Received: 13 September 2021 | Revised: 7 October 2021 | Accepted: 10 October 2021

DOI: 10.1111/and.14285

ORIGINAL ARTICLE

First International Journal of Andrology ANDROLOGIA WILEY

The effect of interleukin-6 level at the time of hospitalisation on erectile functions in hospitalised patients with COVID-19

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Abstract

We evaluated the relationship between erectile dysfunction (ED) and IL-6 levels in males with COVID-19. The study included 80 male patients aged 30–45 years who were hospitalised due to COVID-19. The International Index of Erectile Function (IIEF-5) questionnaire was used to assess erectile function. The IIEF-5 questionnaire was re-administered at a 3-month control visit after discharge, and the change score from baseline was recorded. The patients were divided into three groups according to the IIEF-5 score at 3 months as Group 1 (severe ED), Group 2 (moderate ED) and Group 3 (no ED), and into two groups according to IL-6 level at the time of admission as Group A (IL-6 ≤ 50 ng/ml) and Group B (IL-6 > 50 ng/ml). The change in the IIEF-5 score ($p < .001$) was significantly greater in Group B than in Group A. There was also significant difference in IL-6 between Group 1 and Group 2 ($p = .008$). The correlation analysis revealed a moderate correlation between IL-6 level and the change in IIEF-5 score and D-dimer level (r:0.529, $p < .001$) and a weak correlation between IL-6 level and FSH (r:0.309, $p = .005$). The present study suggests that elevated IL-6 levels in male patients hospitalised due to COVID-19 might be related to the risk of developing ED.

KEYWORDS

COVID-19, erectile dysfunction, IIEF-5, interleukin-6

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) detected at Wuhan city, China, in 2019 that has later been declared a pandemic has been demonstrated to involve all body systems (Atzrodt et al., 2020). Hyperinflammation and immunosuppression are prominent features of COVID-19 (Contini et al., 2020). It was demonstrated that the virus causes endotheliitis and coagulopathy through the overactivation of vascular endothelial cells and the associated endothelial dysfunction (Atzrodt et al., 2020; Contini et al., 2020).

The studies have reported substantial increases in serum levels of cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1), interleukin-4 (IL-4) and tumour necrosis factor-α (TNF-α) as a result of endothelial activation and endothelial dysfunction in COVID-19 patients, and this phenomenon was called the cytokine storm syndrome (Hu et al., 2021). The studies have suggested a direct relationship between the cytokine storm and tissue damage (Mulchandani et al., 2021).

There are many factors implicated in the pathophysiology of erectile dysfunction (ED), which is defined as the inability to achieve or sustain an erection firm enough to have sexual intercourse. However, whatever the reason might be, the main problem is vascular impairment associated with endothelial dysfunction (Irwin, 2019). The studies have established a close relationship between ED and hypertension, dyslipidaemia, diabetes, obesity and neurological disorders (Corona et al., 2015).

To the best of our knowledge, there is no study in the literature evaluating the relationship between IL-6 levels and ED in male patients suffering from COVID-19. The present study hypothesised

that elevated levels of IL-6, a marker of endothelial dysfunction occurring in patients with COVID-19, could be a risk factor independent of other established risk factors. Therefore, the present study evaluates the possible relationship between ED caused by endothelial dysfunction and IL-6 levels serving as a marker of endothelial dysfunction in COVID-19 patients.

2 | MATERIAL AND METHOD

2.1 | Study design

The study was designed as a prospective study. The study was approved by the local ethics committee (Ethics Committee of University of Health Sciences Umraniye Education and Research Hospital Approval Date: 14.01.2021 Number: B.10.TKH.4.34.H.GP.0.01/19) and conducted as per the principles of the Declaration of Helsinki. Written informed consent was obtained from the study participants. For the power analysis, the study of Atar et al was got as reference (Atar et al., 2017). In that study, while the IL-6 level was 33.8 + 29.8 ng/ml in the ED (-) group, it was 56.9 + 26 ng/ml in the ED (+) group (Atar et al., 2017). The sample size was calculated as 25 per group, with the mean difference being approximately 26 units, the Type 1 error in the study was 0.05, and the power of the study was 80%. With a 20% loss, the sample size was calculated as minimum of 30 (total 60) patients per group should have been included in the study. 80 married male patients aged 30–45 years without a known chronic condition who were admitted to the pandemic clinic of our hospital due to COVID-19 (based on Polymerase Chain Reaction positivity) were included in the study. Patients aged below 30 and above 45 years, patients with diabetes mellitus, cardiovascular and neurological disease, acute or chronic infections other than COVID-19, patients with a history of major pelvic surgery, hyperprolactinaemia, malignancy, and those with a history of psychiatric disease were excluded from the study. Patients receiving androgen replacement therapy were also excluded. A detailed medical history was taken from the study participants, and all underwent a physical examination. Smoking status (current smoker, former smoker and never smoker) and alcohol consumption were recorded. Blood chemistry tests were done, and hormone levels were measured. The patients were administered the International Index of Erectile Function (IIEF-5) questionnaire. The patients were invited to attend control visits 3 months after discharge. In this process, patients were asked not to use drugs that increase sexual power. The IIEF-5 questionnaire was re-administered, and the change in the IIEF-5 score from baseline was recorded.

