REVIEW

An Assessment of Men Semen Alterations in SARS-CoV-2: Is Fever the Principal Concern?

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Abstract

The SARS-CoV-2 virus (COVID-19) was identified as a pandemic in March 2020 by the World Health Organization. The virus spreads primarily through saliva droplets or nasal discharges, in addition to coughing or sneezing from an infected person. The most common symptom at the onset of illness is fever, which may appear within 2–14 days after exposure. The high fever (above 38 °C) can persist from one to 4 days. The febrile illness usually has a variable negative impact on sperm characteristics such as sperm output, motility, morphology, and DNA fragmentation. These defects proliferated due to an increase in testicular temperature, and disturbance in the thermoregulatory systems that are responsible for the testicular heat loss. Coronavirus studies suggest that fever from SARS-CoV-2 virus infection induces a reversible negative effect on the sperm parameters until one cycle (74 days) of spermatogenesis. We believe that SARS-CoV-2 can have long-term adverse effects on testicles via immune or inflammatory reactions after the patient has fully recovered. This evidence could be added to the list of the long-term post-COVID-19 syndromes. Long-term follow-up and evaluation of the sperm parameters are necessary for all recovered male patients, especially the young ones.

Keywords SARS-CoV-2 · COVID-19 · Testis temperature · Fever · Sperm parameters · Men

Introduction

The 2019 novel coronavirus disease (COVID-19) was first detected in December 2019 in China. COVID-19 has been rapidly spreading all over the world in February and March 2020, and was recognized as a pandemic in March 2020 by the World Health Organization [1, 2].

Human coronaviruses are endemic in human populations, causing 15–30% of respiratory tract infections each year. Prior to the outbreak of COVID-19, a highly pathogenic severe acute respiratory syndrome coronavirus (SARS-CoV) appeared between 2002 and 2003. This was followed by

Middle Eastern respiratory syndrome coronavirus (MERS-CoV) between 2012 and 2015 [3].

Currently, there are about 240 million confirmed cases and 4.9 million deaths in three consecutive waves of the SARS-CoV-2 virus in 213 countries and territories around the world [4].

Furthermore, it was observed that the SARS-CoV-2 invasion of the host cell begins when the covering glycoprotein spike (S) attaches to the dipeptidyl peptidase 4 (DPP4) and angiotensin-converting enzyme 2 (ACE2)'s cellular receptors for MERS-CoV and SARS-CoV, respectively [5]. The virion-containing vesicles are formed when the viral genomic RNA is produced in the cytoplasm, replicated, and then attached to nucleocapsid proteins and glycoproteins envelope. Subsequently, the virus is spread outside the cell by blending with the plasma membrane [5]. The viral infection from SARS-CoV-2 primarily causes respiratory illness ranging from mild-to-severe disease and death. However, about 80% of the infected people never develop symptoms and may recover without any special treatment or hospitalization [6, 7].

The most common symptoms of patients hospitalized with COVID-19 across a broad clinical spectrum were fever,

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shortness of breath, cough, fatigue, loss of taste and smell, diarrhea, and lymphopenia [8–10].

An observational study on 1420 cases admitted to the hospital with mild or moderate disease reported that the most common symptoms were fever (45%), headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%), and cough (63.2%) [11]. Another study of 4203 patients mostly from China identified fever, cough, and dyspnea (80.5%, 58.3%, and 23.8%, respectively) as the most common clinical symptoms. [12]. In addition, a research group from Wuhan reported that 40 out of 41 patients admitted to the hospital with laboratory-confirmed COVID-19 had a fever as a symptom, 73% of them were men [1]. This study was consistent with the results obtained by Cao et al. described the initial clinical, laboratory, and radiological characteristics symptoms of the infected patients [13]. They conducted a study on 198 patients with COVID-19, 33.3% of the subjects were under 39 years old, and males represented 51.0% of patients. Notably, fever was the most common symptom among those patients, with 86.9% had a body temperature ranging from 38 to 38.9 °C and the other 8.8% had a fever greater than 39 °C [13].

