Author's response to reviews

Title: Procalcitonin as a marker of sepsis and outcome in patients with neurotrauma: an observation study

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Author's response to reviews: see over
Dear Dr. Costoy,

Thank you for your letter and the reviewer’s comments regarding our manuscript (6117234259942249). The comments and proposals by the reviewers were very constructive and helpful for modifying our manuscript. We have modified the manuscript in line with the comments. Hereby we submit the revised manuscript for your consideration for publication. We think that we have addressed reviewers’ comments to the best degree we could, and we hope this has met the reviewers’ and editor’s requests. All the modifications in the script have been marked in red color. Our detailed point-by-point responses to the comments are as follows:

Responses to the reviewer Michael Meisner:

1. The APACHE II score should not be addressed as a severity score.

Thank you for pointing this out. We have followed the reviewer’s suggestion and made some changes. We use the Injury Severity Score (ISS) replaced the APACHE II score to evaluate the severity of injury [1] [page 2 line: 44-45; page 3 line: 49, 75].

2. Does the reader understand correctly that this is isolated brain/head injury or are there other types of trauma coexisting? This should be – if this is the case – expressed by an Injury Severity Score (ISS...), because in this case the GCS is maybe not enough to correlate trauma severity of brain, PCT and overall tissue damage.
Thank you for your comments, and we made some revisions. Actually, it is hard to collect so many isolated traumatic brain injury patients, so this study included 105 neurotrauma patients without or with other body injury but the Abbreviated Injury Scale (AIS)[1] for all other body regions injury<3 and the Injury Severity Score (ISS) was use to evaluate the severity of injury [page 2 line: 35-39].

3. Does the reader understand well that onset of sepsis is possible also during the later course (e.g. day 1-28), or does it mean that sepsis came up during the initial days of the PCT observation period (e.g. day 2, 3, 5, 7)?

Thank you for pointing this out. We followed the reviewer’s suggestion and made modification in the revised version. In this study the various stages of sepsis were defined according to the criteria established by the American College of Chest Physicians/the Society of Critical Care Medicine [2]. We evaluated the onset of sepsis during the first observation week. Patients were allocated to four groups post hoc: (1) NoSIRS (neither SIRS nor sepsis) (2) SIRS (3) sepsis and (4) severe sepsis group (including severe sepsis and septic shock) [page 3 line: 51-56].

4. The difference of SIRS/no SIRS and the Sepsis groups is maximum at day2. The authors should also provide the statistical anlysis and data for this day, because results may be much better and because of the below mentioned consequences. 4b) in Figure 2 the error bars cannot be separated. Thus, the numbers should be mentioned in a table e.g. with median, 90-percentiles etc.

It is really true as Reviewer suggested that we should provide the data of the different sepsis group for day1 and day2. So we made some revisions and the data of the difference of SIRS/No SIRS and the Sepsis groups was showed in Table 2 [page 4 line: 100].

**Table 2** The original data of PCT and CRP in patients of sepsis subgroup
<table>
<thead>
<tr>
<th>Group</th>
<th>PCT(ng/ml)(d1)</th>
<th>CRP(mg/L)(d1)</th>
<th>PCT(ng/ml)(d2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median    IQR</td>
<td>Median    IQR</td>
<td>Median    IQR</td>
</tr>
<tr>
<td>No SIRS</td>
<td>0.093     (0.050,0.093)</td>
<td>4.86     (3.22,10.30)</td>
<td>0.120     (0.080,0.300)</td>
</tr>
<tr>
<td>SIRS</td>
<td>0.105     (0.085,0.328)</td>
<td>21.90    (14.48,42.22)</td>
<td>0.295     (0.148,0.575)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.270     (0.120,0.610)</td>
<td>27.85    (15.12,55.50)</td>
<td>0.555     (0.233,0.857)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>0.570     (0.230,1.450)</td>
<td>34.30    (22.40,154.0)</td>
<td>1.300     (0.360,2.600)</td>
</tr>
</tbody>
</table>

5. The consequences of the data should be updated: Presently PCT is also used to guide antibiotic therapy. Especially the negative predictive value to exclude a risk of sepsis is used. ....But using on a daily base the NPV would be clinically helpful.

