Sonographic findings of COVID-19 related acute scrotal infection and associations with clinical-laboratory data

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Abstract
Background: During the Coronavirus Disease 2019 (COVID-19) pandemic, patients present to hospitals with a wide range of symptoms. Some of these symptoms include acute orchitis and epididymitis. The goal of this research is to see if COVID-19 infection and scrotal infection are associated.

Materials and methods: Patients with a COVID-19 (+) who agreed to a scrotal ultrasound (US) examination were studied prospectively in a tertiary care center between October 2021 and February 2022. The severity of the disease was used to divide patients into groups. Patients diagnosed with acute scrotal infection based on scrotal ultrasonography findings were compared in these groups, as were their age, comorbidities, and laboratory data.

Results: The median age of the 213 participants was 61.7 ± 8.3. During the ultrasonographic examination of the patients, 15 (7%), 8 (3.7%), 17 (7.9%), and 40 (18.7%) were diagnosed with acute orchitis, acute epididymitis, acute epididymo-orchitis, and scrotal infection, respectively. Acute scrotal infection was far more common in patients with a higher clinical severity of the disease. The patients' comorbidities were also assessed, and it was discovered that they were statistically more common in the same group.

Conclusions: Even if there are no clinical symptoms, ultrasonography can help detect acute scrotal infection in COVID-19 patients. Furthermore, in groups with higher clinical severity, this association is more likely to be seen. It is critical to understand this in order to avoid complications.

KEYWORDS
COVID-19, epididymitis, orchitis, pandemic, scrotal, ultrasound

1 INTRODUCTION

The novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which has caused a worldwide pandemic since December 2019 in the Chinese city of Wuhan, caused over 458 million illnesses and over 6 million deaths in March 2022.1,2 It continues to cause an increase in morbidity and mortality due to novel variations created during the process.3-5 Coronavirus Disease 2019 (COVID-19) was once thought to only affect the respiratory system, but it has since been discovered that it can affect a variety of organs and systems.4,6

The predominant functional receptor for the viral mechanism of SARS-CoV-2 has been identified as angiotensin-converting enzyme 2 (ACE2).7-9 According to immunohistochemical studies, ACE2 is widely expressed in human tissues such as the lung, kidney, small intestine, and testis.9,10 As a result of mediating the inflammatory process, its presence in the male genital system is thought to contribute
in the development of acute orchitis, epididymitis, or both. The viral priming transmembrane protease serine 2 (TMPRSS2) is expressed when the SARS-Cov-2 virus binds to the ACE-2 receptor during cell invasion, and the virus then enters the cell. Viruses that cause viral orchitis-epididymitis, such as HIV, HBV, and mumps, all bind to the same receptor (ACE2) in the testicular cells to enter. Intracellular proliferation and the initiation of cytotoxicity stimulate inflammation and cell death.\(^4\)\(^9\)\(^11\)

In the literature, there are a few studies about the association between COVID-19 disease and acute scrotal infection.\(^4\)\(^9\)\(^12\) In this study, we aimed to reveal the relationship between clinical severity of COVID-19 infection and scrotal infections. We also investigated the correlation between acute scrotal infections and comorbidities, laboratory findings, and the severity of the infection.

2 | MATERIALS AND METHODS

Between October 2021 and February 2022, all adult males who were hospitalized with a positive reverse transcriptase polymerase chain reaction (rt-PCR) test for COVID-19 and accepted for scrotal US testing and had no exclusion criteria were prospectively enrolled in a tertiary health care facility in Turkey. Participants could enroll at any point during their stay in the hospital. We excluded participants whose US examination took more than 15 days after the first diagnosis of COVID-19. Study protocol was approved by a tertiary health care facility ethics committee (EBYU-KAEK-2020-02-8752). All patients provided their written informed consent for participating in the study. Written informed consent of the patients on mechanical ventilation were taken from their family.

