Author's response to reviews

Title: Failure of available scoring systems to predict ongoing infection in patients with abdominal sepsis

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Author's response to reviews: see over
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Dear editor,

Thank you reviewing our manuscript and considering our paper for publication after revisions made. Please, accept our apologies for the late response. The critical appraisal and amendments contributed to further improvement of our work. Hopefully the revised version of our manuscript will again be considered for publication.

We have responded to the remarks made by the editorial board and reviewers and revised our work wherever appropriate. Please regard the text below.

**Reply to the reviewers**

**Associate Editor**

The authors should change their study design to a retrospective analysis even that the data in the RELAP trial were collected prospectively.

In respect of the change of study design we would like to emphasize that data on patient characteristics, operation characteristics and laboratory values on consecutive days (day 1 to 14 every day, afterwards weekly until discharge or death) were actually collected prospectively for the RELAP trial per protocol. Upon ICU admittance somewhat more variables were collected than strictly specified by MODS, APACHE II and MPI.

Reviewer 1 is concerned about data collection regarding the SAPSII and SOFA scores. Most data incorporated in these scores are also used in MODS, APACHE II or MPI scores (Table 1). To specifically attend to the data singularly used in either the SAPSII or the SOFA, we give an overview below:

**SAPSII**

Type of admittance – collected prospectively as baseline characteristic

Mechanical ventilation – collected prospectively per protocol as ICU parameter

HCO3 – collected with bloodgas analysis which is performed routinely every day at ICU admittance was considered normal when not admitted to the ICU and no sign pulmonary complications

Urea – collected prospectively per protocol as part of measurement of renal functioning

**SOFA**

Cardiovascular state (defined as administration of and dosage of (nor)epinephrine, dopamine or dobutamine at ICU) – collected prospectively per protocol as ICU parameter

We were dependent on participating doctors for data collection in multiple hospitals. Unfortunately, datasets were not fully complete despite close conduct of our study coordination. Furthermore, multiple imputation of missing data is a widely acknowledged method to reduce uncertainty when analyzing compository scores with missing values which were intended to be collected prospectively.

We feel that to actually change our design to a retrospective study as a whole incorrectly states our methods of data collection and data analyses. We have changed our title to reduce the emphasis on the prospective character of this study. Furthermore we explained data collection somewhat more extensively in the methods section

- Title, p.1 and ‘Methods’ section, Missing values, 1st paragraph, p.7
Editorial requirements

Conclusion Section: Please include a Conclusions section as the last section of the text. This should state clearly the main conclusions of the research and give a clear explanation of their importance and relevance. Summary illustrations may be included.

A ‘Conclusions’ section was added to the manuscript (p.13).

Furthermore, reference citations and references were adjusted according to BMC formatting throughout the manuscript (and ‘References’ p. 16-17). According to your journal’s format we have first stated the figure legends which are followed by the tables (p.18).

Reviewer: Magnus Kaffarnik

Major Compulsory Revisions

It is not a prospective study, but a retrospective trial: The RELAP-trial included the APACHE II score, MPI and MODS. SAPS II and SOFA scores were not mentioned in this trial. These data seems to be collected retrospectively. Also the replacement of missing values (page 7) with statistical methods speaks for a retrospective collection of data. One of the reasons of a prospective Trial is to avoid missing values.

Please, address the answer given to the first editorial remark above.

The group "patients with no relaparotomy but dead <14 days" is unclear. Did they all have an ongoing infection needing relaparotomy? They may die because of other reasons than abdominal infection. It would be interesting to know about the reasons for death.

Death in this group was ‘all cause’. We believe that at this short time interval from emergency laparotomy for secondary peritonitis this underlying condition is related with the cause of death; even when peritonitis is not so evident that relaparotomy or percutaneous intervention was performed. The time frame of 2 weeks was chosen as we believe that most severe complications – or consequences – will occur within this time window, including deterioration of the patients overall condition.

An extra statement was included in the manuscript to further enlighten on cause of death within this time frame.

- Methods, outcomes, ongoing infection needing relaparotomy, first paragraph, p.4.

The group "no relaparotomy but percutaneous drainage with drains left in situ" seems to be matched in the group "ongoing infection". Why should they get a drainage without infection?

Patients without a new or residual intra-abdominal infection should indeed not receive percutaneous drainage. Therefore, they were incorporated in the ‘ongoing infection’ group.

Please refer to the ‘Methods’ section (outcomes, ongoing infection needing re-intervention), p.5
As the authors mentioned, all scores, except the MPI, have been developed to predict death for ICU (page 10 ff). Therefore the failure of these scores in predicting the need for relaparotomy is not unexpected.

