Author's response to reviews

Title: Limitations of the MELD score in predicting mortality or need for removal from waiting list in patients awaiting liver transplantation

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

we would like to thank you and the reviewers for the excellent and encouraging comments and hope, that we address all topics completely and satisfactorily resulting in a substantially improved manuscript that is appropriate and interesting for the readers of BMC Gastroenterology. Please find below the point-by-point response to the remarks of the editorial office and of the reviewers.

Comments of the Editorial Office:

Due to the different recommendations made by the reviewers, our Medical Editors have also assessed your manuscript, and, although we have serious concerns that your manuscript may not warrant publication in BMC Gastroenterology, we would like you to revise your manuscript before we can reach a final editorial decision. We would particularly like you to justify the statistical methods used, provide the additional statistical data requested and ensure that your conclusions are fully supported by your data. Please note that we will be seeking further advice once we receive your revised manuscript.

Obviously we did not succeed in pointing out that the focus of our main analysis was laid on showing that the optimal cut-off of CTP discriminated better than the optimal cut-off of MELD. In addition our analysis includes patients removed from waiting list and incorporates a longer observation period than the regularly assessed 3 or in some studies 6 months survival analysis. So it does not focus on short term prediction for organ allocation, but may have implications for generation of new improved scoring systems. We included the requested statistical data. We changed the title and the conclusion to a more accurate in some extent more cautious wording, thereby ensuring that the conclusions drawn are well supported by our data.

The statistical methods used were described in more detail. A major goal of our trial was to evaluate the reliability of both scores in discriminating patients still on the waiting list from patients died or removed. For this goal we chose the method of minimizing false positive and false negative estimations of each score to determine optimal cut off values. In addition the c-statistics to compare the area under the ROC curves was included. Both methods are regularly used for analyzing scoring systems. The p-values for each test were included in the results in the revised version of the manuscript.

In addition to the concerns raised by the reviewers and our Medical Editors, please also address the following points:

1. Please document ethical approval. Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm). A statement to this effect must appear in the Methods...
section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

We included the following statement regarding ethical approval: “The study protocol conformed to the ethical guidelines of the Helsinki Declaration and was approved by the ethics committee of the University of Heidelberg.”

2. We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional copyediting service. Examples are those provided by the Manuscript Presentation Service (www.biomedes.co.uk), International Science Editing (http://www.internationalscienceediting.com/) and English Manager Science Editing (http://www.sciencemanager.com/). BioMed Central has no first-hand experience of these companies and can take no responsibility for the quality of their service.

As suggested we sent the manuscript to a professional copyediting service and hope that it now fulfils the expected standard of written English.

Figure 1, panel A and B mistakenly read “still on WL or dead” and has been exchanged to “still on WL”. This reflects the analysis and how it is described in the text and the figure legends.

Referee 1: Reviewer: Teh-la Huo
Reviewer's report:
The authors investigated the predictive accuracy for the outcome between the CTP and MELD system. They concluded that CTP is superior to the MELD for outcome prediction. There have been abundant studies in this regard during the past 6-7 years. This study does not provide new or novel information. The MELD has been chosen by the UNOS since 2002 in the US as the major reference system for organ allocation in liver transplantation. The authors provided data to argue against this strategy.

1. However, the case number in this study was relatively small (n=268).

We agree with the reviewer, that the case number of our trial is relatively small. However, the advantage of CTP in discriminating patients still on the wait list from patients died or removed, which was our major aim of the trial, is supported by our data. Further evaluations, i.e. inclusion of subgroup analysis or other co-factors are not feasible due to the small number of patients.

2. More importantly, the authors did not report the AUC values for CTP and MELD, and the p value for the statistical difference (Fig. 2), which I suppose there is no statistical difference between CTP and MELD.
We thank The-la Huo for reading our manuscript very critically and pointing out these topics. Our main analysis focused on which scoring system discriminated better. We found that both scores, CTP and MELD discriminated well regarding death on or removal from waiting list. But the p-value for the CTP score was 0.00009, whereas the p value for the MELD score was 0.002. Thus the level of significance for the CTP score of 9 was superior to the MELD of 14.4 concerning the predictive ability. In addition to this analysis we did AUROC analysis of both scores. The AUROC for CTP was 0.73, whereas for MELD it was 0.68. The test for difference between these AUROC showed a p=0.091, not reaching statistical significance, but showing a strong trend in favour of CTP. All this information has now been included in the manuscript.

3. Therefore, their findings do not justify the conclusion.

The-la Huo argues that the findings of our analysis do not justify the conclusions made in the original version of the manuscript. With new data included and referring to our response to topic 2 of his review we are now confident, that our data support our conclusion that CTP is superior to MELD in predicting death or removal from waiting list in our long term follow up. In addition we termed our conclusions more cautiously and more accurately regarding this special analysis. This as well led to a change of the title of the manuscript. Our revised manuscript is now entitled: The title now reads: “Limitations of the MELD score in predicting mortality on or need for removal from waiting list in patients awaiting liver transplantation”

The conclusion in the revised manuscript now reads: “The increasing numbers of standard exceptions for MELD score, e.g. cholestatic diseases reflect the clinical need to improve this allocation system. Although our study does not argue against the use of the MELD score for short term allocation of organs and prioritization of recipients, the long term prediction of mortality or removal from waiting list in patients awaiting liver transplantation might be better assessed by the CTP score than the MELD score. This might have implications for the development of new improved scoring systems.”

