Author's response to reviews

Title: Analysis of Factors Predicting Mortality of New Patients Commencing Dialysis Therapy in a Single Year after 10 Years Follow-Up

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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 in a Single Year after 10 Years Follow-Up”

We thank you very much for your kind invitation to submit a revised version of our paper. We certainly appreciate the comments of the three reviewers, which were very valuable and which helped us in substantially improving our manuscript. We have taken good care in addressing the reviewers’ concerns and have addressed them as follows:

Reviewer 1

I would be interested to know the process by which cause of death was arbitrated. The reason for asking this is that there is the potential for ambiguity – for example a patient who is fluid overloaded due to failure of dialysis therapy would die a cardiac death, or a patient who discontinues dialysis may for example die of pneumonia.

Death was attributed to what was documented in the medical notes, death certificate where available or from the General practitioner (primary care physician in the case of patients dying in the community). We acknowledge this this may be subject to error, especially if sudden death occurred where the diagnosis as cause of death may be inaccurate but the collection was consistent throughout the study.

I would be interested to know whether primary modality of dialysis therapy influenced long term survival – although this can be confounded by unplanned vs planned presentation for dialysis.

At 5 years the analysis was not significant and again as detailed in the methods section (para 4) this was again compared. Of course the size of the sample is small with 80% of patients being on haemodialysis versus 20% on peritoneal dialysis. We have looked at the deaths in peritoneal dialysis patients and 3 died of cardiac causes, 1 from lung cancer, one from sepsis and 3 had treatment withdrawn. Finally as the reviewer alludes the analysis can be confounded as he has stated.

There is no mention of biochemical methodology (albumin assay for example) and the approach to co-morbidity scoring (was this done prospectively at entry to the study). How was presence of
vascular disease identified or defined? eGFR is described in the methodology – but table 2 uses “GFR” – is this an inconsistency?

The biochemistry was analysed including serum albumin which may be a marker of nutritional status but this was significant in univariate analysis (see table 2). We do not believe that detailing the laboratory methodology of measurement adds any value to the paper but can include it if the editor feels it would add to the article.

Co-morbidity was documented prospectively at the time of commencement of dialysis at a single time point and not subsequently as this would confound the data further. Vascular disease was defined clinical with symptoms or previous investigations to confirm this or a priory intervention such as angioplasty and stenting of a peripheral artery.

*Table 2 should read eGFR as the reviewer has kindly pointed out*

Reviewer 2.

This reviewer indicates that the paper is generally well written but this is not reflected in his final summary of the Written English. We are therefore unclear where the issues are but have reviewed the manuscript and adjusted any anomalies in grammar and English with the assistance of a colleague.

1) Firstly, I’d like to emphasize that I do not feel the current analysis is an update to the previous data. An update would be, in my eyes, an inclusion of more patients, newly acquired parameters or more sophisticated statistical approaches (along these lines it may be mentioned that in the previous publications the authors stated that multivariable analysis was not possible due to the low sample size – however in the current analysis it appeared to be possible (in regard of the fact that it is the same cohort and thus sample size).

We agree with some of the comments. We have adjusted the abstract and removed the term update which adds confusion to the paper and replaced it as follows

“To examine the change in the previously published 5 year data on predialysis and co-morbid risk factors for mortality at 10 years”

In this new analysis we sought the further advice of a statistician, who has subsequently reviewed the manuscript and data and revised those areas which have been highlighted.

The reviewer is correct in part and perhaps an error on our part. It should state the number of events rather than rely totally on the sample size. Events are therefore higher in the 10 year data. Our statistician has confirmed that multivariable analysis would be possible however we do recognise the possible phenomena of regression to the mean which may occur with longer studies.

2) Along these lines a very small sample size needs to be emphasized – there is literature available on observational data which shows factors relating to survival in larger datasets (even providing insight in race and ethnicity as predicting factors).
The revised manuscript does emphasise the sample size as a limitation as confirmed by reviewer one but we have further emphasised this in the revised manuscript to highlight the possibility of a type 2 error. We agree with the reviewer’s comments above but it must be remembered that this is somewhat of a unique UK population of mainly Caucasian dialysis patients (98%) in a deprived region and hence adds valuable insight and support of other larger studies.

