Author's response to reviews

Title: Epidemiologic trends in chronic renal replacement therapy over forty years:
A Swiss dialysis experience

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Author's response to reviews: see over
Dear Dr. Henderson

We very much would like to thank you for considering our manuscript for publication in *BMC Nephrology*, and the reviewers for their insightful comments. We have revised our paper accordingly and implemented all suggestions stated by them. Please, find below a point-by-point reply regarding all concerns and modifications. All changes in the manuscript are highlighted and underlined in blue or red. Specifically, the recommendations regarding statistical calculations implementing a time-dependent Cox regression analysis have been fully adopted. Also, the advice of the reviewers with respect to conclusions from our findings has been incorporated into the revised manuscript. Obviously, in a study reaching back over more than 40 years, certain aspects have to remain unresolved due to partially incomplete data. However, we feel confident that the paper has improved significantly, and, in its current form, can be of substantial interest to the readership of *BMC Nephrology*.

We are looking forward to your decision.

Sincerely yours

Patrice Ambühl

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**Point-by-point reply to reviewer’s comments**

**Reviewer Tobias Breidthardt**

We very much appreciate the positive appraisal of our study by Dr. Breidthardt.

- **Differences in the development of incident age between HD and PD patients:**
  
  An additional figure depicting age at dialysis initiation for the respective quartile and therapy modality has been added (→ figure 3).

- **Survival of "younger" vs. "older" patients after transplantation:**
  
  This is a very interesting aspect indeed! After recalculation of our data in the overall study population, age at time of dialysis initiation was no longer an independent variable for survival (refer to table 3 of the revised manuscript and also to comments to reviewer Seung Hyeok Han). Moreover, analyses regarding age effects on transplant outcomes have been performed more thoroughly by others and were not the main topic of our study. Therefore, we have adapted our conclusions somewhat
in this regard (i.e. page 18, line 2 of the first paragraph, stating that "age beyond 65 is not always associated with a survival benefit...").

- **Percentage of male vs. female patients on PD:** the statement has been changed to "comparable between women and men".

- **Figure 2** has been replaced with a color graph in order to improve readability.

- **Data regarding vascular access and dialysis time:** unfortunately, data are not available on these treatment variables.

- **Recommendations to increase survival in elderly and polymorbid patients:** Our analysis does not allow - and was not designed - to draw conclusions regarding treatment recommendations in various patient groups.

**Reviewer Seung Hyeok Han**

We are very thankful for the critical comments of Dr. Han and his important suggestions regarding the **statistical analysis of our data**. After reconsideration of our approach, we completely agree with Dr. Han’s assessment with respect to the necessity to use Breslow-test in Kaplan-Meier analyses and to perform a time-dependent Cox regression analysis rather than multiple logistic and linear regression analyses. Thus, all statistical calculations have been redone as asked for by the reviewer. As a result - and correctly presumed by Dr. Han - age has turned out **not** to be a relevant factor explaining worse outcome in more recent years of dialysis initiation. Similarly, dialysis vintage - unlike in our first analysis - is associated with survival, at least between the second versus the first quartile.

- **Changes in these regards have been performed throughout the manuscript:**
  - the paragraph on statistics has been entirely replaced
  - the former table 3 and 4 have been dropped and replaced by a revised table 3
  - in both table 1 and 2 results on "time to death" and "survival time" for the respective quartiles have been dropped in order to avoid misinterpretation due to differences in observation time

With regard to the **limitations of our analysis**, again, we basically agree with the reviewer. Specifically, the lack of data on comorbidities substantially reduces more in-depth conclusions from our findings. However, we feel that these limitations are adequately revealed and discussed throughout the manuscript. Moreover, although the interpretation of our results may be limited, the findings per se are valid, and, in our opinion, of epidemiological importance. In fact - and contrary to Dr. Han’s statement - we were unable to come up with any published analysis of comparable follow-up and size on the topic of our paper.
The following changes have been made in order to further emphasize the limitations of our analysis and the criticism of the reviewer:

- Abstract: the conclusions have been modified, adding a statement on the limitations of the study design. Also, the relative contributions of technical/medical advances and changes in comorbidity over time have been rephrased.
- Discussion: similarly, conclusions throughout the discussion section have been adapted in order to present conclusions regarding the interpretation of our findings in a more neutral way.

Of course, we recognize - and accept - that the importance of our analysis is subject to personal opinion. However, we feel that many of the criticisms by this reviewer are now accounted for.

Reviewer Patrick Saudan

Thank you very much for the assessment of our manuscript.

- Impact of "technicalities" versus "clinical covariates" on outcome:

In essence, we agree with Dr. Saudan. To many of his comments has been related to in the replies to the other reviewers. Nevertheless, we would like to summarize the most important aspects:

- Statistical reanalysis of our data has revealed that age at dialysis initiation, in fact, is not responsible for differences in outcome between the different time intervals (decades).
- Similarly, technical advances may indeed have impacted on survival, as shown by the (statistically significant) improvement between the second and first decade.
- We are very much aware of the limitations towards a more in-depth interpretation of our findings lacking information on clinical data. However, be assured, we would have included them if they were available! Nevertheless, we are confident that our findings are still interesting and important, as comparable data are not available from the literature. Also, we feel that the limitations stated by Dr. Saudan are openly declared and adequately discussed, leaving it to the reader how to interpret certain aspects.
- Stratification according to age as suggested by this reviewer may be an option. However, correction for age in fact has been performed using the multivariate time-dependent Cox regression approach.
"No systematic lack of information" regarding missing data: this refers to the circumstance that missing data in our analysis are due to partial and random incompleteness of data recording (i.e. incomplete or missing date of birth and/or death) throughout the first two quartiles. There is no indication, whatsoever, that data have been omitted for specific patients or patient groups.

- **First dialysis by Scribner:** The correct year (1960) is now stated in the introduction.

- **Statistical analysis by three different multivariate models:** We agree! Please, refer to the statements above made in this regard to Dr. Seung Hyeok Han.

- **Time point of analysis:** Every patient initiating dialysis patient at our institution has been included after the first dialytic treatment. Evaluation has been performed at time of death or end of study follow-up.

- **Allocation of grafts between men and women:** Unfortunately, we do not know the reasons for the higher number of transplants performed in men vs. women. Also, the available data do not allow to come up with a reasonable hypothesis. Therefore, we prefer to refrain from unsubstantiated speculations.

- **Impact of "technicalities" on survival:** Again, please, refer to our previous responses in this regard.

- **Transplantation in the elderly:** Similarly, please, see comment to Dr. Breidhardt in this regard.

For the authors

Patrice M. Ambühl, April 12, 2012