Quality of written English: Needs some language corrections before being published

In addition to the reviewer’s comments on grammatical and spelling issues the manuscript has now been copyedited by a professional service.

Referee 2: Reviewer: Ilka Boin
Minor essencial revisions about reference, table titles and put the confidence intervals results

We thank Ilka Boin for encouraging comments. As suggested we included confidence intervals, where applicable and improved table titles.

Quality of written English: Needs some language corrections before being published
In addition to the reviewer’s comments on grammatical and spelling issues the manuscript has now been copyedited by a professional service.

Referee 3: Reviewer: Michael A Fink
Major compulsory revisions:

1. The crux of the paper is the comparison of CTP and MELD score with respect to prediction of waiting list mortality. The paper asserts that CTP is superior in this regard. However, statistical analysis to support this is not presented. I think that it is essential that the C-statistic for CTP and MELD are given and a P value for the comparison be given.

   We thank Michael Fink for critically reading our manuscript and pointing out these important topics. As reviewer The-la Huo he argues for a c-statistics of CTP and MELD. Regarding this issue we would like to refer to our reply to The-la Huo topic 2 and 3 and the general comments of the editorial office.

2. Optimal cut-offs for CTP and MELD are given, but the method of determining these is not described. This should be corrected.

   The optimal cut off for CTP and MELD was achieved by minimizing the false positive and false negative results. This has been mentioned in the revised version of the manuscript.

3. The first 2 paragraphs of the discussion reproduce information contained in the introduction. These should be removed from the paper. They could be replaced by a very brief summary of the introduction.

   As suggested by Michael Fink we replaced the first two paragraphs of the discussion by a brief summary and agree that this improves readability of the manuscript.

4. Tables 5a and 5b do not contribute any substantial additional information and are not further considered in the paper. They should be removed.

   Michael Fink points out that Tables 5a+b are in some aspects redundant to Fig. 1 A and B reflecting the discrimination of CTP and MELD. Since one of our main analysis is this determination of the optimal cut off and its performance, we would like to keep these tables in the manuscript. They do provide some additional, more precise information of the cut off values of each score.

Minor essential revisions:

1. There are some minor grammatical issues that need to be corrected. For example, Results page 1, last paragraph: "Of 29 patients died or removed..."
should read "Of 29 patients who died or were removed..."

This issue has been changed as suggested by the reviewer.

2. Discussion page 1, 3rd paragraph: "In our study that compromised ..." should read "In our study that comprised ..."

This issue has been changed as suggested by the reviewer.

2. Discussion, page 2, 1st paragraph: "indicating, that patient with compensated cirrhosis" should read "indicating that patients with compensated cirrhosis"

This issue has been changed as suggested by the reviewer.

Discretionary revisions:

1. The mean MELD score of all patients in the study was 14.2. This seems relatively low. It has previously been demonstrated that below a MELD score of 15, patients have a higher risk of death from transplantation than waiting list death (Merion et al Am J Transpl 2005;5:307-13). This issue deserves some consideration in the discussion.

   The evaluation of the study population of our trial was performed in data sets of patients listed for transplantation between 2003 and 2005. In this time interval MELD was not implemented for organ allocation in the euro-transplant community. Waiting time was a major factor for organ allocation and therefore patients were listed in an earlier stage of their disease, which may be one factor for the relatively low MELD score on average of the whole study population. This issue has been implemented into the discussion.

2. The authors assert that other studies evaluating MELD and CTP "did not take into account patients removed from the waiting list due to poor condition". In fact, in one paper evaluating risk factors, including CTP and MELD, for waiting list mortality, patients who were listed for transplantation and were removed from the waiting list due to poor condition and subsequently died were included in the waiting list mortality group (Fink et al. J Gastroenterol Hepatol. 2007;22:119-24)

   In regard to this comment we changed the wording accordingly and included this publication in our discussion.

Quality of written English: Needs some language corrections before being published

   In addition to the reviewer’s comments on grammatical and spelling issues the manuscript has now been copyedited by a professional service.
Reviewer's report:
The article wrote is showing an interesting point, once we are seeing the world accepting MELD score as the best method for liver graft allocation. Regarding to this issue, the authors shown a better correlation with Child-Pugh in predicting survival on and need for removal from waiting list in patients awaiting liver transplantation. We do know that MELD score has failed in some cases and we do have to improve our methods to predicting survival on the waiting liver transplant lists.

We thank Ben-Hur Ferraz-Neto for its encouraging review and hope that in our new conclusion we reflect the need for improvement of the current scoring systems even better.