Original Article

Sperm concentrations do not correlate with semen parameters and hormone profiles in males recovered from COVID-19

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Background: Although the negative impact on fertility of men recovered from coronavirus disease 2019 (COVID-19) has been suggested, there is insufficient evidence, and the data are limited and contradictory. The present prospective study aimed to evaluate the sex-related hormones, semen parameters, erectile dysfunction (ED), and lower urinary tract symptoms (LUTS) in a cohort of men who recovered from COVID-19 and age-matched control men.

Methods: Semen samples were collected from twenty-two men recovered from COVID-19 with a median time of 91.5 days and thirty-six control males. The semen parameters were evaluated according to the World Health Organization (WHO) laboratory manual to examine and process human semen. The blood samples were collected to assess the male hormone profile. ED and LUTS were evaluated with the International Index of Erectile Function 5 (IIEF-5) and the International Prostate Symptom Score (IPSS), respectively.

Results: The follicle-stimulating hormone (FSH) (3.819±1.515 IU/L), luteinizing hormone (LH) (4.023±1.792 IU/L), prolactin (PRL) [12.60 (10.72–15.20) ng/mL], and testosterone (T) [4.345 (3.565–5.525) ng/mL] levels were at normal range in all males enrolled in the study. Levels of semen volume (control: 2.5 mL *vs.* COVID-19: 1.9 mL; P<0.05) and sperm concentration (control: 59×10^6/mL *vs.* COVID-19: 41.5×10^6/mL; P<0.005) were significantly lower in males recovered from COVID-19, but still technically well within normal regardless of WHO edition. All variables were examined through logistic regression analysis, demonstrating that only sperm concentration was an independent variable associated with men recovered from COVID-19 [odds ratio (OR) =1; 95% confidence interval (CI): 0.999–1.098; P=0.016]. According to correlation analysis, there was no correlation between sperm concentration and other semen parameters and sex-related hormone profiles. Furthermore, an absence of ED and LUTS in men who recovered from COVID-19 was evidenced using the IIEF-5 and IPSS, respectively.

Conclusions: Reproductive-age males recovered from COVID-19 have normal sperm concentration. Sperm concentration did not correlate with other semen parameters, sex-related hormones, IIEF-5, and IPSS. Further studies should be performed to evaluate whether the lower sperm concentration and semen

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volume that were still within the normal range are a transient or prolonged downregulation resulting from the COVID-19 attack.

Keywords: Coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); sex-related hormones; semen parameters; sperm concentration

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Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is classified into asymptomatic, mild, moderate, severe, and critical (1). Mild COVID-19 includes upper respiratory symptoms such as cough, fever, and sore throat without dyspnea (2). In addition, COVID-19 presents a large spectrum of extrapulmonary manifestations (2). In this regard, SARS-CoV-2 invasion of other organs is related to its receptor, angiotensin-converting enzyme-2 (ACE-2) (3). This membrane receptor is highly expressed on the testis, specifically in Sertoli and Leydig cells, seminiferous tubules, and spermatogonia (4,5). Moreover, SARS-CoV-2 infection might affect the testis inducing an alteration in spermatogenesis and testicular endocrine function (6). Hence, the testis is likely vulnerable to SARS-CoV-2 infection.

ACE2 is also higher expressed in male gonads of younger patients, therefore, they are prone to gonadal SARS-CoV-2 involvement (7,8). Viruses such as Zika virus (ZIKV), human immunodeficiency virus (HIV), human papillomavirus (HPV), cytomegalovirus (CMV), influenza, and mump s virus can cause testicular injury and affect male reproductive function (9). HIV and hepatitis B/C viruses cause alterations in semen parameters and sperm DNA integrity (10). Although previous studies have reported the presence of SARS-CoV-2 in semen and its effects on sex-related hormones and semen parameters, these results are limited and conflicting (11-15). Since more research is required to know aspects of the COVID-19 effect on the male reproductive system; we recruited reproductive age males who had recently recovered from COVID-19, and compared to healthy controls to assess COVID-19 effect on their sex hormones and semen. We present the following article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-22-638/rc).

Highlight box

Key findings

- Sperm concentrations do not correlate with the semen volume, total motility, progressive motility, non-progressive motility, viability, semen leukocytes, serum testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, International Index of Erectile Function 5 (IIEF-5), and International Prostate Symptom Score (IPSS).

What is known and what is new?

