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LETTER TO THE EDITOR

In response to the article, *'Hypothalamic-Pituitary-Adrenal Axis Activity in SARS-CoV-2 Infected Noncritically Ill Hospitalized Patients,'* by Banu H, et al., published in JAFES Vol. 38 No. 2.

Before Low Serum Cortisol Can Be Attributed to SARS-CoV-2 Infection, Alternative Causes Must Be Ruled Out

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We read with interest Banu et al.,'s article about a cross-sectional study of adrenal function using blood levels of cortisol and adrenocorticotropic hormone (ACTH) in 91 patients with acute SARS-CoV-2 infection. It was found that 27% of patients with severe COVID-19, 26% with mild COVID-19 and 4% with moderate COVID-19 had adrenal insufficiency. Decreased cortisol reserve was found in 6.6% of all patients. It was concluded that the adrenocortical response was impaired in a significant number of non-critically ill COVID-19 patients, with the percentage being highest in patients with severe COVID-19 disease.[1] The study is impressive, but some points should be discussed.

The major limitation of the study is that imaging of the pituitary gland and hypothalamus was not performed. To rule out pituitary adenoma, hypophysitis, pituitary apoplexy, pituitary abscess, sellar tuberculoma, or hypothalamic stroke or bleeding, magnetic resonance imaging (MRI) of the pituitary gland and the hypothalamus with contrast agent must be performed. Like any other infection, SARS-CoV-2 infection can trigger the appearance of symptoms of a pituitary pathology.[2]

A second limitation is that imaging of the suprarenal glands was not performed. To assess whether there was adrenal atrophy, adenoma, ischemia, bleeding, or carcinoma, adrenal imaging is mandatory.[3]

A third limitation is that current medication was not reported. Several medications are known to affect serum cortisol levels, making it imperative to know all medications regularly taken by the included patients. Ketoconazole, isilodrostat, vitamin D and omega-3 fatty acids in particular are known to be able to reduce cortisol levels in the blood.[4] A fourth limitation is that no ACTH stimulation test was performed to determine whether primary or secondary suprarenal insufficiency was present. Determining cortisol levels alone without ACTH stimulation testing is not reliable with regard to cortical adrenal function.

A fifth limitation is that serum dehydroepiandrosterone (DHEA) levels were not measured. Since DHEA is the antagonist of cortisol and decreases with age, it is conceivable that high levels of DHEA promoted the reduction of serum cortisol.[5]

Since low thyroxine levels may be associated with low cortisol levels,[6] it would also be desirable to know whether thyroid function was normal or abnormal in the included patients.

In summary, the excellent study has limitations that should be addressed before drawing conclusions. Clarifying the weaknesses would strengthen the conclusions and could improve the study. Serum cortisol levels may be low not only due to SARS-CoV-2 infection but also due to several other causes. Before adrenal insufficiency can be attributed solely to inadequate cortical cortisol production, the entire hypothalamic-pituitary-adrenal axis must be thoroughly examined.

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CRediT Author Statement
JF: Conceptualization, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Supervision, Project administration, Funding acquisition; **ASMS:** Methodology, Investigation, Writing – review and editing, Supervision; **SM:** Methodology, Investigation, Writing – review and editing

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