Dear Editor,

We read with interest the study by Tomo and colleagues investigating serum cortisol and dehydroepiandrosterone sulfate (DHEAS) levels at the time of admission in 76 COVID-19 patients and 79 healthy controls. Total serum cortisol concentrations were found to be higher in patients than in controls, whereas DHEAS and the DHEAS/cortisol ratio were decreased [1]. The authors, however, appear to have overlooked and therefore do not discuss the following: (i) circadian rhythmicity in cortisol secretion, as they did not correct for differences in the time of sampling; (ii) the significant impact of age and sex on DHEAS levels; and (iii) the impact of changes in binding proteins when assessing total serum cortisol levels in conditions of critical illness, as is COVID-19.

Firstly, the pulsatile secretion of both cortisol and adrenocorticotropic hormone is maintained in critical illness; thus, significantly different serum total cortisol results may be obtained at different time-points of sampling. By not recording the sampling time, the authors of the study [1] fail to adjust for potential differences; hence, the results should be interpreted with caution.

Secondly, healthy controls were not age- and sex-matched with the COVID-19 patients in the study by Tomo et al. [1], and this poses a significant challenge when interpreting results regarding circulating DHEAS levels. DHEAS, a prohormone secreted by the adrenal gland, plays a role in the synthesis of the sex hormones androgens and estrogens by altering their levels, and, although throughout life its secretion remains stable during the day, it nevertheless undergoes a significant overall decline with advancing age in both sexes. In additional analyses with age-matched groups of COVID-19 patients and controls (using as a cut-off value the median age of 42 years), results were similar, but the confounding effect of sex was not accordingly eliminated. Indeed, DHEAS level differed significantly only in male COVID-19 patients, compared to controls; however, this analysis was not adjusted for age [1].

Thirdly, more than 90% of circulating cortisol in serum is protein-bound and, thus, the changes in the binding proteins, as occurs in conditions of critical illness, significantly alter measured serum total cortisol concentrations without affecting the concentrations of free cortisol. While serum free cortisol measurement is not routinely available, serum total protein concentrations should be considered when estimating serum total cortisol concentrations.

We have previously reported that morning cortisol levels in saliva, reflecting free circulating cortisol levels, are not increased in COVID-19 [2]; these results were not discussed by Tomo et al. [1]. In our study, patients exhibited higher median levels of evening (measured at 6 pm) and nocturnal (measured at 10 pm) salivary cortisol compared to age- and sex-matched controls, resulting indeed in higher time-integrated area under the curve. In contrast, the sequential measurements of DHEA in saliva at different time-points during the day in our cohort of COVID-19 patients, irrespectively of disease status, were similar to those of controls. As a result, daily DHEA secretion did not differ between COVID-19 patients and controls, whereas the DHEA/cortisol ratios, measured at 12:00 noon, 6 pm, and 10 pm were significantly lower in COVID-19 patients compared to controls, probably reflecting the higher salivary cortisol levels at these time-points. Interestingly, the IL-6 serum levels measured by Tomo et al. were not correlated with serum cortisol levels, DHEAS levels, or DHEAS/cortisol ratio [1]. In contrast, we showed that IL-6 strongly correlates with nocturnal cortisol salivary levels in COVID-19, suggesting that IL-6 may partially replace ACTH as a stimulus of the glucocorticoid-secreting adrenal zona-fasciculata without influencing the secretion of DHEA [2].

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Increased total serum cortisol levels have also been previously reported in a cohort of 403 COVID-19 patients and 132 controls, whereas doubling of serum cortisol was associated with a 42% increase in mortality after adjusting for age, comorbidities, and laboratory tests [3]; again, these results were not discussed by Tomo et al. [1].

To conclude, the impact of circadian rhythmicity and other conditions that may affect the total concentrations of the adrenocortical hormones cortisol and DHEAS should be considered cautiously when interpreting results in COVID-19 patients.

Declarations

Ethical approval  Not applicable.

Informed consent  Not applicable.

Conflict of interest  The authors declare no competing interests.

References

1. Tomo S, Banerjee M, Karli S, Purohit P, Mitra P, Sharma P, Garg MK, Kumar B (2022) Assessment of DHEAS, cortisol, and DHEAS/cortisol ratio in patients with COVID-19: a pilot study. Hormones (Athens) 8:1–4. https://doi.org/10.1007/s42000-022-00382-x

2. Yavropoulou MP, Filippa MG, Mantzou A, Ntziora F, Mylona M, Tektonidou MG, Vlachogiannis NI, Paraskevis D, Kaltas GA, Chrousos GP, Sfikakis PP (2022) Alterations in cortisol and interleukin-6 secretion in patients with COVID-19 suggestive of neuroendocrine immune adaptations. Endocrine 75:317–327. https://doi.org/10.1007/s12020-021-00818-2

3. Tan T, Khoo B, Mills EG, Phylactou M, Patel B, Eng PC, Thurs- ton L, Muzi B, Meenan K, Prevost AT, Comninos AN, Abbara A, Dhillo WS (2020) Association between high serum total cortisol concentrations and mortality from COVID-19. Lancet Diabetes Endocrinol 8:659–660. https://doi.org/10.1016/S2213-8587(20)30216-3

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