Typically, the average period of the symptoms for patients infected with COVID-19 is 11.5 ± 5.7 days. The occurrence of symptoms significantly differed according to age and sex [11]. However, the symptoms may last weeks or months after the infection has gone. These circumstances are called post-COVID-19 syndrome or long COVID. Certainly, the testis is one of the organs most affected by COVID-19 [14–16]. Given that spermatogenesis could be affected by COVID-19 associated fever, semen parameters such as sperm concentration and motility may decrease for a period of 72 to 90 days after the viral infection [17]. Moreover, fever is a symptom of COVID-19 diagnosed in more than 70% of cases. Thus, fever may affect testis and semen quality [18].

In men, the functions of the testis and the epididymis are highly sensitive to the temperature increase of only a few degrees [19], and considerable effort has been devoted to analyzing this response.

Several reports have demonstrated that increased body temperature by fever is a factor affecting sperm parameters [20–22]: an acute fever of 39.9–40 °C for 1 to 4 days, harmed sperm parameters such as sperm output, motility, morphology, and DNA fragmentation. This defect may lead to changes in the metabolism of the germ cells, such as a decrease in the synthesis of DNA, RNA, and proteins. In addition, testicular heating may lead to vascular changes[23].

Moreover, studies reported that exposure of scrotal/testicular to temperatures of several degrees above core body temperature 37 °C [24–29], and/or below core body temperature 35–37 °C [30–36] may induce a disruption of spermatogenesis. This effect depends on two important factors: temperature exposure rate (high or mild) and/or the duration of heat exposure [23].

SARS-CoV-2 virus (COVID-19) is an unprecedented challenge to healthcare systems. Few studies reported the impact of the SARS-CoV-2 virus on the reproductive system, or whether it might change the sperm parameters and sexual hormones for recovered male patients. Here, we discuss the impact of the SARS-CoV-2 virus or accompanying symptoms on testes function and quality of sperm. We also exam the potential mechanisms by which the SARS-CoV-2 virus affects sperm parameters and sexual hormones for recovered male patients.

Materials and Methods

A classified and comprehensive search in previous studies in PubMed, Embase, Web of Science, Scopus, and Cochrane Library Databases was conducted in accordance with the guidelines of PRISMA (2020) (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Literature reviews, both published and peer-reviewed existing articles in English, were studied from online publications between the years 2020 to 2021. Additional sources of citations were from retrieving articles, and there was no limitation on sample size. We reviewed all appropriate titles of all reports, including testicular heat stress and sperm quality, and male gonadal function during and after fever. Similarly, prior publications of clinical studies to coronaviruses were few numbers: articles with information regarding male reproduction, the presence of virus in reproductive tissues, and effects on gametes.

We used a comprehensive and extensive search strategy in order not to miss a formative contribution that might relate to our topic. Search keywords used for different database strategy included the following: fever, male infertility, testis, heat exposure, sperm parameters, genital heat stress, SARS-CoV-2, COVID-19, viral infection, angiotensin-converting enzyme 2 receptors (ACE20), spermatogenesis, reproductive system.

The Viral Infection and Male Fertility

Viruses are known for their capability to infect testes, for example; mumps viruses were found in human Leydig cells and human immunodeficiency virus (HIV) infects human germ cells. HIV, hepatitis B virus (HBV), herpes simplex virus (HSV), and adenoviruses were detected in semen as shown in (Table 1) [37–44]. Additionally, over 20 types of viruses that infect humans have been found in semen and testis such as; Ebola, and Zika virus (ZIKV) [45, 46].

Table 1 Review of the literature on the influence of virus semen infection on sperm parameters

Virus	Studies	Present in semen	Sperm Count	Motility	Normal morphology
HBV	Lorusso et al. [37], Zhou et al. [38], Karamolahi et al. [39]	+	↓	↓	↓
HCV	Hofny et al. [40], Lorusso et al. [37], Safarinejad et al. [41]	+	↓	↓	↓
HIV	Kehl et al. [42], Lorusso et al. [37], Pavili et al. [43]	+	↓	↓	↓
HPV	Bezold et al. [44]	+	↓	↓	↓
Zika	Joguet et al. [45]	+	↓	↓	↓

Review of the literature on the influence of virus semen infection on sperm parameters. (+): Positive in semen sample (↑): increase. (↓): decrease. (HBV): hepatitis B virus. (HCV): hepatitis C virus. (HIV): human immunodeficiency virus. (HPV): Human papillomavirus

Many studies have shown that the presence of HIV, HBV, or HCV in semen impairs sperm parameters, DNA integrity, and reduces forward motility. Other viruses, such as Epstein-Barr virus, Papillomavirus, and mumps virus, were reported to cause viral orchitis [47–49].