- Studies have shown that the sperm concentration and progesterone of the patients who recovered from SARS-CoV-2 infection was significantly lower than those of the controls.
- This manuscript suggested that the levels of sperm concentration were significantly lower but still technically well within normal regardless of WHO edition and associated with reproductive-age males recovering from COVID-19.

What is the implication, and what should change now?

- Men who recovered from mild COVID-19 could have a normal sperm concentration. Further studies should be performed to evaluate whether the lower sperm concentration is a transient or prolonged downregulation resulting from the SARS-CoV-2 infection, and the mild- and long-term impact of COVID-19 on male fertility.

Methods

Study design

This prospective, cross-sectional, and analytical study was conducted in a third-level reference hospital [UMAE H. E. No. 14, Mexican Institute of Social Security (IMSS), Mexico]. Reproductive-age males with a confirmed diagnosis of COVID-19 and healthy participants without previous SARS-CoV-2 infection were prospectively evaluated.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethical and research committee from the UMAE H. E. No. 14, Mexican Institute of Social Security (IMSS) (No. 2020-3001-061), and informed consent was taken from all individual participants.

Participants

The study included hospital residents with a confirmed diagnosis of COVID-19 that were invited and voluntarily agreed to participate. Some of these participants were part of a previous descriptive study carried out by our work team (16). The exclusion criteria were: (I) testicular or endocrine diseases; (II) previous exposure to treatments such as gonadotropins and anti-estrogens; and (III) previous urogenital tract hepatitis B/C virus, HIV or paramyxovirus infections history. The study was performed from April to December 2021. The COVID-19 diagnosis was determined with the New Coronavirus Pneumonia Prevention and Control Program (7^{th} edition). All COVID-19 males were positive for SARS-CoV-2 RNA by real-time reverse transcription-polymerase chain reaction (RT-PCR) assays. SARS-CoV-2 infection was classified as mild based on illness severity. The males recruited for this study filled in a questionnaire regarding their history and familial diseases and exposure to potentially harmful factors to the male reproductive system. The recovery stage refers to the condition with lessened symptoms and negative SARS-CoV-2 RNA tests. The control group was composed of sex/age matched hospital residents who had not suffered from SARS-CoV-2 infection and were invited, voluntarily recruited and were willing to participate. All the participants underwent a comprehensive clinical examination of the secondary sexual features and genitals, including regular features and typical testicular sizes.

Semen analysis

The hospital residents were informed about the appropriate semen collection procedure. Semen samples were collected by masturbation three months after the initial COVID-19 diagnosis, considering the individual's psychological and physiology during the recovery phase. Five days of sexual abstinence were asked before sperm samples were collected into sterile containers provided by the study center. The total sperm count, sperm viability, motility, and morphology were evaluated according to the World Health Organization (WHO) laboratory manual to examine and process human semen (5^{th} edition). Semen assessment was performed within 1 hour of ejaculation using a light microscope (Olympus Corporation, Tokyo, Japan) at ×100 magnification.

Sex-related hormone levels analysis

The blood samples were collected for male hormone profile detection. Serum testosterone (T), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were measured using chemiluminescence immunoassay on the VITROS 3600 Immunodiagnostic System (Ortho-Clinical Diagnostics Inc., Raritan, NJ, USA).

Statistical analysis

Categorical variables were represented as numbers and percentages (%). The data distribution was analyzed with the Shapiro-Wilks test, histogram, and Q-Q plots. Continuous variables with normal distribution were presented as mean [± standard deviation (SD)], and the differences between groups were analyzed with Student's *t*-test. Continuous variables with non-parametric distribution were expressed as the median and interquartile range (IQR), and the difference between groups was analyzed using the Wilcoxon rank sum test. The association between the groups and agglutination was performed with Fisher's exact test (two-sided). The correlation between semen volume and sperm concentration was calculated using the Spearman correlation test. Univariable logistic regression analysis was performed to determine the variables associated with COVID-19. Then, significant variables ($P<0.05$) were considered confounders and were included in the multivariable logistic regression analysis. This analysis was adopted to estimate the association between semen parameters and COVID-19. The P value, odds ratio (OR), and 95% confidence interval (CI) were determined for each risk factor. Calibration was assessed using the Hosmer-Lemeshow goodness-of-fit statistic ($P>0.05$). The Akaike information criterion (AIC) was also calculated to evaluate the goodness of fit of the analysis. The model predictive with the lowest AIC value was considered the preferred model, and the lower the AIC, the better the predictive model. A P value <0.05 was considered a significant difference. Statistical analysis was performed using Rstudio software (version 4.03; R Foundation for Statistical Computing, Vienna, Austria).

