Hormozgan Medical Journal

doi 10.34172/hmj.2023.939

Hormozgan Med J. 2023; 27(3): 162-167

Review Article

Coronavirus and Sexual Transmission: A Systematic Review

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Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019 in Wuhan, China. Although the respiratory system is infected by this disease, other tissues are prone to coronavirus attack so that the male reproductive system can be another target for the virus, causing sexual transmission of coronavirus. The extant research systematically reviewed the studies conducted on COVID-19 and the sexual transmission possibility.

Methods: In this systematic review study, the articles and papers were collected by using some keywords such as COVID-19, Semen, Novel Coronavirus, SARS-CoV-2, Angiotensin-converting enzyme 2 (ACE2), and Male Infertility searching through PubMed, Web of Science, Scopus, and Google Scholar databases using OR and AND operators from December 2019 to November 2020. There was not any constraint on publication language when searching through electronic data sources directly or in reviewing the reference list of studies. Thirteen papers as eligible articles were studied finally. The original research studies examining the expression of SARS-CoV-2 in semen fluid or sexual transmission of this virus in men were chosen, while other studies were removed from the investigation. The full text of the articles was reviewed and discussed by two authors to reach a consensus; disagreements were resolved by consensus. We extracted information on study characteristics from each of the considered studies.

Results: According to current studies, ACE2, which is found abundantly in testicles, can perform as a cellular receptor for SARS-CoV-2. This finding is the foundation of this hypothesis that human testis and semen can be infected by SARS-CoV-2. In particular, a study showed that SARS-CoV-2 might be detected in the semen of patients with COVID-19, while other studies found no viral RNA in testicular biopsy tissue. Furthermore, some studies concluded that this virus, even in the acute phase, could not infect the testicles or the male genital system. Accordingly, no evidence confirms that this virus can be transmitted through male genital organs.

Conclusion: Although this virus has not been detected in semen fluid and it has not been sexually transmitted, one study reported this virus in the semen of coronavirus-infected patients and introduced its possible sexual transmission. Therefore, there is a low probability of sexual transmission of coronavirus.

Keywords: COVID-19, Novel coronavirus, SARS-CoV-2, Semen, ACE2, Male infertility

Received: January 29, 2021 **Accepted:** August 9, 2021, **Published Online:** September 28, 2023

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in December 2019 in Wuhan, China, diagnosing several pneumonia cases (1). This virus belongs to the coronavirus family that is named based on the antigen existing in its membrane, making a crown-like appearance to the virus (2). There is an increasing global rate of coronavirus cases (3) so that more than 46 394 012 COVID-19 cases have been reported worldwide until November 1, 2020, including 1 200 397 deaths and 33 487 667 recovered patients (4). Coronavirus symptoms vary from asymptomatic carriers and symptoms such as mild cold to severe illness and death. Some of these symptoms include fever, cough, tiredness, shortness of breath, headache, myalgia, and production of sputum. Furthermore, some patients have reported gastrointestinal symptoms and anosmia (5). The attention of coronavirus is focused on the respiratory system in which there is a life-death battle between the host and hordes of viruses; however, other tissues such as the brain, heart, and kidney are prone to coronavirus infection, thus the male reproductive system, especially spermatogenesis, may be infected by this virus, causing male infertility or facile sexual transmission of this virus (6). Angiotensin-converting enzyme 2 (ACE2) receptor plays a vital role in COVID-19 pathogenesis, which contributes to direct damage to the host's cell as coronavirus binding to the ACE2 receptor leads to its cellular input and proliferation (1). Therefore, patients are more susceptible to coronavirus when ACE2 is more in the cells (7). The virus will be multiplied once it enters the cell and releases mature viruses, infecting the new

cells (2). A study reported that testicles contain almost the highest amount of ACE2 mRNA and protein compared to other body tissues (7). Moreover, reports revealed that SARS-CoV-1 had infected testicles and caused viral orchitis. Compared to women, male patients are more susceptible to SARS and COVID-19 infections, and the symptoms are more common among men than women (2). Nevertheless, few studies have been performed on the side effects of this virus on the male reproductive system.

