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Androgen and SARS-Cov-2: Exploring the impact of COVID-19 on testosterone levels in men

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Abstract
Background: High expression of ACE2 and TMPRSS2 in testes suggests men's vulnerability to SARS-CoV-2 infection, leading to orchitis, oxidative damage, inflammation, and immunological responses that disrupt the hypothalamic-pituitary-gonadal axis and impaired gonadal steroidogenesis, potentially causing hypogonadism, sexual dysfunction, and infertility.
Objectives: To determine the frequency of testosterone deficiency in post-COVID patients and its association with the severity of COVID-19 disease.
Methods: In this cross-sectional study we enrolled 48 post-COVID male patients aged 18-69 years and equal number of age, BMI, and WC matched participants as healthy control. After using a questionnaire to enlist participants, we measured total testosterone, luteinizing hormone (LH), folicle stimulating hormone (FSH), SHBG, and albumin, then computed free (cFT) and bioavailable testosterone. Testosterone deficiency was defined as TT < 264 ng/ml and/or cFT < 220 pmol/L.
Results: Frequency of testosterone deficiency 12 (25%) was significantly (P=0.028) higher in the post-COVID group compared to only 4 (8.3%) in the healthy control group. The recovered COVID-19 patients had significantly lower total (P=0.034), calculated free (p<0.001) and bioavailable testosterone (p<0.001), and higher SHBG (p<0.001) levels in comparison to the healthy individuals. In contrast to post-COVID patients with normal testosterone levels, patients with deficient testosterone had significantly greater rates of central obesity (P=0.040), and sexual dysfunction (P=0.011) as well as hospitalizations requiring oxygen therapy (P=0.007) and COVID-19 disease severity (P=0.004). In regression analysis, COVID-19 was a significant predictor of testosterone deficiency [OR=4.295 (P=0.034, 95% CI= 1.115, 16.548)], and moderate to severe COVID-19 disease increased the odds of testosterone deficiency by approximately 10 times [OR=9.950 (p=0.017, 95% CI= 1.513, 65.454)] in post-COVID group.
Conclusion: Post-COVID male patients were found to have a higher prevalence of testosterone deficiency in comparison to matched control participants. COVID-19 severity was the most significant predictor of low testosterone levels in recovered COVID-19 patients.

Keywords: COVID-19, testosterone deficiency, severity

Introduction
A novel Corona virus emerged in December 2019, termed SARS-CoV-2 by the International Virus Taxonomy Committee due to its genetic similarities to the SARS-CoV-1 virus (79.5%) [1]. The infection caused by SARS-CoV-2 has been termed as "COVID-19" (Coronavirus disease-19), as this is a Corona virus-related disease that was discovered originally in 2019 [2]. COVID-19 has widespread effects throughout the body with lesser known clinical manifestations, and the medium and long-term health consequences experienced by survivors of COVID-19, if any, are currently unknown [3]. It is a systemic disease, affecting the respiratory, cardiovascular, digestive, endocrine, and neurologic systems [4] and the knowledge about the impact of this virus on the endocrine system is growing [5]. Although epidemiological data suggests that men may have an increased risk of COVID-19-related morbidity and mortality, the potential impact on male reproduction and any mechanisms remain poorly understood [6]. At the pathophysiological basis, SARS-CoV-2 exploits the ACE-2 receptor and uses it to facilitate viral entry into the target cells [7] and utilizes cell surface protease transmembrane serine protease 2 (TMPRSS2) for viral S protein priming.