Table 1 Sex hormone levels and semen characteristics of reproductive-aged men recovered from COVID-19

Variable	Total (n=58)	Age-matched healthy controls (n=36)	Recovered COVID-19 men (n=22)	P value
Age (years)	29 [28–31]	29 [28–31]	29 [28–30]	0.592[a]
FSH (IU/L)	3.819 (±1.515)	3.919 (±1.586)	3.655 (±1.411)	0.511[b]
LH (IU/L)	4.023 (±1.792)	3.906 (±1.855)	4.214 (±1.707)	0.522[b]
Prolactin (ng/mL)	12.60 [10.72–15.20]	12.90 [10.12–15.60]	12.25 [11.62–14.60]	0.724[a]
Testosterone (ng/mL)	4.345 [3.565–5.525]	4.345 [3.715–5.3]	4.275 [3.132–6.202]	0.754[a]
Semen volume (mL)	2.2 [1.525–2.775]	2.5 [1.825–3.2]	1.9 [1.5–2.45]	0.0294[a]
Sperm concentration ($\times10^6$/mL)	55.5 [38.75–61]	59 [53.5–70.5]	41.5 [31.2–55.5]	0.0019[a]
Total motility (%)	90 [85–95]	90 [85–90.5]	90 [85–95]	0.682[a]
Progressive motility (%)	80 [70–87.5]	80 [74–86.50]	77.5 [70–88.75]	0.783[a]
Non-progressive motility (%)	10 [5–15]	10 [5–10]	10 [5–15]	0.288[a]
Viability (%)	90.5 [85–95.75]	90 [84.25–95]	91 [86.25–96]	0.572[a]
Agglutination (%)				0.897[c]
Negative	35 (60.34)	21 (58.33)	14 (63.63)	
Tail-tail	18 (31.03)	12 (33.33)	6 (27.27)	
Head-tail	1 (1.72)	1 (2.77)	0 (0.00)	
Head-head	4 (6.89)	2 (5.55)	2 (9.09)	
Leukocytes detected (number)	2.5 [1.25–4]	2 [1–4]	4 [2–4]	0.717[a]
IPSS	1 [0–2]	1 [0–2]	1 [0–2]	0.743[a]
IIEF-5	24 [23–25]	24 [23–25]	24 [23–24.75]	0.652[a]

Data are presented as number (percentage %) for categorical variable and as mean (± SD) or median [range] for continuous variables. P values were calculated using: [a], Wilcoxon sum-rank test; [b], Student's *t*-test, and [c], Fisher's exact test. P<0.05 was considered statistically significant. FSH, follicle-stimulating hormone; LH, luteinizing hormone; IPSS, International Prostate Symptom Score; IIEF-5, International Index of Erectile Function; SD, standard deviation.

Results

Men characteristics and sex-related hormones analysis

Fifty-eight (n=58) male were classified into two groups: healthy un-infected male control group (n=36) and COVID-19 recovered males (n=22). *Table 1* displays participants age, hormone and semen parameters in both groups. The median age of the participants was 29 (range, 28–31) years; with no statistically significant difference between both groups. The mean or median serum FSH, LH, prolactin (PRL), and T of all study participants were 3.819±1.515 IU/L, 4.023±1.792 IU/L, 12.60 (10.72–15.20) ng/mL, 4.345 (3.565–5.525) ng/mL, respectively. All hormone levels were normal in both groups.

Semen parameter analysis

The median sperm total motility, progressive motility, non-progressive motility, and viability of all men were 90%, 80%, 10%, and 90.5%, respectively. These semen parameters were at normal limits. There was no significant difference in agglutination (P=0.897) between groups (*Table 1*). Although leukocytes were detected in semen samples of both groups, there was not statistically significant difference (P=0.717). The comparison of median semen volume (control: 2.5 mL *vs.* COVID-19: 1.9 mL; P<0.05) and sperm concentration (control: 59×10^6/mL *vs.* COVID-19: 41.5×10^6/mL; P<0.005) between groups were significant differences. This difference was associated with

