Author’s response to reviews

Title: Analysis of Factors Predicting Mortality of New Patients Commencing Renal Replacement Therapy 10 Years of Follow-Up

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Version: 5  Date: 13 January 2014

Author’s response to reviews: see over
Dear Sir,

Thank you for your interest in our manuscript “Analysis of Factors Predicting Mortality of New Patients Commencing Dialysis Therapy after 10 Years of Follow-Up”

We once again thank you for your kind invitation to submit a further revised version of our paper. We appreciate the additional comments of the two reviewers, which were valuable and have allowed us to enhance our manuscript. We have addressed these as detailed below and added further data.

Reviewer 3:LP

Minor Essential Revisions

1. There are still several sentence fragments, problems with grammar (e.g., “data” is a plural noun), and misspellings. Please double-check throughout.
   The paper has been reviewed once again for misspellings and errors of grammar and corrected where necessary.

2. In the limitations: the issue is not that the study is cross-sectional (in fact it is longitudinal), but that the only risk factor data are from baseline. Since many (most) of these factors change over time, the association may weaken with time.
   We have added this important point to the limitations section verbatim. There is debate between the reviewers as to the nature of the study and after consultation with a clinician with epidemiology experience we have labelled the study an observational cohort to avoid the terms cross-sectional or longitudinal.

3. The abstract still states that the aggressive management of cardiovascular risk factors accounts for the differences in this updated analysis. The data do not support this, so this must be clearly stated as a speculation.
   We have changed the final comment to a speculation as detailed above.

4. The follow-up time is still confusing. The mean of 11.9 years stated in the abstract is not possible with a 10-year study. In the paper it becomes clear that the authors meant the time from first encounter with nephrology. However, this follow-up is irrelevant to the study, since survival time presumably started at dialysis initiation (this is when the baseline risk factors were measured). Please confirm that survival time started at dialysis and modify the study follow-up time in the paper accordingly.
The abstract now reflects the mean time from dialysis initiation (8.8 years) rather than from first encounter with nephrology. We have included a risk analysis to examine the effects pre-dialysis as Reviewer 1 has suggested this as an important variable to consider. This is detailed below and added to the revised manuscript. In addition we have added the Tangri risk and slope eGFR calculations.

5. Cox regression is not the same as Cox proportional hazards modeling. I assume the authors have done the latter since they present results for proportional hazards assumptions. Please modify the paper accordingly.

We have sought clarification from the statistician. Cox regression (or proportional hazards regression) allows analysing the effects of several risk factors on survival. The terms are interchangeable so she is not clear as to why we need to change but in order to satisfy the reviewer we have replaced the term Cox regression with Cox proportional hazards modelling.

Discretionary Revisions

1. Table 3: What are the adjusters in the multivariable model? If everything else in the table, add this to a footnote.

Table 3 – Adjusters in the multivariable model have been added to a footnote.

2. Also, exp(beta) is better labeled as a hazard ratio, which is more relatable to the reader.

Exp(beta) has been revised in table 3 as suggested to make more relatable to the reader.

Reviewer 1: JGR

From a bird’s eye view – the paper aims to analyze survival over 10 years taking baseline parameters at HD initiation (not including key parameters such as blood pressure, residual renal function, amongst others) in account. The only significant predictor in this analysis remains presence of age and diabetes at baseline (as per the Cox regression model). Potentially modifiable predictors are not significant as compared to a previous analysis from the same group, which was conducted in a similar fashion investigating a 5 years observation period. In regard of all the parameters being affected by treatment regimen (dialysis, anti-diabetic treatment, vitamin D substitution, phosphorus binder, dietary restriction) and thus not necessarily associated to the outcome over a 10 years period, I think that only longitudinal analyses can answer the difficult and interesting research question investigated by the authors. I believe that the current analysis does not satisfactorily answer these questions.

The Reviewer’s first paragraph from our understanding is a statement summarising our changes as previously suggested and that longitudinal analysis may answer the questions directly. The reviewer indicates this is a difficult and interesting research question. This therefore would support our attempt to add valuable data to the literature and give the opportunity for others to direct future research in this challenging field. Hence we believe it adds to the current literature. As previously indicated a longitudinal study may not produce any meaningful data in this small data set. Looking at trends in parameters pre and post dialysis would be of interest but unfortunately not possible and complex as one would need to choose a time period pre and post for the whole population and this would perhaps introduce an element of lead time bias. However we have added data on a risk analysis to attempt to tease out these interesting questions (detailed below).

