Author's response to reviews

Title: Endothelin-1 precursor peptides correlate with severity of disease and outcome in patients with community acquired pneumonia

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

We thank you for your helpful review of our manuscript. Please find bellow the responses to the reviewers comments and an updated version of the manuscript with changes highlighted. We hope that the manuscript is now acceptable for publication in BMC Infectious Diseases.

With best regards,

Philipp
Major Revisions

1. You suggest in the abstract, that proendothelin-1 levels are superior to C-reactive protein and leukocyte count in predicting mortality risk. However, few would argue that C-reactive proteins or leukocyte counts are reliable prognostic measures; indeed pneumonia specific severity scores are not primarily prognostic measures, but diagnostic measures. Even accepting this, an area under the curve of .69 is really quite weak and the prognostic utility far from optimal.

Response: We agree with the reviewer that the prognostic impact of C-reactive protein and leukocyte count is limited. However, some studies reported an association of CRP concentrations and severity of disease and outcome in patients with CAP (e.g. Almirall et al., Contribution of C-reactive protein to the diagnosis and assessment of severity of community-acquired pneumonia, Chest. 2004; Smith RP et al., C-reactive protein. A clinical marker in community-acquired pneumonia, Chest, 1995). In addition, despite the lack of evidence, in daily routine CRP is often inadequately used to for severity, and thus risk prediction.

We also agree that an area under the curve of .69 of proET1 is rather weak. Accordingly we have added a paragraph in our limitations section “Second, the overall prognostic utility of proET1 with an AUC of 0.64 is rather low reflecting the considerable overlap between survivors and non-survivors, which narrows the clinical applicability of proET1 per se”.

2. You report correlations with renal function, urea level, hospital stay, and blood pressure. Based on the R2 values you show, these correlations are really very weak and the significance level reflects primarily the relatively large sample size.

Response: We discarded the correlation with blood pressure and length of stay. Prof. Vincent suggested to discuss the impact of renal function on proET1 levels, as the correlation of proET1 with renal function might be of interest.” ProET-1 levels showed significant correlations with renal function (serum creatinine ($r^2=0.29$, $p<0.0001$) and urea levels ($r^2=0.32$, $p<0.0001$)).”

3. You report that proendothelin-1 levels are elevated in patients with adverse medical outcome. The medians differ here, but there is substantial overlap in the discriminatory capacity of any given reading is therefore poor as reflected in a low area under the curve of 0.64. What does this tell us practically?

Response: Based on the findings of this study, we believe instead of basing the prognostication on a single biomarker measurement, proET1 measurements could be included in existing scores (such as the PSI or the CURB65 score) and may improve its prognostic utility. In this regard, the finding that proET1 is independently predictive of the risk scores is of interest. We added a sentence in the discussion section "Because the prognostic utility of a single proET1 measurement was only moderate in this analysis,
This biomarker should be inbedded in existing clinical risk scores and may improve their accuracy.

4. Even when choosing an optimal cutoff of 94 pmol/L, the prognostic capacity for death is very modest reflected in a likelihood ratio of only 1.5 or of adverse outcome reflected in the likelihood ratio of 1.8. In general, a good diagnostic test should have a much larger likelihood ratio.

Response: We addressed this point by stating “Second, the overall prognostic utility of proET1 with an AUC of 0.64 is rather low reflecting the considerable overlap between survivors and non-survivors, which narrows the clinical applicability of proET1 per se”

5. How do proendothelin levels correlate with the resolution of infection? In other words, when antibiotics are stopped based on PCT criteria, what are the corresponding positive predictive value and negative predictive value of proendothelin-1?

Response: This is an interesting point. Unfortunately we only have proET1 measurements on admission and upon recovery, but not at the time point antibiotics were stopped.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. In the abstract, you speak of a cohort of “mainly septic patients”; what does this mean?

Response: the statement was rarefied.

2. In the first paragraph of the introduction, you state, “preliminary data suggested beneficial effects of ET-1 antagonism by using the selective ET receptor antagonist during septic shock”. All of these references are to animal studies whereas the use of the word “preliminary” suggests that they might be early phase human studies.

Response: the statement was changed.

3. It seems odd that there is relatively little overlap between the 35 deaths and 36 admissions to the ICU; can you explain this?

Response: The predominant reason for ICU admission was need invasive (n=7) and non-invasive (n=17) ventilation and not sepsis per se. These patients (with often COPD as underlying diagnosis) have the not the same mortality risk as septic shock patients. In addition, some predominately elderly patients, in which death was eminent, might have not been transferred to the ICU because of their age, comorbidity (e.g. cancer) or because patients refused ICU admission.
4. On page #12, you again shift the focus of your discussion to the potential utility of procalcitonin in limiting blood cultures. You have not systematically evaluated PCT levels in this report.

Response: the statement was rarefied.

5. The discussion is overly long, rambles, and overinterprets the data.

Response: the discussion was shortened by one entire page.