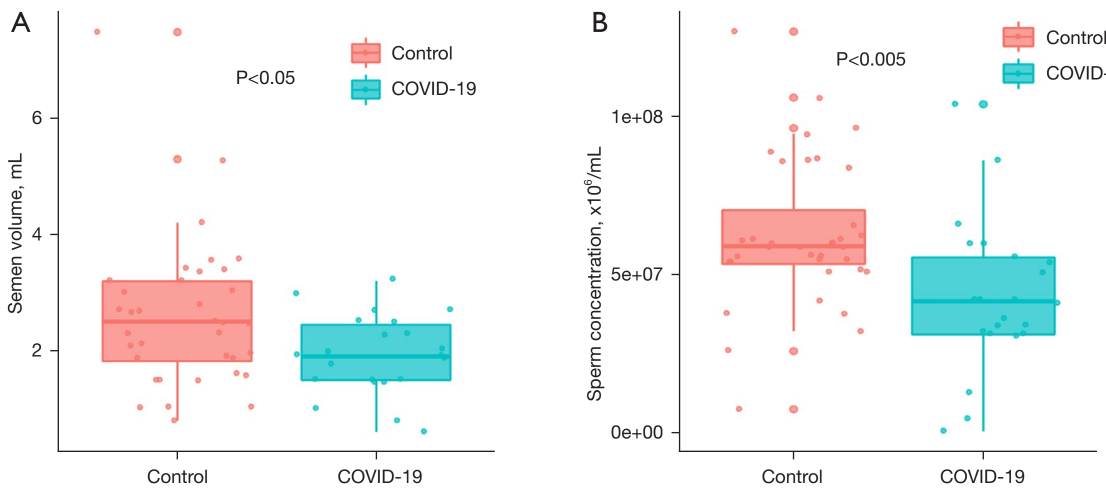

Figure 1 Box plots illustrating the measurements (median, interquartile range, minimum to maximum, all results) of (A) semen volume and (B) sperm concentration in control and men recovered from COVID-19. P<0.05 was considered statistically significant.

lower semen volume (*Figure 1A*) and sperm concentration (*Figure 1B*) that were still within the normal range in the recovered COVID-19 group. Moreover, the correlations between the sperm concentration and sex hormones (*Figure 2A-2D*) or sperm parameters (*Figure 3A-3F*) were statistically non-significant, including the correlation between the sperm concentration and semen volume (R=0.18, P=0.17) (*Figure 3A*).

Sperm concentration is associated with reproductive-age males recovered from COVID-19

The results of the logistic regression analysis are shown in *Table 2*. Univariate analysis demonstrated associations of two factors, semen volume (OR =0.482; 95% CI: 0.226–0.893; P<0.05) and sperm concentration (OR =1; 95% CI: 0.999–1.056; P=0.008). The sperm concentration was retained in the multivariate logistic analysis as an independent variable associated with men recovering from COVID-19. The Hosmer-Lemeshow test (P=0.170) result showed a good model fitness.

Absence of erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) in men recovered from COVID-19

Men recovered from COVID-19 were screened for ED using the International Index of Erectile Function 5 (IIEF-5). The median IIEF-5 score was 24 for both groups and did not show a statistically significant difference in the comparison (P=0.652) (*Table 1*). On the other hand, the LUTS were measured with the International Prostate Symptom Score (IPSS). The mean IPSS in the men who recovered from COVID-19 was 1 in the same way as the control group. There was no statistically significant change in the scores (P=0.743) (*Table 1*). A scattering chart of sperm concentration and IPSS or IIEF-5 scores was presented in *Figure 4*. According to correlation analysis, there was no correlation between sperm concentration and IIEF-5 (R=−0.067, P=0.62; *Figure 4A*) or IPSS (R=0.098, P=0.46; *Figure 4B*) scores of all patients.

Discussion

A broad range of viruses, including HIV, HPV, CMV, ZIKV, influenza, and mumps virus, can cause testicular injury and affect male reproductive function (9). In this study, sex-related hormones and values of semen parameters that are commonly related to fertility causes were investigated in a cohort of 22 reproductive-age males who recovered from COVID-19. The sex hormone profiles between the 22 men who recovered from COVID-19 and 36 age-matched control men did not statistically change. This phenomenon has been observed in other studies where the most sex-related hormones, such as T, LH, and FSH, remain within the normal reference ranges after recovery from COVID-19 (11,13,17). However, Guo *et al.* reported statistically significantly lower progesterone and higher PRL levels in patients who recovered from COVID-19

