



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Disponible en ligne sur

**ScienceDirect**  
[www.sciencedirect.com](http://www.sciencedirect.com)

Elsevier Masson France

**EM|consulte**  
[www.em-consulte.com](http://www.em-consulte.com)



## LITERATURE REVIEW

# Semen parameters and sex hormones as affected by SARS-CoV-2 infection: A systematic review

*Paramètres du sperme et hormones sexuelles affectés par l'infection par le SRAS-CoV-2 : une revue systématique*

J. Bao, Z. Guo, J. He, T. Leng, Z. Wei, C. Wang, F. Chen\*

Jining Medical University, 133, Hehua Road, 272067 Jining, China

Received 16 May 2022; accepted 5 September 2022

### KEYWORDS

COVID-19;  
SARS-CoV-2;  
Male reproduction;  
Semen parameters;  
Sex hormones

### Summary

**Background.** – Impaired semen quality and reproductive hormone levels were observed in patients during and after recovery from coronavirus disease 2019 (COVID-19), which raised concerns about negative effects on male fertility. Therefore, this study systematically reviews available data on semen parameters and sex hormones in patients with COVID-19.

**Methods.** – Systematic search was performed on PubMed and Google Scholar until July 18th, 2022. We identified relevant articles that discussed the effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on male fertility.

**Results.** – A total number of 1,684 articles were identified by using a suitable keyword search strategy. After screening, 26 articles were considered eligible for inclusion in this study. These articles included a total of 1,960 controls and 2,106 patients. When all studies were considered, the results showed that the semen parameters and sex hormone levels of patients infected with SARS-CoV-2 exhibited some significant differences compared with controls. Fortunately, these differences gradually disappear as patients recover from COVID-19.

\* Auteur correspondant.

E-mail addresses: [15668317980@163.com](mailto:15668317980@163.com) (J. Bao), [17852777716@163.com](mailto:17852777716@163.com) (Z. Guo), [hejiarui020303@163.com](mailto:hejiarui020303@163.com) (J. He), [lengtaiyang@163.com](mailto:lengtaiyang@163.com) (T. Leng), [weizichun207001@163.com](mailto:weizichun207001@163.com) (Z. Wei), [19806264362@163.com](mailto:19806264362@163.com) (C. Wang), [chenfei0336@163.com](mailto:chenfei0336@163.com) (F. Chen).

<https://doi.org/10.1016/j.purol.2022.09.004>

1166-7087/© 2022 Elsevier Masson SAS. All rights reserved.

**Conclusion.** — While present data show the negative effects of SARS-CoV-2 infection on male fertility, this does not appear to be long-term. Semen quality and hormone levels will gradually increase to normal as patients recover.

© 2022 Elsevier Masson SAS. All rights reserved.

## MOTS CLÉS

COVID-19 ;  
SARS-CoV-2 ;  
Reproduction  
masculine ;  
Paramètres du  
sperme ;  
Hormones sexuelles

## Résumé

**Contexte.** — Une altération de la qualité du sperme et des niveaux d'hormones sexuelles a été observée chez les patients pendant et après le rétablissement de la maladie à coronavirus 2019 (COVID-19), ce qui a suscité des inquiétudes quant aux effets négatifs sur la fertilité masculine. Par conséquent, cette étude examine systématiquement les données disponibles sur les paramètres du sperme et les hormones sexuelles chez les patients atteints de COVID-19. **Méthodes.** — Une recherche systématique a été effectuée sur PubMed et Google Scholar jusqu'au 18 juillet 2022. Nous avons identifié les articles pertinents qui discutaient des effets du coronavirus 2 du syndrome respiratoire aigu sévère (SARS-CoV-2) sur la fertilité masculine. **Résultats.** — Un nombre total de 1684 articles a été identifié en utilisant une stratégie de recherche par mots-clés appropriée. Après sélection, 26 articles ont été considérés comme éligibles pour être inclus dans cette étude. Ces articles comprenaient un total de 1960 témoins et 2106 patients. Lorsque toutes les études ont été prises en compte, les résultats ont montré que les paramètres du sperme et les niveaux d'hormones sexuelles des patients infectés par le SRAS-CoV-2 présentaient certaines différences significatives par rapport aux témoins. Heureusement, ces différences disparaissent progressivement à mesure que les patients se rétablissent du COVID-19.

**Conclusion.** — Si les données actuelles montrent les effets négatifs de l'infection par le SRAS-CoV-2 sur la fertilité masculine, ces effets ne semblent pas être à long terme. La qualité du sperme et les taux d'hormones reviendront progressivement à la normale à mesure que les patients se rétabliront.

© 2022 Elsevier Masson SAS. Tous droits réservés.