Patients who had scrotal or inguinal surgery, were taking reproductive system medicines, had testicular dysfunction such as cryptorchidism or atrophy, had cancer, or had sexually transmitted infections were all excluded from the study. Patients with a suspected history of testicular infection were also excluded. Prior to the US examination, each participant was assessed for clinical history and any symptoms associated with scrotal infections. They were excluded from the study if they had a history of scrotal symptoms (78 patients).

Patients with a positive rt-PCR test and a chest computed tomography were included in the study. They were divided into groups according to the severity of the clinical disease as defined by Feng et al. They proposed the following clinical disease severity definition for COVID-19: Type 1; patients with mild symptoms and no abnormal radiological findings, type 2; patients with moderate symptoms and evidence of pneumonia on chest CT, type 3; patients with either a high respiratory rate (30/min) or a low oxygen partial pressure/inspired oxygen fraction (300 mmHg) in arterial blood, and type 4; patients who required mechanical ventilation and had shock or organ dysfunction, necessitating ICU admission.\(^13\)

After obtaining informed consent, patients were examined for scrotal findings with US 15 days after the initial rt-PCR (+). We used scrotal US examination for COVID (+) patients solely for research purposes because it was not a routine practice in our facility.

On ultrasonography, unilateral or bilateral involvement, enlargement of the testes and epididymis, heterogeneity in echogenicity, increase in testicular and epididymal blood flow, presence of an epididymal abscess, hydrocele, and scrotal edema were all assessed. The classic triad (enlargement, heterogeneous echogenicity, and increased flow on color doppler of the testis) is the predominant US findings of acute orchitis, whereas minor features include a thickened tunica albuginea, hydrocele, and scrotal wall edema. The presence of all three main characteristics, or any two major features with at least one minor feature, was recognized as the diagnostic criteria for acute orchitis. Enlargement, heterogeneous echogenicity, and increased flow on CDFI of the epididymis are the predominant US findings of acute epididymitis, whereas minor features include an epididymitis abscess, hydrocele, and scrotal wall edema. The presence of all three main characteristics, or any two major features plus at least one minor feature, was recognized as the diagnostic criteria for acute epididymitis. Patients who encountered both epididymitis and orchitis diagnostic criteria were defined as epididymo-orchitis.\(^14\) Two radiologists with 10 and 15 years of experience evaluated the images. Another radiologist with 25 years of experience solved the problem.

All patients were examined with a gray-scale and color doppler ultrasound machine (Toshiba, Xario) with a 12-15 MHz linear transducer.

Scrotal ultrasonography findings of the groups were analyzed and compared separately. In addition, the patients’ ages and laboratory test results were evaluated and classified into groups. Concomitant diseases like hypertension, hyperlipidemia, coronary artery disease, chronic liver disease, COPD, hepatic cirrhosis, and diabetes were also assessed, as well as their association with acute scrotal infections. The presence of comorbidities was determined through a review of medical records and a questionnaire completed by the participant. We used the latter when we couldn’t find the participant’s medical record.

3 | STATISTICAL ANALYSES

Data were analyzed using the IBM Statistical Package for Social Sciences v25 for Windows (IBM SPSS Inc., Chicago, IL). The normal distribution of the data was evaluated with the Kolmogorov–Smirnov test. Numerical variables with normal distribution were shown as mean ± standard deviation, the ones without normal distribution was shown as median (minimum–maximum, interquartile range–IQR). Categorical variables were shown as numbers and percentages. For the comparison of numerical variables between two groups, student t-test was used, for the comparison between multiple groups (disease severity groups) we used one way ANOVA test, and Bonferroni test for post-hoc analysis. We compared the comorbidities, scrotal complaints, sonographic findings, and disease outcome between disease severity groups by Chi-Square test. To evaluate the correlations between the acute scrotal infection presence and age, laboratory parameters, median time after the initial positive rt-PCR test, we used logistic regression analysis.