2.2 | Metabolic parameters

A 25-ml blood sample was withdrawn from a peripheral vein following an 8-hr fasting period to evaluate metabolic parameters. The blood samples were analysed simultaneously in the same laboratory. The laboratory tests included fasting plasma glucose, thyroid-stimulating hormone (TSH), luteinising hormone (LH), total testosterone, prolactin (PRL), follicle-stimulating hormone (FSH), sodium, potassium, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), C-reactive protein (CRP), complete blood count, D-dimer, fibrinogen and IL-6 levels.

Plasma glucose was analysed using an enzymatic assay; creatinine was determined by Jaffe's method; CRP was determined by immunoassay; blood urea nitrogen was determined by spectrophotometric method; sodium and potassium levels were determined by ion-selective electrode analysis method (ARCHITECT Plus Abbott). LH, total testosterone, TSH and PRL levels were determined by chemiluminescence immunoassay (Chiron Diagnostics ACS-180, USA). D-dimer was determined by an immunoturbidimetric assay using NETZSCH's STA 449 F3 analyzer. Complete blood count analysis was performed using Mindray BC6800 electrical impedance-based analysers. Serum IL-6 levels were determined by enzyme-linked immunoassay (ELISA) using human IL-6 test kits (Bender Med Systems GmbH). The interassay coefficient of variation for IL-6 was 4.7%, with a lower detection limit of 0.1 ng/ml and an upper detection limit of 5,000 ng/ml. The patients were divided into two groups according to IL-6 level as Group A (≤50 ng/ml) and Group B (>50 ng/ml).

2.3 | Evaluation of erectile dysfunction

The IIEF-5 questionnaire was administered to the patients to evaluate erectile function. The IIEF-5 questionnaire is a 5-item scale evaluating the erection confidence, penetration ability, hardness, maintenance ability and intercourse satisfaction on a scale of 1 to 5 points (Rosen et al., 1999). The patients were divided into three groups according to the IIEF-5 score at 3 months as Group 1 (5–10: severe ED), Group 2 (11–20: moderate ED) and Group 3 (21–25: no ED).

2.4 | Statistical analysis

Descriptive statistics (mean, standard deviation, minimum, median and maximum) were used for continuous variables. A Mann–Whitney U test was used to compare two independent variables without normal distribution. The Kruskal–Wallis test was used to compare more than two independent groups without normal distribution. A Mann–Whitney U test was used with Bonferroni correction for post hoc pairwise comparison of significant parameters. Spearman's correlation coefficient (Rho) was used to examine the correlation between two variables without normal distribution. The level of statistical significance was set at a p-value of less than .05. The MedCalc Statistical Software version 12.7.7 (MedCalc Software Bvba) was used in the statistical analysis.

3 | RESULTS

A total of 80 male patients diagnosed with COVID-19 with a mean age of 42 ± 3.9 years were recruited. The study was conducted on 75 patients, as three patients did not attend a 3-month control visit and two patients died after recruitment. The mean IIEF-5 score of the participating patients was 15.2 ± 5.6 at the time of hospitalisation and 14.2 ± 5.5 at 3 months; the mean IL-6 level was 87.3 ± 218.4 ng/ml at the time of hospitalisation. Demographic data and clinical and biochemical characteristics of the patients are presented in Table 1.

At the time of hospitalisation, 15 patients (18.75%) had severe ED, 45 patients (56.25%) had moderate ED, and the remaining 20 patients (25%) had no ED. At 3 months after discharge, 30.6% of the patients had severe ED, and 52% had moderate ED. IL-6 levels were above the upper limit (>50 ng/ml) in 34.6% of the patients. Of the patients, 42.5% were never smokers, 46.8% were current smokers, and 10.7% were former smokers. Of the patients, 82% were not using alcohol, and 18% were current drinkers.

