Author’s response to reviews

Title: Impact of initial dialysis modality on mortality: a propensity-matched study

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Reviewer’s response to reviews:

1. TITLE: must be integrated like "Impact of initial modality on mortality in young (or <65') dialysis patients: a propensity-matched study. This change is to avoid generalizations and so extending the research results to the entire considered population.

   Thank you for this comment. Due to comments of reviewer #2, we recognized that the conclusions in the original manuscript were much too focused on subgroup analyses in patients younger than 65 years. The entire PD population was propensity matched with HD patients, and the main aim of the study was to assess all-cause and cardiovascular mortality in patients treated with PD compared to HD as initial RRT, not only patients younger than 65 years. The title is left unchanged, but the discussion and conclusion are rewritten to align with the main aim of the study.

2. page 7 line 1: How is estimated the propensity score? which parameters had taken into account to calculate it?

   A propensity score of being treated with PD as initial dialysis modality was created for each case by a logistic regression model using IBM SPSS statistics with R extension pack as described in the statistics section (Page 6-7). All parameters included in the logistic regression model were listed in the original manuscript on page 6 last paragraph.

3. Discussion. line 54. The analysis was carried out well as statistically than methodologically but remember it may be only for patients under 65 years in both HD and PD.
I am sorry that I am not able to understand this comment. All patients that started PD in the study period in Norway were propensity matched with a HD patient with similar baseline characteristics. Subgroup analyses were then performed in patients below 65 years old.

4. Conclusions. The population is represented by a positively selected subset of patients thanks to the use of propensity score considering the mortality at 2 and 5 years. It should be better emphasized the concept that these results cannot be extended to the general considered population of 3,555 patients from 2005 to 2012. In this period - presumably 8 years - the incidence of ESRD patients in Norway is approximately 87 pts / million / year. This percentage is much lower than the rest of Europe, which in the same period exceeds 160 / patients / million inhabitants. In Norway the population with CKD is followed very closely by showing a more virtuous reality apparently far than other European countries.

Thank you for this comment. Regarding generalization of our results to the entire dialysis population this was stated in the original manuscript in the limitation section (page 11).

“Furthermore, the propensity matched analyses included only HD patients with similar baseline characteristics as patients actually treated with PD in the time period. Thus, generalization of our results to apply for all dialysis patients should be done with care.”

We agree that the matched HD patients included in the study will not be representative of all HD patients. The last sentence is rewritten to better clarify this to the reader (Page 11).

5. Tables needed: it would be interesting to show all parameters showed in table 1 at least in to two interim periods from baseline to the end of observation especially those related to the nutritional status. It is indispensable - for a correct outcome evaluation at least in the population matched - to show dialysis efficiency parameters in both dialysis methods because a discrepancy in dialytic purification may be have considerable influence on the curves in the survival figures Figures 2 no significance showed

Our analyses were restricted to existing data in the Norwegian Renal Registry at the time of dialysis initiation. This is now more clearly stated in the limitation section (page 11). No data on nutritional data or dialysis efficacy were available for the current analyses. As with patient characteristics to be matched in the propensity matching procedure, more variables would further have improved our analyses and improved the reliability of our results. However, we performed the analyses with the available variables. The significance was added in Figure 2 in the revised manuscript.

Reviewer #2:

In the manuscript "Impact of initial dialysis modality on mortality: a propensity-matched study" Authors present a propensity-matched observational study comparing the effect of PD or HD as
first renal replacement treatment on mortality; they conclude PD is not inferior to HD in the short and medium term follow-up while PD yields better survival in younger patients. The major results in the general population are partially confirmatory of previous observations; PD, however, seems to improve survival in younger patients, but this result cannot be conclusive.

Comments

1. A time-dependent logistic regression model was built to create the propensity score and baseline covariates were reported. Which variables entered into the model were time-dependent? More details on this points are needed.

Thank you for this highly relevant comment. We agree that this was not well enough explained in the original manuscript. A propensity score of being treated with PD was calculated separately in patients started in dialysis in the period 2005-2008 and the period 2009-2012 using the same baseline variables. This was done as the characteristics of patients started in PD may have changed during the study period. The Norwegian dialysis population has grown substantially in the last decade and the hemodialysis capacity has been challenged. The population found suitable for PD may therefore have changed in the study period. No individual variables were time-dependent, but were all baseline variables at the time of dialysis start. The statistical analyses section is rewritten to provide details on this point. (page 6)

2. Many factors at start of dialysis are related with outcomes and Authors matched the groups for many variables; nonetheless, several factors lack. At least use of RASi, PCR, phosphate, PTH, central vein should be added to the analysis.

