Dear Editor,

We are pleased to be able to provide a revised version of our article No. 30178, which is entitled "Biliary complications following liver transplantation – Single-center experience over three decades and recent risk factors".

We would like to thank the reviewers for their helpful and constructive criticism which we believe truly enabled a significant improvement of our manuscript. We are glad that all raised concerns could be addressed in the now submitted revised version of our article.

A point-by-point answer to the reviewers' comments is following to facilitate a smooth re-evaluation of the manuscript.

Reviewer: An interesting well-written study. I have a few recommendations regarding your tables and figures. 1) Table 1 is too long. Please split into three tables: recipient data, Transplant specific data, donor data. Also the title of the table should NOT be a description as you wrote (Summarised are the clinical characteristics etc.....) Please modify to "Clinical characteristics of....

> Answer: According to the reviewer's comment, Table 1 was substantially revised and is now divided into three different tables referred to as Table 1 A, B, C. Moreover, the title of the table was changed accordingly.

Reviewer: 2) In table 1 please change the two rows of sex male and sex female to just one row and simply write Male:Female= 915(57%) to 692(43%). In general always use the word "gender " instead of "sex".

> Answer: Table 1 was revised as recommended. Moreover, the term "sex" was changed to "gender" throughout the revised manuscript.

Reviewer: 3) Table 2. Please modify the title to: "Causes of death in transplanted patients over 30 years"

> Answer: The title of Table 2 was revised accordingly.

Reviewer: 4) Table 3: Please modify the title to: "Univariate and multivariate analysis for identification of risk factors for anastomotic biliary complications since 2006"

> Answer: The title of Table 3 was revised accordingly.

Reviewer: 5) Figure 1. Please modify the title to: "Observed biliary complications as a percent of transplants per year over 30 years". This is an interesting figure showing the decline of biliary complications. Can you explain in your discussion why there was a sharp rise again in the rate in 2012?

> Answer: The title of Figure 1 was changed according to the reviewer's comment. As the reviewer suggested, we added a paragraph to the Discussion section on the increase of biliary complications in the year 2012, which reads as follows: "After a relevant drop of the incidence of biliary complications in 2011, the number of observed complications increased again in 2012. The data does not clearly provide insights into the root-causes of this observed development, thus, only assumptions can be discussed here. There was no notable change in

allocation policies at that time, MELD-based allocation was introduced in late 2006 in Germany. Furthermore, the clinical setting did not change significantly, just a slight increase in the application of Histidine-Tryptophane-Ketoglutarat (HTK) preservation solution could be detected in 2012. HTK-solution was suspected to be associated to biliary complications previously and a trend towards this association was shown in our center in previously published research (Stewart et al.; Kaltenborn et al.)" .

Reviewer: 6) Figure 2. Please modify the title to: Kaplan Meier curve showing the cumulative survival of A) Patients with and without biliary complications B) Graft survival of both groups. Write the significance of the colours (blue line=...red line=...) in a legend and also the p-values inside the figures.

Answer: Figure 2 was revised according to the reviewers comment.

Reviewer: 7) Figure 3. Please modify the title to read: "Different Biliary Complications in the MELD era". Inside your box add the number and percent to each complication e.g A anastomotic bile leak n=41 (46%).

Answer: Figure 3 was revised according to the reviewers comment.

Reviewer #2

Reviewer: This is a large single center experience with detailed reporting on the biliary complications after liver transplantation. While many prior reports on similar subject have been written, the authors did attempt to identify risk factors for this complication and found donor BMI/bilirubin/creatinine/sex to be independent risk factors. Donor age, surprisingly, was not a risk factor. Donor quality is a well established risk factor for biliary complications. My main concern therefore is that the method of identifying these risk factors, using "binary" regression, in which continuous variables were dichotomized, may be inappropriate. The authors also did not provide details on how and why each of the variable was dichotomized (age, bilirubin, creatinine). If the authors can provide detailed rational on how they chose the "cutoffs" for the continuous variables, it may be necessary to consider several "sensitivity" analyses on other potential cutoffs. Ultimately, the risk factors identified in the current method of analyses, particularly donor related, likely represent donor quality as many previous papers have found. Nonetheless, if the method can be described more clearly, this "confirmatory" large single center experience remains valuable for the transplant community.

Answer: There seems to be a misunderstanding regarding the method of binary logistic regression analysis, which was applied in the presented study. The term binary just describes that the endpoint, or dependent variable of the regression analysis needs to be a binary variable, such “onset of biliary complication yes/no”. The variables, which were assessed to have a significant influence on that endpoint during regression analysis, do not need to binary or dichotomized for that purposes. Hence, the continuous variables such as age, bilirubin, creatinine etc. were not dichotomized, but included as continuous variable in regression analysis. This approach was intensively described in statistical literature, e.g. Hosmer, Lemeshow, Sturdivant: Applied logistic regression, 3rd edition, Wiley Publishing,

2013; and this methodology was applied by the authors many times before (see for example Kaltenborn et al. 2016. Identifiaction of patients at risk for renal impairment after living-donor kidney transplantation. Langenbecks Arch Surg.; Schrem et al. 2016. The new liver allocation score for transplantation is validated and improved transplant survival benefit in Germany but not in the United Kingdom. Liver Transpl.).

Reviewer #3

Reviewer: 1. Please mention about the way of treatment for biliary complications briefly.

Answer: As the reviewer suggested, a paragraph on the treatment modalities for biliary complications is now part of the revised Patients and Methods section of the manuscript which reads as follows: “There are various therapy options for biliary complications. Early biliary complications, such as biliary leaks can be managed via endoscopic retrograde cholangiopancreatography with stent implantation, whereas late complications, such as biliary stenosis or a diffuse leakage often require a percutaneous transhepatic biliary drainage, surgical revision with a Y-Roux hepaticojejunostomy or at last resort a re-transplantation.”

Reviewer: 2. Figure 1. It should be presented with a bar graph.

Answer: After revision of Figure 1 into a bar graph, all authors discussed the way to present the data and compared the line chart, which was the initial design with the new bar graph, whether there was any value added by the revision. The authors concluded that the line chart is more able to show the development of the complications' incidences than the bar graph, thus, the line chart was not changed in the revised manuscript. Of course, if the reviewer insists on the wish to have the data presented as bar graph, we are eager to provide such a graph.

Reviewer: 3. Standard practices (immunosuppressions, preservation fluids, threads used for biliary reconstruction) should be mentioned.

Answer: As the reviewer suggested, a paragraph on the standard practices is now part of the revised Patients and Methods section of the manuscript.

We hope that the improvements of our manuscript now warrant its publication in the World Journal of Hepatology. If you have any questions please feel free to contact me anytime.

Yours faithfully,

A. Kaltenborn, MD

corresponding author