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Sex-Specific Total Testosterone and Dehydroepiandrosterone Sulfate Status in Noncritically Ill Hospitalized Patients with Coronavirus Disease 2019: A Cross-Sectional Study

Hurjahan Banu, F.C.P.S.[1*], Md Shahed Morshed, M.D.[2], Nusrat Sultana, M.D.[1], Touhida Akter, M.B.B.S.[3], Muhammad Abul Hasanat, M.D.[1], Ahmed Abu Saleh, M.Phil.[4], Shohael Mahmud Arafat, F.C.P.S.[5]

1. Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
2. Kurmitola General Hospital, Dhaka, Bangladesh
3. Department of Medicine, Dhaka Medical College Hospital, Dhaka, Bangladesh
4. Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
5. Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Abstract

Background: In individuals with coronavirus disease 2019 (COVID-19), male subjects have consistently been linked to poor severity and prognosis. Data on sex hormones in non-critical COVID-19-infected patients are scarce. The aim of this study was to assess the status of total testosterone (TT) and dehydroepiandrosterone sulfate (DHEAS) among noncritical patients with COVID-19 according to sex and their associations with clinical and biochemical features.

Materials and Methods: This cross-sectional observational study was done in the COVID-19 unit of a University hospital during the period of September 2021 to February 2022 among 91 adults (18-65 years) with reverse transcriptase-polymerase chain reaction confirmed noncritical COVID-19 patients. Blood was drawn by venipuncture before receiving steroids between 07:00 to 09:00 a.m. in a fasting state to measure serum TT and DHEAS by chemiluminescent microparticle immunoassay. Diagnosis and classification of COVID-19 were done according to World Health Organization's interim guidance. Age- and sex-specific laboratory reference values were used to classify the TT and DHEAS status of the patients.

Results: Only three males (8.1%) had low TT and the rest had normal TT. On the other hand, 15 (27.8%) of the females had high TT with normal levels in the rest. Similarly, 11 (29.7%) males had low DHEAS. Females had low, normal, and high DHEAS in four (7.4%), 48 (88.9%), and two (3.7%) cases respectively. Males with moderate severity of COVID-19 had significantly lower DHEAS (post hoc P=0.038) than the mild group. Both TT (P=0.008) and DHEAS (P=0.023) significantly correlated with neutrophils/lymphocytes ratio and only DHEAS with platelets/lymphocytes ratio (P=0.044) in males. In females, TT significantly correlated with serum sodium (P=0.034).

Conclusion: In noncritical COVID-19 patients, substantial gender variations in TT and DHEAS were detected and correlated with severity markers in males.

Keywords: Androgen, Coronavirus Disease 2019, Dehydroepiandrosterone Sulfate, Noncritical, Testosterone

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Introduction

The global pandemic of coronavirus disease 2019 (COVID-19) has affected people all over the world. Several plausible causes, including immune system abnormalities, behavioral factors, and changes in sex hormones may be associated with an increased predilection for male sex for this respiratory virus (1). Evidence showed a higher prevalence of androgenic alopecia in hospitalized males with COVID-19 but a lower prevalence of the disease in prostate cancer patients on antiandrogen therapy. Similarly, women with polycystic ovary syndrome (a mild hyperandrogenic condition) are at increased risk of COVID-19 (2). These indicate a potential role of male sex hormones in the

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*Corresponding Address: Department of Endocrinology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
Email: hurjahanbanu.endo@bsmmu.edu.bd

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susceptibility to COVID-19. Sex hormones regulate different receptors and proteins such as androgen receptors, angiotensin-converting enzyme 2 (ACE2), and transmembrane serine protease 2 (TMPRSS2) that are related to the pathogenesis of COVID-19 (3). Targeting these sites may have therapeutic implications in COVID-19 that are currently being studied in antiandrogen like spironolactone (4). On the other hand, dehydroepiandrosterone (DHEA) may increase the susceptibility to COVID-19 by inhibiting glucose-6-phosphate dehydrogenase (5).

The causative organism, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes inflammatory and vascular changes in testes via ACE2 leading to Sertoli and Leydig cells' dysfunction with impaired hormonal function and fertility (6, 7). Also, Similar adrenal tropism was observed in autopsy cases (8).

