Authors’ point-by-point response to the Editor and Reviewers’ Comments

Abstract: following the suggested changes in the ‘Discussion’ section, the resulting statement is now confusing. It needs to be reworded for clarity. I suggest removing mention of the Gram positive and Gram negative part.

[Authors’ Response]: Dear Editor, we agree with your comments on the abstract. We decided and had completed rewriting a new Abstract. Please see for yourself and help us to detect any other issues requiring to be tackled. Many thanks.

I also suspect Reviewer 1 doesn’t want any abbreviations in the abstract, rather than defining at first mention. I suggest you not use PCT or LAC – just spell these out throughout.

[Authors’ Response]: We thank the Academic Editor and the Reviewer for the constructive suggestion. We have removed all the abbreviations in the abstract. Moreover, throughout the text proper, procalcitonin and lactate are all spelled out.

Introduction:

What is meant by ‘blood-cultured’ patient? Is this someone who has had a blood culture taken? Or someone with a positive blood culture?

[Authors’ Response]: Dear Editor, we thank you for your attention to details. In the revised manuscript, we have rephrased the sentence as: “In a cohort study, among patients who had blood cultures performed within 72 h of arrival to the medical ED, the overall 30-day mortality rate was 11% (Lindvig et al. 2016).”

Materials and methods:

Please provide the reason for the difference cut-off values in the manuscript and state that these are different from that used in previous sepsis studies. Please provide discussion about how this impacts upon the generalisability of your study.

[Authors’ Response]: We thank the editor for highlighting the difference in the cutoff value of a test between the previous studies and ours. Our research question was to examine the diagnostic value of elevated biomarkers using a cutoff at the upper limit of reference range (procalcitonin, 0.5 ng/mL; lactate, 19.8 mg/dL; and high-sensitivity C-reactive protein, 0.8 mg/dL) for predicting bacteremia, not to derive an optimal cutoff for each single test to obtain the best discriminative power for bacteremia prediction. The different cutoff values you mentioned in the previous studies were resulted from a different study design from ours. We have added the above second sentence to the Materials and Methods section in the new manuscript. We also provide discussion about how this impacts on the generalizability of our results in the Discussion Section. Using a cutoff at the upper limit of reference range for all three biomarkers, the generalizability of our study results will be more easily applied to the real-world practice in the emergency department.

You have now provided details of how contaminants were defined, how about pathogens?

[Authors’ Response]: We thank the editor for this construction suggestion. We feel sorry not to have presented the definition in the Materials and Methods section of the previous versions of the manuscript. In the revised manuscript, we have added the following statements. Pathogenic bacteria were defined in the study as follows: True bacteremia was defined as growth of any significant, pathogenic bacterial species in one or more sets of blood cultures consisting of aerobic and anaerobic bottles. Common skin pathogens often considered as contaminants (namely, coagulase-negative Staphylococci, aerobic and anaerobic diphtheroids, Micrococcus species, Propionibacterium species, or Bacillus species) were excluded from this definition, except when the same species were isolated from at least two consecutive blood cultures (Jaimes et al. 2004; Richter et al. 2002). Mixed cultures were considered pathogenic when bacteria other than the contaminants were isolated.

Discussion:

Please include direct statements that your study assesses predictors of BC positivity, but not of sepsis.

[Authors’ Response]: We have added the statement: “Readers are again reminded here that our study assesses predictors of blood culture positivity, but not of sepsis.” in the Discussion section.

I agree with Reviewer 1 that the discussion needs to include further work to place your study in the context of the broader literature in this area.

[Authors’ Response]: Please allow us to answer this question in the next Reviewer’s comment because both questions/comments refer to the same issue.

Reviewer 1

Basic reporting

It is still a lack of literature references and context in the Discussion. Only a very few of your results are compared with other peoples work (and here only two other works are cited). The Discussion must be extended and the obtained results put in a context, i.e., compared with previous studies reporting the performance of the single biomarkers and/or combined biomarkers for predicting positive blood cultures. Reasons for differences/similarities in findings between studies?

[Authors’ Response]: We thank the editor and the reviewer for reminding us the inadequacy of this part in the Discussion. We have done our best to add relevant references and rewrite the Discussion in the new manuscript. After this rewrite, the word count of the Discussion including conclusions has reached over 1,700 words, and the number of relevant references has reached 38 altogether. We would like you to appreciate what we have accomplished at the moment and feel free to tell us what to change if you think it necessary.