Objectives

The extant research systematically reviewed the studies conducted on COVID-19 and the sexual transmission possibility.

Methods

Data Sources

This is a systematic review study in which the articles and papers were collected by using some keywords such as COVID-19, Novel Coronavirus, SARS-CoV-2, Semen, ACE2, and Male Infertility searching through PubMed, Web of Science, Scopus, and Google Scholar databases by applying OR and AND operators from December 2019 to November 2020. Additional keywords and Boolean operators associated with every database were used to change the strategy. There was not any constraint on publication language when searching through electronic data sources directly or in reviewing the reference list of studies. The manual search was examined through journals, scientific research groups, or reports published by the World Health Organization, proceedings of conferences, seminaries, and dissertations (abstracts of papers). All studies from December 2019 when the first SARS-CoV-2 case was diagnosed in China (1) to November 2020 were entered into the study.

Study Selection

Finally, 13 papers as eligible articles underwent evaluation. The original research studies investigating the expression of SARS-CoV-2 in semen fluid or sexual transmission of this virus in men were selected while removing the other studies. There were no constraints regarding infection and treatment duration. To choose studies, the titles and abstracts of papers and their eligibility were examined in the first step.

Data Extraction

Next, the full texts of the articles were reviewed and discussed by two authors to reach a consensus, and disagreements were resolved by consensus. Then, information on study characteristics was extracted from each of the intended studies (including study design, sample size, place, and period in which the study was conducted, characteristics of the intervention group and control group, main inclusion and exclusion criteria, laboratory findings, and patient-relevant outcomes).

Results

Searching keywords through databases, 1939 papers were detected and examined, and finally, 1845 articles were removed based on the removal of repetitive papers, inclusion and exclusion criteria, titles, and abstracts. After reading the full texts of articles, 81 articles were removed, and 13 articles (Table 1) were eligible, thus they were chosen and entered into the study. The systematic review of studies is illustrated in Figure 1.

SARS is a new viral pandemic with many unknown aspects with limited studies on the case (8). The clinical manifestations of SARS-CoV-2 seem to begin in less than a week and are commonly characterized by fever, cough, nasal congestion, asthenia, anosmia, and ageusia (9). It is essential to study the transmission methods of nCoV-2019 to control virus spread; air droplets and close contact are two main transmission routes. Additionally, there was some evidence of oral-fecal transmission (10). Although the main concern relates to severe infections that cause death, a high number of infected patients indicate that different aspects of this infection should be studied considering infections in other systems (besides the respiratory system), as well as other possible transmission routes of SARS-CoV-2. Evidence indicates that SARS-CoV-2 can affect other systems and can be observed in rectal swabs, as well as blood and urine samples (8). Identification of the virus in various secretions and excretions of the body can indicate the infectious status of the patient (9). Many viruses that infect humans are detectable in semen (11). A wide range of viruses can attack the testicles and affect male reproductive function, including human immunodeficiency virus, influenza, Zika, and mumps (12). Furthermore, previous studies have pointed to the negative effect of other viral infections on semen parameters, including volume, sperm count, and motility (13).

Similar to SARS-CoV-2, SARS-CoV is a virus that belongs to the β-coronavirus family that causes SARS disease, leading to spermatogenic cell necrosis, apoptosis, and interstitial inflammation although its viral genomic sequence has not been detected in testes (11).