3) The longer observation period is used as an argument of the current analysis being an addition to previous data. However, the longer observation period does the opposite – it renders baseline period as even more meaningless for the survival at the end of the observation period. It would be of much greater impacts if the authors would include longitudinal data and trends during the analysis (in time dependent statistical approaches) in the analysis. Alternatively, it would be of interest to look at trends in parameters before and after HD initiation as a predictor of death in the following observation period.

We disagree with this approach as has been suggested the data set is relatively small therefore a longitudinal study may not produce any meaningful data. As indicated above 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. Also new trends may appear post dialysis confounding this analysis. This could form the basis of a much larger epidemiological study extracted from registry data.

4) I repeatedly searched for information on cardiac function and or blood pressure in this analysis and couldn’t find any information. It has been shown that BP change during the first 120 days and also trends during the first year is a strong predictor of death. This is undoubtedly a stronger predictor that Ca*P product and needs to be considered.

We agree Blood pressure was not included due to the poor relationship in measurement in clinical practice and the mounting data of use of home and 24h measurements, however we did use a surrogate marker which has been shown to be a strong predictor, namely the presence of LVH clinically, from the ECG or Echo. This is a more reliable measure. Therefore we have not include BP in this analysis. Indeed Ferro C et al have recently examined the effect of Ca-P in a CKD population in comparison to changes in Cardiac hypertrophy using echo.

5) Patients not surviving the first six years should be excluded (or more interestingly analyzed separated from the rest of the cohort in a subset analysis)– death during this period is not conclusive about general dynamics and also adds a survival bias.

? we do not understand this comment as the first paper analyses 5 year data which therefore we believe would simply be repeating the analysis.

6) The analysis of KTX patients is not uninteresting but appears in the context of the current analysis a little half-heartedly conducted. It can be looked at in a different context but not in this analysis – I’d suggest to censor these patients since KTX patients are more or less considered to be CKD3 patients and thus not really comparable to the cohort analyzed.

We disagree. 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.

7) Residual Renal Function: Abundant literature shows how RRF affects survival and this information needs to be included. Not only at initiation but also trends before and after initiation. Although
comorbidities will affect the dynamics of RRF. RRF can also be influenced by the treatment per se (e.g. volume overload, intradialytic symptoms, etc.).

We agree and have added this to the limitations section.

8) HbA1c at low levels do not necessarily only reflect diabetic treatment but can also be a reflection of malnourishment. Along these lines – no association (an additional point – the authors write about correlations with mortality – this is not really a commonly used term – one may consider speaking about relationships, associations or more accurately termed “statistical predictors” in the context of the results of the analysis) between body composition (which only surfaces briefly and very indirectly as creatinine concentration at HD initiation) and survival. Changes in body composition (e.g. muscle loss) are associated with outcomes – this needs to be addressed in this analysis.

In the discussion section we have revised the text to first of all remove the term association and replace it with “statistical predictor as suggested by the reviewer. We have also added in the comment in relation to HbA1c and malnutrition. However as the reviewer can imagine we were unable to record and analysis every single possible variable and therefore cannot look at this specific parameter but we still believe there is sufficient interesting data contained within the paper to be of value to the reader.

Reviewer 3

1. In the abstract the data about Ca-P should be presented if the authors are going to make conclusions about it.

The abstract has been revised to reflect the above suggestion.

2. Why were MANOVA and Cox regression used? Was the proportional hazards assumption not met over this long period of time?

In relation to the proportional hazards assumption. In a regression type setting this means that the survival curves must have hazard functions that are proportional over time.

The analysis section has been revised to answer this query as detailed below. This makes the approach to the analysis clearer and hopefully answers the several statistical questions posed by the reviewer.

Analysis Section

All continuous data are expressed as means (sd), medians (interquartile ranges). All categorical data are expressed as number and percentage.