Testosterone is the main androgen that is exclusively secreted from male testes with little contribution from the adrenals. However, in addition to synthesis from the ovaries, adrenal DHEA is a significant source of androgen in females. DHEA sulfate (DHEAS) is specific for adrenal glands (9). The levels of these hormones are expected to decrease in COVID-19 patients as the disease is more prevalent in older people who usually have many co-morbidities. However, controversial levels of TT levels are found in recovered patients. Whether low testosterone is a marker of disease severity or a permanent change of COVID-19 is still controversial. TT levels further deteriorated in hypogonadism patients with COVID-19 at admission and even after recovery from COVID-19 (10, 11). Moreover, most of the studies were done among critical patients ignoring the noncritical ones who are the main bulk of the patients and disease survivors. The aim of this study was to see the status of TT and DHEAS among noncritical patients with COVID-19 according to sex and their associations with clinical and biochemical features.

Materials and Methods

This cross-sectional study was done in the COVID-19 unit of a University Hospital during the period of September 2021 to February 2022. The institutional review board of the University approved the study protocol Bangabandhu Sheikh Mujib Medical University (No.BSMMU/2021/557). Informed written consent was taken from each participant.

Adults (18-65 years) with reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed noncritical COVID-19 patients exact test was done as appropriate. Spearman's correlation test was done to see the correlation of TT and DHEAS with different clinical and biochemical that were included after excluding the following criteria: critical COVID-19, known chronic disorders affecting androgen levels (hypogonadism, chronic liver disease, chronic kidney disease, malignancy, heart failure), history of COVID-19 vaccination, history of taking a steroid, testosterone within last three months and serum albumin <2.0 g/dL. For females-pregnancy and lactation, history of taking any hormonal contraceptives within the last three months or having significant hirsutism (modified Ferriman-Gallwey score ≥6), or known cases of any hyperandrogenic disorders were also excluded. History (socio-demographic and symptoms) and relevant physical examinations (height, weight, pulse, respiratory rate, oxygen saturation, and blood pressure) were taken. Initial investigations (complete blood count, electrolytes, C-reactive protein, and D-dimer) at admission were checked and all recorded in a semi-structured questionnaire. The median duration of COVID symptoms was 7 days (4-10 days). Blood was drawn by venipuncture before receiving steroids between 07:00 to 09:00 a.m. in a fasting state within 48 hours of admission to measure serum total testosterone (TT) and DHEAS by chemiluminescent microparticle immunoassay (Siemens, USA).

Diagnosis and classification of noncritical COVID-19 (mild, moderate, and severe) were done according to World Health Organization's interim guidance at admission (12). Age- and sex-specific laboratory reference values were used to classify the TT and DHEAS status of the patients (13).

Data were analyzed by SPSS software version 22.0 (Armonk, NY, IBM Corp). They were expressed in median (inter-quartile range, IQR) or frequency (%). There were some missing data and the available numbers were mentioned within third brackets. Associations between two groups were analyzed by the Mann-Whitney U test and more than two groups by Kruskal-Wallis one-way ANOVA with post hoc Dunn's test for quantitative values. For qualitative variables, Pearson's chi-square or Fisher's variables. Statistical significance was considered with a $P<0.05$.

Results

This study included 91 noncritical COVID-19 patients of whom 37 (40.7%) were males and 54 (59.3%) were females. Both study groups were statistically similar in clinical features and investigation profile except for body mass index (BMI, P=0.026) and neutrophil/lymphocyte ratio (NLR, P=0.046) which were significantly higher in males than females (Table 1).

Considering laboratory reference values, only three males (8.1%) had low TT with the rest of them having normal TT. On the other hand, 15 (27.8%) of the females had high TT with normal levels in the rest of them. Similarly, 11 (29.7%) males had low DHEAS. Females had low, normal, and high DHEAS in four (7.4%), 48 (88.9%), and two (3.7%) cases respectively (Table 2).

Comparison of different clinical and biochemical variables between the different TT and DHEAS statuses showed that males with low DHEAS were significantly younger than those with normal DHEAS (P=0.013). There were no statistically significant differences in any clinical and biochemical variables in females with normal and high TT (Table 3).