Line 249 and 257: No information about the frequency of positive blood cultures for the expanded cohorts. This is important as the group sizes are very important for the performance characteristics. This information must be added in Method and Material section.

[Authors’ Response]: Again, we thank the reviewer for this constructive comment. We have added the information to the Methods and Materials Section. Line 197–202: Since the group sizes are important for the test performance, the prevalence of positive blood culture in the two expanded cohorts are as follows: the expanded cohort that consisted of 923 patients who had procalcitonin, lactate and blood cultures taken on the same day had a prevalence of true bacteremia of 21.9% (202+/923). Another expanded cohort of 2,234 patients who had procalcitonin test result and blood culture results had a prevalence of true bacteremia at 15.5% (347+/2234).

Line 184-186: this sentence is very hard to understand and must be rewritten.

[Authors’ Response]: We thank the reviewer for the attention to details. The poorly understood sentence has been changed to: “We performed ROC curve analyses for every single test, procalcitonin, high-sensitivity C-reactive protein, and lactate in all 886 adult patients to compare their discriminative power in the prediction of the blood culture positive for bacteria (Fig. 1), GNB (Fig. 2), and GPB (Fig. 3).” This change can be found in line 212 to 215.

Line 197- : all the data presented in the text here should be presented by tables only.

[Authors’ Response]: We thank the reviewer for the comment. We used the Tables to display the study results, whereas, in the Result section, these data presented in the text are within the context of study interpretation.

Line 246: threshold for PCT is not defined here.

[Authors’ Response]: We thank the reviewer for the attention of details. We have defined all the cutoff of procalcitonin throughout the manuscript for clarity.

Inconsistent use of hs-CRP vs. high-sensitive CRP. This should be looked over throughout the manuscript.

[Authors’ Response]: We thank the reviewer for highlighting this inconsistency. We have spelled out all the abbreviations and used only the term: high-sensitivity C-reactive protein throughout the main text.

Validity of the findings

In the Abstract: You write "Among patients with elevated PCT and/or LAC, the odds for predicting positive blood culture was nearly five-fold higher compared to that in patients with normal levels (diagnostic odds ratio, 4.83; 95% CI, 42 2.84–8.69). The diagnostic odds ratio was nearly eight-fold higher for the prediction of positive gram-negative bacteria (GNB) culture (diagnostic odds ratio, 7.75; 95% CI, 3.56–20.03) and it was nearly three-fold higher for the prediction of positive gram-positive bacteria (GPB) culture (diagnostic odds ratio, 2.87; 95% CI, 1.43–6.41)." I wonder where these figures come from as I don´t recognize the from the results reported in the manuscript? The abstract should only report exactly the same results as in the Results section.

[Authors’ Response]: Dear Reviewer, in the Abstract, we did extract correctly and report exactly the same figures as in the Results section. Those figures can be found in in Table 2 and Table 3. However, we decided and had completed rewriting a new Abstract. Please see for yourself and help us to detect any other issues requiring to be tackled. Many thanks.

A diagnostic accuracy of only 65% is not acceptable from a clinical point of view (as stated for example in line 275 and line 347). This is considered to be rather poor actually.

[Authors’ Response]: We agree with the reviewer for this important question. We have deleted or rephrased the statement to: Line 293 to 300: “As a single test to predict bacteremia, the procalcitonin test performed even better in a larger expanded cohort of 2,234 adult patients than in the initial cohort of 886 patients in terms of overall accuracy and diagnostic odds ratio, 65% vs. 54% in terms of accuracy and 5.34 vs. 3.64 in terms of the diagnostic odds ratio for predicting blood culture positivity; 65% vs. 53% in terms of accuracy and 10.13 vs. 6.44 in terms of the diagnostic odds ratio for predicting positive GNB culture; and 63% vs. 49% in terms of accuracy and 2.83 vs. 1.89 in terms of the diagnostic odds ratio for predicting positive GPB culture (Supplementary Table 1).”

It is wrong to say that CRP should be abandoned from the ED; it is still useful as a marker for bacterial infections but is limited by it´s slow kinetics and should be viewed from the time point of disease onset.

[Authors’ Response]: We agree with the reviewer on this comment. Line 437-438: We have rephrased as “High-sensitivity C-reactive protein performed poorly for the prediction of positive bacterial culture.”

Reviewer 2

Comments for the author

Thank you for a very improved manuscript.

I have one suggestion to remove the number of patients from the title.

[Authors’ Response]: We thank the reviewer for this kind suggestion. We decided to remove the number of patients from the title.