Original Article

Sperm quality and sexual function after the first COVID-19 infection during the omicron surge: an observational study in southwest China

Tingting Yang[1,2#^], Bo Liu[1,2#^], Xiaohong Luo[1,2^], Lingling Shen[1,2^], Xiao Xiao[1,2^], Yanyun Wang[2,3^], Shiliu Li[4^], Lin Zhang[2,3^], Bin Zhou[2,3^], Fuping Li[1,2^]

[1]Department of Andrology/Human Sperm Bank of Sichuan Province, West China Second University Hospital, Sichuan University, Chengdu, China; [2]Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, China; [3]Laboratory of Molecular Translational Medicine, Center for Translational Medicine, West China Second University Hospital, Sichuan University, Chengdu, China; [4]Wuhou District People's Procuratorate, Chengdu, China

Contributions: (I) Conception and design: T Yang, F Li, B Liu; (II) Administrative support: B Zhou, F Li, L Zhang; (III) Provision of study materials or patients: T Yang, F Li; (IV) Collection and assembly of data: B Liu, X Luo, L Shen, X Xiao; (V) Data analysis and interpretation: T Yang, Y Wang, S Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Bin Zhou, PhD. Laboratory of Molecular Translational Medicine, Center for Translational Medicine, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, No. 1416 Chenglong Road, Jinjiang District, Chengdu 610041, China; Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu 610041, China. Email: zhoubin630@scu.edu.cn; Fuping Li, PhD. Department of Andrology/Human Sperm Bank of Sichuan Province, West China Second University Hospital, Sichuan University, No. 1416 Chenglong Road, Jinjiang District, Chengdu 610041, China; Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu 610041, China. Email: lfpsnake@scu.edu.cn.

Background: As the Omicron variant became the dominant coronavirus disease 2019 (COVID-19) strain and the threat to human health decreased, the impact of COVID-19 on male reproductive health and semen quality may have changed. In this prospective observational study, we aimed to investigate the changes in semen quality and sexual function before and after the Omicron variant infection by self-controlled study and to explore the influence of Omicron variant infection on male reproductive health.

Methods: We recruited 373 participants who provided semen samples before their first COVID-19 infection. During the subsequent follow-up, only 154 participants provided the second semen samples, 11 of whom were not infected with COVID-19. Sperm quality was assessed approximately 45 and 90 days after COVID-19, as well as before infection.

Results: Semen parameters, including total sperm count, total forward sperm, progressive motility, and sperm concentration, significantly declined 45 days after COVID-19 infection. At 90 days after infection, the total sperm count, total forward sperm, and sperm concentration gradually increased to pre-infection levels. Participants who experienced fever showed worse semen quality in terms of total forward sperm, sperm concentration, and sperm progressive rate. However, this phenomenon was not observed in the other group infected with COVID-19 without fever or not infected. In addition, 49 (34.3%) of 143 persons confirmed that the COVID-19 infection resulted in changes in sexual function, with an increase in premature ejaculation diagnostic tool (PEDT) scores.

Conclusions: The results of our self-controlled study indicate that COVID-19 is associated with impaired semen quality early after disease onset. After 1–2 spermatogenesis cycles, the semen quality gradually

^ ORCID: Tingting Yang, 0000-0002-5077-9900; Bo Liu, 0009-0002-1445-1702; Xiaohong Luo, 0009-0002-0417-3788; Lingling Shen, 0009-0001-0426-2636; Xiao Xiao, 0009-0009-9826-2677; Shiliu Li, 0009-0007-6755-5296; Yanyun Wang, 0000-0002-8102-8851; Lin Zhang, 0000-0003-3294-7824; Bin Zhou, 0000-0003-3484-3340; Fuping Li, 0000-0001-5183-4214.

recovers from the infection. These findings are beneficial for better understanding the COVID-19-associated sequelae, which are fundamental for semen collection during assisted reproduction.

Keywords: Sperm quality; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); omicron; sexual function; self-controlled case series study

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Introduction

According to the World Health Organization (WHO), infertility is clinically defined as the failure to achieve pregnancy after 12 months of regular unprotected sexual intercourse (1,2); 72.4 million people are estimated to be affected by infertility, and 40.5 million are seeking infertility medical care. However, accurately estimating of the global burden of infertility and subfertility is challenging (1,3). Overall, the prevalence of infertility has been increasing. Infertility is also associated to reproductive health, psychological, economic, and medical implications, which can result in trauma and stress, especially in societies and cultures with a strong emphasis on childbearing (4). Paternal factors are a primary or contributing cause of infertility in approximately 50% infertile couples (5).

