Original Article

Role of Long-Acting Porcine Sequence ACTH (Acton Prolongatum) Stimulated Cortisol in Assessing Glucocorticoid Status in COVID-19 Patients

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Abstract

Introduction: Conflicting research on cortisol levels and COVID-19 mortality prompted this study to comprehensively assess glucocorticoid status, its links to severity and outcomes, and the role of Acton prolongatum-stimulated cortisol. **Methods:** This is a prospective observational study, conducted in 100 RT-PCR-positive COVID-19 patients of mild, moderate, and severe grades from June 2021 to May 2023. Random cortisol, plasma ACTH, and action prolongatum stimulated cortisol were measured, categorized, and analyzed. **Results:** Among 100 patients, 25 had severe disease, 35 had moderate disease, and 40 had mild disease. In the same study group, 88 recovered and 12 expired from the COVID-19-related cause. The median random basal serum cortisol level (median (IQR): 10.2 (8) vs. 11.6 (9.7) vs. 16.2 (9.5) mcg/dl; *P* value 0.06), median delta value (median (IQR): 6.3 (5.8) vs. 7.6 (4.8) vs. 10.9 (5.6) mcg/dl; *P* value < 0.001), and median plasma ACTH (median (IQR): 13 (14.7) vs. 14.4 (14.1) vs. 22.3 (13) pg/ml; *P* value = 0.002) were lower in severe group subjects than in the moderate and mild group. When patients were labeled as adrenal insufficiency based on random basal serum cortisol < 10 mcg/dl or delta value < 9 mcg/dl, 48% of patients had adrenal insufficiency. There was a linear correlation between random basal and ACTH-stimulated cortisol ($r = 0.908$, *P* value < 0.001). **Conclusion:** The study highlights the significance of adrenal function in COVID-19 prognosis and suggests for routine random cortisol and ACTH assessments for glucocorticoid evaluation.

Keywords: Acton prolongatum, adrenal insufficiency, cortisol, COVID-19

Introduction

Coronavirus disease 2019 (COVID-19) is a highly transmissible infection disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)—a positive-sense, single-strand, enveloped RNA virus belonging to the family of coronaviridae.[1,2] COVID-19 affects multiple systems, including the respiratory, cardiovascular, renal, endocrine, and central nervous system.[3] Despite extensive research, the determinants of severity and mortality during COVID-19 are still poorly understood.

The impact of COVID-19 on adrenal function has been a subject of significant interest and debate. Based on the available data many mechanisms have been proposed for adrenal suppression in COVID-19, e.g., (1) suppression of pituitary function due to inflammatory mediators, (2) direct damage to adrenal glands, and (3) antibodies against ACTH due to molecular mimicry.[4]

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Studies have presented conflicting findings regarding the correlation between cortisol levels and mortality in COVID-19 patients. Some studies have found that higher cortisol levels are associated with higher mortality rates in COVID-19 patients, while others have shown a greater prevalence and severity of hypocortisolism in those with severe COVID-19 disease.[5-7]

The Randomised Evaluation of COVID-19 therapy, RECOVERY trial provided important insights into the

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treatment of COVID-19, demonstrating the significant benefit of dexamethasone in reducing mortality among critically ill patients.[8] This beneficial effect of dexamethasone is linked to its action on alveolar–interstitial pulmonary lesions but possibly to a supplementation of the corticotropic axis with respect to severe infection.

The short synacthen test is one of the commonly used dynamic tests to assess the hypothalamic-pituitary-adrenal axis. Since synacthen is not marketed consistently in many countries including India, Acton prolongatum is used as an alternative option. Many studies have proved the safety and efficacy of injectable long-acting porcine sequence, ACTH 1-39 (Acton prolongatum), which is comparable to the standard synacthen (250 mcg) test.[9-11]

No study completely assessed the adrenal status involving basal cortisol, cosyntropin-stimulated cortisol, and ACTH. This study aims to complete an assessment of the glucocorticoid status, its correlation between severity and outcome, and the role of Acton prolongatum stimulated cortisol levels in COVID-19 patients.