SAR-CoV-2 virus activates oxidant-sensitive pathways via inflammatory responses, thereby inducing oxidative stress (OS) leads to oxidative damage to host tissues and disrupts normal immune responses, leading to the local tissue damage primarily affects the lower respiratory tract and presents as pneumonia, including fever, cough, expectoration, haemoptysis, acute respiratory distress syndrome (ARDS), and multiorgan systemic dysfunctions in terms of sepsis and septic shock, and death [8]. Extrapulmonary damage of COVID-19 includes acute kidney injury, hepatocellular injury, neurological illnesses, myocardial dysfunction, arrhythmia, gastrointestinal and impairment of reproductive function [9]. Epididymoorchitis is recognized as a complication of SARS-CoV-2. Disruption of blood-testis barrier (BTB) in febrile diseases is suspected in the acute phase of the disease enabling viral entry into the testes resulting oxidative damage to germ cells in human testes, a decrease in testosterone synthesis, and an increase in LH and FSH levels [10]. A primary (Hypergonadotrophic) hypogonadism resulted from this. It also disrupts testicular functions and reduces testosterone by suppressing the hypothalamic-pituitary-gonadal axis due to secondary immunological and inflammatory responses, leading to secondary (Hyporgonadotrophic) hyphogonadism [11]. Total and free testosterone was considerably lower in patients with severe COVID19 disease and in those who were admitted into ICU or required oxygen therapy [11, 12]. Therefore, the impact of COVID-19 infection on the hypothalamic-pituitary-gonadal axis attracted attention. But still, it is unclear whether COVID-19 contributes to testicular damage or hypothalamic-pituitary-gonadal axis disruption, resulting in permanent testosterone deficiency with alteration of other reproductive hormones leading to hypogonadism in men. Our aim was to explore the impact of COVID-19 on male reproductive hormones and to determine the frequency of testosterone deficiency and its association with the severity of disease after recovery from acute illness.

Materials and Methods

This cross-sectional observational study was done at the Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbag, Dhaka. Study was conducted on Bangladeshi male patients, who had recovered from acute COVID-19 disease. Purposive non-probability sampling was employed to select the study subjects. Based on the observation of lower testosterone levels in COVID-19 patients reported by Salonia *et al*. [13], at a 95% confidence interval (Z =1.96), 48 post-COVID male patients, aged 18-69 years, within six months of confirmed COVID-19 diagnosis and 48 control participants were recruited. After scrutiny of all inclusion and exclusion criteria, study participants were recruited from the post-COVID follow up clinic of BSMMU. The control group consisted of healthy males with no history or documentation of COVID-19 infection. Participants were matched by age, body mass index (BMI), and waist circumference (WC). Both married and unmarried individuals were included. We excluded participants who had a history of gonadal disease or other endocrine disorders, including diabetes mellitus and thyroid disorders affecting testosterone levels, preexisting chronic kidney or liver disease, and prior use of testosterone or glucocorticoid before COVID-19. Approval of the research protocol was received from the Institutional Review Board (IRB) of BSMMU. Informed written consent was obtained from every participant in this study.

Data were collected using a semi-structured case record form. History and physical examination, including measurements of height, weight, WC, and blood pressure, were recorded. BMI was calculated. Fasting morning blood samples were collected within 7-10 AM for biochemical assays of total testosterone, LH, FSH, SHBG, and albumin levels. Calculated free and bioavailable testosterone levels were derived using a specific calculator developed at the hormonology department, University Hospital of Ghent, Belgium. The cut off levels of cFT and total testosterone were set at 220 pmol/L and 264 ng/dL, respectively, while the levels of luteinizing hormone (LH) was set at 9.4 mIU/mL [14, 15].

SPSS version 25 was used for the analysis of the data. Frequencies and percentages were expressed for qualitative data, while means (±SD) and medians (IQR) were used for quantitative data. Normality was assessed by the Shapiro-Wilk test. Comparisons between groups were made using the Student's t-test or Mann-Whitney U test, as appropriate. The chi-square test was used for categorical variables. Spearman's rho was employed to assess correlations, and multiple linear regression and binary logistic regression were used to evaluate the impact of COVID-19 on testosterone levels and deficiency. Statistical significance was set at $p \leq 0.05$.

Results

From January 2022 to December 2022, a total of forty-eight post-COVID male patients within 6 months of diagnosis of confirmed COVID-19 disease, and equal number age, BMI, and WC-matched healthy participants were enrolled to estimate the frequency of testosterone deficiency and its association with severity of COVID -19 disease. The median ages of the post-COVID patient and control were 34 (28.2-42) and 31.5 (29.2-42.7), respectively. During comparison of clinical and laboratory parameter, we observed, there was statistically significant difference between the percentages of sexual dysfunction which is more in the post-COVID group (33.3% vs. 14.6%) and the median values of total testosterone, calculate free and bioavailable testosterone were significantly lower, and sex hormone binding globulin was significantly higher in the post-COVID group than in the matched control group. But we have not noticed any significant differences between the two groups in median LH, FSH, albumin, or testosterone to LH ratio. All the clinical and laboratory differences between the two groups are demonstrated in Table-1.