Population increase is crucial for national economies, food production, the environment, and global climate (6). The total fertility rate is a key driver of population size and composition (7). Declining fertility is a key driver behind the rapid aging of populations worldwide (7). Furthermore, population aging can induce social problems such as serious financial challenges for all institutions and a lack of labor. Since December 2019, the global coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in high morbidity and mortality worldwide. The COVID-19 pandemic has adversely affected economies, consumption, and lifestyle, directly or indirectly leading to an accelerating decline in the birth rate (8,9). A study across the USA revealed that the pre-pandemic [2016–2019] national annual change in average monthly fertility rate was −10.6 births per month per 100,000 women of reproductive age per year (births/month/100,000 WRA/year). However, nine months after COVID-19 Wave 1, the annual change was −17.5 births/month/100,000 WRA/year, indicating a significant decrease (10). The National Center for Health Statistics data revealed a reduction in births between December 2020 and January 2021 (9). Similarly, the number of Chinese births in 2021 and 2022 was 10.62 million and 9.56 million, respectively, less than the 14.65 million births in 2019 (http://www.stats.gov.cn/sj/). The COVID-19 pandemic has complicated and multifactorial influences on the reduction in birth rates, including its impact of COVID-19 on male reproductive health and semen quality (10).

Sperm quality is related to fertility outcomes and is a primary clinical marker of male reproductive health (5). Over the past decades, numerous studies have reported a global downward trend in sperm quality (11). Furthermore, a study by Levine *et al.* revealed that the worldwide decline will continue in the 21st century at an accelerated pace (11). Some studies have focused on COVID-19 infection and semen quality; however, most studies on the effects of COVID-19 on male reproduction have limitations, including being conducted early in the pandemic and having limited sample sizes (12). However, with the widespread use of

Highlight box

Key findings

- Semen parameters significantly declined 45 days after coronavirus disease 2019 (COVID-19) infection.
- Recovery of semen quality to pre-infection levels by 90 days post-infection.
- Participants with fever experienced worse semen quality than those without fever or uninfected.

What is known and what is new?

- COVID-19 can impact male reproductive health.
- This study shows specific declines and recovery timelines in semen quality related to the Omicron variant, particularly highlighting the impact of fever.

What is the implication, and what should change now?

- Understanding the temporary impact of COVID-19 on male reproductive health is crucial for managing fertility concerns.
- Consideration of infection and recovery timelines for COVID-19 infection in semen collection for assisted reproduction.

COVID-19 vaccines and the change in strains and virulence of COVID-19, the signs and symptoms of infection now differ from those reported earlier (13). Therefore, the impact of COVID-19 on male reproductive health and semen quality may have changed.

As the Omicron variant became the dominant COVID-19 strain and the threat to human health decreased, China made significant adjustments to its COVID-19 prevention and control policies. Since December 26, 2022, the National Health Commission of the People's Republic of China announced that China has renamed the Chinese term for COVID-19 from "novel coronavirus pneumonia" to "novel coronavirus infection" and downgraded its management from Class A to Class B in accordance with the country's law on prevention and treatment of infectious disease. According to the data from Chinese Center for Disease and Prevention, from September 26, 2022 to March 30, 2023, a total of 37,165 local cases of COVID-19 genome were analyzed, all of which were Omicron variants, with 114 evolutionary branches; and the main epidemic strains were BA.5.2.48 (45.3%), BF.7.14 (24.8%) and BA.5.2. (https://www.chinacdc.cn/). The extensively mutated Omicron variant was likely to spread across China, with an alleviated severity (14). Consequently, in this prospective observational study, we aimed to investigate the changes in semen quality and sexual function before and after the Omicron variant infection by self-controlled study and to explore the influence of the Omicron variant infection on male reproductive health. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-173/rc).

Methods

Study population

To investigate the potential effect of COVID-19 infection on sperm quality in China, we recruited 373 participants, who were young adult men of age 20 to 45 years old and were sperm donor candidates at the Sichuan Human Sperm Bank of China. Participants who had previously been infected with COVID-19 were excluded from the study. The participants provided semen samples, and we tested their semen quality between July 2022 and November 2022. Since December 26, 2022, COVID-19 management has been downgraded from Class A to Class B, leading to widespread transmission. Volunteers were followed up continuously during the study period. As the severity of infection with the Omicron variant was largely alleviated, the patients in the study had mild (non-hospitalized) COVID-19 infection, as proven by a positive polymerase chain reaction or antigen test.

Only 154 volunteers participated in the next collection and provided more than two semen samples (*Figure 1*). The participants who were first infected with COVID-19 provided the second and third semen samples approximately 45 and 90 days after the first COVID-19 infection, respectively. Eleven patients who were never infected with COVID-19 during the study period provided second semen samples.