Materials and Methods

This is a prospective observational study, conducted on 100 RT-PCR-positive COVID-19 patients of mild, moderate, and severe grades with clinical and radiological signs being admitted at tertiary referral health care center during the study period of June 2021 to May 2023. The sample size was determined based on a similar study by Alzahrani *et al.*,[12] using a 95% confidence interval ($Z = 1.96$), the prevalence of adrenal insufficiency ($P = 0.643$), and a 10% margin of error ($d = 0.1$), applying the formula: ($n = Z^2pq/d^2$). The minimum sample size calculated was 88. We chose to include 100 randomly selected patients attending our hospital.

The study included RT-PCR-positive COVID-19 patients with clinical and radiological signs who were admitted to Gandhi Medical College and Hospital. However, individuals with any hypothalamic–pituitary–adrenal axis disorders or those who had recent usage of corticosteroids were excluded from the study population.

Before enrolment, details about the nature and utility of the present study were explained to all patients and informed consent was taken. All the patients tested positive for COVID-19. Detailed history regarding symptoms, chronic illness, diabetes, hypertension, and drug usage were enquired. Verification of previous health records and referral documents from peripheral health centers, along with an inspection of all medications they brought with them, is conducted. All participants were subjected to detailed clinical examinations including vitals, anthropometry, and major systems examinations. Patients were categorized into mild, moderate, and severe based on guidelines from WHO.[13]

All subjects were attended on the day of admission. For mild cases, blood samples were collected for random basal cortisol, inflammatory markers, complete blood count, renal function test, liver function test, serum electrolytes, and HbA1c. The next morning, between 7-8 am, blood samples were taken for plasma ACTH, followed by an intramuscular injection of Actum prolongatum 0.4 ml (24 units), with serum cortisol samples collected an hour later. For moderate and severe cases, patients admitted late at night or early morning were attended in the emergency section, where blood samples were collected for random basal cortisol and other biochemical parameters. After being shifted to the wards, they were attended again around 7–8 am. Before administering any glucocorticoid, blood samples were collected for plasma ACTH, followed by an intramuscular injection of Actum prolongatum 0.4 ml (24 units), with serum cortisol samples collected an hour later. Care was taken not to delay any standard treatment for sampling purposes. Because of the lack of consistent availability of synacthen in India, we used the long-acting porcine sequence ACTH (Acton Prolongatum), which is a reliable and safe alternative.[9-11]

The serum was separated in a cold centrifuge and stored at -80° C for analysis at a later date. All the stored serum sample was analyzed within 1 month of acquiring samples. Serum cortisol was measured by CLIA method using Seimens Advia Centaur COR Assay Kits on Seimens Advia Centaur Autoanalyzer, with an assay range of 0.50–75 µg/dL (13.80–2096 nmol/L) and a coefficient of variation (CV) of 2.9–6%. Plasma ACTH was measured using the DRG ACTH ELISA kit (DRG International Inc, Germany), which is a two-site ELISA. The coefficient of variation for intra-assay and inter-assay precision was 2.27-6.715% and 6.9-7.1%, respectively, with an assay range of 0.22 pg/ml to 500 pg/ml. Serum TNF-alpha, IL-6, and PLASMA D dimer were measured using solid-phase sandwich ELISA kits. All estimations were done using the Thermofisher Varioskan LUX Multimode microplate reader at our department.

Patients were labeled as Adrenal insufficiency based on the Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017 Task Force guidelines, i.e., delta total serum cortisol of <9 µg/dL after adrenocorticotrophic hormone (250 µg) administration or random total cortisol of <10 µg/dL.[14]

Statistical analysis: Data were entered in MS Excel and analyzed in SPSS V25. Descriptive statistics were represented with percentages for qualitative data, mean with SD, or median with IQR for quantitative data. Shapiro–Wilk test was applied to find normality. The Chi-square test and Fisher Exact test were applied for comparison of proportions. Kruskal–Wallis test and Man–Whitney U test were applied for comparison among medians. Spearman correlation was calculated. $P < 0.05$ was considered as statistically significant.