I acknowledge the hard work the authors have invested in the current manuscript, however I am still not convinced that this paper adds to the current knowledge in the field and would not recommend it for publication. It is acknowledged that it has improved in terms of raised points, but I feel there is still room for improvement. In addition I would like to mention that I believe the dataset the authors have at their disposition could be the basis for the analysis of (more addressable) research questions of equal importance. However, if my fellow co-reviewers recommend the paper for publication I also don’t have objections to its publication if the editorial board deems it valuable and
appropriate for publication in BMC Nephrology.

As detailed above based on the reviewer’s comments this paper does add valuable information to the current knowledge and gives some direction for future research. The reviewer mentions that the dataset could target “more addressable” research questions of equal importance. However no indication of these are mentioned and based on this statement it would suggest that our analysis, although not perfect is important. We have added further interesting data as detailed below.

Previous points raised:

Ad 1) Removing the term update is certainly a good idea – re-analysis sounds like a better term for this analysis. Concerning the terminology: In the methods, the analysis is declared as being cross-sectional, which I am not sure is the appropriate term in regard of 10 years data of dialysis patients’ survival. It appears to me to be a somewhat discussable description of the study design.

The description of the study has been adjusted. As the reviewer indicates it is a discussable description of the study design. There is debate between the reviewers as to the nature of the study and after consultation with a clinician with epidemiology experience we have labelled the study an observational cohort to avoid the term cross-sectional or longitudinal.

Ad 2) The small sample size is now clearly stated as a limitation and the specific mentioning of the high probability of a type II error is important.

No additions needed

Ad 3) I acknowledge your disagreement with my suggestion of using longitudinal analyses and to also include trends of parameters in the analyses (particularly of survival). In regard of several of the parameters strongly being influenced by the dialysis treatment this would have made the analysis much more informative. The analysis incorporating data prior and after HD initiation would be of great interest, but I agree with the authors that it probably should be conducted based on data from larger scale registries/databases.

The above is a summary Statement confirming our previous response. No changes have been recommended.

Ad 4) Regardless of the well-established differences between ABPM measurements, home blood pressure measurements and pre HD in-center BP measurements, the pre HD in-center BP is a well-established predictor of mortality and should be included in the analysis. The analysis of LVH as a predictor of death would be worthwhile to be shown in regard of the high fraction of cardiovascular deaths.

We have searched the literature and the indication is that BP measurements may reflect fluid status of the patient. Indeed the use of surrogate markers have been shown to be a strong predictor, namely the presence of LVH clinically, from the ECG or Echo in this group of patients and therefore are used in preference to BP. It is unclear which blood pressure reading should be used as the guide for therapy and control of CVD. Some data suggest that pre-dialysis systolic blood pressure correlates best with LVH. However in the peritoneal dialysis population which was part of this study, which blood pressure to choose is unclear also. Hence the rational for our reluctance to use this measure in the current study. Also a direct relationship between levels of blood pressure and cardiovascular events has not been clearly established by controlled studies in dialysis patients and there is a lack of a significant correlation between blood pressure and cardiovascular events in dialysis patients. This may be due to poor ventricular function, leading to lower blood pressure in some patients. A previous prospective cohort study of 180 CKD patients on maintenance HD, followed for a mean duration of 52 ± 36 months, has shown that carotid pulse pressure and aortic PWV were strong independent predictors of all-cause
(including cardiovascular) mortality. Brachial blood pressure, including pulse pressure, had no predictive value for mortality. We acknowledge that Stidley et al showed that the relationship between pre-dialysis systolic BP and mortality changes over time in incident haemodialysis patients. However, the fact that many reports using pre-dialysis blood pressure data have failed to demonstrate an association between hypertension and increased mortality might also indicate the drawbacks of assessing BP in the dialysis unit.

Finally it is well recognised that BP is subject to error in measurement and consistency. Caffeine, exercise, and smoking affect levels. Lack of standardization of various factors: the auscultatory method of blood pressure measurement eg Korotkoff sounds; patient position during blood pressure assessment; appropriate cuff size to ensure the cuff bladder encircles at least 80% of the arm is not always performed. If automated blood pressure recordings are used this may overestimate blood pressure by 14/7 mm Hg before dialysis. Blood pressure measurements obtained manually during dialysis sessions generally overestimate blood pressure obtained by ABPM.

Agarwal's study underlines several important points. Firstly, it indicates that BP measurements obtained in the dialysis unit are of limited prognostic value. Zoccali and colleagues reported that the average of 12 pre-dialysis blood pressure measurements obtained in the dialysis unit had equivalent prognostic value to ABPM among patients on haemodialysis without heart failure.