Table 1: Characteristics of the study population with respect to sex (n=91)

Variables	Males	Females	P value
Age (Y)	55.0 (31.50-63.0) [37]	50.0 (37.25-60.0) [54]	0.535
Co-morbidities			
Hypertension	15 (40.5)	26 (48.1)	0.525
Diabetes mellitus	16 (43.2)	21 (38.9)	0.828
OLD	6 (16.2)	7 (13.0)	0.763
Symptoms			
Fatigue	25 (67.6)	46 (85.2)	0.070
Cough	27 (73.0)	41 (75.9)	0.809
Fever	25 (67.6)	36 (66.7)	1.00
Dyspnea	21 (56.8)	33 (61.1)	0.828
Headache	10 (27.0)	26 (48.1)	0.052
Signs			
Pulse (bpm)	88.0 (77.0-101.0) [37]	88.0 (80.75-102.0) [54]	0.639
Resp. rate (pm)	14.0 (12.0-18.0) [36]	14.0 [12.0-15.0) [53]	0.527
Systolic BP (mm-Hg)	120.0 (110.0-132.75) [34]	120.0 (108.50-139.50) [49]	0.636
Diastolic BP	80.0 (70.0-84.25) [34]	79.0 (70.0-90.0) [49]	0.752
BMI (kg/m^2)	21.64 (20.32-25.44) [36]	24.44 (20.90-28.30) [52]	0.026
Severity of disease			
Mild	21 (56.8)	33 (61.1)	0.828
Moderate-severe	16 (43.2)	21 (38.9)	
Investigations			
TWBC ($\times10^3/\mu L$)	7.99 (6.50-12.09) [32]	9.65 (7.0-12.38) [45]	0.321
NLR	4.59 (2.82-9.80) [32]	3.0 (1.89-5.86) [45]	0.046
PLR	131.08 (94.84-226.22) [32]	127.57 (77.73-185.45) [45]	0.247
Na^+ (mmol/L)	135.0 (130.0-137.0) [23]	135.0 (131.25-136.75) [36]	0.851
K^+ (mmol/L)	4.0 (3.50-4.54) [23]	4.0 (3.80-4.42) [36]	0.613
CRP (mg/L)	33.67 (12.0-91.04) [26]	23.30 (7.1-71.74) [23]	0.203
D-dimer (mg/L)	0.52 (0.11-1.60) [23]	0.68 (0.28-3.98) [34]	0.187

Data were expressed in median (IQR) or frequency (%). Available no. of participants. Mann-Whitney U test or Pearson's chi-square test was done as appropriate. OLD; Obstructive lung disease, BP; Blood pressure, BMI; Body mass index, TWBC; Total white blood cell count, NLR; Neutrophil/lymphocyte ratio, PLR; Platelet/lymphocyte ratio, and CRP; C-reactive protein.

Table 2: Total testosterone and DHEAS status of the study population (n=91)

Age group (Y)	Males (n=37)					Females (n=54)				
	n (%)	Reference value (ng/dL)	Low	Normal	High	n (%)	Reference value (ng/dL)	Low	Normal	High
Total testosterone										
18-49 Y	15 (40.54)	270.0-1734.0	1 (2.7)	14 (37.84)	0 (0.0)	26 (48.15)	13.84-53.36	0 (0.0)	20 (37.04)	6 (11.11)
≥50 Y	22 (59.46)	212.0-755.0	2 (5.4)	20 (54.05)	0 (0.0)	28 (51.85)	12.40-35.76	0 (0.0)	19 (35.18)	9 (16.67)
Total	37		3 (8.1)	34 (91.89)	0 (0.0)	54		0 (0.0)	39 (72.22)	15 (27.78)
DHEAS		(µg/dL)					(µg/dL)			
18-20	3 (8.11)	24.0-537.0	0 (0.0)	3 (8.12)	0 (0.0)	2 (3.70)	51.0-321	1 (1.85)	1 (1.85)	0 (0.0)
21-30	5 (13.51)	85.0-690.0	3 (8.12)	2 (5.40)	0 (0.0)	9 (16.67)	18.0-391.0	0 (0.0)	9 (16.67)	0 (0.0)
31-40	4 (10.81)	106.0-464.0	3 (8.12)	1 (2.70)	0 (0.0)	6 (11.11)	23.0-266.0	1 (1.85)	5 (9.26)	0 (0.0)
41-50	4 (10.81)	70.0-495.0	2 (5.40)	2 (5.40)	0 (0.0)	12 (22.22)	19.0-231.0	2 (3.70)	10 (18.52)	0 (0.0)
51-60	11 (29.73)	38.0-313.0	3 (8.12)	8 (21.62)	0 (0.0)	15 (27.78)	8.0-188.0	0 (0.0)	13 (24.07)	2 (3.70)
61-70	10 (27.03)	24.0-244.0	0 (0.0)	10 (27.03)	0 (0.0)	10 (18.52)	12.0-133.0	0 (0.0)	10 (18.52)	0 (0.0)
Total	37		11 (29.73)	26 (70.27)	0 (0.0)	54		4 (7.41)	48 (88.89)	2 (3.70)