A comparison was made between Group A (≤50 ng/ml) and Group B (>50 ng/ml), which were created according to IL-6 levels (Table 2). In the Mann–Whitney U test, the change in the IIEF-5 score was greater and the D-dimer levels were significantly higher in Group B than in Group A ($p < .01$ for both). Although the mean IIEF-5 score at 3 months was lower in Group B, the difference was not statistically significant between the two groups. There was no significant difference between the groups in terms of age, creatinine, CRP, haemoglobin level and neutrophil-to-lymphocyte ratio.

In correlation analysis between IL-6 levels and all other parameters, there was a moderate positive correlation between the change in IIEF-5 score and D-dimer levels and a weak positive correlation between IIEF-5 score and FSH levels. No correlation was found with other parameters (Table 3).

Then, the patients were divided into three groups according to the IIEF-5 score as Group 1, Group 2 and Group 3 (Table 4). The IIEF-5 score at the time of hospitalisation, IL-6, glucose and sodium levels was significantly different between the groups. In post hoc analysis of variance, there was a significant difference in IL-6 levels between the groups (Group 1–Group 2, $p = .008$; Group 1–Group 3, $p = .211$; and Group 2–Group 3, $p = .315$). According to Bonferroni correction, a p-value less than .0166 was considered statistically significant. Although statistically insignificant, the change in the IIEF-5 score and CRP values in Group 3 was lower, and D-dimer was higher in Group 1 than in the other groups. There was no significant difference in other parameters between the groups, including prolactin, testosterone, FSH and LH.

In the analysis of the correlation between the change in the IIEF-5 score and all other parameters, there was a moderate correlation between the IIEF-5 score and IL-6 (r: 0.529; $p < .001$) and D-dimer (r: 0.422; $p < .001$) levels. In binary logistic regression analysis, a 1-ng/mL increase in IL-6 level was associated with 1.923-fold decrease in the change of IIEF-5 score (Unstandardised$^{\beta}$: −0.814; standard deviation: 0.275; standardised$^{\beta}$: −0.220; t value: −2.956; level of significance, $p = .004$; VIF value: 1.089). The regression model for D-dimer was not significant and thus could not be interpreted ($p = .081$).

TABLE 1 Demographic data, and clinical and biochemical parameters of the patients

	Mean ± Standard Deviation	Median (minimum-maximum)
Age (year) $n = 80$	42 ± 3.9	44 (30–45)
IIEF−5 Score (On admission) $n = 80$	15.2 ± 5.6	14 (5–25)
IIEF−5 Score (At 3 Months) $n = 75$	14.2 ± 5.5	14 (6–24)
Change in IIEF−5 Score $n = 75$	1.2 ± 2.9	0 (−3–9)
Interleukin−6 (0–50 ng/ml) $n = 80$	87.3 ± 218.4	25 (0–1602)
D-dimer (0–550 μg/ml) $n = 80$	6.3 ± 11.9	1.4 (0–73)
Glucose (70–100 mg/dl) $n = 80$	201.1 ± 93	177 (78–557)
Sodium (135–145 mEq/L) $n = 80$	138.9 ± 2.8	139 (131–147)
Creatinine (<1 mg/dl) $n = 80$	0.9 ± 0.3	0.9 (0.7–3)
Aspartate Aminotransferase (15–50 IU/L) $n = 80$	21.3 ± 8	20 (10–63)
Prolactin (60–400 μIU/ml) $n = 80$	8.7 ± 6.1	6.6 (2.5–37.2)
Total testosterone (300–1.200 ng/dl) $n = 80$	455 ± 106	452 (305–1010)
C-reactive protein (<3 mg/L) $n = 80$	1.1 ± 1.2	0.7 (0.0–5.9)
Haemoglobin (12.4–14.8 g/L) $n = 80$	14.4 ± 1.4	14.5 (11.5–17.7)
Neutrophil (1.5–8.0 × 10^3/ul) $n = 80$	4.5 ± 1.3	4.4 (2.5–8.9)
Lymphocyte (1.2–5.2 × 10^3/ul) $n = 80$	2.7 ± 0.9	2.6 (1.2–5.6)
Neutrophil-to-Lymphocyte Ratio $n = 80$	1.9 ± 0.7	1.8 (0.5–3.7)
Potassium (3.5–5.5 mmol/L) $n = 80$	4.5 ± 0.4	4.5 (3.3–5.3)
Blood Urea Nitrogen (10–20 mg/dl) $n = 80$	34.3 ± 10.6	34 (11–71)
Alanine Aminotransferase (10–40 U/L) $n = 80$	28.4 ± 19.7	24 (4–140)
Follicle-Stimulating Hormone (1.3–19.3 mIU/m) $n = 80$	5.6 ± 3.7	4.5 (1.8–23.1)
Luteinising Hormone (1–9 IU/L) $n = 80$	4.5 ± 1.9	4.5 (0.3–12.8)

