Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Radiodiagnosis

Coronavirus Disease Patients with Acute Testicular Infection: Ultrasound Imaging Findings

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DOI: 10.36347/sjams.2023.v11i02.026 | **Received:** 14.01.2023 | **Accepted:** 20.02.2023 | **Published:** 24.02.2023

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Abstract **Original Research Article**

Introduction: Objectives: Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic, raising widespread public health concerns. Our team treated hospitalized patients with COVID-19 in SAIMS Indore, where the outbreak first began, and we suspected that SARS-CoV-2 may cause testicular infection in male patients. We conducted this study to explore that observation. ***Methods:*** We enrolled male patients with a confirmed diagnosis of COVID-19 and performed a bedside ultrasound (US) examination of the scrotum, focused on findings of acute inflammation such as tunica albuginea thickening, enlargement and heterogeneous echogenicity of the testis, epididymis, or both, an abscess, scrotal wall edema, and hydrocele. Then we compared the proportions of observed epididymo-orchitis in patients from different age groups and COVID-19 severity groups. ***Results:*** A total of 150 patients with COVID-19 were enrolled in our study, and 32 (22.5%) patients had acute orchitis, epididymitis, or epididymo-orchitis on scrotal US imaging, according to the diagnosis criteria. The observed risk of acute scrotal infection increased with age, with the incidence reaching 53.3% in men older than 80 years. We also observed that men with severe COVID-19 had a significantly higher possibility of epididymo-orchitis compared to the non- severe COVID-19 group (P = .037). ***Conclusions:*** This study shows US imaging evidence that SARS-CoV-2 may cause infection of the testis or epididymis, and the risk is worthy of the attention of clinicians.

Keywords: Coronavirus disease, COVID-19, global pandemic, diagnosis, epididymo-orchitis.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is highly contagious viral illness caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and had a catastrophic effect on the world's demographics, resulting in more than 6 million deaths worldwide as of March 2022, emerging as the most consequential global health crisis since the era of the influenza pandemic of 1918. The first few cases of this predominantly respiratory viral illness were first reported in Wuhan, Hubei Province, China, in late December 2019 [1]. After this, SARS-CoV-2 rapidly disseminated across the world in a short span of time and on 30 January 2020, first case was reported in India. World Health Organization (WHO) declared it as a global pandemic on March 11, 2020. Since being declared a global pandemic, COVID-19 has ravaged many countries worldwide and has overwhelmed many healthcare systems. The primary mode of transmission of SARS-CoV-2 is via exposure to respiratory droplets. Infection can be transmitted through respiratory air droplets or via direct contact with contaminated surfaces. Early and accurate diagnosis of patients, including those with little or no symptoms is crucial, since nearly 80% of all infections have little or no symptoms and yet, these individuals are equally infective and thus, play a major role in spreading the pandemic. Common symptoms include fever, cough, and dyspnea, while the disease has potential to cause a host severe fatal cardio-respiratory complications in vulnerable population, particularly the elder with co-morbid conditions [2].

Previous studies have demonstrated that the virus enters a host cell via its receptor-binding domain, which binds to a specific cell surface receptor. In humans, angiotensin-converting enzyme 2 (ACE2) has been identified as the major functional receptor for the receptor-binding domain of SARS-CoV and SARS-CoV-2 [7, 8]. Immunohistochemical studies have

demonstrated that ACE2 is widely expressed in various human organs, including the lung, kidney, small intestine, and testis, among others [6, 9]. Angiotensin-converting enzyme 2 has been found to be highly expressed on Leydig cells and seminiferous duct cells in the testis [10, 11] leaving open the possibility that SARS-CoV-2 infection may cause testicular infection. We thus designed this study and performed bedside ultrasound (US) examinations of the scrotum on hospitalized patients with COVID-19 to determine whether there is suf*fi*cient US evidence to verify the risk of testicular infection caused by SARS-CoV-2.

MATERIALS AND METHOD

Study Design and Participants

This retrospective study was scarried out from1st april 2021 to 30th September 2022 in the department of Radiodiagnosis, SAMC & PG Institute, Indore which is one of the major authorized institution that can receive and cure patients with COVID-19. All enrolled patients presented with initial symptoms between from1st april 2021 to 30th September 2022, and had a confirmed diagnosis of COVID-19 during their hospitalization. Our study was approved by the Ethics Committee. All patients in this study signed informed consent.

