**Author's response to reviews**

**Title:** Health related quality of life in patients in dialysis after renal graft loss. Effect of gender.

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

Thank you for the thorough and constructive review of our manuscript “Health related quality of life in patients in dialysis after renal graft loss. Effect of gender”. We have taken all proposals into consideration, and have therefore made substantial changes in the manuscript based on the reviewers’ comments and suggestions. We think these changes as suggested by the reviewers have improved the manuscript substantially. We appreciate the meticulous suggestions from the reviewers, and the possibility to expand on some issues. Below the changes are detailed:

Reviewer 1 (KSG):

Comment from the reviewer:

“The patient cohort represents almost 1/3 of the prevalent dialysis patients in Norway and with the interventions performed at the same centre. Despite the relative small number of female patients it is still one of the largest cohorts internationally. There was also a the high proportion of women resuming dialysis after functional graft loss. Losing the graft seems to influence QOL in females more negatively than in males. The authors could try to speculate about the reasons to this a bit more: why is there gender differences in general in the graft- and patient survival, how does the inequity in waiting time for a retransplantation look like in Norway and other countries “

Answer: The highly relevant clinical comments have led to changes in the Discussion section (page 11 and 12). The reason why females with graft loss perceive lower HRQOL compared to males and to females without graft loss is not readily apparent, but we have suggested some possible explanations to the discussion section. We have also extended the discussion with regard to gender differences in graft- and patient survival.

The important question raised with regard to gender inequities in waiting time for the possibility of retransplantation, has not yet been investigated. However, based on our present findings, we are in the process of investigating this based on data accessible in the Norwegian renal registry including all kidney transplantations in Norway the last three decades. Although there is a gender difference in the waiting list for the first transplantation in some countries, data from the national transplantation registry in Norway does not reveal such differences.

Comment from reviewer:
Most patients were Caucasian and the transplantation and dialysis rates are high in Norway, do the authors think that the findings might be the same in other countries?

Answer: We have added a sentence in the Discussion section addressing the limitations of the study: “As transplantation rate is high in Norway, not only for the first transplantation but also for retransplantation, the time in dialysis is short compared to what has been observed in other populations. As time in dialysis and accessibility to transplantation may affect HRQOL, the generalizability of the results may be limited” (page 15, lines 322-325).

Reviewer nr 2

1) “The interaction analyses are not adequately described and reported. Based on the Methods, interaction terms should have been included in the analyses shown in Table 4, and the results reported with the other coefficients and associated p values.”

Answer

This is a very important comment, and has led to major changes to the manuscript. We agree that the interaction analyses were not adequately described and reported. We have changed the description of the multiple regression models and interaction analyses in the methods section (Page 8, line 161-178). The interaction analyses and presentation were thoroughly discussed with an expert in biostatistics.

The interaction term was entered into the planned multivariate regression model to test for its validity. It will be a problem to interpret the other explanatory variables in the model if we include the interaction term in the presentation. We find that the most conservative way to report the data taking the interaction into account is to present the results of gender specific regression models. As a consequence the results section is rewritten and reorganized (page 8), and the previous table 3 and 4 is substituted with the presentation of the gender specific regression models in a new table 3.

We appreciate this comment, the new revised manuscript is improved substantially as a consequence of the new presentation of the data.

2) “The plots to explain the interaction term would be more consistent with the interpretation if gender were along the x axis and prior transplant status shown by color”

Answer: We totally agree that the boxplots are easier to interpret with gender on the x axis. In the new boxplots the use of color may ease the interpretation (Figure 2).

3) “List all covariates investigated but not significant in a footnote to the tables”

Answer: All the covariates which were not statistical significant have been added in Table 3.
4) "A parallel analysis for male patients to that depicted in Table 5 for females is essential to place the Table 5 results in context"

**Answer:** This is a very relevant comment. A parallel analysis for male patients are included in Table 3 (replaces former Table 4 and Table 5, see answer to comment nr 1).