At the time of semen sample collection, demographic information was obtained through an intake survey: weight, height, age, education level, ethnicity, abstinence time, smoking and drinking history, residential address at the time of sample collection, and working address during the study period. Information on SARS-CoV-2 vaccination (vaccination date, vaccination type, and dose number), International Index of Erectile Function (IIEF-5) score, and signs and symptoms of infection were retrospectively collected using a self-reported electronic survey. And in the study, out of the 373 participants, only 8 had not received their first COVID-19 vaccination before providing the first semen sample. And only 5 men of them provided the second semen sample and their vaccination status did not change.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Review Board of West China Second University Hospital, Sichuan University (WCSUH-SCU IRB No. 2021-197). Informed consent was obtained from all subjects during enrollment.

Semen analysis

Semen collection and analysis were performed following the WHO guidelines, 2021. Semen samples were collected via masturbation into sterile containers. Immediately after collection, the samples were incubated at 37 ℃ and analyzed directly. The volume of semen was measured by weighing. Sperm concentration, motility, and movement parameters were assessed following the WHO 2021 guidelines using the Makler chamber and a Computer Assisted Sperm Analysis (CASA) system. The measurements included sperm concentration (millions/mL), percentage of progressive sperm, average path velocity (μm/s), curvilinear velocity (μm/s), amplitude of lateral head displacement (μm/s),

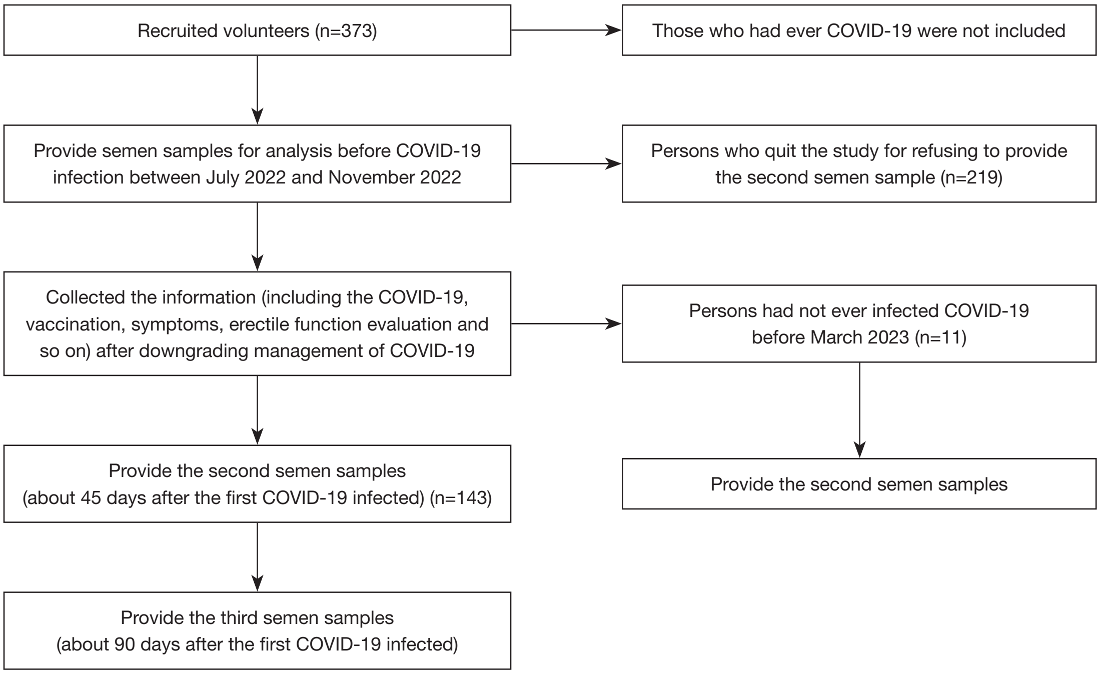

Figure 1 The flow chart and semen collection timeline of this study. COVID-19, coronavirus disease 2019.

straight-line velocity (μm/s), beat-cross frequency (times/s), and straightness (%). More information on semen analysis can be obtained from our previous study (15).

Statistical analysis

SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. The measurement data were expressed as the mean ± standard deviation. A paired *t*-test was used to compare and analyze data before and after COVID-19 infection. P<0.05 was considered statistically significant.

Results

Epidemiologic characteristics

In our study, 373 participants who had never been infected with COVID-19 and had provided their first semen samples were recruited, with a mean age of 25.6 years. Most received an inactivated vaccine (67.0%), and only 2.1% did not received vaccination ever. Most participants (84.2%) were infected with SARS-CoV-2 during the study, and their symptoms of infection were fever (75.5%), cough (62.4%), fatigue and muscle soreness (42.4%), and a stuffy and running nose (39.5%). Only 154 participants provided the second semen sample, and 11 of them were not infected with COVID-19 during the study period. The other epidemiological characteristics were similar to those of all 373 participants (*Table 1*).