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed an extraordinary challenge to public health and safety. It is characterized by a respiratory disease with mild influenza (flu-like) symptoms such as fever, dry cough, myalgia, fatigue, or shortness of breath. The disease can rapidly progress to pneumonia, multi-organ failure, acute respiratory distress syndrome, and even lead to death for a small number of people. According to the World Health Organization, there were more than 556 million confirmed cases globally, including more than 6.3 million deaths as of July 14th 2022, and this number is increasing every day [1]. As a member of the Coronaviridae family, SARS-CoV-2 shares 89.74% amino acid sequence of the N protein with syndrome coronavirus (SARS-CoV) [2]. It is well known that testis damage and defects in spermatogenesis were observed in patients infected with SARS-CoV [3]. Given the similarities between SARS-CoV and SARS-CoV-2, numerous articles speculated in the early phase of COVID-19 outbreak that SARS-CoV-2 infection may lead to potential fertility problems [4,5].

SARS-CoV-2 can invade host cells through binding to cellular angiotensin-converting enzyme 2 (ACE2) receptors [6]. In addition to lung, ACE2 receptors are widespread and highly expressed in other organs, including the heart, kidney, gut, and liver. Correspondingly, damage to these organs was observed in COVID-19 patients [6,7]. Some studies have demonstrated that the protein and mRNA expression of ACE2 in the testes, especially spermatogonia, Leydig cells, and Sertoli cells, is almost the highest in the body [8,9]. Therefore, it has been suggested that the adverse impacts of COVID-19 on male reproduction may primarily be caused by direct infection of SARS-CoV-2 [10]. However, the virus was detected in only one case among testicular tissue samples in 12 patients who died of COVID-19 [11]. Moreover, our previous study has shown that the virus is most likely to come from blood rather than testicular tissue [12]. Similarly, detection of SARS-CoV-2 target genes in the semen of COVID-19 patients may be attributed to viral contamination from non-semen sources [13]. Given that COVID-19 pandemic remains a serious global public health challenge, there is an urgent need to better understand possible mechanism of these changes in SARS-CoV-2 infected individuals. Herein, we conducted a systematic review of studies

investigating semen parameters and sex hormones in patients with COVID-19 in order to provide a reference for further investigations and treatments.

## Methods

The literature search was conducted under the direction of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

### Search strategy

We performed a systematic search for English-language literature on PubMed and Google Scholar databases to find the papers related to the effect of SARS-CoV-2 infection on male fertility. The database was analyzed with the following keywords and search strategy: ("Semen Analysis" [MeSH terms] or "Semen Analyses" [all fields] or "Semen Quality Analysis" [all fields] or "Semen Quality Analyses" [all fields] or "semen" [MeSH terms] or "Spermatozoa" [MeSH terms] or "sperm parameters" [all fields] or "Semen parameters" [all fields] or "Semen Qualities" [all fields] or "semen quality" [all fields] or "Fertility" [MeSH terms] or "genitalia, male" [MeSH terms] or "male reproductive system" [all fields] or "male reproduction" [all fields] or ("Gonadal Hormones" [MeSH terms] or "Follicle Stimulating Hormone" [MeSH terms] or "FSH" [all fields] or "Luteinizing Hormone" [MeSH terms] or "LH" [all fields] or "Testosterone" [MeSH terms])) and ("COVID-19" [MeSH terms] or "SARS-CoV-2" [MeSH terms] or "COVID-19" [all fields]). Moreover, we checked the reference lists of the included articles or relevant reviews identified through the search in order to ensure the comprehensiveness of the search results.

### Eligibility criteria and study selection

The specific inclusion criteria were as follows: 1) healthy men and COVID-19 patients aged 18 and above; 2) literature published from 2020 to 2022; 3) clinical trial outcome measures include at least one or more semen parameters or hormones. Documents that meet one of the following conditions were excluded: 1) non-original researches (e.g. review, commentary, editorial, book chapter, letter to the editor); 2) non-full-text articles (e.g. meeting abstract); 3) animal/in vitro studies; 4) if the data of the literature included in the subsequently published literature, the former was excluded.

Two independent reviewers (Leng T and He J) scrutinized the titles and abstracts of all retrieved records for duplication. Any duplicate documents were consolidated. If there were differences in opinions between both reviewers, the corresponding author was consulted to resolve the discrepancy. A relevant PRISMA flow chart was constructed to detail the number of papers retrieved and the steps undertaken.

### Data extraction

All data were extracted by two independent investigators and consensus was reached after the involvement of a third

investigator where required. Full texts of all potentially pertinent articles were then studied independently to determine the final study selection. The following information was extracted for each identified document meeting the inclusion criteria: the number of subjects and controls, study design, and clinical data.

## Results

### Search strategy results

Our primary search identified a total number of 1,684 articles (including 701 duplicates). The title and abstract screening procedure resulted in the exclusion of publications for these reasons: irrelevant studies ( $n = 721$ ), editorial letters and review articles ( $n = 194$ ). The eligibility of 68 full texts was examined. 26 articles were finally included in this systematic review after screening (Fig. 1).