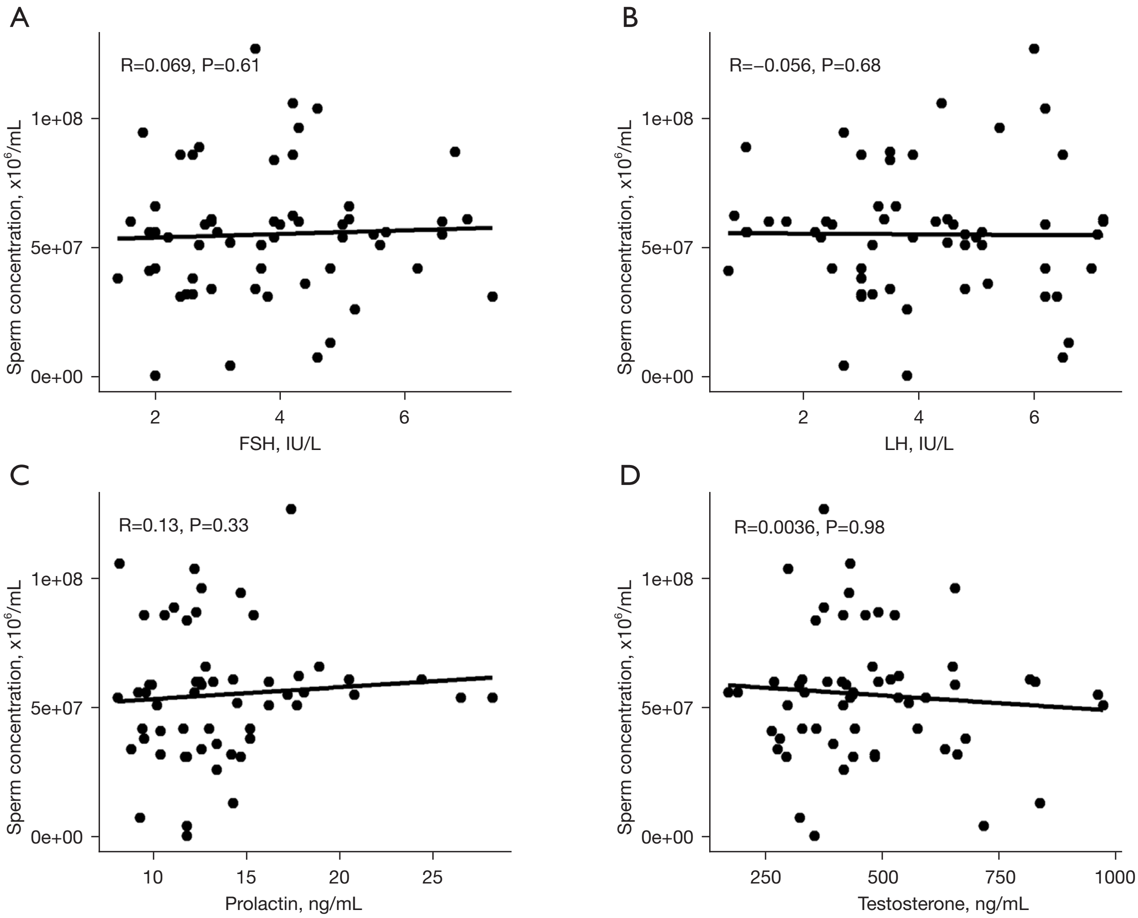

Figure 2 Correlation analysis between the sperm concentration and sex hormones in men recovered from COVID-19. Scatter graph illustrating the correlation between the sperm concentration and (A) FSH, (B) LH, (C) prolactin, and (D) testosterone. P<0.05 was considered statistically significant. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

than those in controls (11). Temiz *et al.* evidenced that all the hormone levels were similar between the COVID-19 patients treated before and after with azithromycin and hydroxychloroquine (15). The males included in this study did not receive azithromycin or hydroxychloroquine. They were treated with paracetamol. Although there are data that raise questions about the effects of acetaminophen on hormonal homeostasis (18), this association was neither analyzed nor confirmed.