Ethical aspects

Approval from the Institutional Ethics Committee (Approval number: IEC/GMC/2021/02/19; Approval date: July 19th, 2021) was taken before the conduct of the study. Written informed

consent was obtained for participation in the study and use of the patient data for research and educational purposes. The study procedures followed were by the ethical standards of the responsible committee and with the Helsinki Declaration of 1964, as revised in 2013.

Results

Baseline demographic and clinical characteristics

Among 100 patients, 25 had severe disease, 35 had moderate disease, and 40 had mild disease. In this same study group, 88 recovered and 12 expired from COVID-19-related causes. There was male predominance (65%). When compared between severity groups, none of the clinical parameters were significant, except for the SpO_2 (84.1 ± 4.5 vs. 91.2 ± 2.3 vs. 93.2 ± 1.3; *P* value < 0.001) and dose of the methylprednisolone given (54.4 ± 18.7 vs. 44.3 ± 25.2 vs. 31.6 ± 11; *P* value = 0.003) [Table 1].

Hematological and biochemical parameters

Various Hematological and biochemical parameters were analyzed between the groups [Table 2]. None of them had a significant correlation except for the serum urea (39.7 ± 19.3 vs. 29.4 ± 11.1 vs. 24.8 ± 12.4; *P* value = 0.025) and serum potassium (4.4 ± 0.5 vs. 4.4 ± 0.4 vs. 4.1 ± 0.5; *P* value = 0.029). Though there was a decreasing trend in serum albumin with severity (3.3 ± 0.5 vs. 3.5 ± 0.5 vs. 3.6 ± 0.5; *P* value = 0.029) and an increasing trend in HBA1c with severity (8 ± 2.3 vs. 7.4 ± 1.47 vs. 7 ± 1.5; *P* value = 0.029) but was not statistically significant.

Glucocorticoid status assessment

The parameters like random basal serum cortisol, ACTH stimulated cortisol, Delta value, and 8 am ACTH sample, which are indicative of glucocorticoid status were compared against the severity of the disease [Table 3].

The median random basal serum cortisol level (median (IQR): 10.2 (8) vs. 11.6 (9.7) vs. 16.2 (9.5) mcg/dl; *P* value 0.06), median delta value (median (IQR): 6.3 (5.8) vs. 7.6 (4.8) vs. 10.9 (5.6) mg/dl; *P* value < 0.001), and median plasma ACTH (median (IQR): 13 (14.7) vs. 14.4 (14.1) vs. 22.3 (13) pg/ml; *P* value = 0.002) were lower in severe group subjects than in the moderate group and mild group. None of the patients experienced any side effects from Inj Acton prolongatum.

Upon comparing the different outcome groups, the nonsurvivors had significantly lower levels of random basal serum cortisol (7.2 ± 3.5 vs. 15.4 ± 9; *P* value < 0.001), ACTH stimulated cortisol (14 ± 2.7 vs. 21.7 ± 10.2; *P* value = 0.015), Delta value (5.2 ± 1 vs. 8.8 ± 3.1; *P* value = 0.002), and 8 am ACTH (11.2 ± 9.6 vs. 22.8 ± 17.5; *P* value = 0.004) [Table 4].

When patients were labeled as adrenal insufficiency based on random basal serum cortisol <10 mcg/dl or delta value < 9 mcg/dl, 48% of patients had adrenal insufficiency. Importantly, the proportion of adrenal insufficiency patients in the severe group was higher than in the moderate and mild groups, which is statistically significant (*n* (%): 18 (72%) vs 21 (60%) vs 9 (22.5%), *P* value < 0.001).

In patients with adrenal insufficiency compared to those without, inflammatory markers D-dimer, s.ferritin, CRP, TNF-alpha, and IL-6 showed significantly elevated levels across all markers [Table 5].

In the analysis of adrenal insufficiency in different outcome groups, all the nonsurvivors (100%) had adrenal insufficiency in comparison to 40.9% of survivors.

The study identified a strong linear correlation between random basal and ACTH-stimulated cortisol (*r* = 0.908, *P* value < 0.001) [Figure 1].

Discussion

The present study was designed to assess complete glucocorticoid status assessment including ACTH and high-dose Acton prolongatum stimulation study.

