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Increased Lower Urinary Tract Symptoms in Female COVID-19 Patients: A Clinical Trial

Kadın COVID-19 Hastalarında Artan Alt İdrar Yolu Belirtileri: Klinik Bir Deney

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ABSTRACT Objective: The coronavirus disease-2019 (COVID-19) outbreak is the latest and greatest disease affecting all over the world recently. Despite the measures being taken in countries, data related to the COVID-19 outbreak is increasing day by day. The diagnosis of COVID-19 patients with atypical/non-specific symptoms is likely to be overlooked during this pandemic process. This study aimed to investigate the changes in lower urinary tract symptoms (LUTS) in females after COVID-19 infection. **Material and Methods:** A total of 62 female patients who were diagnosed with COVID-19 were included in the present study. The International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) scores of patients measured before and during COVID-19 infection were compared. Furthermore, the ICIQ-FLUTS scores after COVID-19 infection were compared with thoracic computed tomography findings. Urinary tract infections and other causes affecting urinary frequency were excluded from the study. **Results:** Total ICIQ-FLUTS scores after COVID-19 infection were found statistically increased in female patients ($p<0.0001$). However, increased LUTS were not correlate with violence of lung involvement ($r=0.063$, $p=0.629$). **Conclusion:** Information about COVID-19 is limited since it is a quite new disease. The LUTS were found to significantly increase in female patients after COVID-19 infection, regardless of the severity of the disease.

Keywords: COVID-19; female; lower urinary tract symptoms

ÖZET Amaç: Koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)], salgını son zamanlarda tüm dünyayı etkileyen en son ve en büyük hastalıktır. Alınan önlemlere rağmen COVID-19 salgınına ilişkin veriler her geçen gün artmaktadır. Atipik/spesifik olmayan semptomları olan COVID-19 hastalarının teşhisi, bu pandemi sürecinde muhtemelen gözden kaçmaktadır. Bu çalışma, kadınlarda COVID-19 enfeksiyonu sonrası alt üriner sistem semptomlarındaki (AÜSS) değişiklikleri araştırmayı amaçlamıştır. **Gereç ve Yöntemler:** Bu çalışmaya, COVID-19 tanısı konan toplam 62 kadın hasta dâhil edildi. Hastaların COVID-19 enfeksiyonu öncesi ve enfeksiyon sırasında ölçülen Kadın Alt Üriner Sistem Semptomları -Uluslararası İnkontinans Anketi [The International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS)] puanları karşılaştırıldı. Ayrıca COVID-19 enfeksiyonu sonrasındaki ICIQ-FLUTS skorları, toraks bilgisayarlı tomografi bulguları ile karşılaştırıldı. İdrar yolu enfeksiyonu ve idrar sıklığını etkileyen diğer nedenler, çalışma dışı bırakıldı. **Bulgular:** Kadın hastalarda COVID-19 enfeksiyonu sonrası toplam ICIQ-FLUTS skorları istatistiksel olarak artmış bulundu ($p<0,0001$). Ancak bu artmış AÜSS akciğer tutulum şiddeti ile ilişkili değildir ($r=0,063$; $p=0,629$). **Sonuç:** COVID-19, oldukça yeni bir hastalık olduğu için hakkındaki bilgiler sınırlıdır. AÜSS'nin, hastalığın şiddeti ne olursa olsun, COVID-19 enfeksiyonundan sonra kadın hastalarda önemli ölçüde arttığı bulundu.

Anahtar Kelimeler: COVID-19; kadın; alt üriner sistem semptomları

The coronavirus disease-2019 (COVID-19) outbreak was first detected in the Chinese city of Wuhan at the end of 2019. The disease is, then, rapidly spread all over China and the world, and became a major outbreak.[1] COVID-19 was declared a pandemic by the World Health Organization (WHO) on 11 March

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2020.[2] Although many countries have adopted strict measures, the spread of the disease could not have been prevented. According to data reported by WHO, more than 18 million people around the world have been diagnosed with COVID-19 and about 700,000 patients died up until this study.[3]

One of the most serious challenges in combating this outbreak is the inability to differentiate COVID-19 patients with non-specific or subclinical symptoms from healthy individuals. Although several symptoms are known like predominantly fever and cough, other findings and characteristics of the disease are unclear yet.[4] In a recent study, it was reported that urinary frequency, one of the most seen findings in urology diseases, is also common in COVID-19 patients.[5] Female patients hospitalized in our COVID-19 clinic have been observed suffering from increased lower urinary tract symptoms (LUTS) and dysuria after COVID-19 infection. Therefore, the effect of COVID-19 on LUTS in female patients was aimed in this study.

