Reviewer's report

Title: Serum cortisol predicts death and critical disease independently of CRB-65 score in community-acquired pneumonia: a prospective observational cohort study

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Reviewer: Yoon Kong Loke

Reviewer's report:

Thank you for this submission which studies the value of cortisol as a prognostic factor in CAP..

Major Compulsory Revisions

According to table 2, mortality is more associated with CRB65, congestive heart failure, chronic renal failure, malignancy and male sex compared to cortisol. Is there any increase in predictive value in morality if cortisol is added to any of these variable which are more associated with mortality? It’s not clear if the authors are recommending cortisol as a an add-on, or as a stand alone marker for clinical use..

Like many other pneumonia biomarker studies, the clinical impact is hardly ever discussed in this manuscript. The authors state that the AUC with CRB-65 alone is 0.76 – 0.77, and this improves to 0.81 if cortisol is added. Now, as a practicing clinician faced regularly with pneumonia patients in the admissions room, my response is ‘So what?’ How many extra patients would I correctly send home, and how many extra patients would I correctly refer to the intensive care unit, if I somehow managed to persuade my laboratory colleagues to run urgent cortisol measurements for me 24 hours a day? The lack of clinical relevance is a major limitation of prognostic score research (admittedly not just in pneumonia). I suggest that some insights into estimating clinical impact can be gained from looking again at our meta-analysis (reference 1 in this article).

Minor Essential Revisions

Comment 1: The advantage of CRB65 is that it is based purely on clinical factors and is particularly suitable for use where the patients are still outside of hospital. Comparison of CRB65 with and without cortisol is out of context in the management of many pneumonia patients, since the cortisol levels are not going to be available as an outpatient test. If hospital laboratory and radiological data are collected, then CURB65 or PSI should be used as reference.

Comment 2: Serum cortisol varies significantly across the day. It typically peaks in the early hours of the morning. Unless levels are low there is uncertain value in random measurements. How does this study account for random variation in levels with diurnal variation? The patients may all have been sampled at different times.
Comment 3: How is use of exogenous steroids accounted for in non-respiratory patients? Patients may use prednisolone orally for inflammatory conditions that are not associated with chronic respiratory illness.

Unless the two limitations are addressed it is difficult to comment on the value of this study.

Comment 4: The authors should expand the section on mechanisms as to why patients with high cortisol is associated with poorer survival – is it a marker or a mediator? It is not clear what possible mechanisms lead to differential response to respiratory infection.

Comment 5: The authors should comment on the evidence of steroid use in pneumonia and how it affects outcome. The potentially beneficial effects of dexamethasone in pneumonia seem counter-intuitive to the findings that higher cortisol levels and associated mortality.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests