Author's response to reviews

Title: Age-related differences in symptoms, diagnosis and prognosis of bacteremia

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Author's response to reviews: see over
Thank you very much for the helpful comments. Here are our Point-to-Point response:

**Reviewer: Anna Levin**

**Reviewer's report:**

My main concern regarding this study is that, although thorough, it is confusing as to its objectives. Initially it seems to evaluate factors associated with outcomes (organ failure and death within 14 days of hospitalization) however the authors present a lot of data on the characteristics and outcomes by age category and on how CPR and SIRS criteria predict organ failure as well as the microorganism (S. pneumoniae) and infection site.

We agree with the referee, and have now been more precise and consistent throughout the manuscript.

It is not clear why factors such as CRP, SIRS 2 and SIRS 3 were not included in the multivariate analysis.

CRP was not included in the multivariate analyses because it was not significantly associated to the outcomes in the bivariate analyses. Regarding SIRS, we decided to include the single markers of inflammation, partly overlapping with SIRS-criteria, rather than SIRS as an entity to be able to compare to similar studies: Leukopenia has been identified as a risk factor for poor outcome. Moreover, as fever has been indicated to be absent in elderly patients with infection more often than in younger patients, we wanted to look into this point as well. As the single markers are not independent of SIRS as an entity, it would not be correct to include them and SIRS in the multivariate analyses.

Should one of the main objectives of the study be to compare the characteristics of infection, clinical presentation and outcome between different age groups?

Yes, this was one of the main objectives, and it has now been included in the abstract and throughout the manuscript.

I feel also that Tables 4 and 5 should present data on the bivariate analyses of all factors evaluated not only the ones that were included in the multivariate analyses.

We agree with the reviewer, and have now included these data in both tables (now table 2 and 3).

In summary, I believe that the study should be revised. Each specific objective should be presented and the methods and results should be simplified in order to answer the objectives.

Each specific objective is now presented more clearly, and the methods and results are simplified in order to answer the comments.
Reviewer: Mette Søgaard

Reviewer's report:

- **Major Compulsory Revisions**

1) **Title**: The title is quite long and could be improved

   We have shortened the title, as well as improved it to prevent unnecessary confusion regarding the objectives of the study described in point 2.

2) **Page 2: Introduction**: The objective stated in the introduction is not really the same as in the title. The title indicates that this study describe prognostic factors associated with bacteremia whereas the objective in the abstract concern with the risk of contracting a severe infection. Please revise this. A review by a native English speaker could be very helpful.

   We have now revised the abstract thoroughly to better present the objectives. A native English speaker has edited the MS.

3) **Page 2: Methods.** Please describe which statistical analyses that were used, and whether the estimates were adjusted for potential confounders.

   Because of constraints regarding number of words in the abstract we have chosen not to include the description of the methods used.

4) **Page 2 results**: How many patients had E. coli and S. pneumonia bacteremia, respectively? Is now included in the abstract. From Table 1 it appears that 72 (10%) and not 92 (14%) died within 14 days of admission. Please revise. Has been corrected.

   Actually, throughout the paper it is a bit unclear to me whether you have follow-up for 14-day mortality for all patients or only for those who are still admitted? Moreover, what is the rationale for reporting 3-day, 14-day and in-hospital mortality? I am skeptical about the value in-hospital mortality since you do not have uniform follow-up for these patients. Therefore, I would recommend that you drop in-hospital mortality and focus on 3-day, 14-day and 1-year mortality.

   We have mortality data from in-hospital and outside-hospital at both 3 days and 14 days of admittance. Reporting in-hospital mortality allows comparison to similar studies. In-hospital mortality truncated at 14 days was chosen in order to separate those who died late during their hospital stay, and thus were more likely to have died from other reasons than severe infection. Regarding the 3-days in-hospital mortality, there are reports that elderly patients with infection die earlier during hospital stay than do younger patients, and we wanted to test this in our material by dichotomizing at 3 days after admittance. We have clarified this throughout the MS.
5) Page 2: I am not entirely sure what is meant by the concluding remark “reproduction of other risk factors underlines the validity of these findings”? This concluding remark has been deleted from the MS.

6) Page 3: Both in the title, abstract, introduction and discussion as well as key messages, the authors are recommended to be more specific regarding the aims of the study. It appears from the title of the paper that the aim is to examine prognostic factors and age-related clinical presentation. However, the abstract gives an entirely different impression. A lot of the results section is focused on identifying predictors of organ failure, but this do not really appear from the aims.

We have clarified this throughout the manuscript, including the revision of table 2 and 3 (now 1 and 2). The variables are presented in a much more logical order that also illustrates the distinction between clinical presentation and severity of infection; these are the two outcomes studied by multivariate analyses (new tables 3 and 4). The discussion and conclusions have been rearranged accordingly.

7) Page 4 Comorbid illnesses: From the description I am not sure whether you used a list of prespecified comorbid illnesses or whether you simply recorded whatever was stated in the medical record?

We had predefined list of illnesses, into which information from the patients charts were categorized. This is now made clear in the manuscript.

Table 2 would convey much more information if you could provide data on the distribution of separate comorbid conditions (e.g. number and proportion of patients with diabetes, COPD, CHF) rather than providing the median number of comorbid conditions. This information is now included in the revised table.

8) Page 5: Criteria for organ failure: I suggest that you move Table 1 to the Appendix. Has been done.

9) Page 7: Statistics: Please specify which survival analyses that you used. Was it Cox regression analysis?

We agree that Cox-regression would have been the correct choice if the observation period had been longer. We chose to use binary logistic regression as advised by our statistician (specified in acknowledgments).

In the analyses of one-year mortality we used Kaplan Meier survival analysis. This is now clarified in the manuscript.

The authors are also recommended to provide further description about what is meant by “sensitivities of CRP and SIRS…”.

Sensitivities related to what? By reading the results section it appears that it is for
identifying #1 organ failures. Is that correct? Please, also see my next comment regarding this analysis and Figure 1. Yes, that is correct. We have tried to clarify.

10) Figure 1. I am very confused about Figure 1 and do not really understand the rationale behind this figure. Shouldn’t the sensitivities be specified on the Y-axis or perhaps it is just me who haven’t seen this kind of figure before? I also suggest that you specify the three age categories in the figure.

The figure is now revised with specification of both sensitivity (Y-axis) and age-categories.

Regarding the interpretation of the Figure (at the top of page 9), the authors comment that there was a significant difference between the middle group and the youngest age-group. Looking at the Figure I would also conclude that the sensitivity for the oldest patients are different from the youngest patients. This estimate is just not statistically significant because the estimate is very imprecise (wide confidence interval). I suggest that the authors put less emphasis on statistical significance.

We have changed this according to the reviewer’s suggestion.

- Minor Essential Revisions


12) Abstract + introduction: Please write the whole genus and species name the first time the name of the bacteria is presented. Done.