In our study, we observed a decreasing trend in random basal serum cortisol levels and the delta value with increasing disease severity. A similar study by Alzahrani *et al.*[12] found that cortisol levels were at the lower end of the normal range or low in patients with COVID-19. In contrast, a study by Tan and colleagues reported higher median cortisol levels in COVID-19 patients, but the lack of concurrent ACTH and DHEAS levels and comparison with non-COVID patients limited the analysis of the entire axis integrity.[5]

In our study, the corresponding ACTH levels measured were also at the lower end of the normal range in severe subjects than in the moderate group and mild group, indicating that this was

Table 1: Demographic and clinical parameters according to severity of COVID-19. Values expressed as mean±SD

	Severe (*n*=25)	Moderate (*n*=35)	Mild (*n*=40)	*P*
Mean Age (year)	58.3±15.1	51.9±15.1	47.4±16.3	0.06
Percentage of males (%)	64%	60%	45%	--
BMI (kg/m^2)	26.5±5.1	25±4.1	26.5±4.7	0.35
Day of onset of symptoms	5.1±1.8	6.5±4.5	2.7±1.4	0.08
Dose of methylprednisolone (mg)	54.4±18.7	44.3±25.2	31.6±11	0.003
Pulse (beats/min)	105.5±9.7	102.4±8.9	97.7±24.2	0.339
Systolic BP mmHg	121.8±15.7	122.1±18.6	122.6±14.2	0.915
Diastolic BP mmHg	80.1±9.9	81.4±9.6	83.5±7.7	0.394
SpO_2 (%)	84.1±4.5	91.2±2.3	93.2±1.3	<0.001

because of secondary adrenal insufficiency. Similar findings were found in the study done by Alzahrani and Liza Das.[7,12]

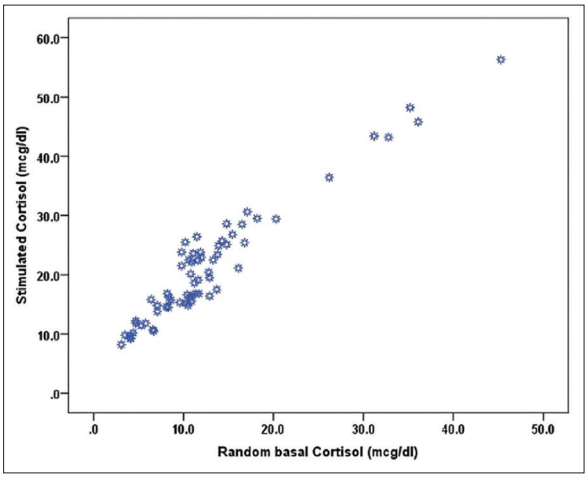

Figure 1: Correlation between random basal and ACTH-stimulated cortisol at the time of admission

Table 2: Hematological and biochemical parameters at the time of admission across different severity groups. Values expressed as mean±SD

	Severe (*n*=25)	Moderate (*n*=35)	Mild (*n*=40)	*P*
Hemoglobin (g/dl)	11.4±1.9	12.1±2.1	11.8±1.9	0.524
TLC (cell/mm^3)	10±4.3	7.9±3.2	8.6±2.3	0.651
Neutrophil (%)	74.1±7.2	70.5±8.2	71.9±7	0.322
Lymphocyte (%)	21±6.6	24±6.5	21.9±6.8	0.184
Eosinophil (%)	4±2.3	3.3±1.4	3.7±1.7	0.523
Platelets (lakh/mm^3)	3±1.1	2.6±1.1	2.7±0.9	0.307
Serum creatinine (mg/dl)	1±0.5	0.8±0.3	0.8±0.2	0.34
Blood Urea (mg/dl)	39.7±19.3	29.4±11.1	24.8±12.4	0.025
Sodium (mEq/L)	140.8±4.7	141.8±4.4	141.5±5.2	0.734
Pottassium (mEq/l)	4.4±0.5	4.4±0.4	4.1±0.5	0.029
HBA1c (%)	8±2.3	7.4±1.47	7±1.5	0.061
SGOT (IU/L)	48.4±30.4	41.5±19.3	45.8±19.3	0.175
ALP (IU/L)	81.8±54.8	68.1±23.2	71.9±28.5	0.755
Albumin (g/dl)	3.3±0.5	3.5±0.5	3.6±0.5	0.142