5) "In their interpretation of the significant interaction terms found, authors consider only one mechanism, graft loss, as causal. Their cross-sectional design cannot eliminate other explanations. Given that women report lower HRQOL than men in the general population and in other studies of transplant and dialysis patients, alternative explanations should be pointed out in the Discussion. Longitudinal confirmation is needed"

**Answer:** Due to the cross-sectional design, causality cannot be explained. We have expanded on alternative explanations in the Discussion part.

6) "Response shift has been associated with HRQOL perceptions after pancreas transplantation. Address issue of response shift in QOL assessment after kidney graft loss."

**Answer:** We find this an exciting issue, and are grateful for the possibility to address this. The phenomenon response shift is probably important after graft loss. Our findings might indicate that there could be gender differences in response shifts in patients with renal graft loss, this could need further explored in longitudinal studies. We have included the possibility of response shift in the Discussion page 13, line 286-299.

7) "Analysis of BMI should be based on standards for under/overweight and obesity, not a median split, to facilitate a meaningful interpretation of findings"

**Answer:** We agree with the reviewer on this comment. BMI has been dichotomized with the split value of 25 kg/m$^2$ in two standardized groups: Underweight/normal weight versus overweight/obesity. A total of 18 patients (6.4%) were classified as underweight (BMI < 18.5 kg/m$^2$), and 46 (16%) as obese (BMI ≥ 30 kg/m$^2$). This number of patients is too low to split them in more groups. The dichotomized BMI are used in the regression models (description of variable in the Methods section (Page 8 line 173)

8) "In the Results, for every finding, be explicit about whether the analysis was or was not adjusted, and make the direction of the relationship clear, and for clarity, replace "reduced “ effect of kidney disease
with “poorer” or “worse”; otherwise it sounds like greater comorbidity was associated with better HRQOL on the effect of KD and other subscales”

**Answer:** We have rephrased our sentences as suggested to improve the clarity of the results, and this has been emphasized in the Result section (page 9 and 10, lines 203-210).

9) “Include the number of men and women with graft loss to the abstract”

**Answer:** This had already been done in the abstract, but we have done slight rephrasing so it should be clearer for the reader (Page 2, line 44-46 (Abstract)).

10) Use “loss” not “failure” in the short title

**Answer:** Changed «failure» into «loss», this is consistently performed in the entire manuscript.

11) “In the Methods, state how missing data are handled”

**Answer** We have now inserted the sentence “Missing data were treated by pairwise deletion in the statistical analyses.” in the Method section (page 6, line 137-138).

12a) “Abstract – have not has in line 3 of abstract and reword this sentence clarify that transitions may affect HRQOL, they will not affect the sex of the patient”

**Answer:** Changed “has” into “have” (page 2, line 28).

“...but whether transition in disease state affects gender differently is not known” into “...but whether transition in disease state affects HRQOL differently in respect to gender is not known” (Page 2, line 29)

12b) “Drop or Reword to replace the term “gender-wise” in the Abstract and Methods”

**Answer:** We have rephrased the sentence in the abstract (Page 2, line 38)

12c) Page 9 – Sentence beginning “In addition to graft loss...” does not make sense - reword.

**Answer:** We have rephrased the sentence in page 8 (former page 9) in Statistical analyses into: “To identify explanatory variables to be used in the different regression models, correlation coefficients (Spearman rho) between the HRQOL item “effect of kidney disease” and demographic and clinical
variables were calculated. Variables with $p < 0.1$ could be entered in the regression models together with age, gender and graft loss.” (page 9, lines 165-170).

12d)

“Refer to the rates of “missing data” on the SF-36 and KDQOL; these are not response rates”

**Answer:** The missing data are given in page 9, lines 184-186.

12e)

“Page 13 – replace mill with million”

**Answer:** This has been replaced with million (page 14 line 314).

12f)

“Page 14 – replace manifold (which means diverse) with many times”

**Answer:** This has been changed page 15, line 321.