Table 1: Clinical and laboratory parameters of study participants (N=96)

Variables	Post-COVID Patient (n=48)	Matched control (n=48)	p-value
Age	34(28.2-42)	31.5(29.2-42.7)	0.849
BMI (kg/m^2)	24.7(22.7-27.4)	24.5(21.7-26.5)	0.395
Waist circumference (cm)	89.33±7.03	87.68±9.52	0.338
SBP	120(110-130)	120(110-120)	0.144
DBP	80(70-90)	80(70-80)	0.084
Sexual Dysfunction	16 (33.3)	7(14.6)	0.031
HTN	9(18.8)	5(10.4)	0.247
COVID-19 vaccinaton	43 (89.6)	46(95.8)	0.435
TT (ng/dl)	391.5(311.2-444)	429.5(360.7-510.7)	0.034
LH (mIU/ml)	3.24(2.1-4)	2.56(2.1-3.5)	0.132
FSH (mIU/ml)	3.0(2.0-4.8)	3.42(2.2-4.5)	0.650
SHBG (Nmol/L)	24.8(15.1-32.5)	11.3(9.3-13.9)	<0.001
Albumin (gm/L)	47(45-48.7)	46.5(44.25-47.0)	0.105
cFT (pmol/L)	296.69(234.7-362.2)	474.8(376-520)	<0.001
BAT (ng/dl)	212.5(168.5-268.5)	337.5(266-384)	<0.001
T/LH (nmol/IU)	4.35(2.7-7.5)	5.5(3.6-7.7)	0.069

(Within parenthesis are percentages over column total) Data were expressed as mean ± SD (if normally distributed) or median (IQR) (if skewed). P- value according to the independent sample t-test, Mann-Whitney U test, Chi-square test and Fisher's Exact Test as indicated.

Of all, a total testosterone level <264 ng/dl and/or a cFT level <220 pmol/L were observed in 12 (25%) post-COVID patients and 4 (8.3%) healthy controls, respectively. So the frequency of testosterone deficiency we observed in our study was significantly higher (P = 0.028) in the post-COVID group than the control group (Figure-1). While in the post-Covid group, levels of total testosterone, cFT, LH, and FSH suggestive for the frequency of secondary and primary hypogonadism were 10 (83.3%) and 2 (16.7%), respectively (Figure-2).

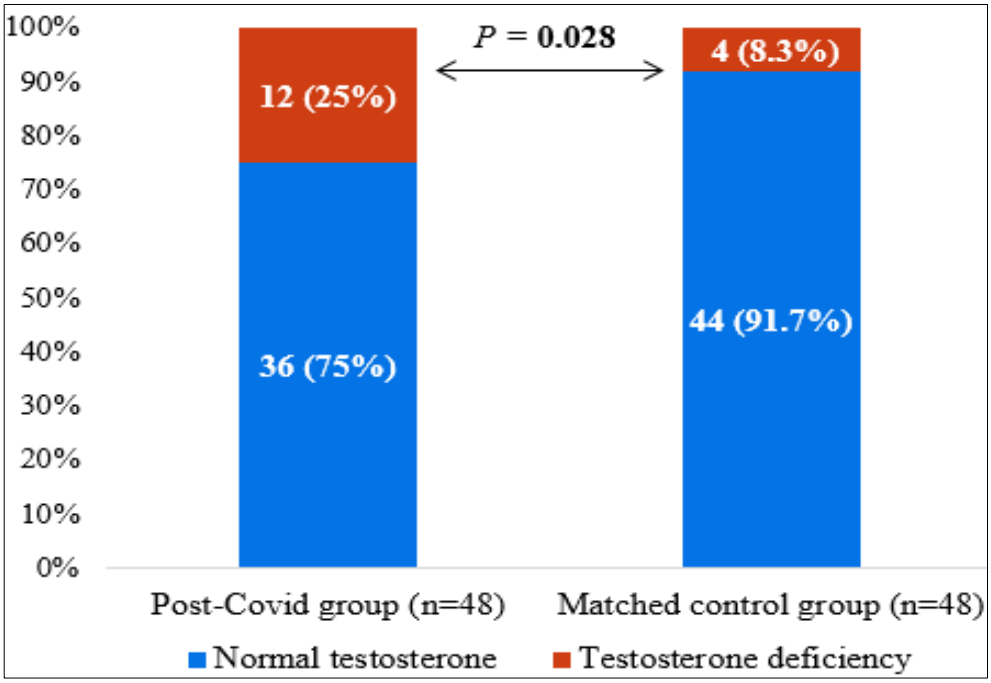

Fig 1: Frequency of testosterone deficiency in post-COVID (n=48) and in matched control (n=48) group (*P* value obtained by Chi-square test)