In our study, 48% of patients were identified as having adrenal insufficiency, characterized by random basal serum cortisol <10 mcg/dl or a delta value <9 mcg/dl. Alzahrani *et al.*[12] found that 30–50% of COVID-19 patients had cortisol levels less than 200 nmol/l (7.4 mcg/dl) when measured on multiple days. Mao *et al.*[6] observed that 66.6% of COVID-19 patients had cortisol means of <10 µg/dl, while half of the non-COVID-19 subjects had elevated cortisol levels. Leow *et al.*[15] reported that 40% of patients who recovered from the previous SARS infection had evidence of central adrenal insufficiency 3 months after recovery from their disease.

The study found that the proportion of adrenal insufficiency patients in the severe group was higher than in the moderate and mild groups, which is statistically significant (72% vs 60% vs 22.5%, *P* value < 0.001). Additionally, the adrenal insufficiency group had significantly higher levels of inflammatory markers, proving its association with the disease severity. Liza Das *et al.*[7] showed a prevalence of hypocortisolism of 38.5% in those with moderate-to-severe disease, whereas nearly 13.6% of patients had mild disease. In contrast, Kumar *et al.*[16] showed that adrenal insufficiency was present in 14% of patients, most of whom belonged to asymptomatic or mild categories (88%), and CIRCI in 18.3% of patients. However, they defined adrenal insufficiency with basal cortisol of <3 µg/dl or 1 h post-ACTH cortisol <18.0 µg/dl and delta cortisol of <9 µg/dl.

The prevalence of adrenal insufficiency was analyzed in different outcome groups, and it was found that all nonsurvivors had adrenal insufficiency compared to 40.9% of survivors. A study by Ahmadi *et al.*[17] also revealed that individuals with SARS-CoV-2 who had lower cortisol levels had a greater fatality rate, and cortisol levels that rose by one unit correlated with a 26% lower mortality risk. In contrast, Tan and colleagues found that doubling cortisol concentration was associated with a significant 42% increase in the hazard of mortality.[5] The study by Kumar *et al.*[16] had findings that were in contrast to the current study, with basal and post-ACTH cortisol levels being significantly higher among nonsurvivors. These conflicting results suggest that further research is needed

Table 3: Hormonal parameters indicatives of HPA status in different severity groups

Variable	Stage	Minimum	Maximum	Mean	SD	Median	IQR	*P*
Random basal Cortisol (mcg/dl)	Severe (*n*=25)	2.9	35.2	9.9	6.8	10.2	8.0	<0.001
	Moderate (*n*=35)	3.1	45.3	14.3	9.8	11.6	9.7	
	Mild (*n*=40)	4.1	38.4	17.3	8.2	16.2	9.5	
ACTH Stimulated Cortisol (mcg/dl)	Severe (*n*=21)	9.2	48.2	18.4	9.2	15.8	10.4	0.24
	Moderate (*n*=32)	8.2	56.3	22.8	12.2	19.1	13.8	
	Mild (*n*=38)	9.8	28.6	20.6	5.3	22.1	9.5	
Delta (mcg/dl)	Severe (*n*=21)	3.80	13.50	7.4	3.3	6.3	5.8	0.019
	Moderate (*n*=32)	3.50	12.20	8.0	2.6	7.6	4.8	
	Mild (*n*=38)	5.70	15.30	10.2	3.2	10.9	5.6	
ACTH (pg/ml)	Severe (*n*=22)	2.8	36.1	15.0	10.1	13.0	14.7	0.002
	Moderate (*n*=30)	4.1	81.6	19.7	16.6	14.4	14.1	
	Mild (*n*=36)	6.8	125.6	26.7	19.3	22.3	13.0	

Table 4: Hormonal parameters indicatives of HPA status in different outcome groups