Sperm quality between the first and second semen sample

During the study follow-up, 143 participants were confirmed to have COVID-19 by a positive polymerase chain reaction test or antigen test, and 11 participants did not have COVID-19 infection during the study period. Semen quality parameters measured before and after COVID-19 infection revealed significant declines 45 days after infection, including total sperm count, total forward sperm, progressive motility, and sperm concentration, compared to pre-infection levels. Ninety days after infection, the semen parameters, such as total sperm count, total forward sperm, and sperm concentration, gradually returned to pre-infection levels, although the sperm progressive rate remained lower than their previous levels (*Table 2*). In contrast, the semen quality of participants without COVID-19 did not differ significantly between the first and second semen samples, except for the progressive rate (P=0.006) (*Table 3*).

Table 1 Distribution of the demographic data of the participants

Variables	All participants (n=373)	Participants provided more than two semen samples (n=154)
Mean age (years)	25.6	25.4
Vaccination information		
Received one shot	9 (2.4)†	5 (3.2)†
Received two shots	92 (24.7)†	40 (26.0)†
Received three shots	256 (68.6)†	103 (66.9)†
Received four shots	8 (2.1)†	4 (2.6)†
No received	8 (2.1)†	3 (1.9)†
The types of vaccine		
Inactivated vaccine	250 (67.0)†	118 (76.6)†
mRNA vaccine	17 (4.6)†	6 (3.9)†
Recombinant new coronavirus vaccine (CHO cells)	8 (2.1)†	3 (1.9)†
Unknown or forget	70 (18.8)†	20 (13.0)†
Mixed vaccine	20 (5.3)†	5 (3.2)†
COVID-19 infection (yes or no)	314 (84.2)†	143 (92.8)†
Without symptom	13 (4.1)‡	6 (3.9)‡
Fever (yes or no)	237 (75.5)‡	112 (72.7)‡
Maximum body temperature (℃)	38.6	38.4
Duration of fever (days), mean	1.7	1.7
Cough	196 (62.4)‡	99 (64.3)‡
Stuffy and running nose	124 (39.5)‡	54 (35.1)‡
Decline of taste or smell	84 (26.8)‡	38 (24.7)‡
Fatigue and muscle soreness	133 (42.4)‡	53 (34.4)‡
Chest tightness	44 (14.0)‡	21 (13.6)‡

Data are presented as n (%) unless otherwise specified. †, percentage of all participants in this column; ‡, percentage of participants infected with COVID-19 in this column. CHO, Chinese hamster ovary; COVID-19, coronavirus disease 2019.

Sperm quality of participants with or without a fever

In this study, 112 participants were infected with COVID-19 accompanied by a fever, and while 42 participants were either infected with SARS-CoV-2 without fever or not infected at all. Semen quality parameters before and after COVID-19 infection with fever revealed that the total forward sperm, sperm concentration, and sperm progressive rate declined compared to those before infection (*Table 4*). Conversely, for participants infected with SARS-CoV-2 without fever or those not infected, semen parameters, including total sperm count, total forward sperm, sperm concentration, volume, and progressive motility, did not differ significantly between the first and second semen samples (*Table 5*).

Evaluation of sexual function before and after COVID-19 infection

During the follow-up of the study, 49 (34.3%) of 143 persons reported that COVID-19 infection resulted in changes in sexual function. The scores of the premature ejaculation diagnostic tool (PEDT) and the IIEF-5 before and after COVID-19 infection suggested that after infection, the scores of PEDT increased, but the scores of IIEF-5 were not significantly different (*Table 6*).

Discussion

Our results revealed that semen parameters, such as total sperm count, total forward sperm, progressive motility, and sperm concentration, significantly declined 45 days after COVID-19 infection. Ninety days after infection, the total sperm count, total forward sperm, and sperm concentration gradually returned to the levels before infection. After infection accompanied by a fever, the semen quality appeared worse in terms of total forward sperm, sperm concentration, and sperm progressive rate. However, this phenomenon was not observed in the other group infected with SARS-CoV-2 without fever or not infected. Some studies have investigated the relationship between COVID-19 and male reproductive health. However, they had limitations, such as a small sample size and a lack of before-after studies in the same patients (16). Moreover, few studies have evaluated sexual function after infection (17,18). In our study, 49 (34.3%) patients reported changes in sexual function after infection, with higher PEDT scores. The male reproductive system may be vulnerable to SARS-CoV-2 infection, and the mechanism of spermatogenic dysfunction mainly includes SARS-CoV-2 viral replication, the influence of a fever, and systemic inflammatory responses and inflammatory factors (19,20) (*Figure 2*).