A two-tailed value of \(p < 0.05\) was considered statistically significant.
RESULTS

There were 213 patients enrolled in our study. On ultrasonography, 15 (7%) patients were diagnosed with acute orchitis, 8 (3.7%) patients with acute epididymitis, 17 (7.9%) patients with acute epididymo-orchitis. In total, scrotal infection findings were found in 40 of the participants. The mean age among all patients was 61.7 ± 8.3 years and for type 1 was 53.3 ± 9.1 years, for type 2 was 67.8 ± 10.7 years, for type 3 was 72.8 ± 9.1 years, and for type 4 was 86.9 ± 6.2 years. Regression analysis revealed a significant and positive association between age and the incidence of acute scrotal infection (OR: 2.12, \( p = 0.001 \)).

Table 1 details the presence of clinical symptoms, comorbidities, laboratory results, and outcome data.

From the initial PCR (+) to the USG examination, it took an average of 7 days (2–15 days, IQR: 5 days). There was no correlation between the median day and the development of acute scrotal infection. (\( p = 0.13 \)).

Clinical scrotal symptoms are present in 24 (11.2%) of the patients, with the occurrence of scrotal complaints in higher severity groups being statistically significant.

We assessed the comorbidities of the patients including hypertension, hyperlipidemia, coronary heart disease, chronic kidney disease, chronic obstructive pulmonary disease, hepatic cirrhosis, and diabetes mellitus.

### TABLE 1  Patients with COVID-19: demographics, comorbid diseases, laboratory results, and outcome

| Characteristics | Whole population (n = 213) | Type 1 (n = 97) | Type 2 (n = 81) | Type 3 (n = 21) | Type 4 (n = 14) | p   |
|-----------------|---------------------------|----------------|----------------|----------------|----------------|-----|
| Age (mean)      | 61.7 ± 8.3 (18–91)        | 53.3 ± 9.1     | 67.8 ± 10.7    | 72.8 ± 9.1     | 86.9 ± 6.2     | 0.001|
| Scrotal complaints | 24 (11.2%)                | 10(10/97 = 10.3%) | 8 (8/81 = 9.8%) | 3(3/21,14.2%)a | 3 (3/14, 21.4%)a | 0.003|
| Comorbid disease |                           |                |                |                |                |     |
| Hypertension    | 70 (30%)                  | 18 (18.5%)     | 24 (29.6%)     | 17 (80.9%)a    | 11 (78.5%)a    | 0.002|
| Hyperlipidemia  | 29 (13.6%)                | 6 (6.1%)       | 7 (8.6%)       | 10 (47.6%)a    | 6 (42.8%)a     | 0.005|
| Coronary heart disease | 10 (4.6%) | 0 (0%)   | 2 (2.4%)       | 3 (14.2%)a     | 5 (35.7%)a     | 0.03 |
| Chronic kidney disease | 3 (1.4%) | 0 (0%)   | 0 (0%)         | 1 (4.7%)       | 2 (14.2%)a     | 0.02 |
| Chronic obstructive pulmonary disease | 25 (11.7%) | 5 (5.1%) | 7 (8.6%)       | 5 (23.8%)a     | 8 (57.1%)a     | 0.002|
| Hepatic cirrhosis | 2 (%0.9)                  | 1 (%1)        | 0 (0%)         | 0 (0%)         | 1 (7.1%)       | 0.06 |
| Diabetes        | 28 (13.1%)                | 4 (4.1%)       | 11 (13.5%)     | 8 (38%)a       | 5 (35.7%)a     | 0.002|
| Laboratory values |                          |                |                |                |                |     |
| D-dimer (μg/L) (mean) | 1.12 ± 0.43            | 0.34 ± 0.23    | 1.28 ± 0.68    | 2.69 ± 1.1     | 3.38 ± 4.72    | 0.001|
| Fibrinogen(mg/dL) (mean) | 337.3 ± 98            | 281 ± 71      | 329 ± 79      | 479 ± 117     | 563 ± 194     | 0.02 |
| CRP (mg/dL) (mean) | 2.23 ± 0.95            | 0.97 ± 1.34    | 2.57 ± 0.17    | 4.87 ± 5.87   | 5.15 ± 3.83   | 0.03 |
| Neutrophil count (× 10⁹/L) (mean) | 3.9 ± 0.93         | 3.6 ± 1.86    | 3.82 ± 0.2    | 4.32 ± 1.27  | 5.92 ± 1.9    | 0.12 |
| Lymphocyte count (× 10⁹/L) (mean) | 2.91 ± 2.2          | 3.3 ± 1.9     | 3.1 ± 2.7     | 1.6 ± 7.2     | 1.1 ± 3.7     | 0.03 |
| Outcome         |                           |                |                |                |                |     |
| Cured/discharged | 208 (97.6%)              | 97 (45.5%)     | 81 (38%)       | 20 (95.2%)     | 10 (71.4%)     | 0.001|
| Deceased        | 5 (2.3%)                 | 0 (0%)        | 0 (0%)        | 1 (4.7%)      | 4 (28.5%)      | 0.001|

