Does Covid-19 affect lower urinary tract symptoms (luts) of male patients?

Soner Çoban[1], Atilla Satır[1], Salim Zengin[1], Özgür Ekici[2], Anıl Erkan[1], Muhammet Güzelsoy[1], Ali Rıza Türkoğlu[1], Metin Kılıç[1], Murat Öztürk[1], Ali Asan[3], Abdulbaki Kalkan[1], Abdullah Gül[1], Akif Koç[1]

[1]Department of Urology, University of Health Sciences, Bursa Yuksek Ihtisas Education and Research Hospital, Bursa, Turkey
[2]Department of Urology, Erzincan Binali Yildirim University, Erzincan, Turkey
[3]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Bursa Yuksek Ihtisas Education and Research Hospital, Bursa, Turkey

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ABSTRACT

Objectives: We investigated the effect of COVID-19 on lower urinary tract symptoms (LUTS) in male patients.

Methods: 110 patients diagnosed with COVID-19 were prospectively included in the study. Fifty-five male patients over the age of 40 who were hospitalized with the diagnosis of COVID-19 at University of Health Sciences, Bursa Yuksek Ihtisas Education and Research Hospital between May 2020 and April 2021, who did not meet the exclusion criteria, were included in the study. As a control patient, 80 patients in the same age group who applied to the urology outpatient clinic for reasons other than LUTS were included. Demographic data of the patients such as age, total prostate specific antigen (tPSA), free PSA (fPSA), International Prostate Symptom Score (IPSS), height and weight were recorded and analyzed. Patients were classified as mild (0-7), moderate (8-19), and severe (20-35) according to their IPSS. These forms were filled in by patients to avoid possible influence from the practitioner. All patients with 5 or more nocturia numbers were considered to have 5 nocturia numbers.

Results: There was no age difference between the groups (p = 0 .29). Although the IPSS value in the COVID-19 group was lower than the patients in the control group who applied to the outpatient clinic, the difference was found to be statistically insignificant (p = 0.07). Similarly, although nocturia and prostate volume was lower than the control group, the difference was not statistically significant. The tPSA and fPSA examined were found to be statistically significantly lower in the COVID 19 group (p = 0.01, p = 0.009, respectively). However, there was no difference between f/t PSA (p = 0.3).

Conclusion: We found that COVID 19 did not affect LUTS in male patients.

Keywords: COVID-19, free/total PSA, lower urinary system symptoms, nocturia

Benign prostatic hyperplasia (BPH) is a histologic definition that develops because of the simultaneous overgrowth of epithelial and stromal cells of the prostate [1]. It is the most common cause of benign prostatic obstruction. Lower urinary tract symptoms (LUTS), which are closely related to benign prostatic obstruction, develop

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Address for correspondence
Özgür Ekici MD., Department of Urology, Erzincan Binali Yildirim Unıversity, Erzincan 24000, Turkey
E-mail: ekici_1990@hotmail.com

because of disruption of both bladder and prostate dynamics [1]. International prostate symptom score (IPSS), prostate specific antigen (PSA) and finger rectal examination are the first tests for the diagnosis of LUTS which increases with age and significantly impairs quality of life.

Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2), which was first isolated in Wuhan province of China in November 2019, has been in our lives for more than 2 years and despite improved vaccines, it causes more than 100 deaths per day according to data from the Turkish Ministry of Health. Although the organs and systems most responsible for deaths are the lungs, heart and cardiovascular system, the virus has been isolated in many organs [2, 3]. SARS-CoV-2 enters the cell through cells expressing angiotensin converting enzyme-2 (ACE-2) and transmembrane serine protease-2 (TMPRSS2). In a study examining the distribution of ACE-2 expression using RNA sequences from different organs, it was reported that it was expressed at a rate of 4% in renal proximal tubule cells and 2.4% in bladder uroepithelial cells [4]. According to this study, the most sensitive organs were lung, heart, esophagus, kidney, ileum and bladder.