Deterioration in semen quality may result from direct viral invasion of the gonads, and fever-induced gonadal

Table 2 Summary of semen quality parameters before and after COVID-19 infection

Semen quality parameters	Before COVID-19 (n=373)†	Before COVID-19 (n=143)‡	45 days after COVID-19 (n=143)	90 days after COVID-19 (n=143)	Pair-wise *t*-test P value (a/b)
Abstinence (days)	4.5 (1.2)	4.5 (1.1)	4.1 (1.1)	4.3 (1.2)	0.050/0.07
Total sperm count (mil)	436.0 (256.5)	429.7 (265.9)	390.8 (159.6)	453.1 (256.3)	0.04/0.81
Total forward sperm (mil)	289.3 (186.3)	289.5 (192.5)	234.8 (159.6)	270 (177.9)	0.001/0.97
Sperm concentration (mil/mL)	119.9 (64.7)	118.2 (66.1)	102.5 (54.6)	119.3 (67.0)	0.001/0.70
Volume (mL)	3.8 (1.5)	3.9 (1.7)	3.9 (1.5)	3.9 (1.5)	0.97/0.53
Progressive rate (%)	65.1 (11.4)	65.7 (10.9)	59.1 (13.8)	58.6 (15.9)	<0.001/<0.001
VCL (μm/s)	38.0 (14.5)	38.6 (13.8)	45.1 (13.7)	45.3 (16.1)	<0.001/<0.001
VAP (μm/s)	24.6 (9.1)	25.0 (8.7)	31.5 (9.6)	31.5 (11.2)	<0.001/<0.001
VSL (μm/s)	18.4 (7.0)	18.7 (6.8)	24.6 (8.3)	24.2 (9.4)	<0.001/<0.001
STR (%)	0.4 (0.1)	0.4 (0.1)	0.5 (0.1)	0.5 (0.1)	<0.001/<0.001
ALH (μm/s)	2.9 (1.0)	2.9 (0.9)	3.0 (0.9)	3.0 (1.0)	0.07/<0.18
BCF (%)	8.3 (2.6)	8.4 (2.4)	10.8 (3.0)	10.4 (3.3)	<0.001/<0.001

Data are presented as mean (SD). †, all participants were recruited in the study; ‡, participants provided more than two semen samples. a: P value of pair-wise *t*-test before COVID-19 and 45 days after COVID-19 infection; b: P value of pair-wise *t*-test before COVID-19 and 90 days after COVID-19 infection. COVID-19, coronavirus disease 2019; VCL, curvilinear velocity; VAP, average path velocity; VSL, straight-line velocity; STR, straightness; ALH, amplitude of lateral head displacement; BCF, beat-cross frequency; SD, standard deviation.

Table 3 Summary of quality parameters of semen from the participants without COVID-19 infection in the study

Semen quality parameters	The first semen sample (n=11)	The second semen sample (n=11)	Pair-wise *t*-test P value
Abstinence (days)	4.5 (1.1)	5.0 (1.5)	0.35
Total sperm count (mil)	543.0 (254.7)	436.7 (289.1)	0.32
Total forward sperm (mil)	360.7 (166.3)	227.5 (167.8)	0.76
Sperm concentration (mil/mL)	141.2 (45.4)	103.3 (44.4)	0.055
Volume (mL)	3.8 (1.7)	4.0 (1.7)	0.64
Progressive rate (%)	66.8 (7.4)	60.3 (14.1)	0.006
VCL (μm/s)	35.6 (9.2)	38.6 (13.7)	0.47
VAP (μm/s)†	23.1 (6.0)	25.7 (6.7)	0.31
VSL (μm/s)†	17.6 (5.2)	18.9 (5.3)	0.54
STR (%)†	0.4 (0.1)	0.4 (0.1)	0.68
ALH (μm/s)†	2.8 (0.6)	2.8 (0.8)	0.94
BCF (%)	8.4 (2.4)	9.3 (2.5)	0.35

Data are presented as mean (SD). †, quality of sperm motion analysed by CASA. COVID-19, coronavirus disease 2019; VCL, curvilinear velocity; VAP, average path velocity; VSL, straight-line velocity; STR, straightness; ALH, amplitude of lateral head displacement; BCF, beat-cross frequency; SD, standard deviation; CASA, Computer Assisted Sperm Analysis.