Recent reports have suggested that ACE2 may induce SARS-CoV-2 access to male reproductive organs. ACE2 is abundantly expressed in testes, including Sertoli cells, Leydig, and spermatogonia (13). Moreover, this finding assumes that human testicles and semen are targets for SARS-CoV-2 infection (14). On the other hand, the viral effects of SARS-CoV-2 have raised concerns that SARS-CoV-2 may cross the testicular-blood barrier and invade the male reproductive system (8). The blood-testis barrier (BTB) is a structure located between the interstitial capillary lumen and the seminiferous tubule lumen, consisting of capillaries, endothelial cells, a

Table 1. Studies Included in This Systematic Review

Author	Year	Type	Sample Size	Study Place	Age (y)	Subject	Results
Kayaaslan et al (8)	2020	Prospective	16	Turkey (Ankara)	18-54 years	Investigation of SARS-CoV-2 in semen of patients in the acute stage of COVID-19 infection	SARS-CoV-2 was not detected in the semen of patients with acute COVID-19.
Paoli et al (9)	2020	Case report	1	Italia (Rome)	31 years old	Study of SARS-CoV-2 in semen and urine samples of a volunteer with positive nasopharyngeal swab	Semen and urine sample search for SARS-CoV-2 RNA was negative.
Song et al (10)	2020	Cross-sectional study	13	China (Wuhan)	Patients in recovery, n=12 (22-38 years) Dead patient, n=1 (67 years old)	Detection of 2019 novel coronavirus in semen and testicular biopsy specimens of COVID-19 patients	The nCoV-2019 virus was not detected in semen and testicle biopsy of COVID-19-positive patients, indicating that nCoV-2019 could not infect the testicles and male genital organs.
Yan et al (11)	2020	Clinical implications	12	China (Tongji Medical College)	42-87 years	pathological findings in the testes of COVID-19 patients: clinical implications	There was not any evidence of SARS-CoV-2 presence in testes.
Ma et al (12)	2020	Cross-sectional study	12	China (Wuhan)	20-49 years	Evaluation of sex-related hormones and semen characteristics in reproductive-aged male COVID-19 patients	SARS-COV-2 was not detected in semen samples of COVID-19-positive men.
Li et al (13)	2020	The first part of the study is a case series The second part of the study is the cross-sectional cohort	In the first part, 6 cases and 6 controls In the second part, 23 cases and 22 controls	China (Tongji Medical College)	The first part Case: 51 to 83 years Control: 56 to 85 years The second part Case: 27 to 55 years Control: 30 to 54 years	Impaired spermatogenesis in COVID-19 patients	All semen samples searched for SARS-CoV-2 RNA were negative in hospitalized COVID-positive patients.
Nora et al (14)	2020	Prospective cohort study	34	Germany (Duesseldorf)	Mild, n=14 (42.7±10.4) Moderate, n=4 (40.8±8.7) Control, n=14 (33.4±13.1)	Assessment of SARS-CoV-2 in human semen—a cohort study	A mild COVID-19 infection is not likely to affect testis epididymis function, and the negative impact of SARS-CoV-2 infection was not detected in sperm parameters of recovered patients with mild symptoms. In addition, SARS-CoV-2 RNA could not be detected in the semen of recovered and acute COVID-19-positive patients.
Ning et al (15)	2020	Retrospective study	112	China (Wuhan)	23-83 years	Effects of the 2019 novel coronavirus on the male reproductive system: A retrospective study	The nCoV-2019 virus was not detected in the reproductive system of men with confirmed COVID-19.
Ruan et al (16)	2020	Prospective cohort study	74	China (Tongji Medical College)	20-50 years	No detection of SARS-CoV-2 from urine, expressed prostatic secretions, and semen in 74 recovered COVID-19 male patients: a perspective and urogenital evaluation	SARS-CoV-2 RNA was undetectable in urogenital secretions, indicating that testicles do not function as extra-pulmonary reservoirs.
Li et al (17)	2020	Cohort study	38	China (Shangqiu)	aged 15 years and older	Clinical characteristics and results of semen tests among men with coronavirus disease 2019	The SARS-CoV-2 virus might be detected in the semen of men infected by COVID-19; further, SARS-CoV-2 might be detected in the semen of recovered patients.
Guo et al (18)	2020	Cohort study	23	China (Shandong)	20-62 years	Absence of SARS-CoV-2 in semen of a COVID-19 patient cohort	SARS-CoV-2 RNA was not detected in the semen of COVID-19-infected patients, indicating that the testicles and genital system of men could prevent viral infection regarding this virus.
Pan et al (19)	2020	Observational, cross-sectional study	34	China (Wuhan)	31-49 years	No evidence of severe acute respiratory syndrome-coronavirus 2 in the semen of males recovering from coronavirus disease 2019	SARS-CoV-2 was not found in the semen of patients recovering from COVID-19 one month after COVID-19 diagnosis.
Pavone et al (20)	2020	Letter to Editor	9	Italia	28-60 years	Italian males recovering from mild COVID-19 show no evidence of SARS-CoV-2 in semen despite prolonged nasopharyngeal swab positivity	There was a low probability of sexual transmission of SARS-CoV-2 by men recovered from mild COVID-19.