Although typical symptoms include fever, cough, headache and diffuse muscle pains, new symptoms related to the involvement of many organs emerge as the disease becomes better understood. Symptoms and findings may also be observed in urinary system involvement, including tightness due to uroepithelium involvement, increased urinary frequency, microscopic haematuria, and acute renal failure [5, 6]. According to the results of a multicentre study, although no lower urinary system symptoms were reported in any patient, the virus was isolated in urine in 19% of the patients [7]. Such a high incidence of uroepithelium has led urologists to investigate the relationship between LUTS and COVID-19 [6, 8].

Our study aimed to investigate whether coronavirus infection affects LUTS in male patients.

METHODS

This prospective study was conducted in accordance with the Declaration of Helsinki and the Ethical Principles of Clinical Research. It was approved by the Clinical Research Ethics Committee of Health Sciences University Bursa Yuksek Ihtisas Education and Research Hospital (decision number 2011-KAEK-25 2020/05-14 dated 27.05.2020). 55 male patients over 40 who were hospitalised with a diagnosis of COVID-19 at University of Health Sciences, Bursa Yuksek Ihtisas Education and Research Hospital between May 2020 and April 2021 were included in the study. As control patients, 100 patients of the same age group who applied to the urology outpatient clinic with complaints other than LUTS were included. Patients included in the study signed an informed consent form.

Exclusion criteria were patients with a PSA value >10 ng/ml or prostate malignancy detected as a result of prostate biopsy with a PSA value between 4-10 ng/ml, previous use of alpha-blockers or 5-alpha reductase inhibitors, Diabetes Mellitus, Chronic Obstructive Pulmonary Disease, TUR-P and/or any interventional treatment for BPH, patients with urethral stricture and/or lower urinary tract surgery (such as urethrotomy, urethroplasty, hypospadias repair, cystolithotomy) for any reason, patients diagnosed with prostate cancer and/or radical prostatectomy, patients with neurological examination findings and/or neurological disease (such as cerebrovascular accident, spinal trauma, multiple sclerosis), patients with a history of diuretic and alcohol use. The patients included in the study were divided into COVID-19 and control groups. The COVID-19 group included hospitalised patients who were definitively diagnosed with reverse transcriptase-polymerase chain reaction (RT-PCR) (Device-Biorad (USA), Kit-Qiagen (USA) test. PCR tests were performed in the acute period when symptoms started the patients whose symptoms regressed after treatment were routinely discharged without PCR testing.

Demographic data of the patients, including age, total PSA (tPSA), free PSA (fPSA), IPSS, prostate volume measured by USG, number of nocturia, height, weight, and medical history, were recorded. According to IPSS, 7 questions were asked to the patients, each receiving a score between 0 and 5 (9). Patients were classified as mild (0-7), moderate (8-19) and severe (20-35) according to IPSS. The quality-of-life index of the IPSS form was used as a quality-of-life scale [10]. The patients filled in these forms to prevent the possible influence of the practitioner. However, it was stated that patients could request information from us for questions they needed help understanding. The number of nocturia was accepted as 5 in all patients with 5 or more than 5 nocturia.

Data were analysed using Statistical Package for Social Sciences (SPSS) version 22.0™ (IBM Corpo-

Table 1. Mean age of patients and results of investigations

	COVID-19 group (n = 55)	Control group (n = 80)	*p* - value
Age (year) mean ± SD	59.46 ± 11.3	61.6±7.8	0.29
Creatinine (mg/dl) mean ± SD	0.9 ± 0.2	0.9±0.1	0.36
Total PSA (ng/ml) median (IQR)	0.8(1.1)	1.3(2.2)	0.01*
Free PSA (ng/ml) median (IQR)	0.3(0.3)	0.5(0.7)	0.009*
f/t PSA median (IQR)	0.4(0.2)	0.3(0.2)	0.3

PSA: prostate specific antigen *$p < 0.05$

ration). The distribution of variables was measured using the Shapiro-Wilk test. Statistical analyses were performed using Student's ttest, the Mann-Whitney U test with and without normal distribution, respectively. Categorical variables were compared using chi-squared test. $P < 0.05$ was considered statistically significant.