Regarding semen parameters, sperm concentration and semen volume were significantly different between the two groups, in contrast with the pre- and post-COVID-19 semen analyses performed by Pazir *et al.* (14). The logistic regression analysis in this study revealed that sperm concentration, but not semen volume, was associated with the men who recovered from COVID-19. Holtmann *et al.* performed a semen analysis between 18 males who had recovered from COVID-19 and 14 healthy volunteers; they found that men exhibiting moderate symptoms had a significant decrease in sperm concentration compared with those who had recovered from mild-COVID-19 and the healthy volunteers (12). Guo *et al.* and Ghosh *et al.* demonstrated that the sperm concentration for the patients recovered from SARS-CoV-2 infection was significantly lower than those for the controls [(86.8×10^6/mL *vs.* 49×10^6/mL; P<0.011), (42.5×10^6/mL *vs.* 24×10^6/mL; P=0.013), respectively] (11,19). There is evidence that patients who recovered from COVID-19 (median 84 days after hospital discharge) had a significant increase in sperm concentration, suggesting a recovery of sperm numbers (11). Here, the sampling was conducted at a median of 91.5 days after COVID-19, suggesting that a longer time may be needed to

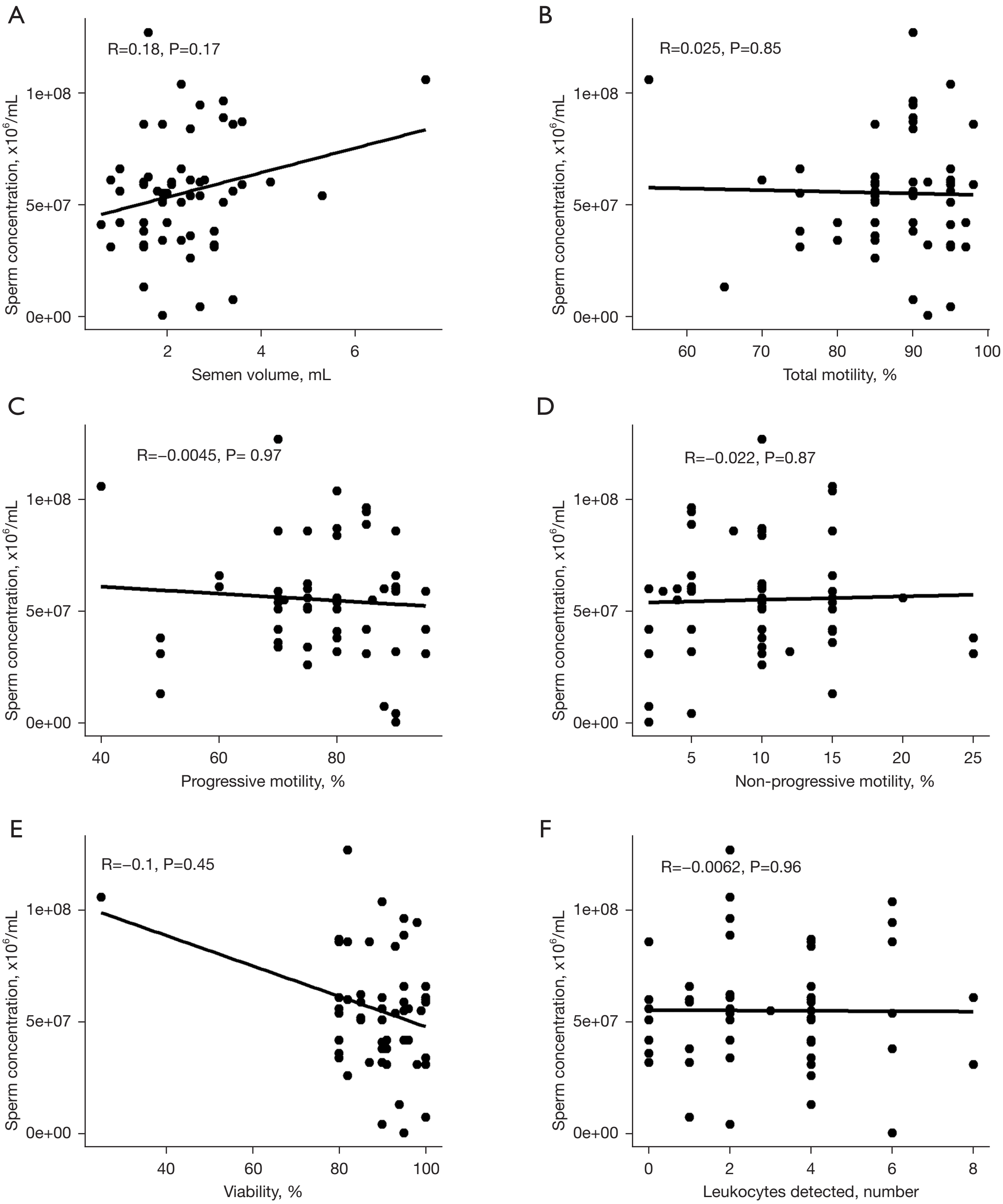

Figure 3 Correlation analysis between the sperm concentration and sperm parameters in men recovered from COVID-19. Scatter graph illustrating the correlation between the sperm concentration and (A) semen volume, (B) total motility, (C) progressive motility, (D) non-progressive motility, (E) viability, and (F) leukocytes detected or semen leukocytes (number). P<0.05 was considered statistically significant.