TABLE 2 Comparison of all parameters between Group A and Group B

	Group A (IL−6 ≤ 50 ng/ml)		Group B (IL−6 > 50 ng/ml)		
	Mean ± Standard Deviation (*N*)	Median (Minimum-Maximum)	Mean ± Standard Deviation (*N*)	Median (Minimum-Maximum)	*p**
Age (Year)	42.2 ± 3.6 (54)	44 (30–45)	41.5 ± 4.4 (26)	43 (30–45)	.552
IIEF−5 Score (On admission)	14.6 ± 5.4 (54)	14 (5–25)	16.5 ± 5.8 (26)	15 (6–25)	.151
IIEF−5 Score (At 3 Months)	14.5 ± 5.2 (52)	13.5 (6–24)	13.3 ± 6 (23)	14 (6–24)	.403
Change in IIEF−5 Score	−0.13 ± 1.0 (52)	0 (−3–2)	4.1 ± 3.8 (23)	5 (−1–9)	**<.001**
D-dimer (0–550 μg/ml)	2.2 ± 4.7 (54)	1.2 (0–32)	14.7 ± 17.1 (26)	12.5 (0.2–73)	**<.001**
Glucose (70–100 mg/dl)	194.22 ± 92.2 (54)	172 (78–420)	217.6 ± 94.4 (26)	203 (100–557)	.214
Sodium (135–145 mEq/L)	138.7 ± 3 (54)	139 (131–144)	139.5 ± 2.3 (26)	140 (135–147)	.288
Creatinine (<1 mg/dl)	1.0 ± 0.3 (54)	0.9 (0.7–3)	0.9 ± 0.2 (26)	0.9 (0.7–1.6)	.055
Aspartate Aminotransferase (15–50 IU/L)	21.4 ± 8.4 (54)	20 (12–63)	20.9 ± 7.2 (26)	19.5 (10–43)	.971
Prolactin (60–400 μIU/ml)	8.5 ± 5.7 (54)	6.8 (2.5–37.2)	8.9 ± 6.9 (26)	6.4 (2.6–36.4)	1
Total testosterone (300–1.200 ng/dl) $n = 80$	456 ± 109 (54)	452 (305–1010)	454 ± 109 (26)	452 (312–663)	.762
C-reactive protein (<3 mg/L)	1.2 ± 1.4 (54)	0.8 (0–5.9)	1.0 ± 1.0 (26)	0.7 (0.1–3.6)	.559
Haemoglobin (12.4–14.8 g/L)	14.5 ± 1.3 (54)	14.6 (11.7–17.7)	14.2 ± 1.6 (26)	14.3 (11.5–17.7)	.306
Neutrophil (1.5–8.0 × 10^3/ul)	4.5 ± 1.3 (54)	4.2 (2.5–7.8)	4.6 ± 1.4 (26)	4.5 (2.5–8.9)	.797
Lymphocyte (1.2–5.2 × 10^3/ul)	2.7 ± 0.9 (54)	2.6 (1.2–5.2)	2.6 ± 1.0 (26)	2.5 (1.2–5.6)	.447
Neutrophil-to-Lymphocyte Ratio	1.8 ± 0.7 (54)	1.8 (0.5–3.5)	1.9 ± 0.8 (26)	1.8 (1.0–3.7)	.685
Potassium (3.5–5.5 mmol/L)	4.4 ± 0.4 (54)	4.5 (3.3–5.2)	4.5 ± 0.4 (26)	4.5 (3.6–5.3)	.828
Blood Urea Nitrogen (10–20 mg/dl)	34.1 ± 10.3 (54)	33.1 (11–62)	34.9 ± 11.3 (26)	34 (21–71)	.922
Alanine Aminotransferase (10–40 U/L)	29.6 ± 21.4 (54)	24 (4–140)	25.9 ± 15.6 (26)	24 (7–87)	.414
Follicle-Stimulating Hormone (1.3–19.3 mIU/m)	5.1 ± 2.8 (54)	4.1 (1.8–12.4)	6.8 ± 5 (26)	5 (2.4–23.1)	.138
Luteinising Hormone (1–9 IU/L)	4.4 ± 1.6 (54)	4.5 (1.0–8.1)	4.5 ± 2.6 (26)	4.3 (0.3–12.8)	.607

*Mann–Whitney U test.