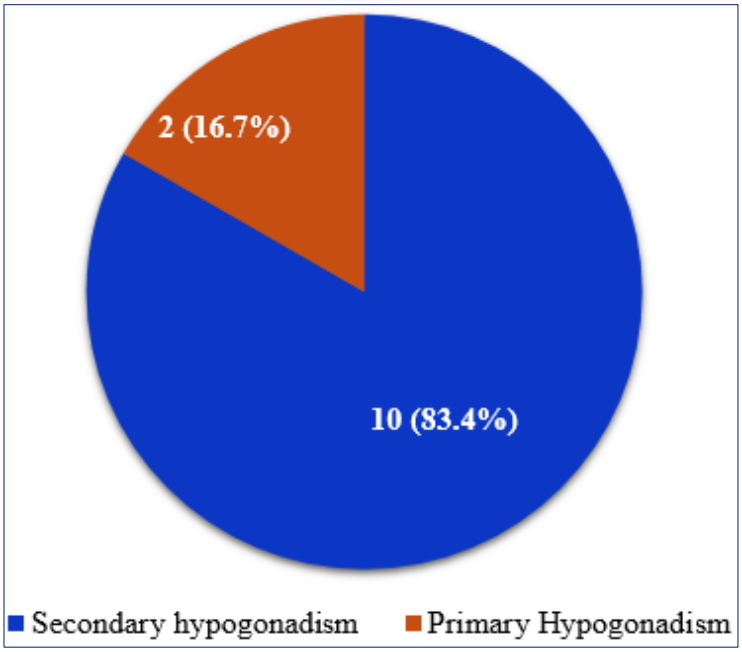

Fig 2: Frequency of primary and secondary hypogonadism in post-COVID group (n=48)

Clinical and laboratory parameters between 12 (25%) post-COVID testosterone deficient and 36 (75%) post-COVID-19 testosterone-sufficient patients summarized in table 2. The median age was significantly higher in testosterone deficient group (41.5, IQR: 32.5-48.7 years) than in the testosterone sufficient group (32, IQR: 27-40.7 years). The testosterone-deficient group had significantly higher rates of central obesity, sexual dysfunction, hospitalization requiring oxygen therapy, and moderate to severe COVID-19 disease, and significantly lower testosterone-to-LH (T/LH) ratio compared to the testosterone-sufficient group.

Table 2: Comparison of clinical and laboratory characteristics between the post-COVID patients with and without testosterone deficiency (N=48)

Variables	Normal testosterone (n=36)	Deficient testosterone (n=12)	p-value
Age	32 (27-40.7)	41.5 (32.5-48.7)	0.021
Time since start of COVID-19 symptoms to the interview date (Days)	131.5 (101.2-150.5)	119 (82-154.2)	0.793
Smoker	11(30.6)	6(50)	0.300
High grade Fever	16(44.4)	9(75)	0.067
Dyspnoea	9(25)	6(50)	0.152
Testicular pain	2(5.6)	2(16.7)	0.257
Sexual dysfunction	8(22.2)	8(66.7)	0.011
Hospitalization	2(5.6)	5(41.7)	0.007
Oxygen therapy	2(5.6)	5(41.7)	0.007
Moderate to severe COVID-19	3(8.3)	6(50)	0.004
HTN	5(13.9)	4(33.3)	0.199
Overweight and obesity	24(66.7)	10(83.3)	0.460
BMI	24.7±3.05	25.54±3.62	0.467
WC	88.13±7.03	92.91±5.90	0.040
LH (mIU/ml)	3.14(1.9-3.6)	3.4(2.8-6.3)	0.125
FSH (mIU/ml)	2.7(2-4.8)	3.2(2-8)	0.552
SHBG (nmol/L)	24(15.7-28)	34.5(9.9-46.7)	0.411
T/LH (nmol/IU)	5.1(3.1-7.7)	2.19(1.6-3.9)	0.001

(Within parenthesis are percentages over column total) Data were expressed as mean ± SD (if normally distributed) or median (IQR) (if skewed). P-value according to the independent sample t-test, Mann-Whitney U test, Chi-square test and Fisher's Exact Test as indicated.