### SARS-CoV-2 infection and semen parameters

Six trials assessed the impact of COVID-19 on semen parameters in patients during infection (Table 1) [14–19]. Temiz et al. [14] found that there were no significant differences in main semen parameters between COVID-19 patients and health controls except for normal morphology. However, Best et al. [15] reported that the sperm concentration and total sperm count of men infected with COVID-19 were lower than men who tested negative. A study found significantly lower sperm concentration, sperm motility, and normal morphology in COVID-19 patients compared to controls [16]. Li et al. [17] found that patients hospitalized with COVID-19 had significantly lower sperm concentrations compared to age-matched control males, and nine out of 23 COVID-19 inpatients had oligospermia. Enikeev et al. [18] reported that progressive sperm motility, sperm motility and normal morphology decreased, while sperm concentration increased in COVID-19 patients compared to controls. One study showed that patients had significantly reduced semen volume, sperm motility, progressive sperm motility, and normal morphology after COVID-19 diagnosis compared to before COVID-19 diagnosis [19]. Another nine studies reported results of semen analysis in patients recovered from COVID-19 (Table 2) [18,20–27]. Although semen parameters can be affected by COVID-19 infection, most parameters gradually returned to normal as the patients recovered.

### SARS-CoV-2 infection and male reproductive hormones

Among the included studies, 12 trials assessed the effects of COVID-19 on different hormonal parameters in patients during the infectious period (Table 3) [14,16,18,19,28–35]. Temiz et al. [14] reported that the serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone (T) levels in the COVID-19 patients were similar to those in the control group. Cinisloglu et al. [28] reported that the serum total testosterone (TT) level of the COVID-19 patients was significantly lower than that of the controls. Furthermore, the serum TT levels were statistically significantly

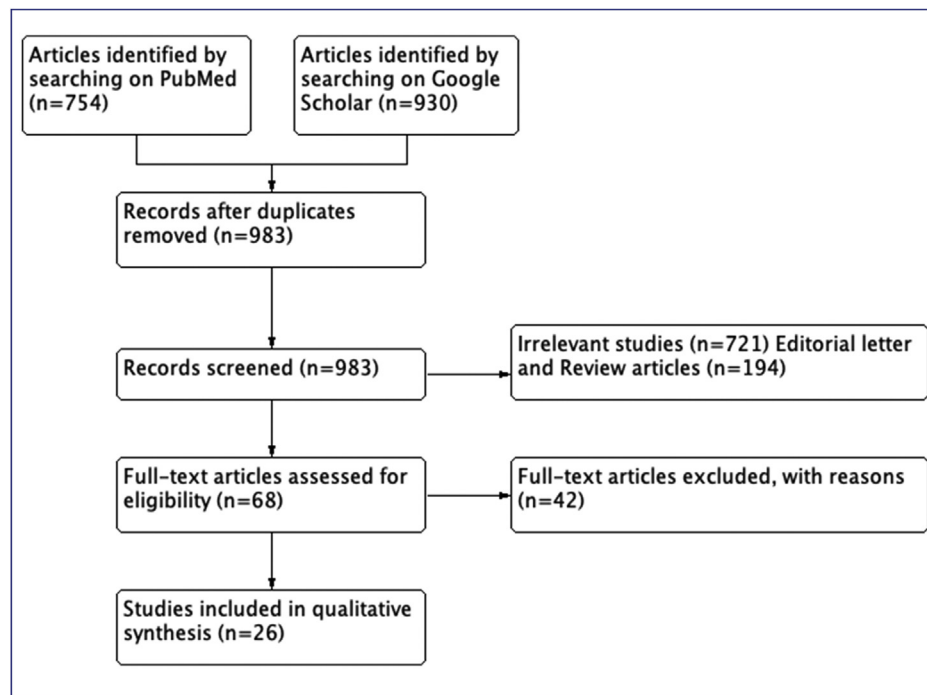


Figure 1. Flow diagram of literature search.

Table 1 Comparison of sperm parameters in SARS-CoV-2 infection patients and control group.

Experimental group/control group (n)	Study design	Semen volume	Sperm concentration	Total sperm count	Progressive sperm motility	Sperm motility	Normal morphology	Reference
10/10	Cross-sectional study	—	—	—	—	—	↓	Temiz et al. [14]
30/30	Prospective observational study	—	↓	↓	NP	NP	NP	Best et al. [15]
60/40	Case-control study	—	↓	NP	NP	↓	↓	Piroozmanesh et al. [16]
23/22	Cross-sectional cohort study	NP	↓	NP	NP	NP	NP	Li et al. [17]
44/44	Prospective two-arm study	—	↑	—	↓	↓	↓	Enikeev et al. [18]
21/21	NP	↓	—	—	↓	↓	↓	Koc et al. [19]

↑ : increase; ↓ : decrease; —: no effect; NP: not provided.

lower in patients with severe COVID-19 compared to those with mild-to-moderate COVID-19. Okçelik [29] investigated 44 patients in a COVID-19 outpatient and found that there was no statistically significant difference in FSH, LH, and TT values between COVID-19 patients and controls. Of the 42 patients who had chest computer tomography scans, 23 were diagnosed with COVID-19 pneumonia. TT levels were significantly lower in the pneumonia group compared with patients without pneumonia. A cross-sectional study involving 30 male patients with endocrine abnormality showed that the serum levels of FSH, LH, and estradiol (E2) in infected men were higher than those in healthy men [30]. Kadihasanoglu

et al. [31] investigated 89 patients with COVID-19 and 143 age-matched controls and found that serum LH and prolactin (PRL) levels were higher in COVID-19 patients than in controls, while TT levels were lower. Additionally, serum TT levels in COVID-19 patients were significantly negatively correlated with hospitalization time. A case-control study reported that 60 COVID-19 patients had increased serum LH levels and decreased T levels and T/LH ratios compared with 40 healthy participants. Besides, there was no difference in serum FSH levels between the two groups [16]. One case-control study showed that decreased TT levels and increased E2 levels were observed in men with COVID-19 at hospital