Note. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 19.

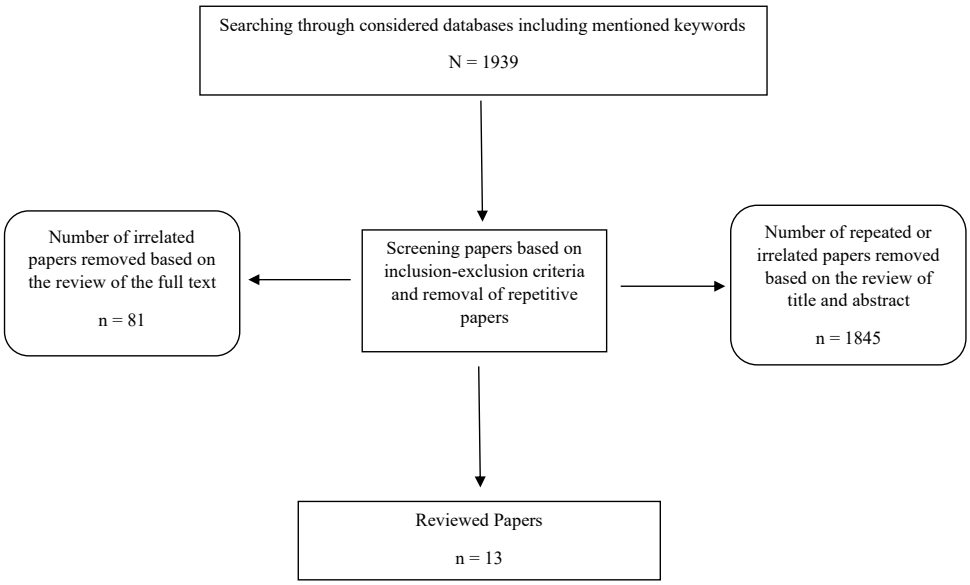

Figure 1. Preferred Reporting Items for Systematic Reviews

basement membrane of lymphatic, myocyte-like cells, a basilar membrane of seminiferous, and Sertoli cells, and can form an immune barrier in testes (15). Under viremia conditions, the male reproductive system might be infected by the virus because the BTB is not suitable enough for full viral isolation (21). It has been reported that Leydig cells and testicular macrophages have a strong antiviral ability, which can produce interferon α and γ simultaneously after contact with viruses, thereby resisting viruses and tumors and enhancing immune regulatory function. It indicates that, in addition to the BTB, the testicular system is also an ideal antiviral system (15). In a study conducted by Ruan et al, SARS-CoV-2 was absent in the semen of patients who had recovered from the disease, indicating that the testes do not act as an extrapulmonary reservoir for the virus. Furthermore, viral nucleic acid was not detected in expressed prostatic secretions, implying that the prostate might not be involved in the infection either (16). In particular, a study showed that SARS-CoV-2 might be present in the semen of COVID-19-positive patients (17). However, Song et al suggested the absence of a viral virus in testicular biopsy tissue; further, it was found that this virus does not infect the testes or male genital tract directly, and no evidence represents that this virus can be transmitted through the male genital tract (10). Moreover, Ma found no SARS-CoV-2 in semen after a certain interval since the symptom onset (at a median time of 78.5 days), suggesting that there was no risk of sexual transmission (12).

