Author's response to reviews

Title: All-cause and cause-specific mortality associated with diabetes in prevalent hemodialysis patients.

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Author's response to reviews: see over
Date: Aug 20, 2012

To:
David Holmes, PhD
Assistant Editor, The BioMed Central Editorial Team

Subject: All-cause and cause-specific mortality associated with diabetes in prevalent hemodialysis patients (MS: 1817787453726721).

Dear Editor:

Thank you for your letter dated June 21, 2012. We were pleased to know that our submitted manuscript was reviewed by two reviewers which subject to revision and response to the comments raised by the reviewers can be resubmitted. We thank the reviewer for their thorough and constructive review of the manuscript.

We have revised the manuscript including figure legend based on the comments made by you as well as the reviewers. Please find our point-by-point response to the comments raised by the reviewer below this letter. We agreed with most of the comments raised by the reviewer. We would like to take this opportunity to express our sincere thanks to the reviewer who identified areas of our manuscript that needed corrections or modification. We would like also to thank you for allowing us to resubmit a revised copy of the manuscript.

I hope that the revised manuscript is accepted for publication in the Journal of BMC nephrology.

Sincerely Yours,

Abdus Sattar, Ph.D
Title: All-cause and cause-specific mortality associated with diabetes in prevalent hemodialysis patients.

Reviewer: Bo Hu

We want to thank Dr. Hu for the thoughtful critique. We have addressed each of the concerns below and made appropriate changes to the text.

Major comments

1. For all the estimated hazard ratios shown in Table 2 and 3, please provide corresponding confidence intervals. Also, for variables such as blood pressure, it is not clinically meaningful to express HR as per 1mmHg change.

Response: We have provided confidence interval (CI) for all HR estimates obtained from the Cox proportional hazard model and Cox’s time varying coefficient model. However, we could not provide CI for the HR estimates obtained from the Gray's model due to a large number of HR estimates. For each covariate there are 10 time-varying HR estimates, and hence 10 CIs. It would be clumsy to present 10 HR estimates and their corresponding CIs for each covariate in the Table 2 and Table 3. Therefore, we have presented a range of the HR estimate obtained from the Gray's model. The details HR estimates and the corresponding CI can be found in the supplementary tables.

2. For time-varying coefficient (Gray's) model, please provide the details of the time intervals. Are these results sensitive to the selection of the time intervals and the number of the intervals? How about using a cubic spline or other types of splines that allow a smooth curve of HR, instead of a linear spline as in Gray’s model?

Response: We have provided details of the time intervals in page 8. Results obtained by fitting the Gray's model are not sensitive to the number and location of knots. The knots are determined in a fashion that the number of events are in each time intervals are approximately equal (Gray: JASA 1992; 87:942-951). Quadratic and cubic penalized splines tend to be unstable in the right tail of the distribution. Thus linear and piecewise-constant penalized splines are favorable choice (Valenta and Weissfeld: Stat. Med. 2002; 21:717-727).

3. Was GFR collected in HEMO study? It would be better to adjust the result for GFR variables.

Response: GFR was not collected in HEMO as the study enrolled patients with minimal residual renal function (<0.5 ml/min), so that adjustment for the level of residual renal function would not have been possible (or clinically meaningful). This exclusion criteria was a purposeful part of the design of the HEMO Study since it was felt at the time of designing the study that the impact of dialysis dose would be attenuated among ESRD patients with substantial residual renal function. Furthermore estimating equations (eGFR) have not been validated for use in dialysis patients, so that adoption of e.g. MDRD to convert creatinine to renal fx estimates would be erroneous. Finally, even if eGFR estimates had been validated in dialysis, creatinine in dialysis patients mostly reflect muscle mass and protein intake and is subject to "reverse epidemiology" considerations, with patients with higher creatinine having better survival, limiting the potential use of estimated GFR in this patient population.
4. For the analysis of cause-specific mortality, was each cause-specific mortality outcome analyzed separately as all-cause mortality? If so, there could be an issue of competing risk.