†Statistically significant at $p \leq .05$.

A receiver operating characteristics (ROC) curve analysis was performed to determine the cut-off point for IL-6. The analysis determined a cut-off value of 14.2 ng/ml for IL-6 in detecting ED at 3 months, and the area under the curve (AUC) was statistically significant ($p < .01$). The AUC value (0.828) was considerably high (95% confidence interval: 0.737–0.919). The analysis revealed that a cut-off point of 14.2 ng/ml for IL-6 yielded a sensitivity of 77.8% and a specificity of 71.5% in detecting the risk of developing ED.

4 | DISCUSSION

The present study was conducted on young males without a chronic condition hospitalised due to COVID-19 and evaluated the possible relationship between ED and IL-6 levels, one of the biomarkers of disease prognosis. The study found that a significant relationship exists between IL-6 levels and IEFF-5 scores in this patient population. The study also found a decrease in erectile functions with increasing IL-6 levels on the admission of young male patients with COVID-19. The present study is valuable for being the first study in the literature on this subject.

COVID-19 has rapidly spread worldwide, and the pandemic situation has been declared with a crude mortality rate of 3% (Atzrodt et al., 2020). COVID-19 manifests itself with symptoms such as fever, myalgia, flu-like illness and mild pneumonia, while 15% of the patients suffer from severe pneumonia accompanied by respiratory failure, and 5% suffer from a severe disease manifesting as septic shock and multiple organ failure (Contini et al., 2020).

COVID-19 may cause cytokine storm, which is defined as increasing plasma concentrations of various cytokines triggered by an uncontrolled immune response, increased proliferation of immune system cells and overproduction of signal molecules (Hu et al., 2020; Mulchandani et al., 2021). The release of cytokines affects unfavourably all organ systems, particularly the lung tissue (Hu et al., 2021). The studies have reported elevated plasma levels of various cytokines in COVID-19, such as tumour necrosis factor-alpha (TNF-α),

TABLE 3 Analysis of correlation between IL-6 levels and all other parameters

	r*	p
IIEF−5 Score (On admission) $n = 80$	0.112	.321
IIEF−5 Score (At 3 Months) $n = 75$	−0.138	.238
Change in IIEF−5 Score $n = 75$	**0.529**	**<.001**
D-dimer (0–550 μg/ml) $n = 80$	**0.615**	**<.001**
Glucose (70–100 mg/dl) $n = 80$	0.102	.367
Sodium (135–145 mEq/L) $n = 80$	0.037	.746
Creatinine (<1 mg/dl) $n = 80$	−0.091	.42
Aspartate Aminotransferase (15–50 IU/L) $n = 80$	0.036	.754
Prolactin (60–400 μIU/ml) $n = 80$	0.033	.77
Total testosterone (300–1.200 ng/dl) $n = 80$	0.014	.98
C-reactive protein (<3 mg/L) $n = 80$	−0.039	.732
Haemoglobin (12.4–14.8 g/L) $n = 80$	−0.156	.168
Neutrophil (1.5–8.0 × 10^3/ul) $n = 80$	−0.05	.657
Lymphocyte (1.2–5.2 × 10^3/ul) $n = 80$	−0.039	.729
Neutrophil-to-Lymphocyte Ratio $n = 80$	−0.031	.786
Potassium (3.5–5.5 mmol/L) $n = 80$	−0.113	.317
Blood Urea Nitrogen (10–20 mg/dl) $n = 80$	0.089	.431
Alanine Aminotransferase (10–40 U/L) $n = 80$	−0.116	.308
Follicle-Stimulating Hormone (1.3–19.3 mIU/m) $n = 80$	**0.309**	**.005**
Luteinising Hormone (1–9 IU/L) $n = 80$	0.163	.148

*Spearman's Rank Correlation Coefficient (Rho).

†Statistically significant at $p \leq .05$.

interferon-γ, IL-2, IL-4 and IL-10 (Li et al., 2020). These cytokines may lead to multiple organ dysfunction and subsequently to death by increasing the risk of vascular hyperpermeability (Mulchandani et al., 2021).

IL-6 is one of the critical pro-inflammatory molecules involved in the cytokine storm (Coomes & Haghbayan, 2020). IL-6 has various biological actions, including the regulation of acute-phase response and the modulation of autoimmune disorders and the nervous system, but it also acts as a regenerative, anti-inflammatory and pro-inflammatory cytokine (Rose-John, 2018). Recent studies have shown that IL-6 levels are substantially elevated in patients with COVID-19 and that IL-6 levels could be used to predict organ dysfunction, morbidity, and mortality (Coomes & Haghbayan, 2020). IL-6 levels were found to be above the upper limit of normal (>50 ng/ml) in 34.6% of the patients included in the study.

A particular focus has been placed on endothelial dysfunction in COVID-19 (Nägele et al., 2020). Because postmortem examinations have found evidence of vascular dysfunction at various levels, including pulmonary embolism, alveolar haemorrhage, microangiopathy and vasculitis (Menter et al., 2020). The data deriving from the outbreak of severe acute respiratory syndrome virus that occurred at the beginning of the 2000s suggest that cardiovascular sequels such as microangiopathy, cardiomyopathy and endothelial dysfunction can also be expected in COVID-19 patients (Noor, 2021).

It is known that ED, defined as the inability to achieve or sustain an erection firm enough to have sexual intercourse, affects more than 150 million adult males in the world (Irwin, 2019). The main factor in the pathophysiology of ED is endothelial dysfunction characterised by inflammation, thrombosis and endothelial cell activation that is associated with atherosclerosis, smoking, hypertension, dyslipidaemia, diabetes mellitus, obesity and sedentary lifestyle (Corona et al., 2015). Despite these well-established mechanisms, many details related to the pathophysiology of ED remain controversial. It has been demonstrated that the COVID-19 pandemic itself affects sexual functions due to various reasons such as the isolation period, psychological pressure and anxiety disorder (Okpechi et al., 2021). However, the problem becomes worse in patients contracting COVID-19. Indeed, the mean IIEF-5 score was 15.2 at the time of hospital admission and decreased to 14.2 at 3 months. Although 20 patients did not have erectile dysfunction at the time of hospital admission, this number decreased to 13 at 3 months after the diagnosis of COVID-19.

The studies have reported that the markers of endothelial functions such as circulating vascular cell adhesion molecule-1, soluble intercellular adhesion molecule-1 and selectin are risk factors for ED (Bocchio et al., 2004). In addition to these findings, the present study also showed that IL-6, a marker of endothelial dysfunction in COVID-19, could serve as a marker for ED. The present study suggests that IL-6 used to indicate inflammatory response in COVID-19 could be used as a marker of ED in young males.

The significant relationship found between IL-6 levels and ED in the present study can be explained by several mechanisms. In the first possible mechanism, it is considered that IL-6 expressed by the Schwann cells generally protects the neurons and possesses neuroprotective effects by facilitating the regeneration of the damaged neurons (Hu et al., 2020). However, overexpression of IL-6 is known to inhibit axonal growth and thus acts negatively on the nervous system (Lacroix et al., 2002). This mechanism can be speculated to affect erectile function negatively in COVID-19 patients who have extensive vascular damage.

In the second possible mechanism, Varga et al. detected viral inclusion bodies in the peritubular interstitium and endothelial cells of glomerular capillary vessels in a pathological examination study of COVID-19 patients (Varga et al., 2020). Angiotensin-converting enzyme 2 (ACE2) is one of the critical viral entry sites for SARS-CoV-2 (Aleksova et al., 2021). It was demonstrated that endothelial cells possessing ACE2 receptors could be directly infected by SARS-CoV-2 (Aleksova et al., 2021). The authors consider that extensive vascular inflammation, hyperactivation, endothelial apoptosis and necrosis in endothelial cells can lead to endothelial dysfunction and subsequent ED. IL-6, which is known to indicate endothelial