Diagnosis and Grading of COVID-19

All patients enrolled in the study had diagnosis and grading according to the interim guidance issued by the World Health Organization [12]. The diagnosis of COVID-19 was confirmed by positive results from a nasopharyngeal swab and respiratory pathogen nucleic acid testing with high-throughput sequencing or a real-time reverse transcriptase polymerase chain reaction [14]. All patients underwent chest computed tomography and were confirmed to show changes characteristic of viral pneumonia [15, 16].

According to their signs and symptoms, computed tomographic results, and laboratory results, COVID-19 severity can be classified into 4 types: mild, moderate, severe, and critical. Severe COVID-19 must meet 1 of the following 3 criteria: respiratory distress and a respiratory rate greater than 30 breaths per minute; resting fingertip blood oxygen saturation less than 93%; and partial arterial oxygen pressure/fraction of inspiration oxygen less than 300 mm Hg. Critical COVID-19 disease is based on the following criteria: respiratory failure requiring mechanical ventilation; shock; and multiple organ failure requiring intensive care management. For this study, patients were classified into 2 groups: group 1, including patients with non-severe COVID-19 (mild and moderate types); and group 2, including patients with severe COVID-19 (severe and critical types).

Ultrasound Examination and Data Collection

The clinical data for the enrolled patients were collected from electronic medical records and included demographic information, clinical symptoms and signs, comorbid conditions, imaging findings, laboratory results, treatments, and clinical outcomes. Ultrasound examinations of the scrotum were performed at the bedside during hospitalization with a delay between 1 week to 1 month after the initial disease symptom appeared or after the admission date for patients whose time of initial symptoms was uncertain in their medical history. The scrotal US examinations focused on the acute orchitis /epididymitis /epididymo-orchitis related imaging manifestations, including a thickened tunica albuginea, enlargement of the testis, epididymis, or both, heterogeneous echogenicity of the testis, epididymis, or both, increased vascular flow on color Doppler imaging, an abscess of the epididymis, hydrocele, and scrotal wall swelling. The major US features of acute orchitis were the classic triad (enlargement, heterogeneous echogenicity, and increased flow on color Doppler flow imaging [CDFI] of the testis), and the minor features included a thickened tunica albuginea, hydrocele, and scrotal wall swelling. The diagnostic criteria for acute orchitis were defined as the presence of all 3 major features or any 2 major features plus at least 1 minor feature. The major US features of acute epi- didymitis were enlargement, heterogeneous echogenicity, and increased flow on CDFI of the epididymis, and the minor features included an abscess in the epididymis, hydrocele, and scrotal wall swelling. The diagnostic criteria for acute epididymitis were defined as the presence of all 3 major features or any 2 major features plus at least 1 minor feature. Patients who met both epididymitis and orchitis diagnostic criteria were classified as having epididymo-orchitis [17].

Statistical Analysis

Binary and ranked variables were expressed as counts and percentages. Continuous variables were expressed as the mean and standard deviation or median and interquartile range (IQR), as appropriate. Continuous parameters were compared by an independent- samples *t* test when the data were normally distributed or the Mann–Whitney test when non-normally distributed. The binary and ranked data sets were analyzed by a cross-table χ^2 test or Fisher exact test when the expected frequency was less than 5. Statistical significance for all analyses was defined as 2-tailed $P < .05$.

RESULTS

Demographics, Clinical Characteristics, and Outcomes

The demographics and clinical characteristics of patients with COVID-19 enrolled in this study are summarized in Table 1. There were a total of 150 hospitalized male patients with confirmed diagnosis of COVID-19 in our study population. The median age

was 58.3 years (IQR, 43.0–78.0 years; range, 24.0–93.0 years). Of the 150 patients hypertension (45 [29.7%]), chronic kidney disease (20 [14.1%]), and diabetes (21 [16.2%]) were the most common. The most common initial symptoms were fever (80 [59.6%]), sore throat (70 [50.4%]), cough (51[40.7%]), chest pain/tightness (49 [36.3%]), and shortness of breath (43 [31.7%]) fifteen (10.2%) patients had acute scrotal symptoms, including enlargement, swelling, and pain, before the US scanning.

Fifty-nine (41.5%) of the patients with severe COVID-19 were categorized into group 2, whereas 83 (58.5%) were categorized into group 1. In comparing these groups, patients in the severe group were significantly older (mean age, 64.0 years versus 54.2 years [IQR, 38.0–69.0] years.

