Author’s response to reviews

Title: Serum Copeptin Levels in the Emergency Department Predict Major Clinical Outcomes in Adult Trauma Patients

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Version: 2 Date: 18 Jan 2020

Author’s response to reviews:

Dear Editor and Reviewers,

We would like to thank you again for this second round of comments and for the opportunity to further improve our manuscript. We have now revised our manuscript according to your comments.

Point-by-point response to the reviewers’ comments is attached below. All modifications made in this second revision are highlighted in red in the manuscript.

We are looking forward to knowing your final decision and we hope our article is now finally suitable for publication on BMC Emergency Medicine.

Thank you.

Sincerely,

Fulvio Salvo, MD
Reviewer reports:
Reviewer 2 (Reviewer 3): GENERAL COMMENTS: Overall, I found this study to be interesting and clinically relevant. The authors have conducted a study to assess the test characteristics of copeptin to predict ISS > 15 and compare its performance to lactate. Overall, the authors have strengthened the manuscript based on the prior review. However, many questions remain that could improve this work.

REQUESTED REVISIONS:
1) The statement that it is superior to lactate is not true for all the outcomes listed in the abstract (review table 2 please).
We thank this reviewer for her/his observation that allowed us to correct the misleading statement. The paragraph has been revised as:
“In a heterogeneous group of trauma patients, a single copeptin determination at the time of ED admission proved to be an accurate biomarker, statistically superior to lactate for the identification of major trauma, hospital admission, and blood transfusion, while no statistical difference was observed for ICU admission and emergency surgery.”

2) There are some spelling errors that exist (line 5 "hormon", and a few others).
We have used this opportunity to revised once again the manuscript and correct the few spelling errors and typos still present.
These include: prohormone (page 2, line 5); immunofluorescence (page 8, line 6); neuroendocrine (page 16, line 18)

3) More description is needed about what RTS 7.84 means and why that particular number was chosen for the subgroup analysis.
The revised trauma score (RTS) is calculated as: 0.9368*(GSc) + 0.7326*(SBPc) + 0.2908*(RRc), using a coded value for each clinical parameter. When all three parameters are in a normal (or “almost normal”) range (i.e. GCS≥13; SBP≥90; respiratory rate 10-29) the result of the equation is 7.84. This subgroup includes the patient that at the time of the evaluation may be considered at low risk of bad outcome. We decided to use this value for two main reasons: first, it is already part of our electronic medical record, calculated in every trauma patient accessing the ED; second, the authors favored using these widely accepted thresholds instead of identifying arbitrarily new ones.
In the paragraph describing the subgroup analysis a detailed description of the RTS calculation was added. Page 10 line 17-22.

4) There is no discussion of the secondary role of lactate as a marker of resuscitation and the value in this population in the context of the results.
As pointed out by this Reviewer, it has been indeed well established that poor lactate clearance is associated with increased mortality in trauma patients [Marie-Alix Régnier, et al. Prognostic Significance of Blood Lactate and Lactate Clearance in Trauma Patients. Anesthesiology 2012;117:1276-1288; Odom SR, Howell MD, Silva GS, et al. Lactate clearance as a predictor of mortality in trauma patients. J Trauma Acute Care Surg 2013;74:999-1004]. Hence, it has been postulated that lactate levels during resuscitation can be assessed as a mean for monitoring the patient's response to treatment. Serial evaluation of blood lactate in the critically ill trauma patient could therefore influence both the diagnostic strategy and the therapeutic effort, and this must be regarded as
a major benefit provided by lactate measurement.
Yet, this study was focused on the first evaluation of trauma patients upon arrival in the ED. We sought to determine the prognostic role of the first measurement of serum copeptin in the prognostication of trauma patients, and its specific relevance among other widely used clinical (e.g. hemodynamics) and laboratory (i.e. lactate) parameters gathered at this early step of patient evaluation. Thus, we did not perform serial measurements of serum copeptin, nor we included in our analysis later measurements of serum lactate. However, taking into account this valuable comment made by this Reviewer, it would be interesting to compare the possible role of copeptin clearance as a marker of resuscitation in this population, and compare it to lactate clearance, in our future planned studies.
5) Perhaps the greatest concern that I have is that is unclear how copeptin would be used in this population. There are some references to using it as a triage marker, but given the imperfect sensitivity and specificity, it is unlikely that this would replace imaging as the primary means of diagnosing the critically ill trauma patient. It would be useful for the authors to discuss what clinical decision might change with access to copeptin results (i.e. in situations without access to advanced imaging?).
This is a very interesting point that was somehow compressed in the original manuscript due to word limits. In our opinion a new reliable biomarker for the triage of traumatic patients should be able to fill the gap of other scores/biomarkers, by performing efficiently in the group of subjects in which these scores/biomarkers give a normal or negative result. Copeptin performed well in the subgroup of patient with normal vital signs (both in primary and secondary outcomes) and this might be particularly useful from a real life perspective.
A brief discussion on potential practical applications of copeptin in these patients was added to the manuscript (Page 15, line 17-21).
6) In the introduction, other studies of trauma patients are described as "conflicting" but there is no further discussion of this literature and how it compares and how this particular study resolves this conflicting literature (or not).
We agree with the reviewer that this is a very interesting point and warrants further discussion.
More details were added in the introduction about the only two studies evaluating copeptin in trauma patients (page 5, line 10-16). In the discussion results of both studies are briefly discussed (page 12 line 20 to page 13 line 4).