TABLE 4 Comparison of parameters among Group 1, Group 2 and Group 3

	Group 1		Group 2		Group 3		
	Mean ± Standard Deviation (*N*:23)	Median (Minimum-Maximum)	Mean ± Standard Deviation (*N*:39)	Median (Minimum-Maximum)	Mean ± Standard Deviation (*N*:13)	Median (Minimum-Maximum)	*p**
Age (Year)	42.5 ± 3.7	44 (30–45)	42.1 ± 3.9	44 (30–45)	40.6 ± 4.6	41 (30–45)	.404
IIEF−5 Score (On admission)	10.2 ± 3.4	9 (5–16)	15.9 ± 4.3	14 (9–25)	22.8 ± 1.6	23 (20–25)	**<.001**
Change in IIEF−5 Score	2.3 ± 3.5	1 (−3–9)	0.9 ± 2.9	0 (−2–9)	0.1 ± 1.0	0 (−1–1)	.065
Interleukin−6 (0–50 ng/ml)	188 ± 380.9	40 (0.1–1602)	39 ± 60.1	18 (0.1–265)	38.5 ± 33.4	26 (1–96)	**.026**
D-dimer (0–550 µg/ml)	11.4 ± 19.1	2.4 (0.3–73)	3.3 ± 5.3	1.2 (0–19)	4.9 ± 8.8	1.6 (0–32)	.092
Glucose (70–100 mg/dl)	158.7 ± 72.8	131 (78–362)	222.2 ± 100.8	196 (108–557)	211.4 ± 93.5	206 (90–351)	**.026**
Sodium (135–145 mEq/L)	139.8 ± 2.5	140 (131–144)	138.3 ± 2.8	139 (132–144)	138.2 ± 2.2	138 (134–141)	**.036**
Creatinine (<1 mg/dl)	1.0 ± 0.5	0.9 (0.7–3.0)	0.9 ± 0.2	0.9 (0.7–1.8)	0.9 ± 0.2	0.9 (0.7–1.2)	.84
Aspartate Aminotransferase (15–50 IU/L)	18.7 ± 4.1	18 (10–28)	22.9 ± 9.9	20 (12–63)	21.2 ± 6.5	21 (10–31)	.279
Prolactin (60–400 µIU/ml)	8.9 ± 5.4	7 (3.6–20)	7.2 ± 3.3	6.3 (2.5–15.9)	10.1 ± 8.9	6.7 (3.3–37.2)	.587
Total testosterone (300 –1.200 ng/dl) $n = 80$	459 ± 108	454 (308–1010)	455 ± 108	452 (305–905)	450 ± 101	408 (106–508)	.473
C-reactive protein (<3 mg/L)	1.2 ± 1.3	0.8 (0.1–5.5)	1.2 ± 1.3	0.8 (0–5.9)	0.5 ± 0.6	0.2 (0.1–2.2)	.06
Haemoglobin (12.4–14.8 g/L)	14.2 ± 1.5	14.2 (12–17.7)	14.5 ± 1.5	14.5 (11.5–17.7)	14.1 ± 1.3	14.3(11.7–16)	.604
Neutrophil (1.5–8.0 × 10^3/ul)	4.5 ± 1.	4.2 (2.5–8.9)	4.4 ± 1.2	4.3 (2.5–7.7)	4.7 ± 1.4	4.7 (2.5–6.7)	.794
Lymphocyte (1.2–5.2 × 10^3/ul)	2.6 ± 0.9	2.6 (1.2–5.6)	2.6 ± 0.8	2.5 (1.3–4.6)	2.8 ± 1.2	2.7 (1.3–5.2)	.96
Neutrophil-to-Lymphocyte Ratio	1.9 ± 0.7	1.8 (0.9–3.5)	1.8 ± 0.6	1.7 (0.8–3.0)	2.0 ± 1.0	2 (0.5–3.7)	.827
Potassium (3.5–5.5 mmol/L)	4.6 ± 0.4	4.6 (3.8–5.3)	4.4 ± 0.3	4.4 (3.6–5.2)	4.4 ± 0.6	4.6 (3.3–5.3)	.099
Blood Urea Nitrogen (10–20 mg/dl)	36.5 ± 10.4	35 (24–64)	34.4 ± 10.6	32 (21–71)	30.8 ± 12.1	32 (11–56)	.395
Alanine Aminotransferase (10–40 U/L)	27.4 ± 17.3	23 (4–87)	30.2 ± 23.	24 (7–140)	25.2 ± 9.1	23 (11–49)	.825
Follicle-Stimulating Hormone (1.3–19.3 mIU/m)	6 ± 3.3	5.2 (2.5–14)	5.4 ± 3.4	4.2 (2.2–17.9)	4.6 ± 2.0	4.1 (1.8–9.8)	.504
Luteinising Hormone (1–9 IU/L)	4.8 ± 2.5	4.8 (0.3–12.8)	4.5 ± 1.8	4.4 (2–9.7)	3.7 ± 1.5	4 (1.0–5.8)	.298

*Kruskal–Wallis Test.

†Statistically significant at $p \leq .05$.

dysfunction and be directly related to cytokine storm, can also serve as a marker of ED.

On the other hand, adult Leydig cells have been demonstrated to express ACE2 in males (Wang & Xu, 2020). Therefore, it is likely that testicular damage occurs in patients with COVID-19. In fact, autopsy studies in post-COVID-19 patients have provided evidence for Leydig cell atrophy and associated decrease in testosterone and LH hormone levels along with oedema and inflammation in the testis interstitium (Yang et al., 2020). It has been suggested that the resulting hypogonadism might cause testicular dysfunction and thus ED (Yang et al., 2020). However, androgenic hormone levels of males in the present study were within the normal ranges and did not correlate with either IIEF-5 score or IL-6 levels. Therefore, the findings of the present study suggest that ED occurs in post-COVID-19 patients before Leydig cell damage and hypogonadism occur and that ED is related to IL-6, which is one of the main components of the cytokine storm.

