

## The Impact Of Post-COVID-19 Syndrome On Serum Sex Hormones And Sexual Functions In Males

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### KEYWORDS

post-COVID 19 syndrome, sexual dysfunction, testosterone, erectile dysfunction, hormonal imbalance.

### ABSTRACT

**Background:** COVID-19 has been associated with various long-term effects and multisystemic damage, including potential disruptions in endocrinal and sexual functions. This study investigated the impact of post-COVID-19 condition on serum sex hormones and sexual functions in male patients.

**Methods:** This hospital-based cross-sectional case-control study has been carried on 200 male participants and involved two groups: 100 men with post-COVID-19 syndrome and 100 healthy age-matched controls. Assessments included detailed medical histories, physical and genital examinations, body mass index (BMI), and questionnaires to evaluate sexual functions, including erectile dysfunction (ED), and premature ejaculation (PE). Also, Hormone levels of total testosterone (TT), free testosterone (FT), estradiol (E2), luteinizing hormone (LH), and prolactin (PRL) were measured and compared.

**Results:** The post-COVID-19 group exhibited significant reductions in TT, FT, and LH levels and increases in E2 and PRL compared to controls ( $p < 0.001$ ). Sexual dysfunction was notably higher among the post-COVID-19 group, with 28% reporting decreased sexual desire, 43% experiencing ED, and 10% experiencing PE, compared to minimal or no dysfunction in controls. Age, diabetes, and hypertension were significantly associated with decreased sexual desire and ED severity.

**Conclusion:** Post-COVID-19 condition appears to, significantly, impact serum sex hormone levels and sexual function in men, suggesting that hormonal imbalances may contribute to long-term sexual dysfunction in this population. These findings highlight the need for endocrinological and sexual health assessments in men recovering from COVID-19.

### Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to widespread health and socioeconomic impacts globally. While the majority of patients experience mild to moderate symptoms, a significant number suffer from severe cases, often requiring hospitalization and intensive care (Docherty et al., 2020). Studies have shown that male patients are at a higher risk of severe COVID-19 complications and mortality compared to females, possibly due to variations in immune response influenced by biological sex. In men, COVID-19 has also been linked to altered endocrine function, particularly affecting serum testosterone levels, which are critical for overall health and sexual function (Gebhard, et al., 2020).

Emerging evidence suggests that hormonal disturbances, specifically testosterone deficiency, may

contribute to the poorer prognosis observed in male COVID-19 patients (Çayan et al., 2020). This testosterone deficiency is thought to arise from inflammatory responses and alterations in cholesterol biosynthesis triggered by SARS-CoV-2 infection. Although some endocrine disturbances seem to improve post-recovery, there is a growing concern regarding the long-term effects of COVID-19 on hormone levels and sexual function in men (Lanser et al., 2021)

Post-COVID-19 syndrome, also known as long COVID, is characterized by persistent symptoms such as fatigue, shortness of breath, and cognitive impairments (Brodin et al., 2022). However, its impact on sexual health and hormone balance remains underexplored. Given the role of testosterone and other sex hormones in male health, understanding the relationship between post-COVID-19 syndrome and sexual dysfunction is crucial (Hebert et al., 2024).

This study aimed to investigate serum sex hormone levels in men with post-COVID-19 syndrome and evaluate their effects on sexual functions, providing insights into potential endocrine and sexual health implications in this population.

### **Patients and methods:**

#### **Sample size calculation:**

Calculating sample size for studying "Evaluation of serum sex hormones in male patients with post covid-19 condition and their impact on sexual functions", through Clin calc.com sample size calculator soft ware, at 5% alpha error (95.0% significance) and 20.0  $\beta$  error (80.0% power of the study), assuming the percentage of hypo-gonadism (decrease in testosterone) was 55% after 7 months post covid-19 patients (Salonia, et al., 2021) and expected to be 30% in persons not suffering from covid-19. The calculated sample size is 60 subjects in each group; we can add 20% for better collected data to reach 72 post covid-19 patients compared to 72 matched non covid-19 persons.

#### **Study Design and Participants:**

This hospital-based cross-sectional case-control study was carried out on 200 men recruited and involved two groups, Post-COVID-19 Group (100 men) who had previously been diagnosed with COVID-19 via PCR testing and were experiencing post-COVID-19 symptoms, following up at Mansoura University Hospital's post-COVID-19 outpatient clinic, compared to 100 healthy, age-matched COVID-19-negative men with no symptoms of chronic illness, recruited from the general public as a control group.

#### **Ethical approval:**

This research was carried out in accordance with the declaration of Helsinki for experiments involving humans. The institutional review board of Mansoura university approved the study protocol (MD.22.05.643). Also, all participants provided written informed consent.

#### **Inclusion and Exclusion Criteria:**

Inclusion criteria required male participants to be aged 18 or older, with a confirmed history of COVID-19 for the patient group. Exclusion criteria included patients with pre-existing chest diseases, known testosterone deficiencies, or those undergoing treatments known to affect hormonal levels. Control persons were selected from healthcare workers and patients' accompanying persons. Sampling was carried out by the non-probability purposive technique. Consecutive eligible men who followed both inclusion and exclusion criteria were included in this study.

#### **All participants provided informed consent and underwent a comprehensive assessment, including:**

1. Medical History: Detailed histories were taken, emphasizing past medical conditions, medications, and any symptoms of hypogonadism.

2. Physical Examination: General and genital examinations were conducted, and body mass index (BMI) was calculated.
3. Sexual Function Questionnaires:
  - A. International Index of Erectile Function (IIEF) for evaluating erectile dysfunction (ED), used to diagnose the presence and assess the ED severity. The severity of ED was described as mild, moderate or severe, where a score of 5–7 indicating severe, 8–11 moderate, 12–16 mild–moderate, 17–21 mild and 22–25 no ED (rosen et al., 1999).
  - B. Arabic Index of Premature Ejaculation (AIPE): The patients were evaluated with (AIPE) questionnaire. PE severity was classified into the following five categories based on AIPE scores; severe (7 – 13), moderate (14 – 19), mild to moderate (20 – 25), mild (26 – 30), and no PE (31 – 35) (Arafa and Shamloul, 2007).
4. Laboratory Investigations: PCR – COVID-19, CBC ( involving differential leucocytic count), CRP, Serum Ferritin, D-dimer, HBA1C, Serum creatinine, SGOT, SGPT and Serum cholesterol. Assessment of the following hormones: Serum levels of total testosterone (tT), free testosterone (fT), LH, estradiol (E2) and prolactin were assessed using the enzyme-linked immunosorbent assay (ELISA) method (Bioassay Technology Laboratory, Shanghai, China). Then, these derived parameters LH /tT, fT/tT and tT/E2 will be calculated. Blood samples will be collected between 7 a.m and 11 a.m (considering the circadian rhythm of testosterone release), after fasting at least 12 hours. Laboratory evidence of hypogonadism will be considered when total testosterone level is  $\leq 230$  ng/dl. Its level can be further classified into: reduced, when it is  $\leq 230$  ng/dl, borderline, when it is between 231 – 350 ng/dl and normal, when it is  $> 350$  ng /dl.
5. Radiological investigations: CT chest, Testicular ultrasound (U.S) and Pharmaco-Penile color Doppler U.S.

### Statistical analysis:

Data were revised, coded, and tabulated using IBM SPSS Statistics (version 25.0). Descriptive statistics, including mean, standard deviation, and median, were used to summarize continuous variables, while frequencies and percentages were used for categorical variables. Normality of data was assessed using the Kolmogorov-Smirnov test. For hypothesis testing, Student’s t-test and Mann-Whitney U test were applied to compare continuous variables between the two groups, depending on data distribution. Chi-square and Fisher’s exact tests were used to examine associations between categorical variables. Additionally, one-way ANOVA and Kruskal-Wallis tests were employed for comparisons involving more than two groups. Significance was set at  $p < 0.05$ , and all analyses were conducted at a 95% confidence level.

### Results:

The mean age of cases was 51.71 years, and 64% of them were immunized. While the BMI values for the patients were significantly higher than those for the control group, with a mean difference of 2.63 kg/m<sup>2</sup> ( $p < 0.05$ ). The difference in the distribution of smoking status between the two groups was statistically significant, where the patients had a significantly lower prevalence of smoking compared to the control group ( $p < 0.05$ ). While incidence of immunization did not differ significantly between cases and controls. Table (1)

**Table 1.** Comparison of demographics among the studied groups.

|                          | Patients<br>n = 100 | Control<br>n = 100 | Test        | P     |
|--------------------------|---------------------|--------------------|-------------|-------|
| Age (years)              |                     |                    |             |       |
| Mean $\pm$ SD.           | 51.71 $\pm$ 12.69   | 49.89 $\pm$ 13.63  | t=<br>0.977 | 0.330 |
| BMI (kg/m <sup>2</sup> ) |                     |                    |             |       |

|                   |              |              |           |         |
|-------------------|--------------|--------------|-----------|---------|
| Mean ± SD.        | 29.11 ± 5.38 | 26.48 ± 3.50 | t= 4.097  | <0.001* |
| Smoking (n%)      | 16(16%)      | 44(44%)      | X2=18.667 | <0.001* |
| Immunization (n%) | 64(64%)      | 71(71%)      | X2=1.117  | 0.291   |

SD: Standard deviation, t: Student t-test; X2, chi square test; P: Comparing control versus cases. \*: Significant

Based on Table 2, the most common comorbidities in the patient group were DM and hypertension, both present in 25% of patients. Metabolic syndrome was less common, seen in 15% of patients. Hyperthyroidism and prostatitis were notably absent in the patient group.

**Table 2.** Associated comorbidities among the patient group.

|                    | Patients<br>n = 100<br>No.(%) |
|--------------------|-------------------------------|
| DM                 | 25(25%)                       |
| Hypertension       | 25(25%)                       |
| Metabolic syndrome | 15(15%)                       |
| Hyperthyroidism    | 0(0%)                         |
| Prostatitis        | 0(0%)                         |

The prevalence of decreased sexual desire was significantly higher in the patient group compared to the control group (p<0.001). For erectile dysfunction (ED), 43 patients (43.0%) in the patient group had ED versus only 7 persons (7.0%) in the control group. This indicates that the prevalence of ED was significantly higher in the patient group compared to the control group (p=0.001).

For the severity of ED, in the patient group, the severity of ED ranged from mild to severe, with 12 patients (12.0%) had mild ED, 2 patients (2.0%) had mild to moderate ED, 14 patients (14.0%) had moderate ED, and 15 patients (15.0%) had severe ED. While in the control group, only 7 persons (7%) had mild ED. Regarding PE, none of the controls had PE, while 10% of patients had PE (p=0.001). Table (3)

**Table 3.** Comparison of the impaired sexual function among the studied groups.

|                         | Patients<br>n = 100<br>No.(%) | Control<br>n = 100<br>No.(%) | Test (X2) | P       |
|-------------------------|-------------------------------|------------------------------|-----------|---------|
| Decreased sexual desire | 28(28%)                       | 0(0%)                        | X2=32.558 | <0.001* |
| ED                      | 43(43%)                       | 7(7%)                        | X2=10.526 | 0.001*  |
| Mild                    | 12(12%)                       | 7(7%)                        | MC=13.280 | 0.001*  |
| Mild to moderate        | 2(2%)                         | 0(0%)                        |           |         |
| Moderate                | 14(14%)                       | 0(0%)                        |           |         |
| Severe                  | 15(15%)                       | 0(0%)                        |           |         |
| 2ry PE                  | 10(10%)                       | 0(0%)                        | X2=10.526 | 0.001*  |

PE, premature ejaculation; ED, erectile dysfunction; x2: Chi-Square, MC, Monte Carlo test, \*: Significant

The patient group had significantly lower levels of TT, FT and LH, and significantly higher levels of E2 and PRL, compared to the control group (p= 0.001 each). table (4)

**Table 4.** Comparison of hormonal levels between the studied groups.

|                      | Patients<br>n = 100   | Control<br>n = 100    | Test      | P       |
|----------------------|-----------------------|-----------------------|-----------|---------|
| <b>TT (ng/mL)</b>    |                       |                       |           |         |
| Median (Min. – Max.) | 4.50 (2.30 – 5.90)    | 5.60 (3.90 – 10.90)   | U= 1736.5 | <0.001* |
| <b>E2 (ng/dL)</b>    |                       |                       |           |         |
| Median (Min. – Max.) | 31.90 (14.80 – 49.00) | 23.50 (10.80 – 38.20) | U= 6997.5 | <0.001* |
| <b>PRL (ng/dL)</b>   |                       |                       |           |         |
| Median (Min. – Max.) | 4.70 (2.20 – 9.50)    | 3.50 (1.30 – 6.70)    | U= 7442.5 | <0.001* |
| <b>FT (nmol/L)</b>   |                       |                       |           |         |
| Mean ± SD.           | 24.03 ± 4.84          | 44.45 ± 7.78          | t= 22.273 | <0.001* |
| <b>LH (IU/mL)</b>    |                       |                       |           |         |
| Median (Min. – Max.) | 3.60 (2.00 – 6.30)    | 3.70 (2.40 – 7.90)    | U= 3693.0 | 0.001*  |

SD: Standard deviation, Min.: Minimum, Max.: Maximum, t: Student t-test, U: Mann-Whitney test, \*: Significant.

There were significant differences in the values of all three ratios between the two groups. Both FT/TT and TT/E2 ratios were significantly lower in the patient group versus the control group ( $p < 0.001$ ), while, the LH/TT ratio was significantly higher in the patient group versus the control group ( $p < 0.001$ ). table (5)

**Table 5.** Comparison of calculated hormonal ratios among the studied groups.

|                      | Patients<br>n = 100   | Control<br>n = 100    | Test      | P       |
|----------------------|-----------------------|-----------------------|-----------|---------|
| <b>FT/TT</b>         |                       |                       |           |         |
| Median (Min. – Max.) | 0.005 (0.002 – 0.012) | 0.008 (0.004 – 0.012) | U= 2648.0 | <0.001* |
| <b>LH/TT</b>         |                       |                       |           |         |
| Median (Min. – Max.) | 0.78 (0.36 – 2.35)    | 0.71 (0.26 – 1.20)    | U= 6556.5 | <0.001* |
| <b>TT/E2</b>         |                       |                       |           |         |
| Median (Min. – Max.) | 14.10 (6.09 – 29.40)  | 26.30 (10.90 – 63.20) | U= 1548.0 | <0.001* |

Min.: Minimum, Max.: Maximum, U: Mann-Whitney, \*p: Significant

Table (6) presents the association of laboratory parameters, with ED among the studied cases. Only total testosterone showed a statistically significant association where the median TT level is lower in cases with severe ED compared to those with mild to moderate or no ED ( $p = 0.042$ ). However, there was no statistically significant association between any of the other laboratory data levels with ED, as  $p > 0.05$  for each.

**Table (6):** Association of laboratory parameters with ED among studied cases.

|  |  | ED |                  |        | Test | P |
|--|--|----|------------------|--------|------|---|
|  |  | No | Mild or moderate | Severe |      |   |
|  |  |    |                  |        |      |   |

|                            | N=57         | N=28         | N=15        |         |        |
|----------------------------|--------------|--------------|-------------|---------|--------|
| <b>Cholesterol (mg/dL)</b> |              |              |             |         |        |
| Mean ± SD.                 | 134.16±34.41 | 138.64±32.15 | 154.2±34.38 | F=2.089 | 0.129  |
| <b>TT (ng/mL)</b>          |              |              |             |         |        |
| Median                     | 4.70         | 4.65         | 4.00        | H=6.344 | 0.042* |
| Min. – Max.                | 2.3-5.8      | 2.3-5.9      | 3.2-5.1     |         |        |
| <b>E2 (ng/dL)</b>          |              |              |             |         |        |
| Median                     | 33.00        | 28.80        | 36.00       | H=4.674 | 0.097  |
| (Min. – Max.)              | 15.2-49      | 14.8-45      | 16.2-44     |         |        |
| <b>PRL (ng/dL)</b>         |              |              |             |         |        |
| Median                     | 4.70         | 4.45         | 5.00        | H=0.881 | 0.644  |
| (Min. – Max.)              | 2.2-9.5      | 2.2-9        | 2.5-6.6     |         |        |
| <b>FT (nmol/L)</b>         |              |              |             |         |        |
| Mean ± SD.                 | 23.57±4.98   | 25.1±4.9     | 23.8±4.15   | F=0.958 | 0.387  |
| <b>LH (IU/mL)</b>          |              |              |             |         |        |
| Median                     | 3.40         | 3.80         | 3.20        | H=3.947 | 0.119  |
| (Min. – Max.)              | 2-5.9        | 2.7-5.8      | 2.9-6.3     |         |        |

SD: Standard deviation, Min.: Minimum, Max.: Maximum, F: ANOVA test; H, Kruskal Wallis test. \*: Significant p<0.05.

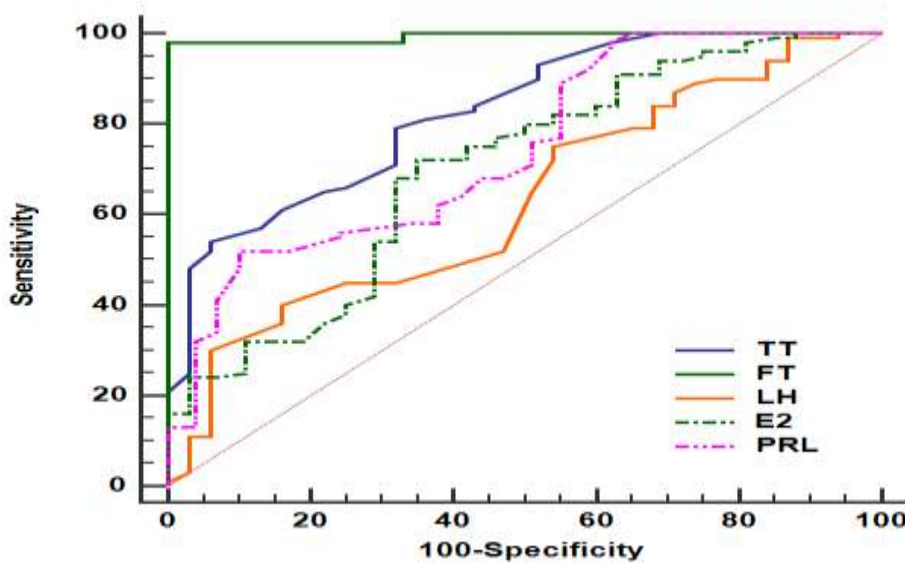
Receiver operating characteristic (ROC) curve of TT, FT, LH, E2, PRL, FT/TT, LH/TT, and TT/E2 levels was conducted for discrimination between POST-COVID 19 cases and healthy subjects. FT showed the highest accuracy AUC. TT, E2, FT/TT, TT/E2 showed moderate accuracy AUCs, while LH, LH/TT showed the lowest accuracy AUCs. Best cut off values and performance characteristics are shown in table (7).

**Table (7):** Validity of hormonal levels and ratios for discrimination between cases and controls using ROC curve

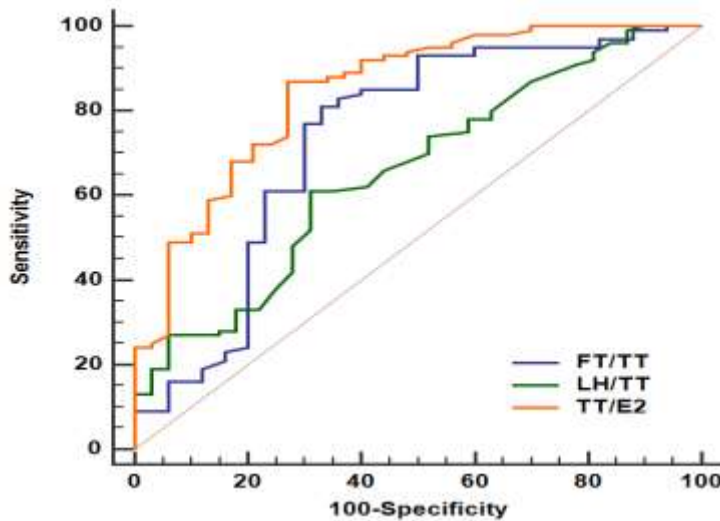
| AUC          | 95% CI        | p      | Cut off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|--------------|---------------|--------|---------|-----------------|-----------------|---------|---------|--------------|
| <b>TT</b>    |               |        |         |                 |                 |         |         |              |
| 0.826        | 0.767 - 0.876 | <0.001 | ≤5.1    | 71              | 68              | 68.9    | 70.1    | 69.5         |
| <b>FT</b>    |               |        |         |                 |                 |         |         |              |
| 0.993        | 0.970 - 1.000 | <0.001 | ≤31.9   | 98              | 100             | 100.0   | 98.0    | 99.0         |
| <b>LH</b>    |               |        |         |                 |                 |         |         |              |
| 0.631        | 0.560 - 0.698 | 0.001  | ≤3.6    | 52              | 53              | 52.5    | 52.5    | 52.5         |
| <b>E2</b>    |               |        |         |                 |                 |         |         |              |
| 0.700        | 0.631 - 0.762 | <0.001 | >28     | 68              | 68              | 68      | 68      | 68           |
| <b>PRL</b>   |               |        |         |                 |                 |         |         |              |
| 0.744        | 0.678 - 0.803 | <0.001 | >3.8    | 62              | 62              | 62      | 62      | 62           |
| <b>FT/TT</b> |               |        |         |                 |                 |         |         |              |
| 0.735        | 0.668 - 0.795 | <0.001 | ≤0.0064 | 77              | 70              | 72.0    | 75.3    | 73.5         |

|       |               |        |       |       |    |      |      |      |
|-------|---------------|--------|-------|-------|----|------|------|------|
|       |               |        |       | LH/TT |    |      |      |      |
| 0.656 | 0.585 - 0.721 | <0.001 | >0.74 | 61    | 69 | 66.3 | 63.9 | 65.0 |
|       |               |        |       | TT/E2 |    |      |      |      |
| 0.845 | 0.787 - 0.892 | <0.001 | ≤16.5 | 74    | 73 | 73.3 | 73.7 | 73.5 |

AUC: Area under the curve; CI: Confidence interval, PPV, positive predictive value; NPV, negative predictive value. \*: P value Significant <0.05



**Figure 1 1.** ROC Curve of hormonal levels for discrimination between post-COVID 19 cases and control groups.



**Figure 22.** ROC Curve of hormonal ratios for discrimination between COVID 19 cases and control groups. ordinal regression analysis was conducted for prediction of ED severity among post-COVID 19 cases, , using age, BMI, cholesterol, TT, FT, LH, E2, PRL, FT/TT, LH/TT, and TT/E2 as confounders. Only older

age was considered as predictor of more severe ED among post-COVID 19 cases. Table (8)

**Table (8):** Ordinal regression analysis for prediction of ED severity among post-COVID 19 cases.

|             | P       | OR    | 95% C.I |       |
|-------------|---------|-------|---------|-------|
| Age         | <0.001* | 1.081 | 1.047   | 1.116 |
| BMI         | 0.169   | 1.041 | 0.997   | 1.088 |
| Cholesterol | 0.160   | 1.007 | 0.998   | 1.014 |
| TT          | 0.146   | 0.835 | 0.654   | 1.065 |
| FT          | 0.465   | 1.018 | 0.970   | 1.070 |
| LH          | 0.882   | 0.980 | 0.753   | 1.276 |
| E2          | 0.160   | 0.980 | 0.953   | 1.008 |
| PRL         | 0.263   | 0.929 | 0.818   | 1.057 |
| FT/TT       | 0.181   | 1.243 | 0.002   | 5.516 |
| LH/TT       | 0.748   | 1.113 | 0.580   | 2.136 |
| TT/E2       | 0.801   | 1.006 | 0.961   | 1.053 |

OR: Odd Ratio; CI, confidence interval. \*: Significant <0.05

### Discussion:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) is a systemic disease, affecting respiratory, cardiovascular, gastrointestinal, neurologic and urogenital systems. It may mainly cause acute respiratory distress syndrome, leading to relatively high risk of death (Paoli et al, 2023).

Epidemiological data have identified male gender as a risk factor for more severe COVID-19 and increased mortality. This inequality is likely due to mixture of behavioral/ lifestyle patterns, gender-specific incidence of comorbidities, aging and intrinsic biological differences between the sexes either on hormonal (i.e., the different effects of testosterone, estrogens or progesterone) or genetical basis (Chaturvedi et al, 2022).

The current study aimed to investigate serum sex hormones in male patients with post COVID-19 condition and their impact on sexual functions in these patients. The study included 100 males with post COVID-19 syndrome versus 100 age-matched healthy controls.

In the present study, the mean age of cases was 51.71 years, and 64% of them were immunised, in addition to 100 healthy control subjects, matched regarding age and immunization ( $P>0.05$ ). While the BMI values for the patients were significantly higher than those for the control group, with a mean difference of 2.63 kg/m<sup>2</sup>. The difference in the distribution of smoking status between the two groups was statistically significant, where the patients had a significantly lower prevalence of smoking compared to the control group.

In the current study, the most common comorbidities in the patient group were DM and hypertension, both present in 25% of patients. Metabolic syndrome was less common, seen in 15% of patients.

In disagreement with our results, Al-Kuraishy et al, (2023) study evaluated 39 patients with ED and 20 healthy controls 3 months after recovering from mild-to-moderate COVID-19 pneumonia. They found non- statistically significant differences between patient group and control group as regarding BMI and smoking ( $P>0.05$ ). The most common comorbidity in the patient group was hypertension, in (23.07%) of patients.

Interestingly, the current study showed that (28.0%) of patients had decreased sexual desire versus none of the control group. This indicates that the prevalence of decreased sexual desire was significantly higher in the patient group compared to the control group ( $p<0.001$ ). In agreement with our study, (Harirugsakul et al., 2022) informed that stress and anxiety associated with COVID-19, along with the

physical toll of the illness itself, can significantly lower sexual desire. The virus can cause inflammation and blood vessel damage, potentially leading to erectile dysfunction (ED) and decreased libido.

For erectile dysfunction, (43.0%) of patients had ED versus only (7.0%) of controls. This indicates that the prevalence of ED was significantly higher in the patient group compared to the control group ( $p=0.001$ ).

Also, the current study showed that, as regard the severity of ED, 12 patients (12.0%) had mild ED, 2 patients (2.0%) had mild to moderate ED, 14 patients (14.0%) had moderate ED, and 15 patients (15.0%) had severe ED. While, in the control group, only 7 persons (7%) had mild ED. Regarding premature ejaculation, none of the controls had PE, while 10% of patients had 2ry PE ( $p=0.001$ ).

In agreement with our results, Harirugsakul et al., (2022) highlighted that 37.7% of recovered patients experienced at least one symptom of long COVID, with ED being a notable concern.

Many other Studies indicated a significant link between COVID-19 and erectile dysfunction (ED). Various studies have reported that men who have recovered from COVID-19 show a higher prevalence of ED compared to those who have not had the virus. For instance, a systematic review and meta-analysis found that COVID-19 patients had a 33% prevalence of ED, compared to 0.4% in control groups without COVID-19 (Zhang et al., 2023).

Erectile dysfunction in post-covid 19 patients has a complicated etiology and not simply attributable to low testosterone serum levels, as endothelial dysfunction, oxidative stress, pro-inflammatory cytokine hyper-activation, and high Ang II serum levels are also interrelated in the onset of ED. Additionally, the psychological impact of the pandemic, including stress and anxiety, can contribute to ED (Kalyanaraman, 2020).

Notably, the autonomic nervous system is crucial for the regulation of male erection and ejaculation, and autonomic dysfunction is associated with the development of ED (Karupasamy and Karthick, 2018). Interestingly, different studies have revealed that post-COVID-19 patients experience dysautonomic features because auto-antibodies against muscarinic receptors and  $\beta$  adrenoceptors have developed (Johansson et al, 2021).

A systematic review and meta-analysis on the effects of COVID-19 on sexual functioning, performed by (Masoudi et al., 2022) found that the pandemic has negatively impacted sexual behavior and functioning, including increased reports of PE among affected males. The psychological stress, anxiety, and depression induced by the pandemic contribute to sexual performance issues, including PE. The physical impacts of COVID-19, such as vascular damage and inflammation, also play a role in exacerbating these conditions.

Regarding the laboratory findings, the current study showed no significant difference between the patient group and the control group regarding cholesterol. ( $p=0.427$ ). However, the patient group had significantly lower levels of TT, FT and LH, and significantly higher levels of E2 and PRL, compared to the control group ( $p=$  at least 0.001 each).

In agreement with our findings, Al-Kuraishy et al, (2023) study found that patients with ED have low TT and FT serum levels, and high LH serum levels compared with controls. Also, Okcelik (2021) confirmed that COVID-19 was associated with low TT serum levels due to suspected testicular injury induced by SARS-CoV-213. It has been shown that Leydig cells and seminiferous tubule damage due to severe SARS-CoV-2 infection may impede spermatogenesis (Li et al, 2020).

Also, In harmony with the above mentioned results, it was found that reduced testosterone levels have been reported in long COVID patients, highlighting the risk of persistent hypogonadism following infection (Moreno-Perez et al, 2022). This finding is highly relevant, not only because of the fundamental role of androgens in sexual response, but also because of the worse outcomes being reported in patients with lower testosterone levels (Rastrelli et al, 2021).

The current study found significant differences in the values of all three calculated hormonal ratios between the patient group versus the control, where, Both FT/TT and TT/E2 ratios were significantly lower in the patient group versus the control group ( $p<0.001$ ), while, the LH/TT ratio was significantly higher in

the patient group versus the control group ( $p < 0.001$ ).

In agreement with our results, Infante et al., (2021) indicated that men with post-COVID-19 often exhibit hormonal imbalances, particularly involving testosterone and estradiol and reported lower total testosterone levels and a higher estradiol to testosterone ratio in men who had COVID-19. This study also observed that hospitalized men with COVID-19 had significantly reduced testosterone levels alongside elevated estradiol levels, which contributed to a hyperinflammatory state and higher mortality rates.

The FT/TT ratio was significantly lower in the post-COVID-19 group compared to controls. A reduced FT/TT ratio suggests a substantial drop in free testosterone levels, despite total testosterone levels that may sometimes appear within the lower-normal range. This finding supports the hypothesis that COVID-19 may specifically impact the bioavailability of testosterone, perhaps through increased binding of testosterone to sex hormone-binding globulin (SHBG) or through direct impairment of testicular function. Lower FT levels are closely associated with symptoms such as fatigue, reduced libido, and ED, and have been documented in previous studies investigating long-term COVID-19 effects (Infante et al., 2021). Lower bioavailable testosterone could directly contribute to the higher prevalence of sexual dysfunction observed in the post-COVID-19 group.

As regarding LH/TT ratio, The post-COVID-19 group showed an elevated LH/TT ratio compared to controls, which may indicate a compensatory response of the pituitary gland to low testosterone levels. An increased LH/TT ratio suggests that, despite heightened luteinizing hormone levels, testosterone production remains suboptimal, potentially due to testicular dysfunction induced by COVID-19-related inflammation or damage. Similar patterns have been documented in other studies, such as those by (Çayan et al., 2020) where elevated LH with low TT levels was observed in male COVID-19 patients, indicating possible impairment in the HPG axis. This compensatory elevation of LH suggests that the body attempts to stimulate testosterone production, but testicular response may be inadequate, particularly in post-COVID-19 patients.

Moreover, the current study investigated the association of clinical, laboratory and demographic characters with erectile dysfunction (ED) among the studied cases. Only the age showed a statistically significant association with severity of ED ( $p < 0.001$ ), where the older the age, the more severe is the ED. In addition, All the three comorbidities (DM, HTN and metabolic syndrome) showed statistically significant association with the severity of ED ( $p < 0.001$ , 0.01, 0.009 respectively).

In harmony with our results, (Sivitrepe et al, 2020) investigated the presence of ED after three months of hospital discharge for COVID-19 detecting a further worsening of IIEF scores compared to the scores at hospital admission, linking this worsening to IL-6 levels. However, Unfortunately, the recruited subject also had high glycemic levels, suggesting diabetes and cardiometabolic comorbidities as possible causes of ED in these patients.

There was a statistically significant association between presence of PE and severity of ED in the current study, as the proportion of participants with PE was higher among those with moderate ED and severe ED compared to those with no or mild ED ( $p = 0.020$ ). Only total testosterone showed a statistically significant association between its levels and severity of ED, where, the median TT level was lower for those with severe ED compared to those with mild to moderate ED ( $p = 0.042$ ).

Therefore, ED in post-covid 19 patients has a complicated etiology and not simply attributable to low testosterone serum levels alone, as endothelial dysfunction, oxidative stress, pro-inflammatory cytokine hyper-activation, and high Ang. II serum levels are also interrelated in the onset of ED (Kalyanaraman, 2020).

The current study, the ordinal regression analysis was conducted for prediction of ED severity among studied cases, using age, BMI, cholesterol, TT, FT, LH, E2, PRL, FT/TT, LH/TT, and TT/E2 as confounders. Only, older age was considered as predictor of more severe ED among studied cases.

However, This study was challenged by some limitations. Firstly, the patients were recruited from a single center and it was better if recruitment was done from multicenters. Secondly, The study design was cross-sectional, meaning it captures data at a single point in time. This limits the ability to establish causal

relationships between post-COVID syndrome and the observed health outcomes, especially regarding long-term sexual dysfunction and hormonal changes.

### **Conclusions:**

post-COVID-19 syndrome substantially impacts male sexual health, with a notably higher prevalence of sexual dysfunction, including decreased libido and erectile dysfunction (ED), compared to controls.

significant alterations in serum sex hormones among post-COVID-19 male patients. Lower levels of total testosterone (TT) and free testosterone (FT), coupled with higher estradiol (E2) and prolactin (PRL) levels, were observed, which could contribute to the observed sexual dysfunction.

Age and other comorbidities, particularly diabetes mellitus and hypertension, are associated with an increased risk of sexual dysfunction in post-COVID-19 patients. These factors seem to compound the effects of post-COVID-19 syndrome on sexual health.

### **Recommendations:**

#### **1. Routine Hormonal Monitoring**

Male patients recovering from COVID-19, especially those presenting with symptoms of post-COVID-19 syndrome, should undergo routine monitoring of serum sex hormones, including testosterone, estradiol, and prolactin, to detect any imbalances that may affect sexual health.

#### **2. Addressing Sexual Dysfunction in Clinical Practice**

Health practitioners should consider evaluating and managing sexual dysfunction, including decreased libido and erectile dysfunction, in male patients post-COVID-19. This may involve early screening and referral to specialists for appropriate interventions.

#### **3. Targeted Interventions for High-Risk Groups**

Patients with pre-existing conditions, such as diabetes, hypertension, and obesity, who are at increased risk for hormonal and sexual dysfunction, should be prioritized for follow-up and provided with targeted interventions to mitigate the effects of post-COVID-19 syndrome.

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