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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.

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1   Tan T, Khoo B, Mills EG, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. *Lancet Diabetes Endocrinol* 2020; **8:** 659–60.
2   Salluh JIF, Shinotsuka CR, Soares M, et al. Cortisol levels and adrenal response in severe community-acquired pneumonia: a systematic review of the literature. *J Crit Care* 2010; **25:** e1–8.
3   Kolditz M, Höffken G, Martus P, et al. Serum cortisol predicts death and critical disease independently of CRB-65 score in community-acquired pneumonia: a prospective observational cohort study. *BMC Infect Dis* 2012; **12:** 90.
4   Hamrahian AH, Fleseriu M, AACE Adrenal Scientific Committee. Evaluation and management of adrenal insufficiency in critically ill patients: disease state review. *Endocr Pract* 2017; **23:** 716–25.
5   Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Intensive Care Med* 2020; **46:** 854–87.

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)

might confer benefit in severe COVID-19.[4] However, this benefit is less likely to be driven by any treatment of critical illness-related corticosteroid insufficiency per se, than by the anti-inflammatory and immunomodulatory effects of dexamethasone. Indeed, no benefit of dexamethasone was seen in patients with COVID-19 not requiring oxygen in the RECOVERY trial.[4]

Choy points out that our analysis did not examine the effect of binding proteins (eg, cortisol-binding globulin). These proteins do indeed decrease in the context of physiological stress as we have previously documented,[5] and this probably occurs in COVID-19. The net effect of an elevation in total cortisol and a reduction in cortisol-binding globulin will be to increase free cortisol levels.[5] This supports our main finding, which is that COVID-19 is associated with a marked elevation in cortisol. Some immunoassays do indeed exhibit a positive bias versus gold-standard assays due to cross-reaction with other steroids in samples derived from critically ill patients. We used an Abbott immunoassay and we note that Dodd and colleagues[6] showed that this assay exhibits no significant bias in comparison with the gold-standard gas chromatography–mass spectrometry assay in the context of critical illness.[6] Therefore, assay interference does not plausibly explain the markedly elevated cortisol levels in our study.

Both Pal and colleagues and Choy caution against the routine use of serum cortisol as a prognostic biomarker in the context of COVID-19. Cortisol is likely to co-vary with disease severity as a marker of physiological stress. Our dataset does not include all the variables necessary for construction of APACHE-II or SOFA scores to verify this hypothesis. However, we believe that the correspondents' comments support our contention that the potential use of cortisol levels as a prognostic marker in COVID-19 will require validation in a prospective study incorporating validated measures of disease severity.

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1 Tan T, Khoo B, Mills EG, et al. Association between high serum total cortisol concentrations and mortality from COVID-19. *Lancet Diabetes Endocrinol* 2020; **8:** 659–60.
2 Gibbison B, Keenan DM, Roelfsema F, et al. Dynamic pituitary–adrenal interactions in the critically ill after cardiac surgery. *J Clin Endocrinol Metab* 2020; **105:** 1327–42.
3 Annane D, Pastores SM, Rochwerg B, 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.
4 RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med* 2020; published online July 17. https://doi.org/10.1056/NEJMoa2021436.
5 Khoo B, Boshier PR, Freethy A, et al. Redefining the stress cortisol response to surgery. *Clin Endocrinol (Oxf)* 2017; **87:** 451–58.
6 Dodd AJ, Ducroq DH, Neale SM, et al. The effect of serum matrix and gender on cortisol measurement by commonly used immunoassays. *Ann Clin Biochem* 2014; **51:** 379–85.

Draft FDA guidance for assessing the safety of glucose lowering therapies: a missed opportunity?

In 2008, the US Food and Drug Administration (FDA) issued guidance to the pharmaceutical industry to show the cardiovascular safety in new drug applications for treatments of type 2 diabetes.[1] Since then, a plethora of cardiovascular outcome trials have taken place, with some showing cardiovascular benefits, but also unexpected findings such as benefits for heart failure hospitalisation and renal outcomes. These trials have informed evidence-based guidelines and consensus recommendations that have substantially improved patient outcomes. However, these trials are fairly short and are event-driven studies recruiting high–risk populations who are unrepresentative of the general population who are prescribed these agents. The cost of cardiovascular outcome trials has been estimated at US$200–400 million,[1] which might have discouraged industry investment in new diabetes therapeutics with a marked decline in in the number of clinical trials in type 2 diabetes since the publication of the FDA guidance.[2] Another criticism has been that few cardiovascular outcome trials have compared active therapies. In 2018, the FDA's Endocrinology and Metabolic Drugs Advisory Committee met and agreed that the scope of cardiovascular outcome trials should be modified and suggested that their design and conduct could be changed by broadening the population, expediting data collection and review, and expanding to other outcomes of interest. Informed by these discussions, in 2020, representatives from academia, industry, and regulatory agencies published a white paper with several recommendations for future regulatory guidance: "requiring only the 1·3 noninferiority margin for regulatory approval, conducting trials for longer durations, considering studying glucose-lowering therapies as first-line management of type 2 diabetes mellitus, considering heart failure or kidney outcomes within the primary outcome, considering head-to-head active comparator trials, increasing the diversity of patients enrolled,