Table 3: Binary logistic regression model predicting risk of testosterone deficiency in whole study participants (N=96)

	OR	P	95% CI	
Age	1.008	0.817	0.944	1.075
BMI	0.904	0.507	0.671	1.218
Waist circumference	1.175	0.036	1.011	1.367
COVID-19 disease	4.295	0.034	1.115	16.548

R2= 15.3- 25.8%, OR= Odds Ratio
CI= Confidence Interval BMI: Body Mass Index
Testosterone deficiency: Low TT and/or low cFT

The whole study population and post-COVID group underwent binary logistic regression to determine the effect of several factors on testosterone deficiency. The strongest predictor of reporting testosterone deficiency was COVID-19 disease, with an odds ratio of 4.295 (P=0.034, 95% CI= 1.115, 16.548) (Table 3) and in the post-COVID group we observed moderate to severe COVID-19 disease was a statistically significant predictor of reporting testosterone deficiency [OR=9.950 (P = 0.017, 95% CI= 1.513, 65.454)] (Table 4), controlling for all other factors in both model.

Table 4: Binary logistic regression model predicting risk of testosterone deficiency in post-COVID group (N=48)

	OR	P	95% CI	
Age	1.067	0.157	0.976	1.166
BMI	1.042	0.855	0.671	1.617
Waist circumference	1.081	0.471	0.874	1.338
Moderate to severe COVID-19 disease	9.950	0.017	1.513	65.454

R2 = 26-38.5%
OR= Odds Ratio
CI= Confidence Interval
BMI: Body Mass Index
Testosterone deficiency: Low TT and/or low cFT

Discussion

So far, there have been many studies that have shown that SARS-CoV-2 infection in male leads to acute stage hypogonadism with statistically significant deficiency of testosterone and alteration of others reproductive hormone levels in men [16]. Testosterone deficiency has been associated to higher levels of pro-inflammatory cytokines, primarily IL-1, IL-6, and TNF, in both human and animal studies, which are crucial inflammatory mediators in SARS-CoV-2 pathogenesis [17]. The hypothalamic-pituitary-testicular (HPT) axis can, however, be inhibited by an acute, serious inflammatory state, as in the case of COVID-19. However, the majority of these studies were carried out in patients during their acute illness, thus long-term effects are still unknown and require further research [18]. Our study revealed that the levels of both TT and cFT were significantly lower and the testosterone deficiency was significantly higher in post-COVID male patients compared to healthy controls. Nearly 25% of post-COVID patients had significiently low TT and cFT levels that were indicative of hypogonadism, compared to just 8.3% in the healthy control group. Hypogonadism in the post-COVID group was secondary in as many as 83.3% of the cases, whereas levels of low testosterone and high LH, FSH suggestive of primary hypogonadism were only 16.7%. After controlling for known confounders of low testosterone levels (Such as age, BMI, and WC), it is noteworthy that SARS-CoV-2 infection status emerged to be independently linked with lower TT and cFT levels and that is suggestive for hypogonadism. Men between the ages of 18 and 69 were recruited for our study, but the majority of participants were young, with 66.7% being under the age of 40. So these results also suggest that many patients, even young patients, tend to develop testosterone deficiency after the acute phase of COVID-19. Our findings are consistent with some recent research [19]. Our findings supported by a single-center study in Egypt found that recovered COVID-19 patients had lower testosterone-to-LH ratios, lower TT and cFT levels, and higher testosterone deficiency (50.9%) prevalence and mostly secondary hypogonadism (60.7%) [20]. Our study also demonstrated that sexual dysfunction including reduce sexual desire (Libido) and erectile dysfunction (33.3% vs. 14.6%) and testosterone deficiency with sexual dysfunction (16.7% vs. 2.1%) were significantly higher in post-COVID patients than in healthy individuals. Thus, impaired erectile function during and after recovery from COVID-19 disease also reported in some previous studies [21, 22]. In a recent report on a follow-up study including 153 males with COVID-19 disease found that ED prevalence was 50.3% at three months after recovery form acute COVID-19 pneumonia. We provide evidence that SARS-CoV-2 infection is significantly associated with testosterone deficiency and confirm, that testosterone levels correlates with COVID-19 severity. Additionally, the levels of both TT and cFT were significantly lower in men recovered from COVID-19 disease and who had the greatest need for hospitalization and ICU care as compared to those with less severe COVID-19 clinical severity at hospital admission. In our investigation, we discovered post-COVID participants were over four times more likely to report testosterone deficiency than matched control individuals. Testosterone deficiency was observed more frequently (41.7%) in those who were admitted to the hospital and given oxygen therapy, and subjects with moderate to severe COVID-19 disease were over approximately 10 times more likely to develop testosterone deficiency than those with mild disease. In agreement with our findings, a systematic review on the level of male sex hormones revealed that in patients with severe COVID-19 infection, the level of total testosterone decreased significantly, and men with lower levels of testosterone experienced more severe disease and mortality [13]. Similar to our findings, Dhindsa *et al*. explained that hospitalized patients with severe disease had lower testosterone levels than men with mild or moderate disease [10]. Zeggeren *et al*. observed that the level of total and free testosterone was considerably lower in patients with severe disease and in those who died from severe disease compared to survivors in a observational study, which is also consistent with our findings [12]. It is noted that there was no statistically significant difference in LH and FSH levels between the post-COVID and control groups. Both LH and FSH were within normal and low normal levels in all the participants except for two participants in the post-COVID group with high LH, FSH, and low testosterone levels, suggesting secondary hypogonadism. In contrast, in comparison to age-matched healthy controls, several studies on COVID-19 patients who were hospitalized revealed generally lower androgen levels with higher LH and FSH levels, primarily hypergonadotropic hypogonadism, suggesting a testicular origin [23, 24]. As mentioned earlier, in our study, a majority of the study participants with deficient testosterone had normal and low normal LH and FSH suggestive of hypogonadotropic hypogonadism, which is thought to result from hypothalamic or pituitary dysfunction. Therefore, we can surmise that this testosterone depletion could result from a condition known as acute functional hypopituitarism, which could occur after a direct (The virus) or indirect (The cytokine storm) impact on the hypothalamus or pituitary gland, even as a result of the complex SARS-CoV-2 neurotropism [25]. Similar to other severe infections, acute-stage hypogonadism in male COVID-19 patients may be explained by secondary immunological responses and oxidant-sensitive inflammatory pathways that disrupt the HPG axis and may result in an abrupt and significant decline in circulating testosterone. In addition to the role played by the hypothalamus in sex hormone alteration, the impact of mental