*Marks the significantly different groups.

### TABLE 2  Relationship between comorbidities and the presence of acute scrotal infection

| Comorbidities         | Chi-Square | p-value |
|-----------------------|------------|---------|
|                       | Acute orchitis | Acute epididymitis | Acute epididymo-orchitis | Any |
| Hypertension          | 0.07       | 0.10    | 0.30     | 0.09    |
| Hyperlipidemia        | 0.60       | 0.70    | 0.60     | 0.60    |
| Coronary heart disease | 0.08 | 0.30    | 0.25     | 0.60    |
| Chronic kidney disease | 0.20 | 0.09    | 0.18     | 0.20    |
| Chronic obstructive pulmonary disease | 0.21 | 0.18 | 0.26 | 0.28 |
| Hepatic cirrhosis     | 0.80       | 0.18    | 0.60     | 0.5     |
| Diabetes mellitus     | 0.06       | 0.053   | 0.057    | 0.032   |
FIGURE 1  Acute orchitis: 35 year old male, no symptoms or comorbidities. Hypoechoic testis parenchyma (A) with increased vascularization on CDUS (B).

FIGURE 2  Acute epididymitis: 58 year old male, scrotal pain and diabetes mellitus. Increased echogenicity of epididymis (A, arrows) with increased vascularization (B).

FIGURE 3  Acute epididymo-orchitis: 62 year old male, scrotal pain, diabetes mellitus and hypertension. Testis parenchyma is heterogeneous, the echogenicity of the epididymis is increased (A, T: Testis, E: Epididymis). Vascularization is also increased in the testis parenchyma and the epididymis (B).