RESULTS

The study included 110 patients hospitalised in the COVID-19 ward. Of these patients, 7 were excluded because of a PSA result > 10 ng/ml, 38 were excluded because they were using alpha-blockers and/or 5-alpha reductase inhibitors due to LUTS, and 10 were excluded because they had a history of previous prostate and/or urethral surgery. The data of the remaining 55 people in the COVID-19 group were analysed. In the control group, 100 people who were not diagnosed with COVID-19 and who applied to the urology outpatient clinic for reasons other than LUTS were included. In this group, 9 patients were excluded because the PSA result was >10 ng/ml, 5 patients were excluded because prostate cancer was detected as a result of a biopsy taken between 4-10 ng/ml, 3 patients were excluded because they had a history of active or previous malignancy of the urological system, and 3 patients were excluded because renal function tests were impaired and/or chronic renal failure was diagnosed. The data of the remaining 80 patients in the control group were analysed.

The mean age of the patients and the results of the tactics are shown in Table 1. The values in the table are given as mean ± standard deviation or median (interquartile range), with and without normal distribution, respectively.

Information about IPSS, number of nocturia, quality of life scale score and prostate volume are summarised in Table 2. The data in the table are shown as mean ± standard deviation. Although the IPSS value in the COVID-19 group was lower than that in the control group of patients presenting to the outpatient clinic due to LUTS, the difference was statistically insignificant ($p = 0.07$). Similarly, although nocturia and prostate volume was lower in the COVID-19 group compared to the control group, the difference was not statistically significant.

Twenty (36%) patients in the COVID-19 group and 11 (13.8%) in the control group were mildly symptomatic, and the difference was statistically significant ($p = 0.002$) (Table 3). However, the groups in moderate and severe symptomatic patients had no significant difference, according to IPSS. The relationship between IPSS and prostate volume is shown in Figure 1.

Table 2. Comparison of COVID-19 group and control group values

	COVID-19 group (n = 55)	Control group (n = 80)	*p* - value
IPSS	13.3 ± 9.5	15.5 ± 6.6	0.07
Number of nocturia	2.2 ± 1.5	2.6 ± 1.1	0.61
Quality of life scale score	2.8 ± 2.2	4.3 ± 1.5	< 0.001*
Prostate volume	44.3 ± 19.1	52.1 ± 25.9	0.18

IPSS: International Prostate Symptom Score, * $p < 0.05$

Table 3. Frequency of nocturia and IPSS

	COVID-19 group (n = 55)	Control group (n = 80)	*p* - value
Nokturia			
0	6 (10.9%)	0	< 0.001*
1	14 (25.5%)	7 (8.8%)	0.009*
2	13 (23.6%)	39 (48.7%)	0.003*
3	11 (20%)	15 (18.7%)	
4	4 (7.3%)	14 (17.5%)	
5	7 (12.7%)	5 (6.3%)	
IPSS severity			
Mild	20 (36.4%)	11 (13.8%)	0.002*
Moderate	21 (38.2%)	42 (52.5%)	
Severe	14 (25.4%)	27 (33.7%)	

IPSS: International Prostate Symptom Score, *$p < 0.05$

DISCUSSION

COVID-19 primarily affects the lungs, causing respiratory symptoms. On the other hand, it can involve all organs and systems through ACE-2 receptors. Bladder and prostate involvement may lead to de novo lower urinary system symptoms or worsening of existing symptoms, increased urinary frequency, and microscopic haematuria [11]. These complaints and the COVID-19-related cystitis picture are thought to be related to the cytokines released. In fact, it has been reported that the cytokine storm, which is responsible for the disease's rapid progression, causes demyelination in central and peripheral nerves and leads to acute urinary retention [12]. However, in the present study, we showed that COVID-19 did not change the symptom scores, the number of nocturia, and prostate volume of BPH patients and only caused changes in PSA values.

