inflammation and neurological disease that cause detrusor overactivity and decreased compliance caused by neurological disease and fibrosis. Voiding symptoms are mainly seen in bladder outlet obstruction and in neurogenic and myogenic diseases that cause bladder underactivity.

Lower urinary tract infections (UTIs) are common in urological practice, and most urologists are familiar

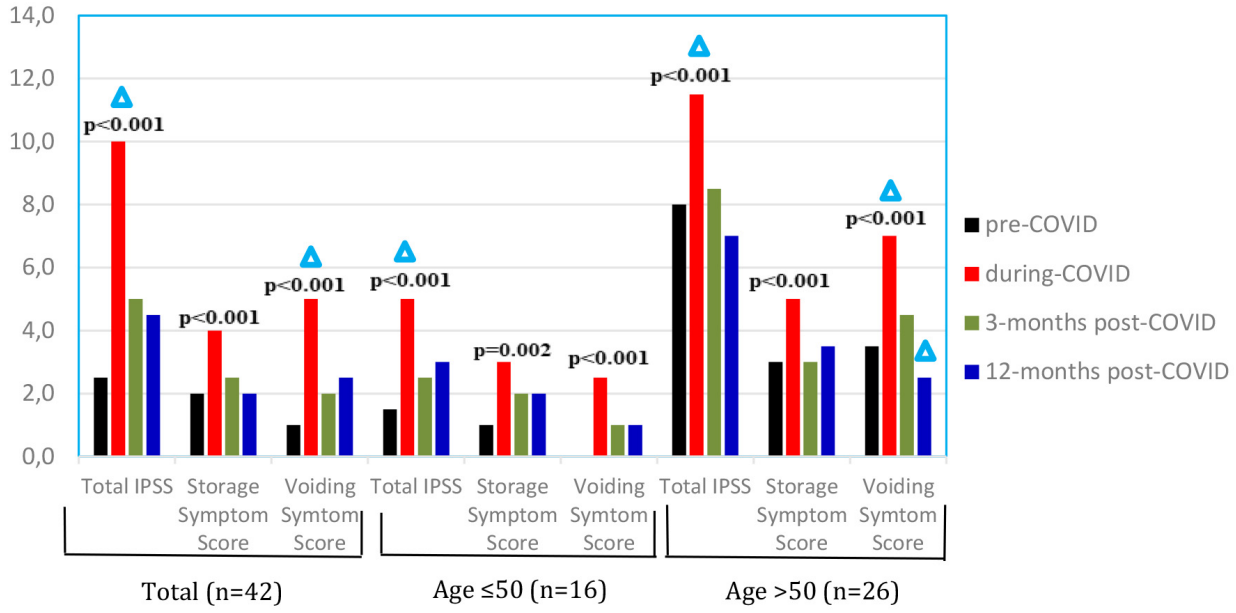

Fig. 1. Comparison of IPSS between pre-COVID, during COVID, and follow-up at 3-months and 12-months post-COVID diagnosis. Δ, change in IPSS of 3 points or more.

Table 3. Change in IPSS before, during and after COVID-19 infection.

	Age ≤50 (n = 16) median (min–max)	Age >50 (n = 26) median (min–max)	*p* value*
Before COVID-19 total IPSS	1.5 (0–11)	8.0 (0–23)	0.004
During COVID-19 total IPSS	$\Delta^{3.5}$ 5.0 (0–20)	$\Delta^{3.5}$ 11.5 (2–29)	0.010
Post COVID-19 3-month IPSS	2.5 (0–18)	8.5 (0–21)	0.020
Post COVID-19 12-month IPSS	3.0 (0–17)	7.5 (0–20)	0.077
p value**	<0.001	<0.001	
Before COVID-19 storage subscore	1.0 (0–5)	3.0 (0–11)	0.006
During COVID-19 storage subscore	3.0 (0–10)	5.0 (0–13)	0.041
Post COVID-19 3-month storage subscore	2.0 (0–8)	3.0 (0–12)	0.050
Post COVID-19 12-month storage subscore	2.0 (0–8)	2.5 (0–12)	0.168
p value**	0.002	<0.001	
Before COVID-19 voiding subscore	0 (0–7)	3.5 (0–18)	0.020
During COVID-19 voiding subscore	2.5 (0–14)	$\Delta^{3.5}$ 7.0 (0–18)	0.021
Post COVID-19 3-month voiding subscore	1.0 (0–11)	4.5 (0–13)	0.038
Post COVID-19 12-month voiding subscore	1.0 (0–9)	3.5 (0–14)	0.091
p value**	<0.001	<0.001	

*, Mann-Whitney U test; **, Friedman test; Δ, change in IPSS of 3 points or more.

Table 4. Multivariate analysis of various factors potentially affecting LUTS for in patients over 50 years of age.