A study conducted in 2002 reported that six male patients infected with SARS-CoV suffered from orchitis as observed through testicular autopsy. They found that orchitis was one of the post-infectious complications that may lead to disruption in spermatogenesis, germ cell apoptosis, and consequently affecting semen quality [42].

On the other hand, Zika virus (ZIKV) has been reported to cause pathological damage in the male reproductive system and detected in the testis and epididymis several weeks after the virus has disappeared from the blood [50].

Viral infection of the testicular cells may cause changes in testicular function, risk of fertility, and general health of the individual (such as a fall in testosteronemia which may lead to cachexia), plus possible transmission of virus-induced mutations to subsequent generations [41].

Genital Heat Exposure and Sperm Parameters

In men, the physiological migration of the testis is associated with a considerable cooling of its thermal environment. This procedure results in a scrotal temperature being 2–4 °C lower than the body core temperature [23]. This lower temperature is required for the process of sperm development or spermatogenesis to proceed in normal settings.

Two main thermoregulatory systems are responsible for this lower physiological testicular temperature in human. The first system consists of a countercurrent heat exchange between arterial blood and spermatic vein blood through the pampiniform plexus [51]. The second system is the external heat loss outside the body through passive convection and radiation by the scrotum [51, 52]. Furthermore, several characteristics of the scrotum, such as thin skin with minimal subcutaneous fat, dense sweat glands, and scant hair distribution play a role in regulating testicular temperature as well [23].

Most of the experimental protocols that raise the testicular temperature different methods (electric warming bag, polyester-lined supports, testis supra-scrotal localization, sauna, water bath) have a negative impact on spermatogenesis and the quality of sperm parameters (Table 2). An experimental increase in temperature intensity can be classified into two categories, depending on the body temperature: a mild increase when the testicular temperature remains below body temperature, and a high increase when it exceeds body temperature.

The Effect of the Acute Febrile Illness (Fever) on Sperm Parameters

During the onset of fever, testicular thermoregulation is disrupted, and scrotal temperature is raised along with the core body temperature. Several studies have shown that fever impairs spermatogenesis due to increased testicular temperature [20, 22, 52, 57–59]. Evenson et al. reported that a 1-day fever of 39.9 °C in a fertile man presented with influenza had 36%, 49%, and 30% denatured sperm DNA at 18, 33, and 39 days post fever, respectively, using the sperm chromatin structure assay (SCSA) (Table 3) [21]. Further, they reported alterations in the normal processing of protamine 2 and a slight increase in histone to protamine ratio suggesting a fever related disruption of mRNA synthesis which codes protamine 2 processing enzyme.

MacLeod followed three medical students during a febrile disease (body temperature was 37.7–40 °C) of chickenpox and pneumonia and found a marked decrease in sperm concentration, morphology and motility, and recovery almost 1–2 months after normalization of the temperature [60].

Sergerie et al. showed that fever may affect sperm parameters (total sperm count, motility, and vitality) and DNA fragmentation index (DFI) in a fertile man. Semen parameters were analyzed at 15, 37, 58, 79, and > 180 days after the fever [22]. Total sperm count significantly decreased from 15 to 58 days from the onset of fever and recovered on day 79 post fever. In addition, the percentage of sperm motility significantly decreased on day 15 and 37 and returned to

Table 2 The effects of experimental scrotal/ testicular temperature increase on sperm parameters

Research group	Method of heating	N	H/days	Period	Started effects during T° Increase	Recovery after T° increase	Parameter
Robinson and Rock [53]	Cloth-insulation	10 fertile men	11 H	10 W	3 W During T	11 W after T	Count (↓)
(1) Mieusset et al. [54, 55]	STP	14 fertile men	15H	12 M	2 M During T	6–8 M after T	volume(↓) Count(↓) Morphology(↓) Motility(↓)
(2)Mieusset et al. [56]	STP	6 fertile men	15H	6–24 M	2 M During T	6–15 M after T	Count(↓) Morphology(↓) Motility(↓)
Shafik [32]	Polyester-insulation	28 Men	24H	12 M	3 M During T	6 M after T	Count(↓) Morphology(↓) Motility(↓)
Shafik [33]	Polyester-insulation	14 men	24H	12 M	3 M	6 M after T	Count(↓) Testicular Volume (↓)
Zhang et al. [29]	Water bag	19 fertile men	H/D	3 M	1 M During T	1 M after T	Count(↓) Morphology(↓) Motility(↓) WBC (↑)
Ahmad et al. [34]	STP	5 fertile men	15H	4 M	34 D During T	93 D after T	Count (↓) Motility (↓) Round Cell (↑) Viability (↓) DFI (↑) HDS (↑)