The prostate is a target for SARS-CoV-2, just as

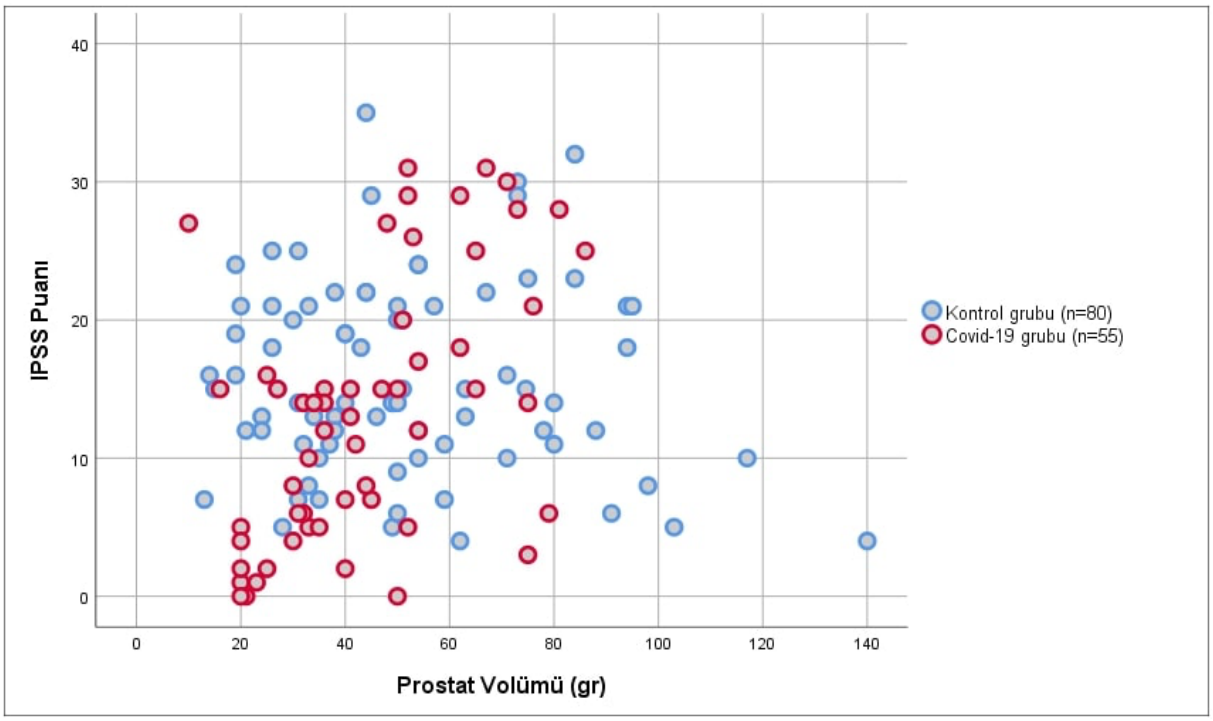

Figure 1. Distribution graph of prostate volume and international prostate symptom score of the patients

other organs are targets via ACE-2 and TMPRSS2 receptors. The possible mechanism is related to tissue damage and disruption of the structure of the ductus, as in prostatitis. Disruption of this structure may lead to an increase in the level of PSA in the blood. In their study investigating the effect of COVID-19 on PSA levels in BPH patients, Cinislioğlu *et al*. found that the PSA value during the COVID period was statistically significantly higher than before and after COVID-19 [13]. In the present study, total and free PSA values of COVID patients in our study population were statistically significantly lower than in the non-COVID control group. According to the authors of the study, antibiotics, anti-virals or steroids taken by inpatients to prevent bacterial co-infections may have led to lower PSA values compared to the control group.