Variable	OR (95% CI)	*p* value
Age	0.944 (0.860–1.037)	0.230
BMI	1.220 (0.942–1.581)	0.132
Hypertension	3.125 (0.460–21.252)	0.244
Diabetes mellitus	1.071 (0.103–11.130)	0.954
Smoking	1.969 (0.293–13.212)	0.486
PSA	0.501 (0.074–3.400)	0.479

with typical bacterial pathogens and current treatment paradigms; however, less is known about viral pathogens that can cause lower urinary tract infections. Generally, infections of the lower urinary tract manifest through suprapubic pain, dysuria, and storage LUTS. When LUT infections accompany prostate infection, voiding symptoms such as intermittency, hesitancy, and fever are added to the clinical picture. Bacterial LUT infection is usually treated without complication if there is no underlying anatomical disorder or immune system pathology. Viral lower urinary tract infection is seen in immunocompromised patients who

have undergone solid organ transplantation or bone marrow transplantation. Viral lower urinary tract infection is extremely rare in patients without a suppressed immune system. In viral LUT infections, macroscopic hematuria is frequently added to suprapubic pain and storage LUTS. Hematuria is the most common symptom of viral LUT infections. The mortality rate from lower UTIs is extremely low in patients with normal immune systems; however, viral UTIs with a high viral load may be associated with high mortality in patients whose immune systems are compromised due to multi-organ viral infections and insufficiency. SARS-CoV-2 has a specific three-dimensional spike protein structure characterized by a strong binding affinity to angiotensin-converting enzyme 2 (ACE2) receptors. In this setting, human cells expressing ACE2 can act as target cells for SARS-CoV-2 [14].

In their study, Mumm *et al*. [15] reported the that urinary frequency of 12.2% of patients with COVID-19 infection. However, this study only evaluated the frequency. In the present study, 80% of patients experienced LUTS with a significantly different IPSS compared to the pre-infection period. Also, when storage and voiding symptoms were evaluated separately, there was no significant difference in the number of symptoms. However, hematuria the leading symptom of viral cystitis was not observed in any of our patients nor was suprapubic pain, another symptom of cystitis. On the other hand, COVID-related symptoms persisted in five (14.7%) patients at the 12-month follow-up. This suggests that SARS-CoV-2 may have a chronic permanent effect on lower urinary tract tissues.

Lamb *et al*. [10] examined urinary cytokine levels in 4 patients with COVID-19 infection. IL-6, IL-8 and IP-10 levels were higher in the urine of all patients with COVID-19 compared to patients without COVID-19, with IL-6 and IL-8 elevations being statistically significant between the two groups. Lamb *et al*. [10] termed this difference as termed this COVID-19 associated cystitis (CAC).

Karabulut *et al*. [16] concluded that COVID-19 infection progressed more severely in patients with higher IPSS symptom scores. The onset period of LUTS in patients included in Karabulut *et al*. [16] was not discussed. The results reported in this paper found that although there was no statistically significant difference between the two groups, both storage and voiding symptoms of IPSS were common in patients with COVID-19 infection over the age of 50 years compared with patients under 50 years.

In acute bacterial infection of the prostate, there is an increase in voiding symptoms that are secondary to obstruction in the prostatic urethra. It is also known that bacterial infections of the prostate can cause an increase in PSA levels above normal. However, a viral infection of the prostate is very rare [17,18]. Studies on viral infections of the prostate in the literature are limited to case reports [18,19]. The present study, although the basal PSA values were not known, it was observed that PSA values did not exceed the normal value; however there was a significant increase in the patients' voiding symptoms, the PSA values remained within the normal range and suggested that COVID-19 infection did not cause inflammation in the prostate.

In the current study, one patient who did not report having any prior urological complaints developed a neurogenic bladder as evidenced by post-infection urodynamic studies. The patient drained their bladder using clean self intermittent catheterization. Hence, it could be hypothesised that a urodynamic study is necessary to understand the functional change in LUT. However, because of ethical concerns, it does not seem possible to conduct such a study in the acute period. It is known that there are changes in the detrusor function in chronic ischemia of the bladder. There are publications in the literature about COVID-19 causing common microangiopathy, but this also seems to be a different research topic.

None of the patients included in the study attended the urology outpatient clinic for LUTS. LUTS is a set of symptoms that affect the quality of life; these symptoms may not be a primary reason for patients to attend an outpatient clinic, especially when they might intend to avoid COVID-19 infection from visiting the hospital. However, patients with a history of lower urinary tract pathologies may have more complaints with COVID-19. The most important limitation of the present study is the low number of participants since face-to-face meetings with participants infected with COVID-19 were not feasible due to the risk of virus transmission.

5. Study Limitations

This study has the following limitations. Known pro-inflammatory cytokines or biomarkers such as hypersensitive C-reactive protein (hsCRP), IL-6, IL-1β, VEGF, COX-2, MCP-1, VCAM-1, etc., were not obtained from the study sample. The AUA-SI was not included and therefore quality of life scores could not be provided. Prostate volume, voiding diary data, uroflowmetry, and residual urine volume were not obtained due to clinical concerns relating to the infectious status of the COVID-19 patients.

6. Conclusions

LUTS may develop *de novo* or prior symptoms may rise, in patients with COVID-19 infection. Questions concerning lower urinary system symptoms should not be omitted during the diagnosis and treatment of COVID-19 patients.

Author Contributions

OKö and OKa conceived of the presented idea and developed the theory. OKö wrote the manuscript with support from YTA, BU. EG and HT were involved in planning and supervised the work. AE and HIC processed the experimental data, performed the analysis, drafted the manuscript.

All authors discussed the results and contributed to the final manuscript.

Ethics Approval and Consent to Participate

Before the beginning, the necessary approval was received from the local committee of our hospital with the 05/06/2020 dated and 317 numbered decision. The study followed ethical principles of the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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