illnesses like stress and depression on sex hormones must also be taken into consideration [26]. Serum testosterone level may be negatively affected by some conditions sush as age, obesity, systemic disease and overall health status. Central obesity may have the primary relationship between COVID-19 and hypogonadism because it is considered a risk factor for both the severity of COVID-19 and testosterone deficiency [27]. In the post-COVID group, we observed a significant negative correlation of age with both TT and cFT, BMI with TT, and diastolic BP with cFT. In the matched control group, both TT and cFT were significantly and negatively correlated with BMI, waist circumference, and diastolic BP. After doing regression analysis, in addition to COVID-19 disease, central obesity estimated by waist circumference was found to be a significant predictor of low testosterone and no effect of age and BMI were observed to predict testosterone deficiency. The prevalence of low testosterone (25%) in post-COVID patients detected in our study is higher than what is stated for the general population. 4.1% of participants in the middle-aged and elderly males in the European Male Aging Study (Age range: 40 to 79 years; mean age: 59.7±0.3) had a TT level less than 8.0 nmol/L (2.3 ng/ml) and 17.0% had a TT level less than 11 nmol/L (3.2 ng/ml) (Wu *et al*., 2010). But estimates of the prevalence of possibly functional hypogonadism in middle-aged and older men range from 2.1% to 12.3% in the community [28]. Our study has some points of strength as it evaluates the impact of COVID-19 on male reproductive hormone levels after recovery from active disease and we found that, testosterone levels emerged to be inversely associated both SARS-CoV-2 infection and severity of COVID-19 disease. Our participants as control were matched according to age, WC and BMI, which are known to affect testosterone levels by a large number of studies. The literature's definition of hypogonadism, typically late-onset hypogonadism, may not perfectly fit the context of androgen level reduction acutely observed after SARS-CoV-2 infection. So The Endocrine Society's specified TT and cFT threshold criteria (i.e., TT 264 ng/dl) were arbitrarily applied in our study to conclude a case of hypogonadism.

Conclusion

COVID-19 may be a risk factor for testosterone deficiency in men, and the frequency of testosterone deficiency was observed in about 25% of post-COVID male patients. COVID-19 severity was the most significant predictor of testosterone deficiency in recovered COVID-19 patients. But any long-term negative impact on male reproductive system remains unexplored and requires longer follow-up to assess the persistent effects of COVID-19 on male reproductive hormone levels to draw a solid conclusion.

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Author's Contribution

Not available.

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