Author's response to reviews

Title: Gastrointestinal failure in intensive care: a retrospective clinical study in three different intensive care units in Germany and Estonia.

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Author's response to reviews: see over
Dear Editor-in-Chief

Enclosed, please find the revised version of the manuscript – Gastrointestinal failure in intensive care: a retrospective clinical study in three different intensive care units in Germany and Estonia. A. Reintam, P. Parm, U. Redlich, L.-M. Tooting, J. Starkopf, F. Köhler, C. Spies, H. Kern

We would like to thank you and the reviewer for providing important comments and criticisms. Revision has been made according to these comments which we do feel have improved the manuscript. Details of the changes made are listed below. We hope that you find the critique adequately addressed, and that the enclosed and revised manuscript can be considered for publication in BMC Gastroenterology.

Annika Reintam
Corresponding author
Answers to the reviewers

We thank all the reviewers for valuable comments, which clearly have helped us to improve the study. Below is the point-to-point response.

Reviewer # 1

*In the present study, of retrospective character there seems to be an additional mortality risk in the patients with low SOFA scores (<8) in predominantly post cardiac surgery patients. This category patients can be complicated by low output syndrome resulting in cardiovascular failure and usually intestinal failure follows. GIF can be considered as a proxy parameter for the severity of cardiac failure. In the discussion authors should elaborate on this matter. Statistical analysis should made clear that GIF is not related to SOFA 3 and 4 points in the SOFA category for cardiovascular failure.*

We agree with the reviewer, that in cardiac surgery patients the GIF may most likely result from intestinal hypoperfusion. Also, detrimental influence of cardiopulmonary bypass cannot be excluded. In the revised version of the manuscript, the discussion is extended respectively (page 12-13).

*Furthermore: the criticism the authors put forward on the Goris score (lack of definitions in the gastrointestinal items) holds also true for their proposed score. Vomiting: how much how often, what about regurgitation.? Gastric retention: what cut-off values are used to discontinue feeding/tube feeding ?. Inability to feed: what percentage of target caloric /volumetric intake ? Presence of blood in retention or stools: coffee grounds, bright red blood, positive guaiac test ??*

We completely agree with the criticism on the definitions, made by all reviewers. In clinical routine, probably, the symptoms like food intolerance, gastrointestinal haemorrhage, and ileus are often used without concerning the clear and exact definition of them. In our database, aimed to document the main factors influencing the outcome of the patients, the symptoms were defined as described in the manuscript. Vomiting was considered important if feeding needed to be stopped. The regurgitation was not specifically addressed. Feeding was discontinued if the amount of the nasogastric aspirate appeared bigger than the volume given enteral previously. The ratio of enteral feeding to total nutritional requirements was not documented in the database; the presence of blood in stool was assessed visually, guaiac or other tests were not applied routinely. We agree that there are substantial drawbacks of the definitions, and this is discussed in the revised manuscript.

Still, even despite of these limitations we believe that our retrospective analysis demonstrates, first, that gastrointestinal failure is a relevant problem with high impact on ICU outcome, and, second, that attention should be paid to the fact that there is no
definition and criteria for this organ failure in modern literature. The need for prospective study with exact definition is obvious, and we are currently working on it. The GIF score is an idea that we are trying to address in our ongoing prospective study.

*It is also not clear when a patient was considered as a GIF positive patient: only once one of their gastrointestinal problems occurred? or during more consecutive days? The score used in the study is not categorised i.e. GIF severity is not categorised. A gastric retention of 500 ml/24 hours with 400 ml of feed is as severe as a gastrointestinal hemorrhage. Authors should comment on this matter in the discussion.*

GIF was defined as presence of at least one of the following gastrointestinal problems documented in the patient data at any period of their ICU stay: food intolerance, gastrointestinal haemorrhage, and ileus.

Yes, in present form of data, the GIF is defined as a “yes or no” phenomenon. This is a clear limitation as the severity of the symptoms is indeed different. Further studies should evaluate the GIF score, where categorized symptoms are included and weighted respectively. The matter is commented in the discussion of the revised version of the manuscript (page 12).

*Figure 1 the ROC curve can be omitted. Does not provide additional information to support the stated issues.*

In the revised manuscript, the figure is omitted.
Reviewer # 2

2. The method section should provide a more detailed description of the patient population and the settings. The specific reasons for ICU admission and underlying co-morbidities should be described. Were there any patients admitted for GI reasons (medical or surgical)? The number of beds and the staffing (physician, nursing, etc) should be described.

In the methods section of the revised manuscript, we attempted to give a better description of the ICUs and the patient population. The majority of the patients were postoperative cardiac surgery patients. Unfortunately, we are not able to provide the exact number of patients that were admitted due to primary GI reasons.