Table 4 Semen quality parameters before and after COVID-19 infection from the participants infected with COVID-19 accompanied by a fever

Semen quality parameters	Before COVID-19 (n=112)	45 days after COVID-19 (n=112)	Pair-wise *t*-test P value
Abstinence (days)	4.5 (1.2)	4.1 (1.0)	0.03
Total sperm count (mil)	469.9 (276.5)	462.2 (252.0)	0.84
Total forward sperm (mil)	296.9 (193.8)	222.6 (138.3)	<0.001
Sperm concentration (mil/mL)	120.7 (65.7)	98.5 (50.0)	<0.001
Volume (mL)	3.8 (1.6)	4.0 (1.4)	0.40
Progressive rate (%)	65.7 (12.1)	58.9 (13.5)	<0.001
VCL (μm/s)	36.9 (14.3)	44.2 (13.1)	<0.001
VAP (μm/s)†	24.1 (9.1)	31.1 (9.3)	<0.001
VSL (μm/s)†	18.0 (7.0)	24.2 (8.1)	<0.001
STR (%)†	0.4 (0.1)	0.4 (0.1)	<0.001
ALH (μm/s)†	2.9 (0.9)	2.9 (0.8)	0.64
BCF (%)	8.2 (2.7)	10.7 (3.0)	<0.001

Data are presented as mean (SD). †, quality of sperm motion analysed by CASA. COVID-19, coronavirus disease 2019; VCL, curvilinear velocity; VAP, average path velocity; VSL, straight-line velocity; STR, straightness; ALH, amplitude of lateral head displacement; BCF, beat-cross frequency; SD, standard deviation; CASA, Computer Assisted Sperm Analysis.

Table 5 Semen quality parameters from the participants without a fever in the study

Semen quality parameters	Results of the first semen sample (n=42)	Results of the second semen sample (n=42)	Pair-wise *t*-test P value
Abstinence (days)	5.0 (1.4)	4.4 (1.4)	0.52
Total sperm count (mil)	424.2 (250.9)	480.3 (304.6)	0.24
Total forward sperm (mil)	269.4 (166.4)	297.2 (205.8)	0.38
Sperm concentration (mil/mL)	121.7 (45.4)	123.9 (61.4)	0.79
Volume (mL)	3.5 (1.7)	3.9 (1.7)	0.13
Progressive rate (%)	63.7 (10.9)	61.0 (9.4)	0.20
VCL (μm/s)	43.0 (15.7)	48.0 (15.9)	0.08
VAP (μm/s)†	27.4 (6.0)	32.8 (10.4)	0.01
VSL (μm/s)†	20.5 (5.2)	25.3 (8.8)	0.01
STR (%)†	0.5 (0.1)	0.5 (0.1)	0.11
ALH (μm/s)†	3.3 (1.0)	3.2 (1.0)	0.68
BCF (%)	9.1 (2.0)	10.7 (3.0)	0.06

Data are presented as mean (SD). †, quality of sperm motion analysed by CASA. VCL, curvilinear velocity; VAP, average path velocity; VSL, straight-line velocity; STR, straightness; ALH, amplitude of lateral head displacement; BCF, beat-cross frequency; SD, standard deviation; CASA, Computer Assisted Sperm Analysis.

Table 6 The scores of PEDT and IIEF-5 before and after COVID-19 infection

The scores	Before COVID-19 (n=49)	After COVID-19 (n=49)	Pair-wise *t*-test P value
IIEF-5 scores, mean (SD)	16.0 (7.1)	15.3 (6.9)	0.39
Severe ED (≤7 scores)	5 (10.2)	8 (16.3)	–
Moderate ED (8–11 scores)	8 (16.3)	6 (12.2)	–
Mild to Moderate ED (12–16 scores)	11 (22.4)	14 (28.6)	–
Mild ED (17–21 scores)	13 (26.5)	12 (24.5)	–
Without ED (22–25 scores)	12 (24.5)	11 (22.4)	–
PEDT scores, mean (SD)	6.8 (5.0)	8.6 (5.4)	0.003
Without PE (0–8 scores)	31 (63.3)	19 (38.8)	–
Potential PE (9–10 scores)	8 (16.3)	14 (28.6)	–
PE (11–20 scores)	10 (20.4)	16 (32.7)	–

Data are presented as n (%) unless otherwise specified. PEDT, premature ejaculation diagnostic tool; IIEF-5, International Index of Erectile Function; COVID-19, coronavirus disease 2019; SD, standard deviation; ED, erectile dysfunction; PE, premature ejaculation.

damage, the immunologic or inflammatory responses following infection. The blood-testis barrier (BTB) cannot completely prevent the spread of the virus; therefore, the male reproductive system is vulnerable to viral infection (21,22). SARS-CoV-2 is not unique in impacting sperm quality (22), and a few viruses (such as mumps virus, Zika virus, human papillomavirus, and human immunodeficiency virus) can cause damage to the testis or semen quality. SARS-CoV-2 receptor angiotensin-converting enzyme 2 is highly expressed in human testes (Leydig and Sertoli cells) and ejaculated sperm, and the testis could be a potential target for direct damage by SARS-CoV-2 (23,24). Luddi *et al.* revealed that human sperm were readily infected, both *in vivo* and *in vitro*, by SARS-CoV-2, as demonstrated by confocal and electron microscopy, and that the seminiferous epithelium and sperm could support SARS-CoV-2 viral replication (25). In other words, the spermatogenetic process may be detrimentally affected by the virus, underscoring the need to implement safety measures and guidelines in reproductive medicine.