MATERIAL AND METHODS

Hospitalized female patients more than 3 weeks for COVID-19 infection were prospectively evaluated. İstanbul Prof. Dr. Cemil Taşcıoğlu Clinical Research Local Ethics Committee approved the study protocol with approval number 230 in 16/6/2020. The study was carried out in line with the Declaration of Helsinki. Approval from the Ministry of Health was obtained for this study. All subjects signed the detailed informed consent form. Those confirmed with COVID-19 infection by real-time reverse transcription-polymerase chain reaction test were included in the study. Patients between 40-65 years were included in the study. Additionally, patients who were hospitalized less than 3 weeks excluded from the study.

All patients received similar supportive treatments and antiviral favipiravir molecule. Patients who took massive intravenous hydration, drug using affecting urine frequency and previously had pelvic or urethral surgery were excluded from the study. Concurrent urinary tract infection was excluded with urine analysis. All patients were treated in COVID-19 clinic service. Patients who needed intensive care unit and developed macrophage activation syndrome were excluded from the study.

The section of the International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS) questionnaire, where urine filling and voiding symptoms were questioned, was used to assess patients' LUTS. The patients answered the questions twice over their symptoms before and during the COVID-19 infection. Symptom scores of the patients before and during COVID-19 infection were compared.

Furthermore, the degrees of lung involvement in COVID-19 patients were classified according to thoracic computed tomography.[6] Score 0 means no evidence of lung infiltration. Score 1 indicates minimal infiltration in single lung. Score 2 indicates minimal or moderate infiltration in both lungs. Score 3 indicates diffuse infiltration in both lungs. Tomography scores and ICIQ-FLUTS scores were evaluated in terms of correlation.

STATISTICAL ANALYSIS

Statistical Package for Social Sciences (SPSS) version 22.0™ (IBM Corporation) was used to analyse the data. Shapiro-Wilk test was used to measure the distribution of the variables. The ICIQ-FLUTS scores were compared using the Wilcoxon signed-rank test. Correlation analyses were performed with Spearman's test. All p values <0.05 were accepted statistically significant.

RESULTS

A total of 62 female patients with COVID-19 were evaluated. General characteristics of patients were presented in Table 1. The average age of the partici-

TABLE 1: General characteristics of patients.

	n=62 (mean±SD)
Age	55.67±14.4
BMI, kg/m^2	28.08±5.55
Cigarette (Yes/No)	8/54
Diabetes mellitus (Yes/No)	22/40
Hypertension (Yes/No)	28/34

SD: Standard deviation; BMI: Body mass index.

TABLE 2: Lower urinary tract symptom scores of female COVID-19 patients.

	Before COVID-19	During COVID-19	p value
Filling scores	4.3±3.7	5±3.2	0.035
Voiding scores	1.4±1.8	1.9±2.6	<0.0001
Total ICIQ-FLUTS scores	5.7±5.1	6.9±5.1	<0.0001

ICIQ-FLUTS: The International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms.

pants was 55.6±14.4 years, and the mean body mass index was 28±5.5 kg/m^2. The ICIQ-FLUTS scores of the patients are presented in Table 2. The filling scores before COVID-19 infection were 4.3±3.7 whereas it was 5±3.2 during COVID-19 infection. This increase in filling symptom scores was found to be statistically significant (p=0.035). The voiding scores before and during COVID-19 were 1.4±1.8 and 1.9±2.6, respectively. This increase in voiding symptom score was found to be statistically significant (p<0.0001). The total ICIQ-FLUTS score was 5.7±5.1 before COVID-19 and 6.9±5.1 during COVID-19. This increase in the total ICIQ-FLUTS score was found to be statistically significant (p<0.0001). The distribution table of ICIQ-FLUTS scores and tomography scores is shown in the Figure 1. There was no correlation between the scores (r=0.063, p=0.629).

