
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

We congratulate Tan and colleagues[1] for their work on serum cortisol concentrations and mortality from COVID-19. Although these results are novel in the context of COVID-19, the practical implications are debatable.

Tan and colleagues[1] showed that cortisol concentrations in patients with COVID-19 were significantly higher than in those without COVID-19. However, disease severity scores (eg, APACHE II, SOFA) of the two groups were not reported. The remarkably high levels of C-reactive protein in the COVID-19 group (median 117·8 mg/L [IQR 58·2–180·4]) compared with the non-COVID-19 group (42·0 mg/L [9·5–123·5]) highlights that the patients with COVID-19 were more severely ill than their counterparts. Cortisol, being a marker of disease severity, is expected to be higher in patients with a more severe disease compared with a less severe disease. Multivariate analysis found that doubling of serum cortisol was associated with a 42% increase in mortality after adjusting for age, comorbidities, and laboratory tests. Median survival was significantly lower in patients with cortisol concentrations of greater than 744 nmol/L in the cohort. Conspicuously, the analysis did not include disease severity. Performing multivariate and survival analyses after adjusting for disease severity would have been reflective of the true predictive potential of cortisol.

The prognostic role of serum cortisol in community-acquired pneumonia has been extensively studied. Elevated cortisol is an independent biomarker predicting adverse outcomes and mortality in patients with community-acquired pneumonia.[2,3] However, serum cortisol is not used in routine clinical practice as a prognostic biomarker in community-acquired pneumonia, mostly because of the inherent interindividual variability in cortisol dynamics in response to stress. The authors have also not ruled out the possibility of an underlying critical illness-related corticosteroid insufficiency, which would ideally require documentation of a cortisol increment of more than 248 nmol/L at 60 min after tetracosactide administration. Nevertheless, even in the context of critical illness-related corticosteroid insufficiency, given the unreliability of cortisol assays in critical illness, most physicians in routine clinical practice prefer to administer a short course of hydrocortisone in patients with septic shock who are pressor-dependent or refractory to fluid resuscitation regardless of serum cortisol levels.[4] The Surviving Sepsis Campaign guidelines also recommend the use of intravenous hydrocortisone (200 mg per day) in patients with COVID-19 with refractory shock without relying on serum cortisol levels.[5]

In summary, the severity of underlying disease needs to be well defined to interpret the stress cortisol response in patients with COVID-19. As in patients with community-acquired pneumonia, serum cortisol in COVID-19 predicts mortality and duration of survival, although its utility in routine clinical practice seems limited.

We declare no competing interests. RP and MB contributed equally.

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## Authors' reply

We are grateful to Rimesh Pal and colleagues and Kay Choy for their interest in our work[1] and their useful comments. As Choy correctly points out, pulsatility could affect cortisol levels. Gibbison and colleagues[2] showed concordance of adrenocorticotropic hormone and cortisol pulses, crucially with significantly less pulsatility in critical illness compared with healthy volunteers. This finding suggests that pulsatility might not have as great an effect on cortisol levels in critically ill patients as they would in healthy patients.

With regard to the comment made by Pal and colleagues on the diagnosis of critical illness-related corticosteroid insufficiency, we note that the consensus statement of Annane and colleagues[3] on diagnostic criteria could not recommend the use of a short Synacthen (tetracosactide) test because the evidence was of low quality. An alternative definition of critical illness-related corticosteroid insufficiency is a cortisol concentration of less than 276 nmol/L (10 µg/dL). Of the 403 patients with COVID-19 in our cohort, we found that only 18 had a cortisol level below this cut-off (compared with 13 of 132 in the patients without COVID-19).[1] This result suggests that critical illness-related corticosteroid insufficiency is not a widespread problem in the context of COVID-19 in a non-intensive care unit setting, but further data are needed. Pal and colleagues also comment that clinical practice for septic shock involves the use of hydrocortisone and other glucocorticoids. Of specific relevance, glucocorticoids (eg, dexamethasone)