Table 2 Association of sex-related hormones and semen parameters in reproductive-age males recovered from COVID-19

Variable	Univariable regression			Multivariable regression		
	OR	95% CI	P value	OR	95% CI	P value
Age	1	0.823–1.214	0.956	–	–	–
FSH (IU/L)	0.888	0.610–1.266	0.516	–	–	–
LH (IU/L)	1.103	0.817–1.501	0.523	–	–	–
Prolactin (ng/mL)	0.976	0.849–1.107	0.713	–	–	–
Testosterone (ng/mL)	1	0.996–1.003	0.950	–	–	–
Semen volume (mL)	0.482	0.226–0.893	0.037	0.500	0.221–0.995	0.069
Sperm concentration ($\times 10^6$/mL)	1	0.999–1.056	0.008	1	0.999–1.098	0.016
Total motility (%)	1.012	0.949–1.087	0.725	–	–	–
Progressive motility (%)	0.997	0.953–1.045	0.902	–	–	–
Non-progressive motility (%)	1.050	0.953–1.162	0.329	–	–	–
Viability (%)	1.027	0.974–1.104	0.400	–	–	–
Leukocytes detected (number)	1.057	0.827–1.354	0.653	–	–	–
IPSS	1.006	0.608–1.639	0.979	–	–	–
IIEF-5	0.881	0.51–1.512	0.644	–	–	–

P<0.05 was considered statistically significant. OR, odds ratio; CI, confidence interval; FSH, follicle-stimulating hormone; LH, luteinizing hormone; IPSS, International Prostate Symptom Score; IIEF-5, International Index of Erectile Function.

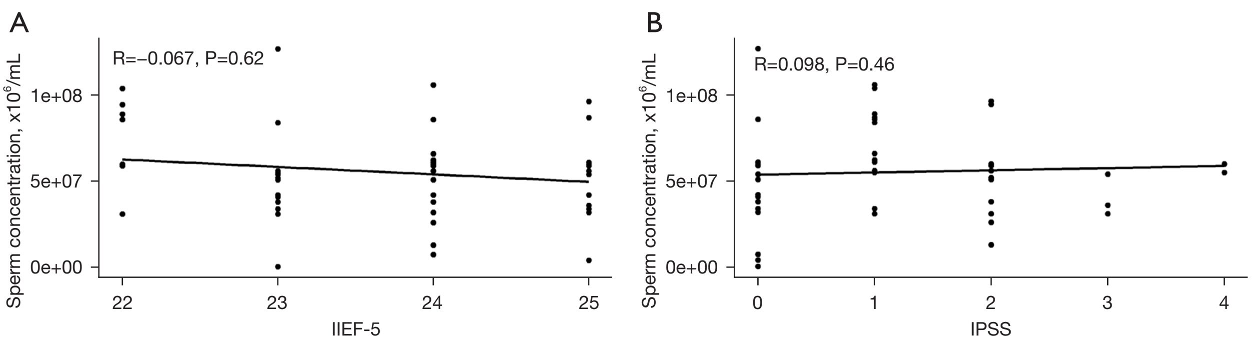

Figure 4 Correlation analysis between the sperm concentration and IPSS or IIEF-5 scores in men recovered from COVID-19. Scatter graph illustrating correlation between the sperm concentration and (A) the IIEF-5 or (B) the IPSS. P<0.05 was considered statistically significant. IIEF-5, International Index of Erectile Function; IPSS, International Prostate Symptom Score.

recover sperm concentration. Since human spermatogenesis is estimated to take 74 days (20,21), these findings might indicate altered sperm physiology post-COVID-19, affecting one spermatogenic cycle. Hu *et al.* performed an evaluation of mild- and long-term impact of COVID-19 on male fertility and they found that a total sperm number after a recovery time of 90 days and an improving trend of about 150 days (22). More studies are required to investigate the persistence of this alteration for a more extended period and its role on male reproductive function. In this sense, the chronic inflammatory response in obesity can cause sperm dysfunction due to reduced sperm concentration (23).