This is a very relevant comment. Our analyses were restricted to existing data in the Norwegian Renal Registry at the time of dialysis initiation. None of the mentioned variables are available in the registry and we were not able to include them in our propensity matched analyses. This is clearly a limitation of our study and should have been mentioned in the limitations section in the original manuscript. In the revised manuscript it is stated that the current analyses were restricted to data available in the Norwegian Renal Registry (page 11). Despite lack of data on important variables, our propensity score were calculated on a larger number of variables compared to similar studies, and this should ensure reliability of our results.

3. Results of this paper are different with respect to another recent very similar propensity analysis (KI 2014); Authors should deeply discuss the differences.
We agree that our results are somewhat different from the study from Kumar et al that you mentioned. In the original manuscript we tried to discuss the difference between our study and previous studies in general, included the study by Kumar et al. Kumar et al found that the cumulative HR favored PD for up to 3 years with no difference thereafter, while we could not find any significant difference between PD and HD in our two year analyses in the entire group. They included more patients than we did, but the propensity score was founded on fewer variables. Thus, our patients could be better matched on baseline characteristics. The difference in the results might be explained by the age difference in the two populations. While in the Kumar study, the mean age was 57 years in the PD patients, mean age in our study was 65 years in PD patients as well as HD patients. In our subgroup analyses in patients below 65 years old, HD was associated with a higher 2-year HR of all-cause mortality in both the as-treated and intention-to-treat analyses (HR= 1/0.39= 2.56 and 1/0.47=2.13 ) which was comparable with the results of Kumar et al (first-year HR 2.68 and 2.10 respectively).

We have added a paragraph in the revised manuscript that more thoroughly discuss the differences between the American and our study, since the methodology in the two studies were similar (page 10)

4. I have some concerns on the generalizability of the results in younger patients. 1) the number of subjects is relatively low; 2) the mortality rate is relatively low as well (report the crude yearly mortality rate); the transplantation rate is unknown; 4) the matching is incomplete.

Thank you for these comments. We agree that the low mortality rate and the high transplantation rate would affect the generalizability of the results in younger patients, especially for longer term follow-up. Short median time in dialysis in this study was aimed as a limitation in the original manuscript (page 11). This will affect our power to perform subgroup analyses especially for longer term follow-up. In the subgroup analyses for younger patients only 32 PD patients remained in the as-treated analyses beyond 2 years (figure 2). Long-term complications would then be difficult to assess. Furthermore we agree that the matching procedure was not designed to subgroup analyses.

The discussion and conclusion is revised to better meet this highly relevant comment. The main results and conclusions now point to the main result of the entire group and the conclusions on subgroup analyses are made less conclusive and more suggestive.

5. Authors state that this paper suggest that PD in more favourable in patients below 65 years. To support this statement they provide two reasons: 1) better clearances, better hemodynamic, lower infections and RRF in PD; this point is speculative since these data were not reported in the paper; also, even if these reasons could explain the better results in youngers they should work also for elderly; 2) improved PD quality in the last decade; also
this hypothesis is too speculative and not supported by data; to prove this hypothesis Authors should compare PD pts starting dialysis between 1980-2005 and 2005-2012.

Thank you for these comments.

1) We agree that these data are not reported in the paper and the statements are too speculative. As a consequence the section is deleted from the revised manuscript.

2) Concerning improved PD quality in the last decade, we agree that our data are not able to prove this hypothesis. However, in the original manuscript we refer to studies that confirm both that survival has improved more in PD than in HD the last decades and the positive effects of the modern PD solutions used in all PD patients in Norway the last decade. We included this part in the original manuscript as an argument not to conclude on survival differences between dialysis modalities with data from the last century when modern treatment principles were not utilized. In our opinion there is a need for ongoing evaluation of treatment effects, and our study is a contribution to evaluate more modern treatment modalities.

6. The last part of the discussion on possible reasons to prefer PD is too speculative and not supported by the data and goes beyond the aim of the paper.

We recognize that this last part was too speculative and beyond the aim of the paper. The section is rewritten and shortened (page 11).