(1)Ensure the permanent localization of the testes close to the inguinal canal but testicles were relatively free to travel due to the elasticity of the fabric. *STP* supra-scrotal position, *WBC* white blood cells, *N* subject number, *H* hour, *W* week, *M* month, *D* days, *T* temperature, *DFI* DNA fragmentation index, *HDS* high DNA stainability. (↑): increase. (↓): decrease. Ensure the permanent localization of the testes close to the inguinal canal but testicles were relatively free to travel due to the elasticity of the fabric

(2)Add to the device a ring of soft material to ensure that the testicles were kept permanently in an inguinal position. *STP* supra-scrotal position, *WBC* white blood cells, *N* subject number, *H*: hour, *W* week, *M* month, *D* days, *T* temperature, *DFI* DNA fragmentation index, *HDS* high DNA stainability. (↑): increase. (↓): decrease

Table 3 The effects of febrile episodes (fever) on testis, scrotal, and sperm parameters

Research group	Body T°	N	H/days	Parameters
Lazarus and Zorgniotti [52]	37.6–37.9 °C	6 men	(–)	Intra-scrotal temperature (↑)
Buch and Havlovec [59]	38.3 °C	14 fertile men	24H	Count(↓)
Evenson et al. [21, 57]	39.9 °C	One case study	24H	DFI (↑) HDS (↑) Free -SH (↑)
French et al. [20]	40 °C	One case study	3 days	Sperm density(↓)
Sergerie et al. [22]	39–40 °C	One case study	2 days	Count(↓) Motility(↓) DFI (↑) HDS (↑)
Carlsen et al. [58]	(–)	15 men	1–11 days	Count(↓) Morphology(↓) Motility(↓)
MacLeod [60]	37.7–40 °C	3 men	3–5 days	Count(↓) Morphology(↓) Motility(↓)

N subject number, *H* hour, *D* days, *T°* temperature, *DFI* DNA fragmentation index, *HDS* high DNA stainability. (–): no date. (↑): increase. (↓): decrease

normal on day 58-post fever. DFI measured by the sperm chromatin structure assay (SCSA) significantly increased by 24% and 36% and by 15 and 37 days, post fever, respectively. However, They decreased to 15% and 8% when approached to 58 and 79 days, post fever, respectively [22].

In the same context, Carlsen et al. analyzed the effect of a history of febrile illness on semen quality in men who experienced one or more episodes of fever. Sperm concentration, morphology, and motility are significantly affected by fever, particularly during the post-meiotic period of spermiogenesis. In addition, the number of days the men experienced fever significantly affected their sperm parameters [58].

Other publications have analyzed the effect of temperature on semen quality. Buch and Havlovec (1991) found that sperm count has decreased in a case report of a semen donor of the patient who suffered an acute viral illness with a fever (38.3 °C for 24 h) [59]. Another study reported that the Intra-scrotal temperature was compared with oral body temperature in six subjects with fever; when the body temperature reached 37.6 to 37.9 °C, the testicular thermoregulatory mechanism appeared to fail, and the intra-scrotal temperature increased. However, the adverse effect seemed to be dependent upon the number of days with fever [52].

Several studies have reported a rise in testicular temperature resulting from fever has induced a reversible decrease in sperm output and quality (motility, normal morphology) as well as in fertility when exposure ranges up to 2 days.

SARS-CoV-2 (COVID-19) and Male Fertility

Statements reported a high rate of infection, morbidity, and mortality among male patients who tested positive for coronavirus. However, very few casuistic reports were conducted on men to show the effects of COVID-19 on sperm parameters, sexual hormones, and the male reproductive system.