There were no significant differences between patients in the groups in terms of the other comorbid diseases and all the initial symptoms recorded in this study. In group 2, more patients had acute scrotal symptoms than group 1 (12 [18.9%] versus 5 [4.2%]).

Table 1: Clinical Characteristics of Patients with COVID-19

Characteristic		Disease Severity Groups		
	All Patients (n = 150)	1(Non-severe) (n=85)	2(Severe) (n = 65)	*P*
Age, y	58.3 (43.0–73.0)	54.2 (38.0–69.0)	64.0 (47.0–78.0)	0.001
Initial symptoms				
Fever	80 (59.6)	39 (55.0)	35 (63.7)	0.699
Cough	51 (40.7)	30 (35.9)	29 (46.1)	0.191
Shortness of breath	43 (31.7)	32 (29.1)	18 (23.9)	0.199
Chest pain/tightness	49 (36.9)	30 (35.2)	20 (34.3)	0.674
Sore throat	70 (50.4)	45 (50.4)	30 (52.2)	0.477
Acute scrotal symptoms				
Swelling/pain	15 (10.2)	5 (4.2)	12 (18.9)	0.006
Comorbid diseases				
Hypertension	45 (29.7)	26 (30.4)	25 (37.9)	0.157
Diabetes	21 (16.2)	12 (12.3)	14 (19.6)	0.201
Coronary heart disease	19 (13.7)	7 (9.4)	12 (21.6)	0.037
Chronic kidney disease	20 (14.1)	10 (12.7)	15 (26.9)	0.059
Chronic obstructive pulmonary disease	16 (14.1)	9 (9.3)	10 (16.6)	0.022
Hepatic cirrhosis	10 (8.1)	4 (3.9)	7 (12.1)	0.123

Scrotal US Imaging Findings

Twenty-one (15.1%) patients had in*fl*ammatory findings in bilateral testes, epididymis, or both, whereas 18 (13.0%) patients had unilateral onset. There was significant difference in the unilateral and bilateral onset risk between the disease severity groups (*P* = .268). The most common manifestations were a thickened tunica albuginea (29 [21.1%]), increased vascular flow on CDFI of the testis (27[19.3%]) and epididymis (22[14.7%]), and heterogeneous echogenicity of the testis (15 [10.9%]) and epididymis (9[6.5%]). Compared with group 1, significantly more patients in group 2 had a thickened tunica albuginea (27 [48.1%] versus 13 [15.1%]; P < .001), heterogeneous echogenicity of the testis (13 [16.6%] versus 5 [5.1%]; *P* = .012), increased vascular *fl*ow on CDFI of the testis (26[43%] versus 8 [9.8%]; *P* = .001), increased vascular *fl*ow on CDFI of the epididymis (18[28.1 %] versus 11 [12.1%]; *P* = .019), and an abscess in the epididymis (6 [8.8%] versus 0 [0%]; *P* = .026).

There were no significant differences between patients in the disease severity groups in enlargement of the testis, enlargement of the epididy- mis, heterogeneous echogenicity of the epididymis, hydrocele, and scrotal swelling.

Table 2: Ultrasound Findings of Acute Scrotal Infections in Patients with COVID-19

		Disease Severity Groups		
US Finding	All Patients (n = 150)	1(Nonsevere) (n = 85)	2 (Severe) (n = 65)	*P*
Unilateral onset	18 (13.0)	9 (10.1)	9 (14.3)	0.158
Bilateral onset In *fl*ammatory characteristics	21 (15.1)	11 (13.2)	14 (24.1)	0.148
Thickened tunica albuginea	29 (21.1)	13 (15.1)	27 (48.1)	<.001
Enlargement of testis	11 (8.0)	5 (5.8)	7 (11.2)	0.301
Heterogeneous echogenicity of testis	15 (10.9)	5(5.1)	13 (19.6)	0.012
Increased vascular flow on CDFI of testis	27 (19.3)	8 (9.8)	26 (43)	0.001