DHEAS; Dehydroepiandrosterone sulfate.

Table 3: Characteristics of COVID-19 male patients with DHEA-S status and female patients with TT status

Variables	Male			Female		
	Low DHEAS (n=11)	Normal DHEAS (n=26)	P value	Normal TT (n=39)	High TT (n=15)	P value
Age (Y)	38.0 (28.0-51.0) [11]	60.0 (42.50-64.0) [26]	0.013	48.0 (38.0-58.0) [39]	55.0 (27.0-60.0) [15]	0.923
Systolic BP (mm-Hg)	122.0 (110.0-126.25) [10]	120.0 (111.50 -143.25) [24]	0.642	120.0 (109.25-140.0) [34]	121.0 (101.0-136.0) [15]	0.803
Diastolic BP (mm-Hg)	81.0 (70.0-85.75) [10]	79.0 (70.0-84.75) [24]	0.381	79.50 (68.0-90.0) [34]	78.0 (71.0-85.0) [15]	0.939
BMI (kg/m^2)	21.77 (20.70-27.55) [11]	21.51 (18.89-24.25) [25]	0.161	24.97 (22.23-28.56) [39]	23.81 (20.16-26.44) [13]	0.228
Disease severity						
Mild	7 (63.6)	14 (53.8)	0.723	26 (66.7)	7 (46.7)	0.220
Moderate-severe	4 (36.4)	12 (46.2)		13 (33.3)	8 (53.3)	
Investigations						
TWBC	7.11 (4.98-9.0) [10]	9.06 (6.94-14.14) [22]	0.077	9.45 (6.63-13.53) [32]	9.65 (8.17-11.13) [13]	0.980
NLR	5.45 (2.09-7.81) [10]	3.46 (2.94-1047) [22]	0.920	3.56 (1.90-8.35) [32]	2.41 (1.66-3.26) [13]	0.157
PLR	146.65 (95.39-243.34) [10]	124.90 (93.04-235.40) [22]	0.675	133.59 (91.19-206.59) [32]	111.96 (64.48-130.54) [13]	0.130
Na^+ (mmol/L)	136.0 (130.0-136.0) [7]	134.0 (130.63-139.0) [16]	0.769	134.0 (131.0-136.25) [30]	136.0 (133.50-138.25) [6]	0.268
K^+ (mmol/L)	3.50 (3.10-4.0) [7]	4.0 (3.69-4.54) [16]	0.089	4.0 (3.80-4.53) [30]	3.95 (3.10-4.19) [6]	0.467
CRP (mg/L)	33.74 (15.45-157.18) [9]	28.0 (12.0-80.0) [17]	0.491	22.20 (7.09-59.68) [16]	24.0 (7.75-123.95) [7]	0.452
D-dimer (mg/L)	0.41 (0.10-3.41) [9]	0.66 (0.11-1.59) [14]	0.926	1.47 (0.39-4.67) [25]	0.33 (0.12-1.84) [9]	0.086

Data were expressed in median (IQR) or frequency (%). Available no. of participants. Mann-Whitney U test or Fisher's exact test was done as appropriate. TT; Total testosterone, BP; Blood pressure, TWBC; Total white blood cell count, BMI; Body mass index, NLR; Neutrophil/lymphocyte ratio, C-reactive protein, and PLR; Platelet/lymphocyte ratio.

Comparison of TT and DHEAS among the severity of illness showed that males with moderate severity of COVID-19 had significantly lower DHEAS (post hoc P=0.038) than the mild group. TT in both sexes and DHEAS in females were statistically similar across the spectrum of noncritical illness of COVID-19 (Table 4).