However, remaining afebrile throughout the SARS-CoV-2 infection does not necessarily protect against spermatogenesis deregulation. Nevertheless, whether the effect of COVID-19 on sperm parameters is due to fever remains controversial. Fever is widely reported as one of the most common clinical manifestations of COVID-19. Our study revealed that fever was a prevailing symptom among the participants, which appeared to correlate with worse semen quality after COVID-19 infection. This aligns with the results of a study by Carlsen *et al.*, who verified that a history of febrile illness adversely affected semen quality (sperm concentration, morphology, and motility), which was also dependent on the fever duration (26). Moreover, the estimated duration of fever in patients with SARS-CoV-2 infection is longer than that in patients with MERS or other viral diseases. Therefore, COVID-19-induced fever may have a greater effect. Spermatogenesis is temperature-dependent and occurs optimally when the temperature is slightly lower than that of the body. Therefore, high temperatures can impair spermatogenesis.

COVID-19 is characterized by hyperinflammation, resulting in a "cytokine storm". This condition is critical for infection, as SARS-CoV-2 can induce autoimmune and autoinflammatory pathways of tissue invasion and the development of both immunosuppressive and hyperergic mechanisms of systemic inflammation. The testis is an organ of immune exemption because of the BTB with an isolated immune-privileged microenvironment for sperm; however, it cannot be protected from the general immune response. Histopathological changes, including inflammatory damage to seminiferous tubules with interstitial edema, congestion, inflammatory cell infiltration, and erythrocyte exudation, were observed in patients with COVID-19 in two separate reports, suggesting that COVID-19 might damage the male reproductive system through inflammation. Increased levels of pro-inflammatory cytokines and leukocytes in the seminal plasma of patients with COVID-19 have also been reported, indicating a systemic inflammatory process even

