INTRODUCTION

Coronaviruses (CoV) cause either self-limiting mild infection or more serious infections that effect to the whole body. CoV disease (COVID-19) has first reported on 7 January 2020, as a result of investigations from pneumonia cases of unknown aetiology in Wuhan, China's Hubei province. COVID-19 caused a pandemic that has spread all over the world. The disease is transmitted mainly through droplets. As the virus can be detected in the respiratory secretions of asymptomatic people, of whom could transmit the disease to another people.

The recommendations of the genitourinary system associated with COVID-19 are generally focused on management of urological diseases or treatment methods. If we evaluated in terms of genitourinary pathologies, acute kidney failure is among the most frequently studied subjects. Studies published of the relationship between the genitourinary cancers and COVID-19 has usually focused on the management of prostate cancer (PCA) or bladder cancer (BC). In these studies, the roles of CoV presence in the diagnosis and treatment of urinary system pathologies were mentioned and disease management was explained with general recommendations.

The relationship between testicular pain and COVID-19 is one of the least informed subjects among the existing urological diseases. In the current literature, only one case report was published regarding...
COVID-19-related scrotal or testicular pain.\textsuperscript{15,16} In this study, we aimed to evaluate COVID-19-related testicular pain in hospitalised patients because of COVID-19 and to review as an aetiological factor for epididymo-orchitis.

2 | MATERIAL METHODS

In this prospective descriptive study, patients who diagnosed and treated because of COVID-19 in our clinic between 1 April 2020 and 31 May 2020 were included. This study was approved by the local Ethics Committee and conducted according to the principles of World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects.” A total of 91 male patients diagnosed with COVID-19 were enrolled to study. Patients with COVID-19 between 18 and 75 years of were included in the study. Patients who were found to have missing data during data recording, evaluation or analysis were excluded from the study. To evaluate testicular pain or epididymo-orchitis in patients with COVID-19, some questions related with urological complaints such as urinary system symptoms, previous surgical and medical history or the presence of epididymo-orchitis were assessed in all patients. Patients’ neutrophil and lymphocyte count, C-reactive protein (CRP) levels, D-dimer values and neutrophil-lymphocyte ratios (NLR) were recorded. Patients with COVID-19 were divided into two groups according to absence or presence of testicular pain as group 1 and group 2. Eighty-one patients in group 1 and 10 patients in group 2 were enrolled to the study. All results of questionnaire form and laboratory tests were compared for both groups.

Data analyses were performed using SPSS Statistics 20.0 software (SPSS Inc, Chicago, IL, USA). The normality hypothesis was tested using the Kolmogorov-Smirnov test during data analysis. All variables were non-normally distributed. Quantitative variables were expressed as median (interquartile range). Qualitative variables were expressed as presence or absence percentage, and Chi-squared test was applied. Mann-Whitney’s U test was used to evaluate all non-normally distributed variables. A \( P < .05 \) was considered statistically significant in all analyses.

3 | RESULTS

A total of 91 patients were analysed. Eighty-one and 10 patients were enrolled in group 1 and 2, respectively. The median age of the patients in group 1 was 37 (28) years and in group 2 was 46 (31.5) years. Presence of dysuria, testicular swelling, history of BCG vaccine, history of epididymo-orchitis and any Urological surgery are shown in Table 1. Median duration of COVID-19 was similar in both groups and no statistically significant difference was found (\( p: 0.465 \)). Median neutrophil and lymphocyte counts, NLR, CRP and D-Dimer levels for both groups are summarised in Table 2. No statistically significant difference was found between in two groups for these parameters (\( P: .395, .069, .909, .478, .193 \)).

Patients were evaluated according to the level of lymphopenia to find any association of stage of COVID-19 disease with testicular pain or epididymo-orchitis. The patients were divided into two groups as those with lymphocyte level below 1.5 \( \times 10^3/\text{mm}^3 \) and above.
1.5 × 10^3/mm^3. Groups were compared for testicular pain and epididymo-orchitis. Patients with lymphocyte level below 1.5 × 10^3/mm^3 were older than the patients with lymphocyte level above 1.5 × 10^3/mm^3 and it was statistically significant (P: .038). No statistically significant difference was found in the groups for other parameters and described in Table 3.