As Reviewer suggested that we should update the data of PCT used to guide antibiotic therapy. We have followed the reviewer’s suggestion and made some changes. There are several studies that have reported using PCT to guide antibiotic therapy in different settings [3-5]. Experts have reached a consensus and developed guidelines for the clinical interpretation of elevated PCT and the risk stratification according to different elevated PCT levels. In particular, the negative predictive value (PCT<0.1 ng/ml) to exclude a risk of sepsis is used. In the present study, we conventionally administered a single shot antibiotic to neurotrauma patients on admission to prevent infection. We determined that the odds ratio for the development of sepsis was increased as PCT>0.215 ng/ml, and according to the daily measurement of the PCT value, if PCT remains lower than 0.1 ng/ml, further antibiotic treatment was not required due to the low risk for sepsis. This finding was consistent with Marc and colleagues [3]. We also determined that PCT concentration rapidly decreased to a near-normal value in patients who did not develop sepsis, thus, during the further course of treatment, if the PCT level remained <0.1 ng/ml and the combined clinical symptoms did not provided any evidence for sepsis, no antibiotics were required. Thus, the daily use of the negative predictive value of PCT would be clinically helpful [page 5 line: 155-168, page 6 line: 191].
Special thanks to you for your good comments.

Responses to the reviewer oluwaseun akeju:

1. While this article is interesting and may have clinical implications. It is impossible to accurately read and opine on the hypothesis, study procedures, and statistical analysis because the grammar is significantly flawed. The authors should have this article reviewed and edited for publication in an English language journal.

We are very sorry for our incorrect English article. According to the Reviewer’s suggestion, we have invited a professional English scriptwriter to help us rewrite and extensively edited this manuscript for an English language journal.

2. I would suggest that the authors make sure this work complies the STROBE guidelines for reporting observational studies (Ann Intern Med. 2007; 147:573-577). Also, a figure illustrating inclusion/exclusion in the study would be appropriate.

Thank you for pointing this out. We have followed the reviewer’s suggestion and made some changes according to the STROBE guidelines for reporting observational studies (page 2, line 35-39; page 3, line 51-59, 69-76; page 4, line 113-116). For the purpose of excluding potential confounding factors to our study, patients with pre-existing febrile illness, suffering from burns, an Abbreviated Injury Scale (AIS) for all other body regions injury $\geq 3$, patients under immune suppressive therapy, patients already on antibiotics for $\geq 3$ days before admission, and patients who did not survive for 48 hours after admission were excluded from the study [page 2 line: 35-39].

3. Statistical—Due to the issue stated earlier with regards to the grammar, an assessment of the statistical methods is difficult. It is unclear to me how group comparisons were made and reported. ....Do the authors mean multivariable logistic
regression vs multivariate logistic regression? Same for univariable vs univariate analysis?

We have re-written this part according to the Reviewer’s suggestion. PCT levels among sepsis groups or GCS groups were carried out using Kruskal-Wallis tests (data not normally distributed), if statistical significance of differences was detected, then the Mann-Whitney U-test (nonparametric analysis) was used for further comparisons between the two sepsis groups or GCS groups. We used the Pearson chi-square test (χ² test) or Fisher’s exact test to compare proportions. Multivariate logistic regression was used to assess the performance of the variables in the prediction of sepsis. Based on the results of univariate analysis, we selected three confounding variables (age (p=0.789), sex (p=0.779), ISS (p<0.05)) that required adjustment to minimize their influence on the results. Because this three variable themselves were related to sepsis [page 3 line: 69-76]. We were so sorry that there was an error in multivariable logistic regression and univariable analysis. We made some modifications (replaced the “multivariable logistic regression” with “multivariate logistic regression” and “univariable analysis” with “univariate analysis”) in revised version [page 3 line: 73-74; page 4 line: 111,113-114; page 5 line: 151].

We have revised the manuscript in line with all the reviewers’ comments and we hope that the manuscript is now acceptable for publication at BMC Anesthesiology journal. We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for your comments and suggestions. If you have any questions, please feel free to contact us. We appreciate your support very much. We look forward to your response.

Yours sincerely,
Shuixiang Deng

References