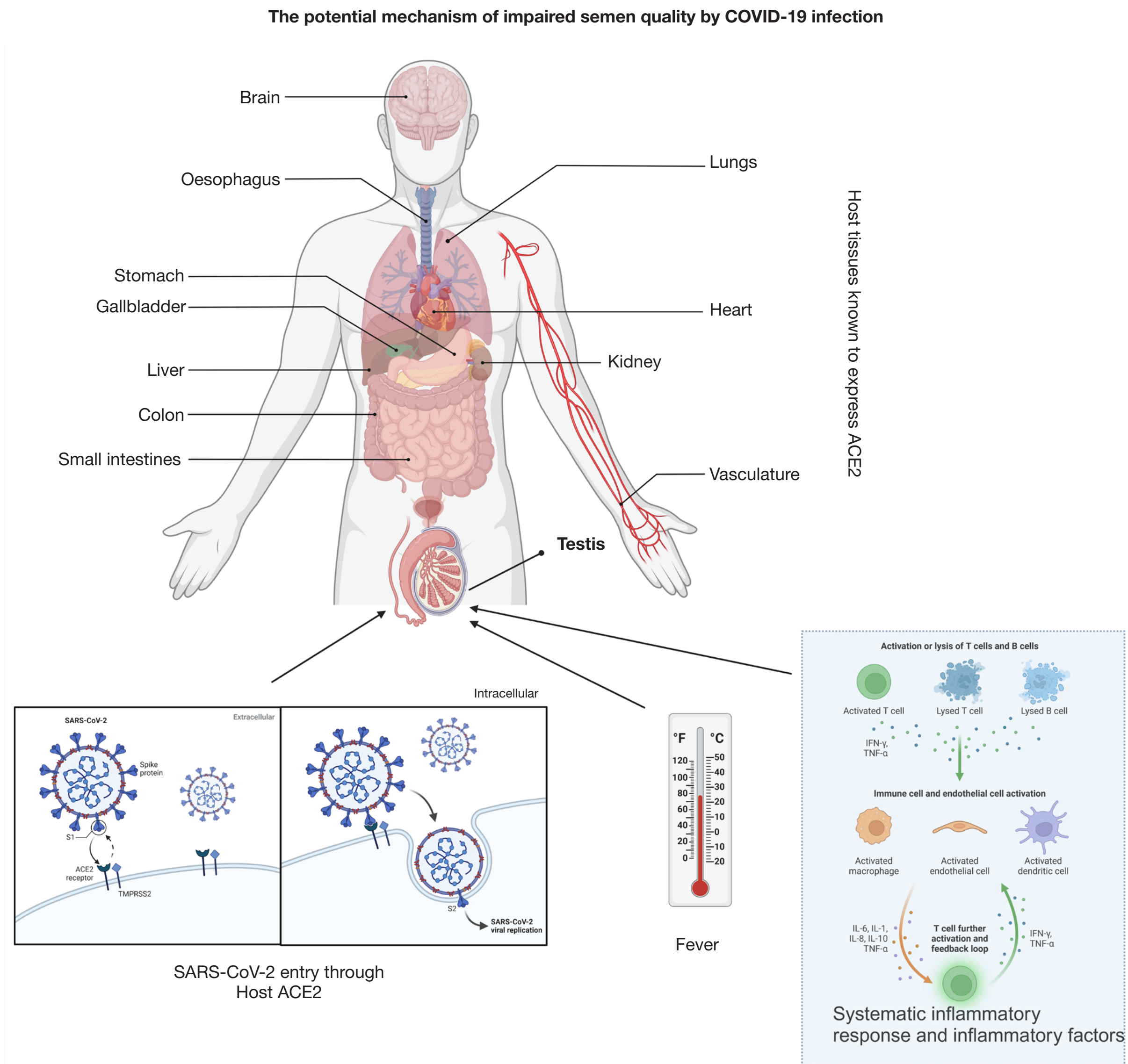

Figure 2 Possible mechanisms of COVID-19 affecting male reproduction. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin converting enzyme-2.

after recovery (27,28).

In addition, it is reported that SARS-CoV-2 infection could generate a dramatic increase in pro-inflammatory molecules and sequentially an intense state of oxidative stress, further leading to tissue damage (29), which occurs when the imbalance between oxidants and antioxidants toward an excess of reactive oxygen species (ROS) (20,30). Interestingly, a study from Transmission electron microscopy observations showed that spermatozoa from SARS-CoV-2-infected patients are themselves involved in ETosis processes and exhibit ETosis characteristics, that spermatozoa produce nuclear DNA-based extracellular traps, probably in a cell-free DNA-dependent manner, similar to those previously described in the systemic inflammatory response to COVID-19 (31). Few studies evaluated male sexual function after the COVID-19 outbreak. Sexual function in patients with acute and severe COVID-19 has rarely been investigated because of the disease severity. Salar *et al.* discovered that the changes in the IIEF-5 scores of patients from the pre-to post-disease period were significant for both mild and moderate groups of SARS-CoV-2 infection, regardless of the disease severity (32). However, in our study, the difference in the IIEF-5 score was not significant after the COVID-19 infection. Previous studies have linked infection to premature ejaculation (33), such as Chlamydia trachomatis infection (34). Anxiety and depression have been hypothesized to contribute to sexual dysfunctions (17).

This prospective observational study has some limitations, including a relatively small sample size and a lack of mechanistic studies. And in the study, 11 participants with non-infection of COVID-19 cannot completely rule out asymptomatic infections, though who had underwent several times PCR or antigen tests before March 2023. And the regular sexual intercourse was not the inclusion criteria, which was a potential study limitation for evaluation of sexual function. And when IIEF5 or PEDT was abnormal, it was not confirmed clinically whether the questionnaires suggested sexual dysfunction. It is worth noting that some studies have shown that environmental factors such as air pollution and diet can affect sperm quality (35). However, this study did not discuss the potential impact of environmental and dietary factors on sperm quality during the COVID-19 pandemic.

However, despite these limitations, this study represents the first comprehensive investigation evaluating the effects of semen quality and sex function on the reproductive health of patients with COVID-19. In the future, researches with larger sample sizes may explore the underlying mechanisms related to these findings.

Conclusions

Our prospective observational study suggested that semen parameters significantly declined 45 days after COVID-19 infection. Ninety days after infection, the total sperm count, total forward sperm, and sperm concentration gradually increased to the levels before infection. Moreover, with infection accompanied by fever, the semen quality appeared worse in terms of total forward sperm, sperm concentration, and sperm progressive rate. Therefore, the male reproductive system is shown to be vulnerable to SARS-CoV-2 infection. Our results underscore concerns regarding sexual function after COVID-19 infection. These data are beneficial for better understanding COVID-19 associated sequelae, which are fundamental to semen collection during assisted reproduction.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-173/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-173/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Review Board of West China Second University Hospital, Sichuan University (WCSUH-SCU IRB No. 2021-197). Informed consent was obtained from all subjects during enrollment.

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