3. The main objectives of the study were to describe the incidence of GI failure and the risk factors associated with it as well as its impact on outcome. The comparison of the three intensive care units does not add any pertinent information to the objectives of the study and some of it should be deleted. Description of the three ICUs is adequate.

In the revised manuscript, the data presentation is changed according to suggestions made by reviewer #3. The comparison of the three intensive care units is omitted.

4. The statistical section needs to be rewritten. I have a hard time in understanding how the data were analyzed. I assume the authors first performed univariate analysis to identify variables associated with the development of GI failure and then developed a logistic regression model by including the predictor variables with a P value of < 0.05. I again assume the AUC was calculated from the logistic regression model. All these should be clearly stated.

In the revised manuscript, we have attempted to improve the description of statistics. The methods and the results sections are rewritten.

2. The authors have clearly highlighted the fact that one of the reasons gastrointestinal failure did not get the attention it deserves was due to lack of acceptable definition. They used food intolerance, gastrointestinal (GI) bleeding and ileus to define GI failure. This is a good start. However, the definitions they used for food intolerance and ileus are incomplete. Ileus is not defined. Food intolerance may result from causes other than nausea and vomiting. For example, diarrhea is one of them. There may also be non-GI etiologies leading to food intolerance.

We agree with the criticism on the definitions, made by all reviewers. In clinical routine, the symptoms like food intolerance, gastrointestinal haemorrhage, and ileus are commonly used to characterise GI dysfunction/failure, while clear and exact definitions of them is often missing. Our ICU database is recorded with the aim to document main factors influencing the outcome of the patients. Originally not much attention was paid to GI symptoms, and they were defined as described in manuscript. Present retrospective
The ileus was defined as an intestinal obstruction due to inhibition of bowel motility.

6. In the results section, the authors mention that 48 variables from the first ICU day were analyzed to assess the risk factors for GI failure. These variables should have been mentioned in the methods section. Moreover, the authors mention that the change in SOFA score during the first two days is a risk factor for GI failure. When talking about risk factors, I suggest looking at the first day variables only.

The following variables from the first ICU day were analyzed:
age; sex; patients’ profile; diagnose group; source of admission; ICU; APACHE II; SOFA; SAPS II; mean arterial pressure; heart rate; glasgow coma scale; pH; CVP; PEEP; op time; reoperation; bleeding; transfusion; haemoglobin; haematocrit; WBC; platelets; glucose; C-reactive protein; albumin; protein; bilirubin; creatinine; urea; pO\textsubscript{2}/FiO\textsubscript{2}; lactate; antithrombine III; readmission; reintubation; mechanical ventilation; use of catecholamines; use of thrombolytics; sedation; enteral nutrition; renal replacement therapy; low cardiac output syndrome; renal failure; liver failure; septic shock; diabetes; reanimation.

Twenty-three from these variables were identified as highly predictive (p<0.01) risk factors for GIF development, including:
patients’ age, medical profile, haematocrit, leucocyte count, platelet count, creatinine, urea, bilirubin, C-reactive protein, lactate, pO\textsubscript{2}/FiO\textsubscript{2}, mean arterial pressure, central venous pressure, APACHE II, SOFA; SAPS II, use of catecholamines, sedation, PEEP, hemodialysis, low-output syndrome, septic shock, and use of blood products.

In results section of revised manuscript, only independent risk factors are given. The change in SOFA score is omitted from the analysis of risk factors.

7. In the results section, the authors state that GI failure was more common in patients who did not receive enteral nutrition on day 1. Since the definition of GI failure included food intolerance, this is the result of the definition. The reason why the authors did not find similar association in Berlin is probably due to the low incidence of GI failure.

We agree and omitted the respective paragraph in the revised version of the manuscript.

8. Based on the logistic regression analysis, the authors calculated the predictive accuracy of the model. The authors need to tell us what the independent predictor variables were included in the model. I strongly recommend that the authors describe the variables independently associated with the development of GI failure.

The most powerful predictors for GIF development appeared to be SOFA score and APACHE II score on admission. Twenty-three variables demonstrated a significant correlation with the development of GIF. In the revised manuscript, logistic regression
analysis is provided. The variables independently associated with the development of GI failure were APACHE II and SOFA scores on admission; patient profile and use of catecholamines.

9. I also suggest that the authors tell us the AUC (with 95% CI) of their model as well as its calibration. The isolated AUCs of SOFA and APACHE II (figure 1) are not adequate.

10. The authors also need to describe how they chose the cut-off points for calculating sensitivity, specificity and negative and positive predictive values of their model. They also need to describe all these predictive test results with their 95% CI.

We agree with the criticism to the analysis shown on figure 1. In the revised version of the manuscript, the figure is omitted.