TT had a moderate negative correlation with age in both sexes (males: r=-0.50, P=0.001; females: r=-0.42, P=0.002). DHEAS had a significant negative correlation with age only in females (r=-0.31, P=0.025). DHEAS had a significant negative correlation with platelet/lymphocyte ratio (PLR) in males (r=-0.36, P=0.044) and TT had a positive significant correlation with serum sodium (Na^+) in females (r=0.36, P=0.034). TT had a significantly negative correlation with NLR (r=-0.46, P=0.008) but DHEAS had a significantly positive correlation with NLR (r=0.40, P=0.023) only in males (Table 5). TT significantly correlated with DHEAS in females (r=0.33, P=0.014).

Table 4: TT and DHEAS in COVID-19 patients with different severity (n= 91)

	Mild	Moderate	Severe	P value
Males (n= 37)	(n=21)	(n=11)	(n=5)	
TT (ng/dL)	391.0 (302.50-472.50)	299.0 (270.0-374.0)	279.50 (301.0-425.0)	0.132
DHEAS (µg/dL)	80.20 (50.85-90.50)	41.0 (34.0-65.0)	67.40 (40.25-97.50)	**0.045**
Females (n= 54)	(n=33)	(n=15)	(n=6)	
TT (ng/dL)	33.0 (25.50-49.55)	32.0 (24.0-48.20)	27.45 (22.05-36.25)	0.430
DHEAS (µg/dL)	49.0 (34.50-83.50)	51.50 (34.20-67.0)	41.75 (19.35-97.0)	0.764

Data were expressed in median (IQR). Kruskal Wallis one-way ANOVA with post hoc Dunn's test was done. TT; Total testosterone and DHEAS; Dehydroepiandrosterone sulfate. Bold indicates significant P.

Table 5: Correlations of TT and DHEA-S with different clinical and biochemical variables

Determinants of 'r'	Males					Females				
	Available no.	TT		DHEAS		Available no.	TT		DHEAS	
		r	P	r	P		r	P	r	P
Age (Y)	37	-0.504	**0.001**	-0.266	0.112	54	-0.419	**0.002**	-0.305	**0.025**
BMI (kg/m^2)	36	0.228	0.181	-0.139	0.419	52	-0.146	0.302	-0.016	0.910
Systolic BP	34	-0.201	0.255	-0.083	0.640	49	-0.231	0.110	-0.063	0.668
Diastolic BP		-0.075	0.674	-0.063	0.723		-0.090	0.538	0.126	0.388
TWBC	32	-0.095	0.604	0.117	0.522	45	-0.107	0.484	-0.134	0.381
NLR		-0.459	**0.008**	0.401	**0.023**		-0.216	0154	-0.175	0.250
PLR		-0.221	0.224	-0.358	**0.044**		-0.129	0.399	-0.095	0.534
Na^+ (mmol/L)	23	0.107	0.626	0.335	0.118	36	0.355	**0.034**	0.120	0.484
K^+ (mmol/L)		0.078	0.724	0.350	0.102		-0.267	0.115	-0.186	0.278
CRP (mg/L)	26	-0.102	0.620	-0.254	0.211	23	0.031	0.888	0.030	0.891
D-dimer (mg/L)	23	-0.393	0.063	-0.407	0.054	34	-0.105	0.553	-0.138	0.435

Bold indicates significant P. BMI; Body mass index, BP; Blood pressure, TWBC; Total white blood cell count, NLR; Neutrophil/lymphocyte ratio, and PLR; Platelet/lymphocyte ratio.

Discussion

In this study, we found that most of the noncritical COVID-19 patients had normal TT and DHEAS. While a few males had low TT, around 30% of females had high TT. About 30% of males had low DHEAS and 10% of females had abnormal (low/high) DHEAS. Males with moderate COVID-19 had lower DHEAS than mild COVID-19. TT had a negative correlation with age in both sexes; with NLR in males and serum Na+ in females. With DHEAS, females had a negative correlation with age but males had a significant correlation with NLR and PLR. TT positively correlated with DHEAS in females.