This study aimed at examining the presence or absence of SARS-CoV-2 in the semen of COVID-19-positive men and subsequently the viral potential for sexual transmission through the male genital tract. There was no definite clinical evidence on the presence of SARS-CoV-2 infection in human semen (18). To address this question, Song et al collected samples from 12 COVID-19-positive patients in their recovery phase using the sterile method through masturbation and testicular samples from one patient who died of COVID-19. None of the patients had severe COVID-19 pneumonia, and all samples were negative regarding SARS-CoV-2 presence in semen and testis (10). In another study conducted by Ruan et al, similar results were obtained despite some differences such as a larger sample size (74 patients with COVID-19 in their recovery phase) and the presence of patients with severe COVID-19 pneumonia, which is similar to the findings of Song et al. In their research, Ruan et al examined 74 patients who recovered from COVID-19, and the median interval between the last positive pharyngeal swab real-time polymerase chain reaction test and semen samples collection was 80 days (16). As this interval of semen sample collection of 80 days after a positive pharyngeal swab seemed so long, we reviewed the study conducted by Pan et al. They studied 34 male patients recovered from COVID-19, and the average time of semen sample collection from patients was 31 days after the certain COVID-19 diagnosis. According to the results, SARS-CoV-2 was not detected in any of the semen samples (19). The higher potential viral transmission phase is the acute phase of illness when the virus is in the infection stage, and viremia might be detected. Current studies argue that the negative results of SARS-CoV-2 presence in semen in infected patients might have been associated with a lack of semen sample collection during the acute phase of infection (22). Additionally, semen examination in patients with mild COVID-19 symptoms may cause the viral threshold is not achieved to cross the BTB (19). Kayaaslan et al studied 16 patients infected by COVID-19. All semen samples were collected during hospitalization and the acute phase of disease.

In addition, the median time of the sampling swab was one day (0-7 days) after the positive nasopharyngeal test of patients. SARS-CoV-2 was not detected in the semen of the mentioned patients (8). Guo et al examined 23 COVID-19-positive patients in acute and recovery phases; of them, 18 subjects showed mild symptoms, and 5 had moderate symptoms. To this end, semen samples were collected in both recovery and acute phases. There was no SARS-CoV-2 detected in semen samples, indicating that the transmission of the virus one month after its initial diagnosis seems unlikely. According to the results obtained by the above-mentioned researchers, there was no evidence of the virus being expressed in human semen samples, indicating that the testis might not be a target organ for SARS-CoV-2 (18). Contrarily, Li et al concluded that SARS-CoV-2 might be detected in the semen samples of patients with COVID-19 and who recovered from the disease. In this research, 38 COVID-19-positive patients were enrolled for SARS-CoV-2 presence in the semen; of which, 23 patients had achieved clinical recovery, and 15 patients were at the acute stage of infection. Ultimately, six patients had positive results for SARS-CoV-2 in semen fluid; of them, four patients were at the acute stage, and two patients were recovering (17). However, as this study did not fully analyze semen, the possibility of viral contamination from sources other than semen was not ruled out completely (18). Since it is a critical issue, further studies with a larger sample size and higher accuracy should be performed in this case.

Conclusion

Various studies examined the effect of SARS-CoV-2 infection on the male genital tract while only one study detected this virus in the semen of infected patients and its possible sexual transmission. There has been no evidence of SARS-CoV-2 presence in semen collected from infected men either in the acute phase or in the recovering stage. Therefore, it is an unlikely possibility that this virus can be transmitted sexually.

Authors' Contribution

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Competing Interests

The authors declare that there are no conflicts of interests.

Funding

The authors received no specific funding for this work.

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