11. The impact of GI failure on outcome is stated in the manuscript. GI failure increases mortality, duration of mechanical ventilation and length of ICU stay. However, the manuscript does not provide convincing evidence about the independent association of GI failure with these adverse outcomes. The data available in the study included APACHE II and SOFA. Was the association of GI failure with adverse outcome independent of the admission APACHE II and the SOFA score on the day GI failure developed?

Yes, GIF was independent factor, in addition to APACHE II and SOFA on admission, in predicting the ICU mortality. The data are presented in the results section of the revised manuscript.

13. The authors need to provide explanations for differences in the incidence of GI failure and outcome of patients among the different ICUs? For example, was stress ulcer prophylaxis administered in all ICUs?

Different incidences of GIF in the three ICUs are most likely explained by the difference in the patients’ profile. In ICU1 and ICU2 mainly postoperative cardiac surgery patients were treated, while ICU3 dealt with surgical and medical emergencies. Stress ulcer prophylaxis was given routinely in all units. In the revised manuscript, the detailed comparison between the units is omitted, and replaced by a classification according to the patient profile (elective surgical, emergency surgical and medical).

14. The time of onset of GI failure should be described.

The time of onset (cumulative incidence) of GIF is illustrated by figure 1 in the revised manuscript.

15. In the discussion section, the authors have mentioned some of the variables associated with GI failure. This should be stated in the results section.

Thank you for pointing this out. In revised manuscript Methods and Results sections have been rewritten accordingly.
Reviewer # 3

We thank the reviewer for valuable comments, which helped us clearly to improve the manuscript.

Introduction:
The authors should however at least somewhere mention the relation between intraabdominal pressure and gastrointestinal failure. Was IAP measured? If not in all patients try to provide some data. If IAP was not measured then this should be discussed as a major limitation of the study and as a possible goal for future studies.

Yes, we agree with that. The sentence about IAP was added to the introduction, and the discussion is changed accordingly. In the present study, the IAP was not measured (retrospective study of patients treated during the year 2002).

Materials and methods:
The definitions for food intolerance, ileus and hemorrhage as they are given are quite vague, they should be better defined.

We completely agree with the criticism of the definitions. In clinical routine, the listed symptoms are often used without concerning the clear and exact definition of them. In our database, aimed to document the main factors influencing the outcome of the patients, that was also the case. The drawbacks of the definitions are discussed in the revised manuscript. In this retrospective study it was impossible to reanalyze the data with the suggested modified definitions. However, even despite of these limitations we still believe, that we are able to demonstrate firstly, that gastrointestinal failure is a relevant problem with a high impact on ICU outcome, and, secondly, to pay attention to the fact that the definition and criteria for this organ failure are almost absent in modern literature. The need for a prospective study with exact definition (including objective parameters such as IAP) is obvious, and we are currently working on it.

Statistics:
I suggest to re-analyse the data as follows:
- tables 1 to 5 should be replaced by only 2 new tables
-first do a univariate analysis (either ANOVA, student t test or mann whitney U) comparing the different variables in survivors versus nonsurvivors and in GIF vs non GIF patients.

The analysis and presentation of data has been changed. The number of tables is reduced from five to two. We decided not to add the table comparing survivors and nonsurvivors in the manuscript because of a little additional information, although it is added to this letter.

Identify the dependent variables for either outcome or GIF development on univariate analysis (p<0.01)
- Enter these highly predictive parameters into the multiple logistic regression model to identify independent predictors for mortality or GIF development.

The results of logistic regression analysis are included in the results section of the revised manuscript.

What about combining SOFA + GIF and looking for mortality as an endpoint – I assume that the AUROC would even be better… Maybe you could quantify GIF by giving some point as with SOFA subscores; eg no GIF afctors = zero points, 1= 1point, etc – problem is that there are only 3 determinants so you’ll need to find out what condition gets 4 GIF points.

In our opinion, it would be hard to expect reliable results form the analysis of the data after a transformation as suggested. SOFA score is measured on admission, and on an everyday basis thereafter; while GIF, in contrast, is documented as a “yes” or “no” phenomenon in our database. The possibility for errors in the data transformation process cannot be eliminated; therefore, we decided not to add such an analysis. The GIF score, however, is an interesting idea, which we are trying to address in our ongoing prospective study.

I also strongly suggest to omit any differentiation between Berlin and Tartu in the manuscript, you performed a MULTIPLE center study so the data should be treated as such! You could do a subgroup analysis afterwards and just explain in a few sentences in the text the results of that.

Please stratify patients according to admission groups: elective surgery (cardiac and other), emergency surgery (cardiac and other), medical instead of pooling medical and emergency surgery together.