Variable	Outcome	Minimum	Maximum	Mean	SD	Median	IQR	*P*
Random basal Cortisol (mcg/dl)	Death (*n*=12)	2.9	13.7	7.2	3.5	6.5	6.5	<0.001
	Recovered (*n*=88)	3.1	45.3	15.4	9.0	12.9	8.9	
Stimulated Cortisol (mcg/dl)	Death (*n*=8)	9.2	17.5	14.0	2.7	14.8	3.7	0.015
	Recovered (*n*=83)	8.2	56.3	21.7	10.2	20.4	10.3	
Delta (mcg/dl)	Death (*n*=8)	3.80	6.70	5.2	1.0	5.0	1.7	0.002
	Recovered (*n*=83)	3.50	15.30	8.8	3.1	8.6	5.2	
ACTH (pg/ml)	Death (*n*=9)	3.8	33.8	11.2	9.6	7.6	9.4	0.004
	Recovered (*n*=79)	2.8	125.6	22.8	17.5	19.0	16.9	

Table 5: Inflammatory markers at the time of admission in the adrenal insufficient and sufficient group

Variable	Adrenal insufficient	Minimum	Maximum	Mean	SD	Median	IQR	*P*
D Dimer (mcg/ml)	Yes (*n*=48)	0.10	2.10	0.7	0.4	0.6	0.5	<0.001
	No (*n*=52)	0.10	1.00	0.4	0.2	0.4	0.2	
Ferritin (ng/ml)	Yes (*n*=48)	36.1	1566.0	505.6	328.8	424.0	394.0	<0.001
	No (*n*=52)	39.0	683.0	272.9	163.0	258.0	243.0	
CRP (mg/dl)	Yes (*n*=48)	1.5	21.8	7.8	4.1	6.6	5.6	<0.001
	No (*n*=52)	1.2	10.4	4.2	1.8	3.8	2.1	
TNF Alpha (pg/ml)	Yes (*n*=48)	26.4	154.7	66.2	27.5	60.5	34.6	<0.001
	No (*n*=52)	25.1	75.1	40.5	11.7	38.4	16.7	
IL – 6 (pg/ml)	Yes (*n*=48)	10.3	143.2	53.7	34.8	43.5	33.2	<0.001
	No (*n*=52)	7.2	73.8	22.0	15.2	18.2	13.8	

to fully understand the relationship between cortisol levels and COVID-19 outcomes.

We found that there is a significant linear correlation between random basal cortisol and stimulated cortisol (r = 0.908, P value < 0.001). However, it does not provide sufficient evidence to conclude that random cortisol and plasma ACTH alone are adequate for evaluating glucocorticoid status during COVID-19. Further research, including direct comparative studies and consideration of clinical guidelines, is necessary to validate the use of these parameters as standalone diagnostic tools.

The study had certain limitations: Cortisol was estimated using CLIA rather than the more sensitive LC-MS; imaging for adrenal and pituitary glands was not included, which could have provided insights into the mechanism of adrenal insufficiency (primary vs. secondary); and testing for the Anti-ACTH antibody was not conducted, which might have explained the mechanism for adrenal insufficiency. Despite these limitations, the study has notable strengths: We included mild cases, which were often neglected in previous studies, and comprehensively assessed the HPA axis, including basal cortisol, ACTH-stimulated cortisol, and plasma ACTH.

Conclusion

This study comprehensively assessed glucocorticoid status in COVID-19 patients by measuring random basal cortisol, ACTH-stimulated cortisol, delta value, and plasma ACTH. A significant linear correlation was found between random basal cortisol and stimulated cortisol (r = 0.908, P < 0.001). The prevalence of adrenal insufficiency was high, affecting 48% of patients, particularly in severe cases, indicating a link with disease severity. Non-survivors exhibited significantly lower levels of random basal cortisol, ACTH-stimulated cortisol, delta value, and plasma ACTH than survivors. These findings underscore the importance of routine cortisol and plasma ACTH assessment in COVID-19 patients to evaluate glucocorticoid status and predict disease severity and outcomes. Although the acute phase of the pandemic has passed, the virus's ongoing circulation and potential new waves make these results pertinent for future clinical management and preparedness.