**Table 2** Comparison of sperm parameters in patients recovered from SARS-CoV-2 infection and control group.

Experimental group/control group (n)	Time between clinical recovery and semen collection	Classification of illness	Study design	Semen volume	Sperm concentration	Total sperm count	Progressive sperm motility	Sperm motility	Normal morphology	Reference
4/14	Mean 25.5 days	Moderate 100%	Cohort study	—	↓	↓	↓	↓	NP	Holtmann, et al. [20]
14/14	Mean 34.9 days	Mild 100%	NP	—	—	—	—	—	NP	Guo et al. [21]
41/50	Median 56 days	Mild 70.7%		—	↓	↓	↓	↓	NP	
		Moderate 24.4%								
		Server 4.9%								
55/145	Median 77.3 days	Mild 12.7%	NP	—	↓	↓	—	↓	NP	Ruan et al. [22]
		Moderate 43.6%								
		Server 43.6%								
37/44	3 months <sup>a</sup>	NP	Prospective two-arm study	—	—	—	—	—	—	Enikeev et al. [18]
24/24	Median 111.5 days <sup>a</sup>	Mild 100%	Prospective cohort study	—	—	NP	—	↓	NP	Pazir et al. [23]
26/26	≥4 months <sup>a</sup>	NP	Retrospective—cohort study		—	—	—	—	↓	Wang et al. [24]
100/100	Range 4–12 months <sup>a</sup>	Mild 42%	NP	—	↓	NP	NP	—	—	Aksak et al. [25]
29/29	Mean 4.52 months	Moderate 58%	Cross-sectional study	—	—	—	—	—	NP	Gul et al. [26]
		NP								
36/45	Median 177.5 days	Mild 11.1%	NP	—	—	—	—	—	NP	Hu et al. [27]
		Moderate 47.2%								
		Server 41.7%								

↓ : decrease; —: no effect; NP: not provided.

<sup>a</sup> Time between a positive swab test and semen collection



**Table 3** Comparison of male reproductive hormones in patients with SARS-CoV-2 infection and control group.

Experimental group/control group (n)	Study design	FSH	LH	T	T/LH	PRL	E2	Reference
10/10	Cross-sectional study	—	—	—	—	—	NP	Temiz et al. [14]
358/92	Prospective cohort study	↑	↑	↓ <sup>a</sup>	NP	NP	NP	Cinislioglu et al. [28]
24/20	NP	—	—	— <sup>a</sup>	NP	NP	NP	Okcelik [29]
30/NP	Cross-sectional study	↑	↑	—	NP	—	↑	Hadisi et al. [30]
89/143	Prospective cohort study	—	↑	↓ <sup>a</sup>	NP	↑	NP	Kadihasanoglu et al. [31]
60/40	Case-control study	—	↑	↓	↓	NP	NP	Piroozmanesh et al. [16]
286/281	Case-control study	—	↑	↓ <sup>a</sup>	NP	NP	↑	Salonia et al. [32]
44/44	Prospective two-arm study	↑	↑	↓	NP	—	NP	Enikeev et al. [18]
119/273	Case-control study	—	↑	—	↓	NP	NP	Ma et al. [33]
81/76	Case-control study	NP	NP	↓	NP	NP	NP	Ahmed [34]
85/25	Prospective cohort study	NP	—	— <sup>a</sup>	NP	NP	NP	Livingston et al. [35]
8/8	NP	—	—	↓	NP	NP	NP	Koc et al. [19]

FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; T: testosterone; PRL: prolactin; E2: estradiol; ↑ : increase; ↓ : decrease; —: no effect; NP: not provided.  
<sup>a</sup> Total testosterone

**Table 4** Comparison of male reproductive hormones in patients recovered from SARS-CoV-2 infection and control group.

Experimental group/control group (n)	Time between clinical recovery and semen collection	Study design	FSH	LH	T	T/LH	PRL	E2	Reference
41/50	Median 56 days	NP	—	—	—	NP	↑	—	Guo et al. [21]
29/29	Mean 4.52 months	Cross-sectional study	—	—	— <sup>a</sup>	NP	—	NP	Gul et al. [26]
348/348	6 months <sup>b</sup>	Cross-sectional study	—	↑	↓ <sup>a</sup>	NP	NP	NP	Karkin et al. [36]
70/50	Within 6 months	NP	—	—	NP	NP	↑	NP	Abbas et al. [37]
60/30	NP	NP	↑	↑	↓	NP	NP	NP	Azzawi et al. [38]
39/22	NP	NP	↓	↓	—	NP	—	↑	Xu et al. [39]

FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; T: testosterone; PRL: prolactin; E2: estradiol; ↑ : increase; ↓ : decrease; —: no effect; NP: not provided.  
<sup>a</sup> Total testosterone  
<sup>b</sup> Time between a positive swab test and semen collection.

admission than in healthy participants [32]. Enikeev et al. [18] reported that COVID-19 infected patients had lower T levels and increased LH and FSH levels compared with healthy controls. A study found that there were no differences in T and FSH levels between the patients and controls. Furthermore, lower T/LH ratios were observed in the COVID-19 group, which was negatively associated with white blood cell counts and C-reactive protein levels [33]. Ahmed [34] reported that the T levels were significantly lower in COVID-19 patients compared to healthy controls. Livingston et al. [35] found that there was no significant difference in serum TT levels between COVID-19 positive and negative males. Koc et al. [19] reported a significant decrease in T levels

in patients diagnosed with COVID-19 than in controls. Six additional trials evaluated the impact of COVID-19 on different hormonal parameters in recovered patients, including FSH (n=6), LH (n=6), T (n=5), PRL (n=4), and E2 (n=2) (Table 4) [21,26,36–39]. Of these studies, Azzawi et al. [38] reported elevated FSH levels in recovered patients, while Xu et al. [39] observed decreased FSH. The remaining four studies showed no significant difference in FSH between recovered patients and healthy controls. Moreover, two studies observed elevated levels of PRL in recovered patients. In addition, LH and T levels were restored to some extent in the recovered patients compared to the infected patients (Table 4).

## Discussion

In this article, we reviewed the effect of COVID-19 on male fertility. According to the current evidence, values for semen parameters including sperm concentration, progressive sperm motility, sperm motility, and normal morphology were significantly worse in men with COVID-19 than in controls (Table 1). The activated inflammatory response in the testes and disease-associated fever might be implicated in the alteration of semen parameters [40]. Generally speaking, fever can induce sperm parameters major alteration and germ cell death even of limited duration [41]. In particular, as one of the most common complications of infection with SARS-CoV-2, fever is observed in more than 80% of patients with COVID-19. However, a Turkey study revealed that there were no significant changes in main semen parameters between COVID-19 patients and healthy controls [14]. It is understandable since the treatment of COVID-19 patients was initiated before the RT-PCR results in this study, which can prevent the complications induced by delay in the treatment. Given the sperm concentration increases with longer periods of abstinence and less sexual activity during COVID-19 infection [42], it also seems understandable to detect higher sperm concentration in patients with COVID-19 [18].

Although semen quality was impaired during viral infection, it will gradually increase to normal as patients recover. Moreover, the recovery in semen quality appeared to be associated with the length of recovery time in COVID-19 patients. Some semen parameters were still significantly different in recovered COVID-19 patients compared with controls in several studies. This result is understandable since spermatogenesis requires a certain duration, but these studies did not allow the formation of new spermatogenesis. However, the differences in semen parameters basically disappeared after 3 months of recovery from COVID-19 (Table 2). Notably, one study found that the total sperm count showed a significant decline after 90 days of recovery time [27]. This could be because spermatogenesis might still be affected during the recovery period of about three months. In fact, the patients who had recovered from COVID-19 have been reported to present persistent physical discomforts such as fatigue, dyspnea, and chest pain at one or two months post-discharge [43,44]. Fortunately, sperm quality in COVID-19 patients was observed to return to normal approximately six months after recovery [27]. Furthermore, the decline in semen parameters appeared to correlate with the severity of symptoms in COVID-19 patients prior to recovery. Patients who recovered from moderate COVID-19 disease reported more changes in semen parameters than those recovered from mild COVID-19 disease [20].

Based on the results, most studies found significantly elevated levels of LH and E2, but decreased levels of T and ratios of T/LH in COVID-19 patients compared to healthy men (Table 3). Given that serum T level is an important factor and predictor of the clinical course of patients, the impact of reduced T levels in patients cannot be underestimated [45,46]. In fact, clinical data also indicate that low T level is common in acute respiratory failure patients requiring assisted mechanical ventilation [47]. It is well-known that the vast majority (95%) of T is produced in the interstitial cells of the testes depending on stimulation with LH [48]. Only a small amount (5%) is produced in

the adrenal glands [49]. Hence, it is not difficult to understand that decreased levels of T may result from testicular failure (primary hypogonadism) or hypothalamic-pituitary failure (secondary hypogonadism) [50]. It is worth mentioning that in the presence of low T levels, elevated LH concentration is a sensitive indicator of primary Leydig cell failure, further explaining the cause of hypogonadism [51]. The changes in E2 may be due to SARS-CoV-2 infection, the body response, or the treatment of patients. However, there are no known side effects of COVID-19 drugs that cause elevated E2 in men, so we suspect that the most likely cause of abnormally elevated E2 in patients is SARS-CoV-2 infection and/or the interactions between SARS-CoV-2 and the host. High levels of E2 would affect the expression of host receptors and proteases, which may be protective agents in certain inflammatory diseases [52]. In addition, there was no significant difference in serum FSH between the patients and control group in most studies. This phenomenon can be explained considering that FSH is predominantly associated with inhibin B secreted by Sertoli cells, which appear to be less perturbed than Leydig cells in COVID-19 infected patients [40].