Ad 5) I apologize for this horrible typo in this comment – meant was six months (instead of years). Including patients which died before formally being prevalent dialysis patients may show different effects of the baseline parameters. Particularly in the Kaplan Meier curves there appears to be a sudden (not unexpected) drop in the fraction of surviving patients which is not consistently found for all patients. I believe that exclusion of subjects not surviving the first 6 months would be of interest since mortality is high in the first months after HD initiation and potentially of different cause than for
prevalent patients. An in depth analysis of mortality in incident patients only may also be of interest in this unique Caucasian (98% - along these lines – what race/ethnicity are the other 2% - didn’t find this mentioned at all in the manuscript) population.

The ethnic differences which amount to 2.1% of the cohort consisted of 1 Asian and one Chinese person. We have added this to the manuscript but doubt whether this will have a huge impact on the data set.

For patients not surviving the first six months, the reviewer presents an interesting question of analysis with exclusion of this group. From our initial QJM paper we analysed the one year mortality in which 56% of the deaths occurred after censoring for transplantation. We have now performed an analysis with exclusion of subjects not surviving the first 6 months after commencement of dialysis therapy but there were only 9 deaths in the first 6 months and therefore this additional analysis adds little to the data set.

The message you are trying to convey to the reader in this underpowered analysis prone to a type II error is that kidney transplantation does not result in a survival advantage to a patient suffering from renal failure – did I understand this right? I consider this a debatable result which should not be made with insufficient statistical power.

Again we apologise for the lack of clarity, as the reviewer indicates although there was no significant difference, there was at least a 12month difference in survival and sub analysis of this group demonstrated that after 10 years 62% were still alive. As the reviewer correctly indicates the numbers are small and difficult to make any conclusions and we have highlighted this in the revised manuscript but it may also reinforce the need for cardiovascular prevention early in this group also.

More importantly patients were censored as previously suggested by the reviewer in the main analysis.

We made the following comments in our previous response to reviewers: “The analysis censored for kidney transplantation because the primary outcome was all cause mortality which is influenced by transplantation and more so the longer patients survive post transplantation”. As detailed in our previous response we believe we have addressed this issue “The current analysis we have carried out details outcomes which are censored for transplantation (see para 3 of results section). – “transplanted patients were censored in the survival analysis”. The paragraph on transplant outcomes does not form a major part of the paper but we believe adds valuable information to the reader on this cohort of patients studies”

Ad 7) I didn’t find any mentioning of residual renal function in the limitation section – did I miss it? The only mentioning I found is eGFR (or GFR as commented on by Reviewer 1 – I agree with his comment that this should be uniform throughout the manuscript). Was this the only assessment of its kind prior to HD initiation? Speaking of HD initiation – I would not talk about “pre HD...” when talking about a value prior to HD initiation – pre HD is considered to be reserved for pre HD assessments prior to an individual treatment.

We have adjusted the terminology regarding “pre Dialysis” to prior to commencement of RRT.

We must point out the eGFR at commencement of RRT appears in Table 2, and therefore eGFR at time of commencement of RRT has been included in the analysis. We have added this to the text and indicated that it was not significant during the analysis. Also it is interesting to note that in the initial QJM paper in which death was analysed at 1 year (see Table 1 in QJM paper), eGFR at first dialysis (as a surrogate measure of residual renal function) in the two groups (survivors and deaths) was significantly different between those who died and those who were
alive but this was not associated with overall mortality on multivariable analysis. However further analysis using slope eGFR produced some interesting findings as detailed below:

Below is detailed the examination of Risk factors in CKD patients before commencement of dialysis

Using the Tangri risk calculator (a predictive model for progression of chronic kidney disease to renal failure) the risk of entering end-stage renal failure was calculated in the cohort. Calculations were made based on; age, sex, eGFR, calcium, phosphate, albumin and bicarbonate, before undertaking renal replacement therapy.

The stratification in level of risk (0-10% = Low risk, 10-20% = intermediate risk and >20% risk of entering ESRF = High risk) The risk calculator was predictive of stating dialysis. Patients stratified to low risk had a significantly longer time to dialysis; an average of 31 months (95% CI 19.5-43.5) compared to high risk individuals who had an average time of 1 year (95% CI 0.46-1.56). However patient mortality was not dependent on risk calculator categorisation

The slope eGFR for this cohort were calculated using linear regression from time of presentation to a nephrologist and just before commencing dialysis. Those crash landing to dialysis within 90 days were censored from the analysis.

The cohort was split into quartiles. The upper quartile (composed of the fastest increasing slope) was compared against the lower three quartiles for mortality. Kaplan Meier survival analysis (Figure) showed that the severe slope eGFR group was associated with an increased mortality but this regressed to the mean after 10 years.

Figure: Kaplan-Meier Survival curves for predicting the mortality of those with severe slope eGFR deterioration (highest quartile) prior to commencement of dialysis compared to the lower 3 quartiles of rate of eGFR progression.
We hope the above-listed alterations render this document acceptable for publication.

Kind regards

In anticipation

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