Our study found no difference between the COVID and the control groups regarding IPSS. In their research, including both genders, Kaya *et al*. had patients hospitalised and discharged due to COVID-19 fill out IPSS and Urinary Symptom Profile (USP) before, during and after hospitalisation. In male patients, only the storage scores of IPSS were found to be different between the three periods. In female patients, stress incontinence and overactive bladder symptoms significantly differed in three periods [14]. Can *et al*. divided COVID-19 patients into low-moderate-severe groups according to lung involvement and analysed the correlations of these groups with IPSS. According to the analysis, no correlation was found between the severity of CT findings and IPSS. In the group over 50 years of age, an increase in IPSS during the COVID period compared to the previous period was found to be statistically significant [15]. Nabeeh *et al*., in their study including 50 BPH patients, found that the IPSS value increased statistically significantly during hospitalisation and in the 1st and 3rd months after discharge compared to the pre-COVID period [16]. In addition, the quality-of-life score worsened during the COVID-19 period in this study. In our research, on the contrary, the quality-of-life score was found to be lower in the COVID-19 patient group.

In our study, there was no difference between the COVID-19 group and the control group regarding the number of nocturia. Swatesitipun *et al*., in their study including 136 COVID-19 patients, reported that 44.85% of patients had storage symptoms, and the group with storage symptoms had a significantly higher number of nocturia than the other group [17]. Although not in a comparative study, Dhar *et al*. reported that all patients had nocturia symptoms, and 87% of patients had nocturia >4 in a study including COVID-19 patients of both sexes with 39 diseases [5]. The prominence of nocturia is probably because viral infections lead to storage disorders. For example, according to a study conducted on patients infected with the HTLV-1 virus, the most common urological finding in these patients was nocturia, with 35.8% [18]. Studies in which cytokine increase was detected in urine samples of patients with storage phase disorders support this theory [19]. Lamb *et al*. reported that IL-6, IL-8 and IL-10 levels were increased in all COVID-19 patients in their study conducted with 4 COVID-19 patients with de novo urinary system symptoms and 4 patients in the control group. They defined the new-onset lower urinary system symptoms associated with COVID-19 as COVID-19-related cystitis [19].

According to the results of our study, COVID-19 does not negatively affect lower urinary tract symptoms and nocturia. The findings in the literature generally contradict our results. However, studies that partially support our results have also been published. For example, Welk *et al*., in their study comparing 5617 COVID-19 patients with 11225 patients who did not have COVID-19, did not observe a significant difference in the COVID-19 group in terms of the use of medication, urology consultation and cystoscopy necessity in terms of the overactive bladder within 2-5 months after COVID-19. Therefore, they stated that it did not lead to significant bladder dysfunction after the acute period [20].

In contrast to our research question, in a study on the effect of lower urinary tract symptoms on COVID-19 prognosis, Karabulut *et al*. divided COVID-19 patients into low-medium-high risk groups in terms of IPSS. They found more hospitalisation time, more intensive care unit hospitalisation and higher mortality rate in the high-risk group compared to patients in the low-risk group [21]. According to the study's authors, lower urinary tract symptoms can be used to predict the prognosis and severity of COVID-19.

Among the study's limitations, antibiotics, and the amount of fluid intake, which may affect nocturia and PSA levels in the patient groups, were not known. These factors may have caused changes in nocturia and PSA levels.

CONCLUSION

We found that COVID-19 did not affect LUTS in male patients. On the other hand, tPSA and fPSA

were statistically significantly lower in the COVID-19 group, which may delay the diagnosis of prostate cancer. Therefore, the decision for biopsy in patients with COVID-19 should be based on the f/t PSA ratio.

Conflict of Interest

There is no conflict of interest between the authors.

Ethics Committee Decision

It was approved by the Clinical Research Ethics Committee of Health Sciences University Bursa Yuksek Ihtisas Education and Research Hospital (decision number 2011-KAEK-25 2020/05-14 dated 27.05.2020).

Authors' Contribution

Authors' Contribution Study Conception: AA,; Study Design: SZ, ÖE, AE,; Supervision: AG, MK, AB,; Materials: AK, MÖ, AA,; Data Collection and/ or Processing: SÇ, AS,; Statistical Analysis and/ or Data Interpretation: SZ, ÖE, AE; Literature Review: AG, MK, AK,; Manuscript Preparation: ART, MG and Critical Review: AK, MÖ, AA.

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