The correlations between sperm concentration, semen parameters and sex-related hormones were statistically non-significant in this study, implying that the sperm concentration might be related to other factors. Donders *et al.* suggested that a reduction in sperm concentration was correlated with the anti-S1 SARS-CoV-2 IgG antibodies and time lapse after COVID-19 (24). Semen proteomics of COVID-19-recovered males identified pathways involved in reproductive functions such as extracellular matrix, cell motility regulation, and sperm-oocyte recognition (19). Furthermore, Ghosh *et al.* revealed significant downregulation of prosaposin and semenogelin 1, two proteins related to male fertility (19). Therefore, to discern fertility-related biological processes triggered by SARS-CoV-2 infection, a protracted assessment of disease impact in men recovered from COVID-19 is required. In this sense, ACE-2 receptor is present and highly expressed on seminiferous tubules, Sertoli cells and the germ cells from the testes, making them a potential site for SARS-CoV-2 infection which could impact spermatogenesis (25,26).

Kidney proximal tubule cells and bladder urothelium, that have ACE-2 expression, are highly at risk for potential SARS-CoV-2 infection (27). In this study, the LUTS were evaluated by IPSS score, where we did not find any significant differences between recovered COVID-19 males and men control group. According to the results of the correlation analysis, there was no correlation between the semen concentration and IPSS score. Interestingly, Can *et al.* reported that LUTS scores increased in elderly patients, and the severity of COVID-19 did not correlate with this score (28). ED was also analyzed in this study through the IIEF-5. Saad *et al.* demonstrated a significant difference in the mean IIEF-5 score between patients with COVID-19 and controls. Their multiple logistic regression model for COVID-19 ED revealed that the IIEF-5 score was an independent variable (29). Nevertheless, the results of this study found no association between IIEF-5 score and men recovering from COVID-19.

To date, the impacts of COVID-19 on male fertility remain uncertain. Li *et al.* observed a decreased sperm concentration and increased seminal levels of MCP-1, IL-6, and TNF-α in COVID-19 subjects compared to control males (30). Possible explanations for the decreased sperm concentration could be associated with an impairment of spermatogenesis due to an elevated immune response in the testis of male COVID-19 patients (30). In addition, the presence of SARS-CoV-2 RNA in semen of men with acute infection or recovered from COVID-19 could play a key role in sperm concentration (31). However, other authors have not detected SARS-CoV-2 in the semen samples of active infection or recovery groups (12,30,32). These findings are supported by a study showing a sparse expression of ACE2, a primary receptor of SARS-CoV-2, in men for 31 days from the COVID-19 diagnosis to the collection of semen, found no evidence of viral RNA in the analyzed semen samples. Our study did not investigate the presence of viral RNA.

The current study does have some limitations. Due to the nature of the study (an exploratory pilot study), a limited number of men were enrolled, making the cohort size a primary limitation of the study. Also, the study recruited mild COVID-19 subjects, and due to this reason, the sample could not be stratified by disease severity to assess its impact on the semen parameters and sex-related hormones. A prospective cohort involving more men is further required. Because the baseline levels of semen parameters and sex hormones in the males before infection are unknown, results should be interpreted with caution. The study's strengths include the enrollment of men without diseases other than COVID-19 that may cause harmful effects on sperm concentration.

This study focuses on a minuscule spermatogenesis cycle, and it is key to understanding SARS-CoV-2 pathophysiology and its clinical implications. Moreover, it is the first study where an univariable and multivariable logistic regression analysis was performed to determine the association between the sperm concentration and the men recovered from COVID-19. In addition, since the study included only males who recovered from mild COVID-19, it permits to analyze a more homogeneous sample. Hence, the findings suggest that men who recovered from mild COVID-19 could have a normal sperm concentration.

Conclusions

In summary, these findings suggested that the levels of sperm concentration were significantly lower but still technically well within normal regardless of WHO edition and associated with reproductive-age males recovering from COVID-19. Further studies should be performed to evaluate whether it is a transient or prolonged downregulation resulting from the COVID-19 attack. Moreover, the mechanism of a long-term effect must be clarified.

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Footnote

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Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-22-638/dss

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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-22-638/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). The study was approved by the ethical and research committee from the UMAE H. E. No. 14, Mexican Institute of Social Security (IMSS) (No. 2020-3001-061), and informed consent was taken from all participants.

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