TABLE 3  Infection types and ultrasound findings in COVID-19 patients

| US findings                        | Whole population (n = 213) | Type 1 (n = 97) | Type 2 (n = 81) | Type 3 (n = 21) | Type 4 (n = 14) | p     |
|------------------------------------|----------------------------|----------------|----------------|----------------|----------------|-------|
| Unilateral                         | 29 (72.5%)                 | 5 (45.4%)      | 8 (57.1)       | 3 (42.8%)      | 2 (25%)        | 0.03  |
| Bilateral                          | 11 (27.5%)                 | 6 (54.5%)      | 6 (42.8%)      | 4 (57.1%)      | 6 (75%)        | 0.03  |
| Enlarged testis                    | 16 (7.5%)                  | 7 (7.2%)       | 6 (7.4%)       | 2 (9.5%)       | 1 (7.1%)       | 0.5   |
| Heterogeneous echogenicity of testis| 18 (8.4%)                  | 5 (5.1%)       | 6 (7.4%)       | 4 (19%)        | 3 (21.4%)      | 0.002 |
| Increased testicular vascular flow | 32 (15%)                   | 8 (8.2%)       | 12 (14.8%)     | 6 (28.5%)*     | 6 (42.8%)*     | 0.001 |
| Enlargement of epididymis          | 23 (10.7%)                 | 10 (10.3%)     | 5 (6.1%)       | 5 (23.8%)*     | 3 (21.4%)*     | 0.002 |
| Heterogeneous echogenicity of epididymis | 18 (8.4%)            | 9 (9.2%)       | 5 (6.1%)       | 1 (4.7%)       | 3 (21.4%)*     | 0.03  |
| Increased epididymal vascular flow | 22 (10.3%)                 | 6 (6.1%)       | 9 (11.1%)      | 3 (14.2%)      | 4 (28.5%)*     | 0.02  |
| Epididymal abscess                 | 5 (2.3%)                   | 0              | 1 (1.2%)       | 2 (9.5%)*      | 2 (14.2%)*     | 0.003 |
| Hydrocele                          | 8 (3.7%)                   | 4 (4.1%)       | 3 (3.7%)       | 0              | 1 (7.1%)       | 0.054 |
| Scrotal edema infection type       | 9 (4.2%)                   | 3 (3%)         | 4 (4.9%)       | 1 (4.7%)       | 1 (7.1%)       | 0.07  |
| Acute orchitis                     | 15 (7%)                    | 5 (5.1%)       | 4 (4.9%)       | 3 (14.2%)*     | 3 (21.4%)*     | 0.01  |
| Acute epididymitis                 | 8 (3.7%)                   | 3 (3%)         | 2 (2.4%)       | 1 (4.7%)       | 2 (14.2%)*     | 0.001 |
| Acute epididymo-orchitis           | 17 (7.9%)                  | 3 (3%)         | 8 (9.8%)       | 3 (14.2%)*     | 3 (14.2%)*     | 0.02  |
| Total                              | 40 (18.7%)                 | 11 (11.3%)     | 14 (17.2%)     | 7 (33.3%)*     | 8 (57.1%)*     | 0.001 |

Abbreviation: US, ultrasound.
*Marks the significantly different groups.
chronic obstructive pulmonary disease and found that comorbidities other than cirrhosis, were found statistically more frequent in type 3 and 4 (Table 1).

We found that diabetes mellitus was independently correlated to the presence of acute scrotal infection when all three pathologies were evaluated together as acute scrotal infection. There was no association between the presence of acute scrotal infection and the other comorbidities (Table 2).

D-dimer, Fibrinogen, CRP, neutrophil, and lymphocyte counts were also assessed. Other laboratory results, with the exception of neutrophils, showed a significant increase in correlation with clinical severity groups. According to the regression analysis, there is a significant and positive relationship between the CRP value and the occurrence of acute scrotal infection (OR: 1.87, p = 0.01).

The number of patients who recovered or were discharged after receiving COVID-19 treatment was evaluated, as well as the number of patients who died. 208 patients (97.6%) recovered from COVID-19 infection in our study, while five patients (2.3%) died as a result of COVID-19 infection. We found a substantial statistical association between mortality and the severity of clinical disease (p = 0.001).

Type 3 and type 4 patients had more heterogeneous echogenicity in the testicles, increased testicular vascular flow, enlargement of the epididymis, and epididymal abscess as a result of the ultrasound findings, while type 4 patients had more heterogeneous echogenicity of the epididymis and increased epididymal vascular flow as a result of the ultrasound findings (Figure 1–3). When patients were divided by diagnostic criteria, cases of acute epididymitis, acute orchitis, and acute epididymoorchitis were found to be significantly higher in type 3 and 4 groups (Table 3).

5 | DISCUSSION

We found a relationship between COVID-19 infection and acute scrotal infection in this study. Although 24 (11.2%) of the 213 patients in our study had scrotal symptoms, diagnostic criteria based on US data revealed the presence of scrotal infection in 40 (18.7%). Higher clinical severity scores were associated with scrotal inflammatory findings, according to our findings. Age was found to have a significant and positive relationship with the occurrence of acute scrotal infection (OR: 2.12, p = 0.001). Furthermore, higher clinical severity groups were found to be more frequently associated with comorbid diseases (types 3 and 4).