4 | DISCUSSION

Testicular pain is divided two groups according to acute or chronic. Acute severe testicular pain is usually related with testicular torsion but chronic testicular pain is a rare condition and be considered as part of the chronic pelvic pain syndrome.17 Infectious or non-infectious causes may induce to acute testicular pain. Isolated acute orchitis is an infrequent phenomenon and usually accompanied by epididymitis.18 There are nearly 600 000 cases of epididymo-orchitis per year in the United States and the majority of epididymo-orchitis cases are aged 20-39 years.19

Testicular pain and epididymo-orchitis caused by bacterial pathogens specifically Chlamydia trachomatis and Neisseria gonorrhoeae, are a common condition in andrology. Orchitis in especially young patients is caused by virus infections such as mumps, rubella, coxsackievirus, varicella, echovirus and cytomegalovirus.20,21 Since the using of the mumps-measles-rubella vaccination, the frequency of mumps orchitis has decreased dramatically.

Mechanisms of occurred COVID-19 infection by binding to Angiotensin-converting enzyme 2 (ACE2) is known main pathway of influencing to host cells.22 ACE2 is expressed in many tissues, including kidney, bladder and testicular cells in genitourinary system, and therefore, virus may affect to testicular tissue and cause to testicular tissue damage.23,24

As in many medical sections, current literature on the genital involvement of coronavirus is limited with a few case reports.15,16 In this case reports, testicular and abdominal pain or both of them continued for 8 days. In another case report, a patient with COVID-19 whose complaint was acute abdominal pain diagnosed and revealed ovarian vein thrombosis. Although it develops in a female patient, but this case was significance in terms of genital involvement and it might explained to testicular pain how to occurs by vascular mechanisms.25 However, pain control was better in our patients of which group 2. Nonsteroidal anti-inflammatory drug therapy was successful in all patients with testicular pain and no patient required more invasive procedures. It can be concluded that this period is shorter than testicular pain because of bacterial pathogens. When the patients’ history was assessed, having a history of epididymo-orchitis increased the probability of CoV-related testicular pain. Blood-testis barrier defect which is the cause or result of previous epididymo-orchitis; may be one of the reasons for this increase.

In the current population, patients with testicular pain or epididymo-orchitis appeared to be slightly older than expected. Testicular pain or epididymo-orchitis was observed 10.98% in the study population. One of the most important reasons for this rate to be high is to have a systemic infection condition and it can be explained by the less response to systemic inflammation in the older population, unlike younger men. But this condition was unrelated to the level of lymphopenia. As we mentioned before, the history of previous epididymo-orchitis increases the probability of testicular pain because of CoV. Sun et al reported that viral RNA was detected in multiple organs in patients with COVID-19 was successfully isolated from urine of patient with COVID-19.26 The possibility of having COVID-19 in urine can lead to epididymo-orchitis by vas deferens reflux secondary to increased voiding pressure in ageing males.

Another important risk for young adults with testicular pathology is the affecting of male reproductive system.27,28 This may be a critical reproductive problem for young patients. “Società Italiana di Andrologia e Medicina della Sessualità” and Aversa et al were reported that in patients recovered from COVID-19, especially for those patients with testicular pain or epididymo-orchitis were older than expected. Testicular pain or epididymo-orchitis appeared to be slightly older than expected. Testicular pain or epididymo-orchitis was observed 10.98% in the study population. One of the most important reasons for this rate to be high is to have a systemic infection condition and it can be explained by the less response to systemic inflammation in the older population, unlike younger men. But this condition was unrelated to the level of lymphopenia. As we mentioned before, the history of previous epididymo-orchitis increases the probability of testicular pain because of CoV. Sun et al reported that viral RNA was detected in multiple organs in patients with COVID-19 was successfully isolated from urine of patient with COVID-19.26 The possibility of having COVID-19 in urine can lead to epididymo-orchitis by vas deferens reflux secondary to increased voiding pressure in ageing males.