To date, most studies reported that the SARS-CoV-2 virus is absent from the semen and testes in men infected in both acute and recovery phases [61–67].

In contrast, a study of 38 male patients with the SARS-CoV-2 virus found that 4 of 15 patients (26.7%) were in an acute stage of infection and 2 of 23 patients (8.7%) in recovery had detectable SARS-CoV-2 presents in semen samples [68]. Similarly, Yang et al. reported that one case (1/12) with a high viral load was positive for viral RNA after post-mortem examinations of testicular tissue [16].

Furthermore, studies have identified the main path for coronavirus entry into the cell—via the viral spike (S) protein that is attached to the angiotensin-converting enzyme 2 (ACE2). Interestingly, at the level of testicular cells, four main cell types, such seminiferous duct cells, spermatogonia, Leydig cells, and Sertoli cells, show a higher rate of ACE2 mRNA expression, where it employs the cellular serine protease (TMPRSS2) for S protein priming both of

which present in the testis. Thus, concern has arisen regarding (1) infection of the testes [69] and (2) possible sexual transmission [70]. However, no experimental studies or epidemiological investigations have described evidence that COVID-19 is a sexually transmitted disease (STD). While angiotensin-converting enzyme 2 receptors were found in the reproductive organs, the lack of co-expression of the TMPRSS2 modulator protein, required for SARS-CoV-2 cell entry, in testicular cells, sperm, or seminal plasma, argues against the hypothesis that gametes may transmit SARS-CoV-2 [18, 67].
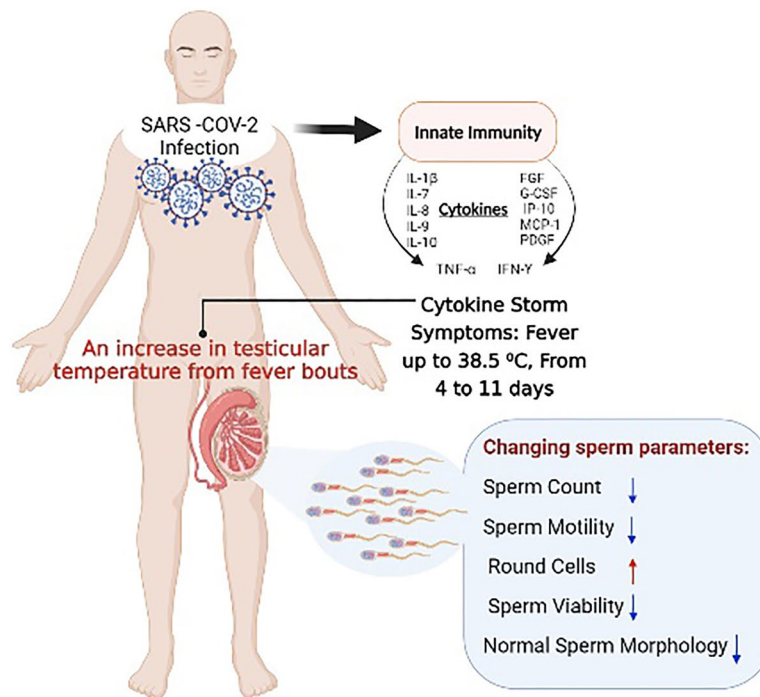
In a recent study, the results reported that the testosterone to luteinizing hormone (T to LH) ratio in 81 patients with the SARS-CoV-2 virus was dramatically decreased in comparison with 100 age-matched healthy counterparts. Serum T to LH ratio (as a predictor of Leydig function) could be a potential marker of impairment of reproductive health in COVID-19 patients [70, 71]. One observation in Hamburg, Germany, showed that majority of male SARS-CoV-2 virus patients present with low testosterone and dihydrotestosterone levels at admission to the intensive care unit (ICU). In addition, 6 out of the 35 male patients with low testosterone levels have elevated levels of the luteinizing hormone (LH) at the same time, suggesting impairment of Leydig cell steroidogenesis in 17.1% of the male patients [72]. Furthermore, an acute critical inflammatory condition, as in the case of COVID-19, may suppress the activity of hypothalamic–pituitary–testicular (HPT) axis. These findings may suggest direct effects of SARS-CoV-2 virus infection in testicular cells rather than via the HPT axis [73].