		Disease Severity Groups		
US Finding	**All Patients (n = 150)**	**1(Nonsevere) (n = 85)**	**2 (Severe) (n = 65)**	***P***
Enlargement of epididymis	13 (9.7)	6 (7.0)	8 (12.2)	0.512
Heterogeneous echogenicity of epididymis	9 (6.5)	4 (4.3)	6 (9.3)	0.212
Increased vascular flow on CDFI of epididymis	22 (14.9)	11 (12.1)	18 (28.1)	0.019
Abscess in epididymis	-2.8	0 (0)	6 (8.8)	0.026
Hydrocele	10 (7.1)	4 (4.3)	9 (12.9)	0.051
Scrotal swelling	4 (7.3)	2 (6.6)	5 (8.2)	0.149
Subcategorized by infection type				
Acute orchitis	11 (9.0)	4 (4.6)	8 (19.1)	0.091
Acute epididymitis	6 (3.9)	6 (4.1)	6 (7.8)	0.399
Acute epididymo-orchitis	25 (20.2)	3 (4.2)	18 (14.9)	0.032

DISCUSSION

In this study, we acquired First-hand and direct US imaging findings of acute scrotal infection in hospitalized patients with COVID-19 on the front line of the pandemic. Thirty-nine (27.5%) patients showed in*fl*ammatory imaging features such as a thickened tunica albuginea, tissue enlargement, heterogeneous echogenicity, increased vascular *fl*ow, hydrocele, abscesses, and scrotal wall swelling. more patients had a diagnosis of as acute orchitis, epididymitis, or epididymo-orchitis according to the diagnostic criteria, and the observed risk appeared to increase with increasing age and COVID- 19 severity.

According to our review of the Human Protein Atlas, the ACE2 protein is highly expressed in the duodenum, small intestine, colon, kidney, testis, and gallbladder [20]. The expres-sion pattern of ACE2 suggests that SARS-CoV-2 mayaffect the function of multiple organs. Some previous and recent coronavirus studies have demonstrated that the virus can indeed affect many organs beyond the lungs, including the kidneys, brain, digestive tract, heart, liver, thyroid gland, and testicles [21–23]. In human testis tissue, ACE2 is primarily expressed in the sper- matogonia, Leydig cells, and Sertoli cells [25]. A 2005 study of autopsy *fi*ndings for patients with SARS found 6 cases of orchitis with various pathologic changes such as widespread germ cell destruction, few or no spermatozoa in the seminiferous tubules, thickening of the basement membrane, and leukocyte in*fi*ltration [24]. Consequently, many scholars consider the testicles as potential infection targets of SARS- CoV-2, given its similar receptor interaction as SARS-Co V [25, 26].

Viral infections can result from hematogenous spreading or from direct extension of adjacent in*fl*am- mation. Therefore, on the basis of the assumption of receptor interaction and the distribution of ACE2, we think that SARS-CoV-2 could attack both the testis and the epididymis. At the same time, however, many patients with COVID-19 were in a state of dimin- ished immunity, and the bacteria from the ascending urinary tract may break out and cause scrotal infec- tions, in which tail-of-epididymis involvement was most obvious [17].

Our results lend credence to the idea that SARS- CoV-2 infection may speci*fi*cally affect the testis, epi- didymis, or both. Thus, we suggest that clinicians remain aware of the risk of acute scrotal infection in hospitalized patients with COVID-19, and for young male patients with COVID-19, especially those who wish to have children, local symptoms and fertility should be carefully monitored and protected.

Admittedly, there was no pathologic evidence to verify the US diagnosis of acute scrotal infections in this study, so we cannot state with surety that SARS-CoV-2 was responsible. Comorbidities and a systemic in*fl*ammatory reaction may have resulted in tissue enlargement and swelling as well. Further research based on biopsy or autopsy should be undertaken to investigate whether pathologic and histologic changes caused by SARS-CoV-2 occur in the testis and epidid- ymis of patients with COVID-19.

CONCLUSION

Viral infections can result from hematogenous spreading or from direct extension of adjacent inflam mation. Therefore, on the basis of the assumption of receptor interaction and the distribution of ACE2, we think that SARS-CoV-2 could attack both the testis and the epididymis. At the same time, however, many patients with COVID-19 were in a state of dimin- ished immunity, and the bacteria from the ascending urinary tract may break out and cause scrotal infec- tions, in which tail-of-epididymis involvement was most obvious [17]. Our results lend credence to the idea that SARS- CoV-2 infection may specifically affect the testis, epi- didymis, or both. Thus, we suggest that clinicians remain aware of the risk of acute scrotal infection in hospitalized patients with COVID-19, and for young male patients with COVID-19, especially those who wish to have children, local symptoms and fertility should be carefully monitored and protected. Admittedly, there was no pathologic evidence to verify the US diagnosis of acute scrotal infections in this study, so we cannot state with surety that SARS CoV-2

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