Sex hormone levels were restored in recovered patients compared with infected patients, such as T (60.0% vs. 41.7%) and LH (50.0% vs. 36.4%) levels (Table 4). This result is understandable because the damage to the testis is physiologically recovered or compensated when the patient recovers from the critical state of infection [39]. It is worth noting that two studies observed elevated levels of PRL in recovered patients. This could be attributed to psychological stress, especially fear of death because of a high number of infections [37]. These pressures will build up as the COVID-19 pandemic continues.

## Conclusion

Present data show that the reductions in sperm concentration, progressive sperm motility, sperm motility, and normal morphology were observed in COVID-19 patients. Changes in these parameters are likely to be associated with the activated inflammatory response in the testes and disease-associated fever. In addition, the decline in semen parameters appeared to correlate with the severity of symptoms in COVID-19 patients prior to recovery. Patients who recovered from mild COVID-19 disease showed fewer changes in semen parameters than those recovered from moderate COVID-19 disease. Moreover, the recovery of semen quality appears to be related to the length of recovery time in COVID-19 patients.

Sex hormone levels are also affected by COVID-19 infection. Patients with COVID-19 had elevated LH and E2 levels compared to healthy controls, whereas T levels and T/LH ratios were reduced. Decreased T levels further exacerbated the severity of COVID-19 patients, leading to adverse clinical outcomes such as hypogonadism. Fortunately, LH and T levels were restored to some extent in the recovered patients compared to the infected patients.

Further long-term follow-up is still required to assess the exact time when sperm quality and sex hormone levels begin to improve. In addition, it is important to understand the dynamics of the virus and know all the possible routes



of transmission in determining the preventive measures we must take. In summary, the effects of SARS-CoV-2 on male reproduction remain to be explored and will be an important consideration in the future.

## Funding

This work was supported by the Natural Science Foundation of Shandong Province (grant No. ZR2020QC100).

## Authors' contributions

Bao J and Guo Z designed the study, reviewed literature, and drafted the manuscript. He J and Leng T retrieved and summarized the literature. Chen F and Wei Z advised on the review and reviewed the final manuscript. Wang C collected and analyzed the relevant data for the article when the manuscript was revised. All authors contributed to the article and approved the submitted version.

## Acknowledgments

None.

## Disclosure of interest

The authors declare that they have no competing interest.