During the COVID-19 pandemic, some patients experienced non-respiratory symptoms such as gastrointestinal, genitourinary, cardiovascular, and even neurological symptoms.9,15,16 Other systemic findings have been related to the expression of the ACE2 receptor in various organs, which allows the SARS-CoV2 virus to adhere to the cell. The viral priming transmembrane protease serine 2 (TMPRSS2) is also expressed when the SARS-CoV-2 virus binds to the ACE-2 receptor, allowing SARS-CoV-2 to invade cells.9,11 The presence of ACE2 receptor expression in the testis and epididymis in COVID-19 patients is thought to be the cause of scrotal complaints.

In the literature, the effect of the SARS CoV-2 virus on the testis and epididymis has been described in two ways. The first is that it affects cells directly through bloodstreaming,9 while the second is that it activates the cytokine system and the inflammatory response.4,17 The ACE2 receptor is primarily expressed in spermatogonia, Leydig cells, and Sertoli cells, according to Wang et al.18 In addition, another study found that LH hormone levels increased significantly after SARS-Cov-2 infection.19 This suggests that the virus may have a negative impact on the reproductive system. SARS CoV-2 was found to be positive in the semen in only one study in six patients,20 whereas it was found to be negative in the others in a review of 28 studies on live and cadavers. It was also discovered that it affected spermatogenesis and resulted in a drop in sperm quality.17

Only a few studies have assessed the effect of COVID-19 disease on acute scrotal infection.4,9,12 The Chen et al. study included 91 COVID-19-infected patients, while the Ediz et al. study included 142. Carneiro et al. also conducted a comprehensive study with 30 patients suffering from mild to severe epididymitis. To the best of our knowledge, our study has the most cases on this specific subject, with 213 patients.

Chen et al.9 revealed that comorbidities are more common in groups with high COVID-19 clinical severity, similar to ours. It was also more common in the high severity groups among the patients with scrotal symptoms. Similarly, when ultrasound findings of acute scrotal infection were compared, heterogeneous echogenicity in testis, increased blood flow in testis and epididymis, and epididymal abscess were observed more frequently in groups with higher clinical severity. Unlike our study, they found no significant differences in epididymis enlargement or heterogeneous epididymis echogenicity between the clinical severity groups. Acute epididymitis, orchitis, or epididymoorchitis were also more common in groups with a high clinical severity. In both studies, there was a strong association between the age and scrotal infection.

Ediz et al.12 analysed the laboratory results of 19 COVID patients with and without testicular symptoms and observed no variations in neophile, CRP, or D-dimer concentrations between the two groups. In our study, however, we discovered that greater CRP levels increase the likelihood of a scrotal infection. The discrepancy may be attributable to population size; we have analysed a larger sample size. Also, population characteristics may be a factor; our population may comprise a greater proportion of individuals with a worse clinical severity.

In the study of Carneiro et al.4 the association between epididymitis and COVID-19 infection and findings of enlargement of the epididymal head was found to be significantly similar to our results. Contrary to our study, only mild–moderate clinical severity group was studied in this research.

There are some limitations of the study. First of all, since we made our diagnosis of scrotal infection with the diagnostic criteria consisting of US findings, there are no pathological study data and this makes it difficult to say that the scrotal infection factor is definitely related to COVID-19. In addition, some ultrasound findings like edema and enlargement can be seen in comorbid diseases such as coronary heart disease, chronic kidney disease, hepatic cirrhosis, diabetes...
mellitus. So it is hard to make certain etiological differentiation. Moreover, we did not study the relationship between increased mortality, length of hospital stay and scrotal infection.

To conclude, acute scrotal infection can be seen in COVID-19 patients, even in the absence of any symptoms. Acute scrotal infection in this population can be diagnosed with sonography and it is also associated with the clinical disease severity of COVID-19.

**FUNDING INFORMATION**

No funding have been received for the study.

**CONFLICT OF INTEREST**

The author declares that there is no conflict of interest.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**ETHICS STATEMENT**

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**CONSENT STATEMENT**

All included patients provided their written informed consent for participating in the study.

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