Thanks to pointing this out. In the revised manuscript we analyzed and presented the data accordingly.

How many CABGs were emergencies?

310 cardiac procedures were emergency cases.

Page 6: omit the formulas for RR and OR.

Omitted.

Page 9, second paragraph: It seems logic that GIF development was more often in patients who did not receive enteral nutrition since it is part of the definition (food intolerance and ileus); this statement should be omitted

We agree with the reviewer, and omitted the respective paragraph in the revised version of the manuscript.
Page 9, paragraph 3: Please put the results of the regression analysis here, state the independent predictors for mortality and GIF according to the results of the analysis as pointed out above.

In the new version of the manuscript, the regression analysis is included.

**Discussion**
Nicely addresses the problem of the lack of acceptance of GIF in current scoring systems. The issue of IAP needs to be addressed here at some point! Discuss the option to add the GI tract into the current SOFA score since as is nicely pointed out the GI tract is NOT included into current organ failure scoring systems... However GI failure will lead to hepatosplanchnic hypoperfusion, bacterial translocation finally triggering a vicious cycle leading to MOF...

The relevance of IAP is discussed in the revised manuscript.

**References:**
We added some recent articles and also our own data presented as an abstract on an ESICM meeting.

**Figures:**
Please add a figure showing the GIF incidence for the whole group during the first week. Please also provide figures for SOFA evolution in survivors vs nonsurvivors during the first week.

Figure of cumulative incidence of GIF is added to the revised manuscript. We decided not to include the figure for SOFA evolution since in our opinion; it would add little information to the results. The Figure is enclosed to the present letter.

**Minor comments:**
- page 8 second paragraph: replace incidence of GIF with the development of GIF...
- page 8, paragraph 4: replace periods of mechanical ventilation with duration of MV
- page 8, par 5, line 4: replace described by found

Respective changes were made.
**Table.** Comparison of survivors and nonsurvivors. Data are presented as medians (with lower and upper quartiles) if not stated otherwise. P-values (Mann-Whitney U-test for continuous variables or chi square test for categorical variables) are calculated for the differences between survivors and nonsurvivors.

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>Total</th>
<th>P-value (survivors vs. nonsurvivors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>2355</td>
<td>233</td>
<td>2588</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(91.0%)</td>
<td>(9.0%)</td>
<td>(100.0%)</td>
<td></td>
</tr>
<tr>
<td>Female/male ratio; number of patients</td>
<td>807/1548</td>
<td>89/144</td>
<td>896/1692</td>
<td>0.229</td>
</tr>
<tr>
<td>Age, years</td>
<td>64 (55-72)</td>
<td>67 (57-74)</td>
<td>64</td>
<td>0.099</td>
</tr>
<tr>
<td>Patients’ profile; number of patients (percentage)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elective surgical</td>
<td>1727</td>
<td>44</td>
<td>1771</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(97.5%)</td>
<td>(2.5%)</td>
<td>(100.0%)</td>
<td></td>
</tr>
<tr>
<td>emergency surgical</td>
<td>466</td>
<td>115</td>
<td>581</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(80.2%)</td>
<td>(19.8%)</td>
<td>(100.0%)</td>
<td></td>
</tr>
<tr>
<td>medical</td>
<td>162</td>
<td>74</td>
<td>236</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(68.6%)</td>
<td>(31.4%)</td>
<td>(100.0%)</td>
<td></td>
</tr>
<tr>
<td>APACHE II score, points</td>
<td>12 (9-16)</td>
<td>21 (15-27)</td>
<td>13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SOFA score, points</td>
<td>5 (4-7)</td>
<td>10 (7-13)</td>
<td>5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incidence of GIF</td>
<td>142</td>
<td>110</td>
<td>252</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(6.0%)</td>
<td>(47.2%)</td>
<td>(9.7%)</td>
<td></td>
</tr>
<tr>
<td>Mechanically ventilated; number of patients (percentage)</td>
<td>1936</td>
<td>220</td>
<td>2156</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(82.2%)</td>
<td>(94.4%)</td>
<td>(83.3%)</td>
<td></td>
</tr>
<tr>
<td>Days on mechanical ventilation</td>
<td>1.0</td>
<td>4.0</td>
<td>1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(1.0-1.0)</td>
<td>(1.0-13.0)</td>
<td>(1.0-2.0)</td>
<td></td>
</tr>
<tr>
<td>ICU stay, days</td>
<td>2.0</td>
<td>5.5</td>
<td>2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(2.0-3.0)</td>
<td>(1.0-15.5)</td>
<td>(2.0-4.0)</td>
<td></td>
</tr>
</tbody>
</table>
**Figure.** Evolution of median and quartile scores in daily SOFA during the first week of stay in intensive care.