## References

- [1] World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. <https://covid19.who.int/>. (accessed July 11, 2022).
- [2] Oliveira SC, de Magalhaes MTQ, Homan EJ. Immunoinformatic analysis of SARS-CoV-2 nucleocapsid protein and identification of COVID-19 vaccine targets. *Front Immunol* 2020;11:587615, <http://dx.doi.org/10.3389/fimmu.2020.587615>.
- [3] Xu J, et al. Orchitis: a complication of severe acute respiratory syndrome (SARS). *Biol Reprod* 2006;74(2):410–6, <http://dx.doi.org/10.1095/biolreprod.105.044776>.
- [4] Illiano E, Trama F, Costantini E. Could COVID-19 have an impact on male fertility? *Andrologia* 2020;52(6):e13654, <http://dx.doi.org/10.1111/and.13654>.
- [5] Tian Y, Zhou F L.Q. Evaluating the impact of COVID-19 on male reproduction. *Reproduction* 2021;161(2):R37–44, <http://dx.doi.org/10.1530/REP-20-0523>.
- [6] Mjaess G, Karam A, Aoun F, Albisinni S, Roumeguere T. COVID-19 and the male susceptibility: the role of ACE2, TMPRSS2 and the androgen receptor. *Prog Urol* 2020;30(10):484–7, <http://dx.doi.org/10.1016/j.purol.2020.05.007>.
- [7] Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. *Eur J Intern Med* 2020;76:14–20, <http://dx.doi.org/10.1016/j.ejim.2020.04.037>.
- [8] Douglas GC, et al. The novel angiotensin-converting enzyme (ACE) homolog, ACE2, is selectively expressed by adult Leydig cells of the testis. *Endocrinology* 2004;145(10):4703–11, <http://dx.doi.org/10.1210/en.2004-0443>.
- [9] Wang Z, Xu X. scRNA-seq profiling of human testes reveals the presence of the ACE2 receptor, a target for SARS-CoV-2 infection in spermatogonia, leydig and sertoli cells. *Cells* 2020;9(4), <http://dx.doi.org/10.3390/cells9040920>.
- [10] Pike JFW, et al. Comparative analysis of viral infection outcomes in human seminal fluid from prior viral epidemics and Sars-CoV-2 may offer trends for viral sexual transmissibility and long-term reproductive health implications. *Reprod Health* 2021;18(1):123, <http://dx.doi.org/10.1186/s12978-021-01172-1>.
- [11] Yang M, et al. Pathological findings in the testes of COVID-19 patients: clinical implications. *Eur Urol Focus* 2020;6(5):1124–9, <http://dx.doi.org/10.1016/j.euf.2020.05.009>.
- [12] Chen F, et al. Effects of COVID-19 and mRNA vaccines on human fertility. *Hum Reprod* 2021;37(1):5–13, <http://dx.doi.org/10.1093/humrep/deab238>.
- [13] Gacci M, et al. Semen impairment and occurrence of SARS-CoV-2 virus in semen after recovery from COVID-19. *Hum Reprod* 2021;36(6):1520–9, <http://dx.doi.org/10.1093/humrep/deab026>.
- [14] Temiz MZ, et al. Investigation of SARS-CoV-2 in semen samples and the effects of COVID-19 on male sexual health by using semen analysis and serum male hormone profile: a cross-sectional, pilot study. *Andrologia* 2021;53(2):e13912, <http://dx.doi.org/10.1111/and.13912>.
- [15] Best JC, et al. Evaluation of SARS-CoV-2 in human semen and effect on total sperm number: a prospective observational study. *World J Mens Health* 2021;39(3):489–95, <http://dx.doi.org/10.5534/wjmh.200192>.
- [16] Piroozmanesh H, Cheraghi E, Naserpoor L, Aghashahi M, Janatifar R. The effect of COVID-19 infection on sperm quality and male fertility. *Jentashapir J Cell Mol Biol* 2021;12(2).
- [17] Li H, et al. Impaired spermatogenesis in COVID-19 patients. *EclinicalMedicine* 2020;28:100604.
- [18] Enikeev D, et al. Prospective two-arm study of the testicular function in patients with COVID-19. *Andrology* 2022, <http://dx.doi.org/10.1111/andr.13159>.
- [19] Koc E, Keseroglu BB. Does COVID-19 worsen the semen parameters? Early results of a tertiary healthcare center. *Urol Int* 2021;105(9–10):743–8, <http://dx.doi.org/10.1159/000517276>.
- [20] Holtmann N, et al. Assessment of SARS-CoV-2 in human semen: a cohort study. *Fertil Steril* 2020;114(2):233–8, <http://dx.doi.org/10.1016/j.fertnstert.2020.05.028>.
- [21] Guo TH, et al. Semen parameters in men recovered from COVID-19. *Asian J Androl* 2021;23(5):479–83, <http://dx.doi.org/10.4103/aja.aja.31.21>.
- [22] Ruan Y, et al. 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. *Andrology* 2021;9(1):99–106, <http://dx.doi.org/10.1111/andr.12939>.
- [23] Pazir Y, Eroglu T, Kose A, Bulut TB, Genc C, Kadihasanoglu M. Impaired semen parameters in patients with confirmed SARS-CoV-2 infection: a prospective cohort study. *Andrologia* 2021;53(9):e14157, <http://dx.doi.org/10.1111/and.14157>.
- [24] Wang M, et al. Investigating the impact of SARS-CoV-2 infection on basic semen parameters and in vitro fertilization/intracytoplasmic sperm injection outcomes: a retrospective cohort study. *Reprod Biol Endocrinol* 2022;20(1):46, <http://dx.doi.org/10.1186/s12958-022-00918-1>.
- [25] Aksak T, Satar DA, Ridvan B, Gultekin EO, Coskun A, Demirdelen U. Investigation of the effect of COVID-19 on sperm count, motility and morphology. *J Med Virol* 2022, <http://dx.doi.org/10.1002/jmv.27971>.
- [26] Gul A, Zengin S, Dunder G, Ozturk M. Do SARS-CoV-2 infection (COVID-19) and the medications administered for its treatment impair testicular functions? *Urol Int* 2021;105(11–12):944–8, <http://dx.doi.org/10.1159/000517925>.

- [27] Hu B, et al. Evaluation of mid-and long-term impact of COVID-19 on male fertility through evaluating semen parameters. *Transl Androl Urol* 2022;11(2):159.
- [28] Cinisiloglu AE, et al. The relationship of serum testosterone levels with the clinical course and prognosis of COVID-19 disease in male patients: a prospective study. *Andrology* 2022;10(1):24–33, <http://dx.doi.org/10.1111/andr.13081>.
- [29] Okcelik S. COVID-19 pneumonia causes lower testosterone levels. *Andrologia* 2021;53(1):e13909, <http://dx.doi.org/10.1111/andr.13909>.
- [30] Hadisi N, et al. COVID-19 and endocrine system: a cross-sectional study on 60 patients with endocrine abnormality. *Cell J* 2022;24(4):182–7, <http://dx.doi.org/10.22074/cellj.2022.8079>.
- [31] Kadihasanoglu M, Aktas S, Yardimci E, Aral H, Kadioglu A. SARS-CoV-2 pneumonia affects male reproductive hormone levels: a prospective, cohort study. *J Sex Med* 2021;18(2):256–64, <http://dx.doi.org/10.1016/j.jsxm.2020.11.007>.
- [32] Salonia A, et al. Severely low testosterone in males with COVID-19: a case-control study. *Andrology* 2021;9(4):1043–52, <http://dx.doi.org/10.1111/andr.12993>.
- [33] Ma L, et al. Evaluation of sex-related hormones and semen characteristics in reproductive-aged male COVID-19 patients. *J Med Virol* 2021;93(1):456–62, <http://dx.doi.org/10.1002/jmv.26259>.
- [34] Ahmed K. Relationship of inflammatory mediators and sex-related parameters in jordanian adult men patients with COVID-19. *J Med Biochem* 2022, <http://dx.doi.org/10.5937/jomb0-35601>.
- [35] Livingston M, Ramachandran S, Hartland A, Plant A, Kirby M, Hackett G. Low testosterone on hospital admission with COVID-19 infection is associated with increased mortality. *Androgens Clin Res Ther* 2022;3(1):14–21, <http://dx.doi.org/10.1089/andro.2021.0029>.
- [36] Karkin K, Gürlen G. Does COVID-19 cause testicular damage? A cross-sectional study comparing hormonal parameters. *Eur Rev Med Pharmacol Sci* 2022;26(10):3745–50.
- [37] Abbas MA, Al-Shakir NM, Amal H. Influence of COVID-19 infections on LH, FSH and prolactin level in group of males recovered from COVID-19 in Baghdad. *Al-Nisour J Med Sci* 2022;4(1).
- [38] Azzawi ATH, Abdulrahman MA. The effect of some hormonal variables on the blood serum of men recovered from COVID-19 in Fallujah city. *Int J Health Sci* 2022;6(S2):13983–9, <http://dx.doi.org/10.53730/ijhs.v6nS2.8872>.
- [39] Xu H, et al. Effects of SARS-CoV-2 infection on male sex-related hormones in recovering patients. *Andrology* 2021;9(1):107–14, <http://dx.doi.org/10.1111/andr.12942>.
- [40] Foresta C, Bettella A, Spolaore D, Merico M, Rossato M, Ferlin A. Suppression of the high endogenous levels of plasma FSH in infertile men are associated with improved Sertoli cell function as reflected by elevated levels of plasma inhibin B. *Hum Reprod* 2004;19(6):1431–7, <http://dx.doi.org/10.1093/humrep/deh255>.
- [41] Bendayan M, Boitrelle F. What could cause the long-term effects of COVID-19 on sperm parameters and male fertility? *QJM* 2021;114(4):287, <http://dx.doi.org/10.1093/qjmed/hcab028>.
- [42] De Jonge C, LaFromboise M, Bosmans E, Ombelet W, Cox A, Nijs M. Influence of the abstinence period on human sperm quality. *Fertil Steril* 2004;82(1):57–65, <http://dx.doi.org/10.1016/j.fertnstert.2004.03.014>.
- [43] D'Cruz RF, et al. Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. *ERJ Open Res* 2021;7(1), <http://dx.doi.org/10.1183/23120541.00655-2020>.
- [44] Carfi A, Bernabei R, Landi F. C-P-A CSG gemelli against persistent symptoms in patients after acute COVID-19. *JAMA* 2020;324(6):603–5, <http://dx.doi.org/10.1001/jama.2020.12603>.
- [45] Rastrelli G, et al. Low testosterone levels predict clinical adverse outcomes in SARS-CoV-2 pneumonia patients. *Andrology* 2021;9(1):88–98, <http://dx.doi.org/10.1111/andr.12821>.
- [46] Dhindsa S, et al. Association of circulating sex hormones with inflammation and disease severity in patients with COVID-19. *JAMA Netw Open* 2021;4(5):e2111398, <http://dx.doi.org/10.1001/jamanetworkopen.2021.11398>.
- [47] Almoosa KF, Gupta A, Pedroza C, Watts NB. Low testosterone levels are frequent in patients with acute respiratory failure and are associated with poor outcomes. *Endocr Pract* 2014;20(10):1057–63, <http://dx.doi.org/10.4158/EP14003.OR>.
- [48] Zirkin BR, Papadopoulos V. Leydig cells: formation, function, regulation. *Biol Reprod* 2018;99(1):101–11, <http://dx.doi.org/10.1093/biolre/iy059>.
- [49] Sher L. Testosterone and suicidal behavior. *Expert Rev Neurother* 2012;12(3):257–9, <http://dx.doi.org/10.1586/ern.12.6>.
- [50] Basaria S. Male hypogonadism. *Lancet* 2014;383(9924):1250–63.
- [51] Costa RR, Varanda WA, Franci CR. A calcium-induced calcium release mechanism supports luteinizing hormone-induced testosterone secretion in mouse Leydig cells. *Am J Physiol Cell Physiol* 2010;299(2):C316–23, <http://dx.doi.org/10.1152/ajpcell.00521.2009>.
- [52] Mateus D, Sebastiao AI, Carrascal MA, Carmo AD, Matos AM, Cruz MT. Crosstalk between estrogen, dendritic cells, and SARS-CoV-2 infection. *Rev Med Virol* 2022;32(3):e2290, <http://dx.doi.org/10.1002/rmv.2290>.