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| TABLE 3 | Statistical comparison of groups according to the lymphocytopenia levels |
| Parameter | Lymphopenia (<1.5 × 10^3/mm^3) (n = 37) | Lymphopenia (>1.5 × 10^3/mm^3) (n = 54) | P value |
| Age (y)^a | 40 (23.5) | 29 (27.5) | .038^b |
| Duration of COVID-19 (d)^a | 11 (10.5) | 12 (6.25) | .704^b |
| Dysuria | 5.4% | 14.81% | .757^c |
| Testicular pain | 10.81% | 12.96% | .159^c |
| Testicular swelling | 5.4% | 1.85% | .786^c |
| History of BCG vaccine | 13.51% | 7.4% | .338^c |
| History of epididymo-orchitis | 2.7% | 1.85% | .786^c |
| Comorbid diseases | 18.91% | 18.51% | .962^c |

^aMedian (IQR). ^bMann-Whitney U test. ^cChi-squared test.
5 | CONCLUSION

COVID-19-related testicular pain was present more frequently than expected in the study. To explain this frequency and also association of between COVID-19 and testicular pain or epididymo-orchitis; future studies which are isolated the COVID-19 in genitourinary system are necessary.

DISCLOSURE
Authors declared no conflict of interest.

AUTHORS’ CONTRIBUTIONS
EC: Contributed to the conception and design of the study. EC, THH, OK, AA, AS: Collected the data. EC, YO, THH, AS: Drafted and revised the manuscript. EC, AS, THH, OE: Participated in preparing tables and performing statistical analysis.

ETHICAL APPROVAL
This prospective descriptive study was approved by the University of Health Sciences Hamidiye Clinical Research Ethics Committee (Hamidiye-KAEK 20/83).

PATIENTS’ CONSENT
Informed consent is not obtained from patients to publish the data concerning this study.

