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Dismissal of the utility of free cortisol measurement is premature

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Dear Editor,

Molenaar et al. [1] observed that free cortisol (FC) measurements correlated closely with those of total cortisol (TC) in critically ill patients and thus concluded that measurements of FC were of marginal benefit. We do not believe this conclusion to be justified.

Plasma TC and FC are dependent variables and this relationship forms the basis of the well-known Coolens equation [2]. Correlation between FC and TC, either between baseline or post ACTH stimulation, is expected. It would have been very unusual if the authors demonstrated a regression line between the TC and FC increment that was not statistically significantly from zero ($P > 0.05$) and as such the observed $P < 0.001$ is entirely in keeping with what has been previously reported.

The correlation coefficient of 0.77–0.79 ($R^2 = 0.59$) does not imply the tests can be used interchangeably. Concordance around the suggested decision limits of 77 and 250 nmol/L was not demonstrated, and formal tests of concordance such as Cohen's kappa and the McNemar test would be more appropriate to demonstrate any relationship. From Fig. 1a and c it is evident that there were samples with an appropriate FC increment and a TC increment below 250 nmol/L, which argues against the authors' conclusion that the increments are interchangeable. Observations from our group have documented significant discordance in diagnosis of adrenal insufficiency using TC and FC criteria in patients with liver disease, and in septic shock [3, 4].

The authors' own observations that relative increases of FC were significantly higher than those of TC, as well as the documented stronger association of FC with sickness severity [5], suggest that FC may be a more valid index of adrenal function. Robust examination of the association of FC with outcome will be required to investigate this issue. It is our opinion that the authors' recommendation that the TC increment was sufficient to assess adrenal reserve, especially in sepsis, is premature and not supported by their data.

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