Moreover, the hyperactivated immune responses along with cytokine storms following SARS-CoV-2 infection affect many organs. There is a direct correlation between an increase in pro-inflammatory cytokines and multiple-organ failure, including the heart, liver, and kidney. In addition, a high inflammatory response associated with fever, immune cell activation, and inflammatory mediators such as interferons and cytokines can affect testicular function (Fig. 1) [74, 75].

Importantly, fever is an additional risk of COVID-19 that may affect male fertility. The average duration of fever in SARS-CoV and SARS-CoV-2 patients is the same (11.4 ± 6.8 days) and it may last for 31 days in COVID-19 patients who receive intensive care services (ICU) [76]. However, the duration of fever observed in MERS and other viruses such as influenza and Zika virus was shorter; the average duration of MERS is 8 days [76–78], the influenza is 3–4 days for the influenza virus [79], and Zika virus was 1–8 days. [80]. Hence, we can conclude that the fever caused by COVID-19 may have a significant effect compared to other viruses.

Within the same family of SARS-CoV-2 virus, Xu et al. stated that pyrexia is a first symptom expressed in SARS

Fig. 1 Schematic overview of the mechanism of the increase in body temperature (fever)-induced SARS-CoV-2 infection. TNF-α and IFN-ϒ synergize to drive the cytokine storm and fever associated with COVID-19 to impair sperm quality. Created by BioRender.com

patients combined with increased apoptotic spermatogenetic cells and a few positive Leydig cells as shown in (Fig. 1) [49].

A recently conducted study by Patel et al. reported that spermatogenesis could be affected by COVID-19-associated fever, and semen parameters such as sperm concentration, morphology, and motility could be decreased at least one cycle of spermatogenesis (74 days) after the viral infection [17]. Additionally, Temiz et al. showed a significant decrease in the percentage of normal morphology of the semen in patients infected with the COVID-19; they attributed this result to the fever seen in all COVID-19 patients [18].

Certainly, it seems prudent to avoid pregnancy if the risk of COVID-19 infection remains high for many of COVID-19 actions have not yet been discovered. The American Society for Reproductive Medicine (ASRM) and the European Society of Human Reproduction and Embryology (ESHRE) issued a recommendation for the patient and clinical management during the coronavirus (COVID-19) pandemic. Similarly, initiation of new treatment cycles, including ovulation induction, intrauterine inseminations (IUIs), and in vitro fertilization (IVF) including retrievals and frozen embryo transfers, as well as non-urgent gamete cryopreservation should be avoided. Also, strongly consider the cancellation of all embryo transfers whether fresh or frozen [81].

There are at least three possible speculations on how the SARS-CoV-2 virus can affect testicular functions and sperm quality: (1) body fever contributes to an increase in testicular temperature which may cause poor sperm quality, this notion has been generally accepted. Several authors showed a negative influence of fever on semen quality with impaired sperm density, progressive motility, and morphology occurring a few weeks after the onset of fever and lasting for 1–3 months [20, 21, 23, 58–60, 82] (Fig. 1). (2) Triggering a secondary autoimmune response leading to autoimmune orchitis [73]. (3) The SARS-CoV-2 binds to the ACE2 receptors for cellular entry and replication. Thus, it may be observed that testicular cells with higher ACE2 expression are more susceptible to the effects of SAR-CoV-2 [83].

Conclusions

COVID-19 affects a wide-range of patients, from youth to the elderly. Fever is consistently the most common symptom of onset, and several studies demonstrated that males are more likely to be infected by COVID-19 and more likely to die. One important aspect of our review is the highlight of one of the COVID-19 virus symptoms (fever) that may affect men's sperm parameters post-recovery of the illness. Physicians must counsel patients about the risk of damage to the testis's cells, sperm parameters, and sperm DNA fragmentation, especially those who had been exposed to severe fever. We recommend adding the effect of the SARS-CoV-2 virus on the testis and on the quality of sperm to the list of

the post-COVID-19 syndrome (long COVID), which may last up to 3 months post-recovery.

Today, the impact of COVID-19 on male fertility is vague in several aspects. Well-designed and controlled studies of reproductive function and evaluation of the sperm quality may be required for men recovered from COVID-19 disease, especially young male patients.

Declarations

Conflict of Interest The authors declare no competing interests.

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