DISCUSSION

The COVID-19 outbreak has brought many countries to the verge of a major crisis both socially and economically, as well as in terms of health systems. Numerical data on COVID-19 are increasing day by day although the measures are taken such as closing the country borders, social distancing, and closing schools and workplaces. All characteristics of COVID-19 disease have not been fully elucidated yet, and different symptoms may be seen in each patient.[7] It is of great importance to prevent disease transmission from patients with asymptomatic or non-specific symptoms.

The most seen symptoms of COVID-19 are fever, cough and lower respiratory tract symptoms.[8] However, in a recent study, urinary frequency was reported to be common in patients with COVID-19.[5] Parallel to this, a statistically significant increase has been observed in the ICIQ-FLUTS scores of the patients included in the present study after COVID-19 infection (p<0.0001). It is believed that this significant increase in both filling and voiding symptoms may be associated with bladder mucosal irritation. The most common routes of virus transmission are known to be nasopharyngeal and lower respiratory tract secretions.[8] Although some studies reporting that COVID-19 may be shown using urinary samples, there is no evidence that urine is a route of transmission.[9,10] There is a strong binding affinity between COVID-19 and angiotensin-converting enzyme 2 (ACE2) receptors. Therefore, higher ACE2 receptor level is more risky for COVID-19 infection. In a study examining the rates of ACE2 expression in organs, kidney and bladder were reported to be high-risk organs since their urothelial epithelium was above the 1% cut-off value.[11] However, it is not clear whether the high ACE2 receptors in bladder cells are expressed from luminal epithelial cells or from basal urothelial cells. Therefore, even if viral RNA is not detected in urine, there is a mechanism that can explain bladder irritation. COVID-19 infection causes endotheliitis in endothelial cells.[12] COVID-19 may have caused increased irritative symptoms and ICIQ-FLUTS

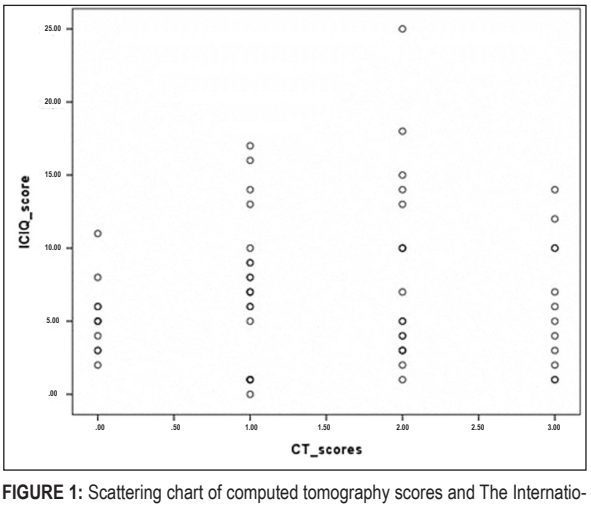

FIGURE 1: Scattering chart of computed tomography scores and The International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms scores (r=0.063, p=0.629).
ICIQ: International Consultation on Incontinence Questionnaire; CT: Computed tomography.

scores by causing endothelial damage in the bladder mucosa.

Different degrees of damage may occur in each patient due to COVID-19 infection, and the viral load of each patient is not the same.[13] Correlation analyzes were performed to evaluate the relationship between the symptom scores that increased during COVID-19 infection and the violence of the disease. However, no correlation was found between the ICIQ-FLUTS and thoracic tomography scores. This result may be a sign of an increase in LUTS of female patients regardless of the severity of the disease.

Some test and symptom scores such as International Prostate Symptom Score, Overactive Bladder Symptom Score, Modified Indevus Urgency Severity Scale and urodynamy were used to evaluate LUTS of females in literature. We used the ICIQ-FLUTS due to including both of filling and voiding symptoms and being specific for female.

Viral RNA in urine was not evaluated to indicate COVID-19 infection in the bladder. Small number of patients is the other limitation of the present study.

CONCLUSION

The COVID-19 outbreak is one of the most remarkable diseases of recent times. The course of this new virus with many unknown features in the coming months is not predictable yet. One of the ways to control the outbreak is to identify COVID-19 patients with sub-clinical or non-specific symptoms. An increase has been observed in LUTS of female patients with COVID-19 regardless of the severity of the disease. Female patients suffering increased LUTS may also be assessed for COVID-19 in case of no other underlying cause. However, large, prospective studies are needed to confirm our results.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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