*Response:* The assignment of cause specific mortality was not done with a mutually exclusive classification scheme (e.g. cardiac is included in cardiovascular), so that a re-analyses with competing risk methods is not possible. Nevertheless, the same model was used for all the different causes.

Minor comments

1. Abstract, in the method section, it should be that “Cox-TVC that allows …”.

*Response:* Corrected the grammatical error.

Last paragraph of the discussion section, the sentence “with an increased risk after that point” is redundant.

*Response:* The phrase “with an increased risk after that point” has been remove.
We want to thank Dr. Villar for the thoughtful comments. We have acknowledged in the text that although the HEMO Study collected severity, it did not discern between Type 1 and Type 2 diabetes. Furthermore, our work confirmed the interaction between gender and diabetes on survival and we have included this in our results. We greatly appreciate the chance to further assess this relationship between gender and diabetes.

Major Compulsory Revisions:

A. The result may be distorted by several biases:

1. Patients are prevalent ESRD subjects. This may bias survival analysis study (lead time bias; see: Tripepi et al Kidney Int 2008)

2. There’s no distinction between type 1 and type 2 diabetes. Previous studies points out that patient’s characteristic and prognosis differ significantly between diabetes types.

3. Years of dialysis (dialysis vintage) differ between diabetic and non-diabetic, as well as co-morbidity ICED scores.

Authors should discuss these clinical issues in the limitation section of their paper. Despite adjustment, these points may have biased the main results.

Response: We chose to address comments 1 and 3 together as the possible source of bias is similar in both cases. Firstly, the nature of bias is more accurately described as survivorship or bias, i.e. the inclusion of patients who had survived the health burden of ESRD up to their inclusion in the study, rather than lead time bias (which Tripepi et al KI 73, 148-53 2008 describe as informational bias occurring in prospective studies evaluating the efficacy of screening). Survivorship bias, stems from the inclusion of the “survivors” whose hazard of death may differ from that of naïve patients (i.e. patients who just started dialysis) and can be thought of an extreme form of “immortal-time” bias that arises in pharmacoepidemiological studies. To mitigate the bias, the use of time varying hazard models has been proposed (usually encoded as time dependent covariates in the context of the Cox model, see e.g. the short reviews by Glesby et al Ann Intern Med 124, 999-1005, 1996 and Suissa Am J Epidemiol 167(4), 492-499, 2008) in order to account for possible changes in the hazard function. We believe that the Gray’s model which is a more general time varying hazard model adequately guards against this bias, and provides a graphically appealing way to visualize the potential of underestimating the impact of diabetes after prolonged follow up of patients receiving dialysis. Furthermore, the explicit testing for interaction between diabetes and time allows us to address potential differences between diabetic and non-diabetic patients. Finally, we accounted for the ICED score in the analysis in order to moderate the confounding bias from the differences in the distributions of the ICED scores between diabetics and non-diabetics.

With reference to Comment 2, information to separate patients with T1 and T2 diabetes is not available in the HEMO analytic files. Furthermore, the convention used to score the ICED co-morbidity instrument excluded diabetes from the scoring algorithm to avoid “double adjustments”. This limitation is acknowledged in the revised manuscript.

B. Analysis of the literature shows that there is an interaction between diabetes and gender regarding survival after first dialysis (Villar et al Diabetes Care 2007; Karame at al Nephron Clin
Pract 2009, Carrero et al Nephrol Dial Transplant 2011). Did authors test this interaction in the HEMO Study dataset?

Response: This is an interesting observation. We have re-ran the analysis to examine the interaction between diabetes and gender. We found that there is a borderline interaction (p=0.06) between diabetes and gender by the Cox-TVC model and significant interaction (p=0.05) by the Gray's model(Table 3). Therefore, we included this interaction term in the both models and presented the adjusted analysis results.