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REFERENCES
1. Borchert A, Baumgarten L, Dalela D, et al. Managing urology consultations during COVID-19 pandemic: application of a structured care pathway. Urolgy. 2020;141:7-11.
2. Heldwein FL, Loeb S, Wroclawski ML, et al. A systematic review on guidelines and recommendations for urology standard of care during the COVID-19 pandemic. Eur Urol Focus. 2020;6;1070-1085.
3. Nowroozi A, Amini E. Urology practice in the time of COVID-19. Urol J. 2020;17:326.
4. Mejean A, Roupret M, Rozet F, et al. Recommendations CCAFU on the management of cancers of the urogenital system during an epidemic with Coronavirus COVID-19. Prog Urol. 2020;30:221-231.
5. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int. 2020;97:829-838.
6. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med. 2020;8:738-742.
7. Zaorsky NG, Yu JB, McBride SM, et al. Prostate cancer radiotherapy recommendations in response to COVID-19. Adv Radiat Oncol. 2020;5:659-665.
8. Bhowmick NA, Oft J, Dorff T, et al. COVID-19 and androgen targeted therapy for prostate cancer patients. Endocr Relat Cancer. 2020;27:281-292.
9. Assi T, Ibrahim N, Abboud RM, et al. The management of patients with metastatic prostate cancer during the COVID-19 pandemic. Future Oncol. 2020;16:1455-1461.
10. Gomez Rivas J, Dominguez M, Gaya JM, et al. Prostate cancer and COVID-19 pandemic: current recommendations. Arch Esp Urol. 2020;73:367-373.
11. de la Pena E, Hernandez V, Guijarro A, et al. Recommendations on bladder cancer Management during COVID-19 pandemic: lessons learned and future plans. Arch Esp Urol. 2020;73:374-383.
12. Teoh JYC, Roupret M, Shariat SF, Herrmann T. Intravesical therapy for bladder cancer in the pandemic of Covid-19. World J Urol. 2020;30
13. Wang T, Liu S, Joseph T, Lyou Y. Managing bladder cancer care during the COVID-19 pandemic using a team-based approach. J Clin Med. 2020;9:1574.
14. Wallis CJD, Novara G, Marandino L, et al. Risks from deferring treatment for genitourinary cancers: a collaborative review to aid triage and management during the COVID-19 pandemic. Eur Urol. 2020;78:29-42.
15. Kim J, Thomsen T, Sell N. Goldsmith AJ. Abdominal and testicular pain: an atypical presentation of COVID-19. Am J Emerg Med. 2020;38:1542.e1.
16. Gagliardi L, Bertacca C, Centenari C, et al. Orchiepididymitis in a boy with covid-19. Pediatr Infect Dis J. 2020;39:e200-e202.
17. Sigalos JT, Pastuszak AW. Chronic orchialgia: epidemiology, diagnosis and evaluation. Transl Androl Urol. 2017;6:537-543.
18. Ludwig M. Diagnosis and therapy of acute prostatitis, epididymitis and orchitis. Andrologia. 2008;40:76-80.
19. Liu JM, Chang YH, Ho TW, et al. Patients with epididymo-orchitis and meteorological impact in Taiwan: a nationwide population-based study. Can J Infect Dis Med Microbiol. 2017;2017:1506857.
20. Azmat CE, Vaitla P. Orchitis. Treasure Island, FL: StatPearls. 2020.
21. Kanda T, Mochida J, Takada S, Hori Y, Yamaguchi K, Takahashi S. Case of mumps orchitis after vaccination. Int J Urol. 2014;21:426-428.
22. South AM, Diz DI, Chappell MC. COVID-19, ACE2, and the cardiovascular consequences. Am J Physiol Heart Circ Physiol. 2020;318:H1084-H1090.
23. Zhang Y, Geng X, Tan Y, et al. New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. Biomed Pharmacother. 2020;127:110195.
24. Fan C, Li K, Ding Y, Lu WL, Wang J. ACE2 expression in kidney and testis may cause kidney and testis damage after 2019-nCoV infection. MedRxiv. 2020. https://doi.org/10.1101/2020.02.12.20022418
25. Mohammadi S, Abouzaripour M, Hesam Shariati N, Hesam Shariati MB. Ovarian vein thrombosis after coronavirus disease (COVID-19) infection in a pregnant woman: case report. J Thromb Thrombolysis. 2020;50:604-607.
26. Sun J, Zhu A, Li H, et al. Isolation of infectious SARS-CoV-2 from urine of a COVID-19 patient. Emerg Microbes Infect. 2020;9:991-993.
27. Illiano E, Trama F, Costantini E. Could COVID-19 have an impact on male fertility? Andrologia. 2020;52:e13654.
28. Vishvkarma R, Rajender S. Could SARS-CoV-2 affect male fertility? Andrologia. 2020;52:e13712.
29. Corona G, Baldi E, Isidori AM, et al. SARS-CoV-2 infection, male fertility and sperm cryopreservation: a position statement of the Italian Society of Andrology and Sexual Medicine (SIAMS) (Societa Italiana di Andrologia e Medicina della Sessualita). J Endocrinol Invest. 2020;43:1153-1157.
30. Aversa A, Jannini EA. COVID-19, or the triumph of monogamy? Minerva Endocrinol. 2020;45:77-78.
31. De Paoli P. Bio-banking in microbiology: from sample collection to epidemiology, diagnosis and research. FEMS Microbiol Rev. 2005;29:897-910.
32. Kurscheidt FA, Mesquita CSS, Damke G, et al. Persistence and clinical relevance of Zika virus in the male genital tract. Nat Rev Urol. 2019;16:211-230.
33. Ma W, Li S, Ma S, et al. Zika virus causes testis damage and leads to male infertility in mice. Cell. 2016;167:1511-1524.e1510.

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