This remark is correct. However, in clinical practice the treating medical team seems to attach value to clinical deterioration or failure to recover – often depicted with incorporated ICU scores – in decision making for relaparotomy or percutaneous intervention. In this study we question whether we can use widely incorporated ICU scores to improve our decision making for relaparotomy or percutaneous intervention for patients with ongoing or persistent intra-abdominal infection.

Text was edited to further clarify the purpose of studying prognostic scoring systems in this manuscript.

- ‘Introduction’, final paragraph, p.3

The sequential scores (SOFA, SAPS II and MODS) are measured only on day 1+2 after initial operation and missed the period between day 3-7. 61 patients of the RELAP trial had 2 and more relaparotomies. It is likely that for many of these patients the period of operations was >7 days. It is reasonable to extend the time frame for measuring the sequential score (e. g. day 4 + 6). It is also interesting to analyze these scores on later days in patients without relaparotomy, but died <14 days (page 11; For the non-operated….).

It would be expected that later sequential scores are lower in patients without relaparotomy and surviving 14 days than in patients with relaparotomy between days 3-7. The statistically difference might be significant and the score might predict need for relaparotomie.

In this study we focus on early identification of patients with ongoing infection needing relaparotomy / re-intervention in the acute phase of the disease. We believe that adequate selection of patients and timing of early re-intervention where necessary will enhance patient survival in abdominal sepsis.

Therefore, in this study the emphasis of patient selection for re-intervention is within a short time period following emergency laparotomy. The proposed analyses will not contribute to early identification of patients for re-intervention and therefore beyond the scope of this manuscript.

Please refer to the ‘Methods’ section (Study population, final paragraph, p.4.) where we explain the need of early patient identification.

Discretionary Revisions

The overall timeframe is short. The experience shows that critically ill abdominal surgery patients die after weeks because of ongoing tertiary peritonitis. It would be interesting to know about the 90-day-mortality rate and the relationship between dead on day 15-90 and ongoing peritonitis.

This study was conducted to try and optimize timing for relaparotomy or re-intervention in the acute phase of abdominal sepsis. In this phase patients are most critically ill and adequate selection of patients and timing of re-intervention is, we believe, associated with reduction of morbidity and mortality.

It would indeed be interesting to study ongoing tertiary peritonitis. We believe, however, that tertiary peritonitis is beyond the scope of this study as tertiary peritonitis is defined as ongoing intra-abdominal infection after adequate source control. Therefore, we believe tertiary peritonitis is a different disease entity and requires a different treatment strategy.
Please refer to the ‘Introduction’ and ‘Discussion’ sections. Amendments were made to further emphasize this study was conducted for patient selection and timing of re-intervention in the acute phase of secondary peritonitis.

- ‘Introduction’, final paragraph, p.3
- ‘Discussion, 3rd paragraph, p. 11

There are some interesting recent papers that could be discussed (e.g.):

Chromik et al. (2009) Identification of patients at risk for development of tertiary peritonitis on a surgical intensive care unit.

Zügel et al. (2011) Predictive relevance of clinical scores and inflammatory parameters in secondary peritonitis.

Egberts et al. (2011) Preoperative risk evaluation of postoperative morbidity in IBD patients--impact of the POSSUM score.


We thank the reviewer for pointing out these recent studies. The manuscripts mentioned are indeed interesting, especially the ones by Zügel et al., Torer et al. and Tan et al. However, these studies looked at mortality and not at patient selection for relaparotomy for ongoing infection.

We have included the articles by Torer et al. and Tan et al. to our Discussion as adequate regression analysis was performed to identify prognostic value of the MPI. However, all three studies describe retrospective data analyses based on only few events. We have also added a remark on the study by Zügel et al. confirming value of the SOFA score regarding prediction of patient outcome in secondary peritonitis.

The article by Chromik et al. on tertiary peritonitis is beyond the scope of this manuscript as we try to detect early ongoing infection due to failure of source control or new intra-abdominal focus. Tertiary peritonitis is defined as severe recurrent or persistent intra-abdominal infection after adequate surgical source control of secondary peritonitis. Also we believe that IBD patients are more complex and cannot be compared to a standard secondary peritonitis group of patients. Therefore, the article of Egberts et al. is not included in our manuscript.

Articles by Zügel et al, Tan et al. (on small bowel perforation [2010] and colon perforation [2011]) and Torer et al. were reviewed in the ‘Discussion’ and added to our references (Discussion, p. 9, 1st paragraph; References 17 to 20, p. 14)

Reviewer: Carolin Kayser

There were no major and/or minor revisions stated.

Kind regards, on behalf of all authors,

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