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Authors contribution

VSRD: Study idea, protocol development, data collection, and manuscript writing and will act as guarantor for the study; CB: Developing protocol, data collection, analysis, and manuscript writing; SP: Developing protocol and manuscript writing; SRP: Developing protocol and manuscript writing; VK: Developing protocol, data analysis and manuscript writing; VSRD, CB, SP, SRP, and VK: Critical appraisal and revision of manuscript. All authors approved the final version of the manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Data availability statement

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

References

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3.
2. Gorbalenya AE, Baker SC, Baric RS, de Groot R, Drosten C, Gulyaeva AA, *et al.* The species Severe acute respiratory syndrome-related coronavirus: Classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020;5:536–44.
3. Carfì A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. JAMA 2020;324:603–5.
4. Vakhshoori M, Heidarpour M, Bondariyan N, Sadeghpour N, Mousavi Z. Adrenal insufficiency in coronavirus disease 2019 (COVID-19)-infected patients without preexisting adrenal diseases: A systematic literature review. Int J Endocrinol 2021;14;2271514.
5. Tan T, Khoo B, Mills E.G, Phylactou M, Patel B, Eng PC, *et al.* Association between high serum total cortisol concentrations and mortality from COVID-19. Lancet Diabetes Endocrinol 2020;8:659-60.
6. Mao Y, Xu B, Guan W, Xu D, Li F, Ren R, *et al.* The adrenal cortex, an underestimated site of SARS-CoV-2 infection. Front Endocrinol 2021;11:593179.
7. Das L, Dutta P, Walia R, Mukherjee S, Suri V, Puri GD, *et al.* Spectrum of endocrine dysfunction and association with disease severity in patients with COVID-19: Insights from a cross-sectional, observational study. Front Endocrinol 2021;12:645787.
8. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, *et al.* Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021;384:693–704.
9. Gundgurthi A, Garg MK, Dutta MK, Pakhetra R. Intramuscular ACTH stimulation test for assessment of adrenal function. J Assoc Physicians India 2013;61:320–4.
10. Wagmode NB, Mathew V, Bantwal G, Ayyar V, George B, Patanjali CP, *et al.* It is time to carpe diem with porcine ACTH-A comparison of porcine sequence corticotropin to tetracosactide hexaacetate in testing the hypothalamic-pituitary-adrenal axis in healthy individuals. Indian J Endocrinol Metab 2018;22:636–40.
11. Nair A, Jayakumari C, George GS, Jabbar PK, Das DV, Jessy SJ, *et al.* Long acting porcine sequence ACTH in the diagnosis of adrenal insufficiency. Eur J Endocrinol 2019;181:639–45.
12. Alzahrani AS, Mukhtar N, Aljomaiah A, Aljamei H, Bakhsh A, Alsudani N, *et al.* The impact of COVID-19 viral infection on the hypothalamic-pituitary-adrenal axis. Endocr Pract 2021;27:83–9.
13. World Health Organization. Clinical Management of COVID-19: Interim Guidance. World Health Organization; 2020. p. 13–5.
14. Annane D, Pastores SM, Rochwerg B, Arlt W, Balk RA, Beishuizen A, *et al.* Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part I): Society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Med 2017;43:1751-63.
15. Leow MK, Kwek DS, Ng AW, Ong KC, Kaw GJ, Lee LS. Hypocortisolism in survivors of severe acute respiratory syndrome (SARS). Clin Endocrinol (Oxf) 2005;63:197-202.
16. Kumar B, Gopalakrishnan M, Garg MK, Purohit P, Banerjee M, Sharma P, *et al.* Endocrine dysfunction among patients with COVID-19: A single-center experience from a tertiary hospital in india. Indian J Endocrinol Metab 2021;25:14–9.
17. Ahmadi I, EstabraghniaBabaki H, Maleki M, Jarineshin H, Kaffashian MR, Hassaniazad M, *et al.* Changes in physiological levels of cortisol and adrenocorticotropic hormone upon hospitalization can predict SARS-CoV-2 mortality: A cohort study. Int J Endocrinol 2022;2022:4280691.