Most of the noncritical COVID-19 patients had normal TT irrespective of sex. We found only 8.1% of males had low TT. Salonia et al. (11) found 90% of cases of hypogonadism among 286 males, and 85% of patients with hypogonadism were secondary (hypothalamic-pituitary). However, most of their patients had severe to critical illness (~80%) that they used a lower cut-off of TT levels to define hypogonadism (<265 ng/dL). Among 89 COVID-19 patients with 53% of mild cases, Kadihasanoglu et al. (14) found 74.2% of males with hypogonadism (TT <300 ng/dL). So, the prevalence of hypogonadism depends on the severity of COVID-19 as well as the cut-off of TT. Similarly, we found a lower prevalence of low TT in males due to the inclusion of higher percentages of mild cases (~57%) as well as using a lower cut-off (<212 ng/dL). Involvement of the hypothalamic-pituitary-testicular axis at each level may be responsible for this low level of TT in males (15). In contrast to males, we found nearly 26% of females had high TT levels. Di Stasi et al. (16) also found higher TT levels in females with a positive association with inflammatory markers, as opposed to that found among males. So, low TT in males has a similar effect to high TT in females. However, estrogen plays a primary role in females providing better immunity than males. Due to an extra X chromosome as well as the anti-inflammatory effects of estrogen, females get advantages over males for the infectivity rate, severity, and mortality from COVID-19 (17). This benefit is lost after menopause. However, despite lower levels of TT older males suffer more than young ones because of less estrogen from aromatization as well as the inflammatory effects of different comorbidities (1, 17).

We observed a trend of lower TT with increasing severity of COVID-19 in both sexes without significant associations. Cinislioglu et al. (18) also found lower TT in moderate to severe cases than in mild cases of COVID-19. Beltrame et al. (13) found significantly lower TT levels in severe cases than in non -severe ones. An inverse association between severity and TT levels has been found in most of the studies (19, 20). TT levels were similar between asymptomatic and mild-moderate hospitalized symptomatic patients (21). Camici et al. (22) found lower TT in severe cases than in mild ones and similar levels of androstenedione, 5α-dihydroxy testosterone, and sex hormone-binding globulin between them. Thus, lower TT is a response to acute illness and may serve as a marker of the severity and prognosis of COVID-19. However, we did not find a significant association because of less severe cases of COVID-19 as well as a small number of participants in the severe group.

DHEAS levels were found significantly lower in males with moderate cases than in mild cases of noncritical illness of COVID-19. About 30% of males had low and 11% of females had abnormal DHEAS. Vaez Mahdavi et al. (23) found lower DHEAS in severe/critical patients than in moderate cases of COVID-19. Alzahrani et al. (24) found 75% of non-severe cases of COVID-19 with normal DHEAS (1.81 - 8.3 μmol/L) with only two cases with high and four cases with low DHEAS. Therefore, it seems that levels of DHEAS may decline with the severity of the illness.

A negative correlation between TT and age was found in both sexes and between DHEAS and age was found only in females. These indicate age-related as well as the

co-morbidity-accumulated decline of androgens along with the minor role of DHEAS in males (25).

We found a negative correlation between TT with NLR in males. Other authors found a negative correlation between TT with neutrophils and a positive correlation between lymphocytes in men with TT (20, 22). So, TT may be a reciprocal inflammatory marker in noncritical COVID-19 patients. A positive correlation between TT with serum Na+ in females may be explained by the role of testosterone in increasing renal reabsorption (26).

There were several limitations of our study. The small sample size especially the small number of severe patients was the main drawback. Besides, there were many missing data. We also could not measure luteinizing hormone, follicle-stimulating hormone, oestradiol, and sex-hormone binding globulin to further clarify the reproductive hormone status of COVID-19 patients.

Conclusion

There is considerable sex-specific differences in TT and DHEAS status in noncritical patients with COVID-19. Moreover, serum DHEAS is associated with the disease severity that both are correlated with inflammatory markers in males.

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Authors' Contributions

H.B., M.S.M., N.S., A.A.S., S.M.A.; Conceptualization, Methodology, and Software. M.A.H.; Validation. H.B., T.A.; Investigation and Data curation. H.B., M.S.M., N.S.; Formal analysis, Writing, Original draft preparation, and Visualization. M.A.H., A.A.S., S.M.A.; Supervision, Writing, Review, Editing, Project administration, and Funding acquisition. All authors read and approved the final manuscript.

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