Another possible mechanism may be capillary microthrombus formation resulting from cell swelling, disruption of intercellular junctions and basement membrane damage observed in pathological examination studies in patients with severe COVID-19 (Chen & Pan, 2021). If it is considered that similar microthrombi are formed in the penile vascular bed, ED occurs as an inevitable complication. The studies have reported a relationship between IL-6 and coagulopathy caused by endotheliitis in COVID-19, and this relationship indirectly supports the present findings. On the other hand, it is worth noting that these venous microthrombotic events are associated with high D-dimer levels in COVID-19 patients (Chen & Pan, 2021). In fact, one of the important findings in the present study was the significant correlation between the change in IIEF-5 score and D-dimer levels.

Endothelial, cardiovascular and metabolic disorders associated with ageing may lead to ED by causing both pituitary and penile hypoperfusion (Corona et al., 2015). However, another interesting point in the present study was that the study population was composed of young patients who did not have a chronic condition. This suggests that the primary cause of ED in the present study group was IL-6 which is associated with inflammation.

A study reporting on patients diagnosed with obstructive sleep apnoea syndrome has found that TNF-α, which is one of the inflammatory cytokines, can predict ED (Matos et al., 2013). The same study also evaluated the relationship between IL-6 levels and ED, but unlike our study, they reported no relationship (Matos et al., 2013). Another study involving diabetic patients had reported no effect of IL-6 on erectile function (Burnett et al., 2009). This discrepancy can be explained by the fact that both studies were conducted on patients with a chronic condition, and the mean IL-6 levels in the two studies were 3.5 ng/ml and 3.25 ng/ml, respectively (Burnett et al., 2009; Matos et al., 2013). The mean IL-6 level in the present study was 87.3 $\pm$ 218.4 ng/ml. The authors of the present manuscript consider that acute elevation of IL-6 to this high level may have caused further damage to the endothelium. ROC curve analysis conducted in the present study showed that a cut-off value of 14.2 ng/ml for IL-6 would predict the development of ED with a sensitivity of 77.8% and a specificity of 71.5%.

In regression analysis of IL-6 and IIEF-5 score at 3 months after COVID-19, a one ng/ml increase in IL-6 level at the time of admission caused a 1.92-fold decrease in the IIEF-5 score, and this finding supports that IL-6 is associated with an inflammatory response that can last up to 3 months. The duration of follow-up was 3 months in our study. Thus, it is difficult to suggest in which direction the degree of ED will change in the ensuing period; however, the present study shows that IL-6 negatively affects erectile function in a short period.

The present study has some limitations. The study was single centred and not designed as a large-scale, long-term cohort study. Therefore, a causal relationship between IL-6 and ED could not be established. Although the number of samples was determined by power analysis, the number of participants was small. Furthermore, IL-6 levels and androgenic hormone levels were evaluated at a single time point. In literature; ED severity is classified into five categories based on IIEF-5 scores: severe (5–7 points), moderate (8–11 points), mild to moderate (12–16 points), mild (17–21 points) and no ED (22–25 points). However, since the number of patients in our study was relatively small and when we divided these patients into five groups, the number of patients per group would be low, so we divided the patients into 3 groups. In addition, psychiatric evaluation of the patients was not performed after discharge. Mood during quarantine can affect sexual functions.

5 | CONCLUSION

The present study provides evidence that IL-6 levels can serve as a marker of ED in COVID-19 patients. The extensiveness of COVID-19 in the world and the fact that the disease will continue affecting many males in the long term make the significant relationship between IL-6 levels and the development of ED a critical finding. Future studies should investigate the utility of IL-6 antagonists in the treatment of ED associated with COVID-19.

ACKNOWLEDGEMENT

The authors would like to thank Sabri Atay MD for his support.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

RS, SUB, AB and EVK involved in conception and design. RS involved in data acquisition. RS, and SUB involved in data analysis and interpretation. RS and SUB drafted the manuscript. SUB and EVK critically revised the manuscript. AB involved in statistical analysis. SUB involved in supervision.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Sivritepe, R., Uçak Basat, S., Baygul, A., & Küçük, E. V. (2022). The effect of interleukin-6 level at the time of hospitalisation on erectile functions in hospitalised patients with COVID-19. *Andrologia*, 54, e14285. https://doi.org/10.1111/and.14285