The first stage in the analysis was to describe the mortality rate at 10 years (Table 1). The independent variables were compared between those who were alive or dead at 10 years using a chi-square test for continuous variables and chi-square tests for categorical variables (Table 2).

For survival over 10 years based on time to death or last follow-up, the Kaplan-Meier method was used. Log rank tests were used to explore the relationship with categorical independent variables
(e.g. presence of vascular disease, diabetes and age (less than or equal to 65 vs greater than 65). This data is presented in Table 4.

To further investigate mortality over 10 years, Cox regression was used, with time to death or last follow-up as the dependant variable, and a range of categorical and continuous variables included in the model (Table 3). The log-log plot is one way to assess graphically whether the assumption of proportional hazards was reasonable. For the assumption to hold then the log-log plot should show the separate lines as approximately parallel to each other.

All statistical analyses were completed on SPSS for Windows (v19). A p-value of < 0.05 was considered statistically significant.

3. Related to the above, even if the proportional hazards assumption is met, a segmented analysis (or equivalently, the addition of an interaction term with time) might be interesting and relevant to the study question. For example, an indicator of < 5 vs. >= 5 years could be created, and this term could be tested in interaction with variables of interest to determine whether there is evidence of effect modification by time (e.g., if Ca-P is associated in early years and not in later years, as the authors suggest). This gets at the question more directly than simply comparing the same analysis with more years.

See above - the proportional hazard is met so an indicator variable does not need to be introduced – the log-log plots were approximately parallel to each other (see attached).

4. Why are there no adjusted analyses (only Kaplan-Meier)? Is this due to small numbers of events? It seems at least half the cohort died (~50) so there is probably some wiggle room for adjustment for 4-5 important confounders.

We have done a cox regression, which seems to have been missed by the reviewer. We have done this in the paper by exploring which variable explained survival.

5. The median follow-up is 8.7 years. This seems extraordinary if those who died at < 5 years were included (which seems to be the case from Table 1). Further, it appears from Table 2 that 1/2 of the patients who started dialysis 10 years prior were still alive, which again seems high. Do the authors have any thoughts on whether this is a highly selected cohort? Or is this typical in the UK? Either way this should be discussed.

It should be pointed out that the data presented in Table 2 are percentages and not actual numbers. Number have been added.

6. Those who dialyzed < 90 days were excluded. Did this include early deaths?

In order to maintain a consistent approach of the definition of chronic rather than acute kidney injury, patients dialysing less than 90 days were excluded. We have examined the data of patients dialysis for less than 90 days and there was one death in a patient with acute kidney injury and the other patients recovered renal function to become dialysis in depended. There were no deaths in patients presenting in the first 90 days for the proposed chronic referrals that we can ascertain but this is subject to error.
7. While the exclusion above could have resulted in selection bias if it were differential by variables of interest, I am not sure why the results that show kidney graft is protective are indicative of selection bias (see first paragraph of Discussion). Could the authors clarify?

We have removed this statement as the reviewer alludes it is perhaps confusing rather than helpful. 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.

8. Table 3 needs the beta estimates, not just the CIs. Or, perhaps, exp(beta) since this is a risk ratio (from Cox regression). The Wald statistic is not of interest.

On re-running the analysis the figures have changed slightly. We agree that we need the exp(b) estimates along with the CI’s.

In table 2 we have included the numbers along with % and mean (sd) for age.

9. Limitations should include: confounding by both known and unknown factors (since there was no adjustment); misclassification of the outcome (cause of death only) and of potential confounders; and lack of longitudinal data on all the risk factors, as biomarkers (like Ca-P), vascular access, and comorbid conditions could change dramatically in 10 years, making them less relevant closer to death.

We have added the above suggestion to the limitations section of the revised paper.

10. The conclusion is not supported by the data. The authors don't present longitudinal data on CVD/diabetes treatment nor do they adjust for it, so it is speculative that changes in treatment account for the changes in deaths. (Further, it would require a comparison of cohorts who started at different times to examine this issue, since there are competing risks within the same cohort.) It seems more likely that the distribution of causes of death changes because those who die of CV or infectious causes die earlier.

We agree that the changes are speculative and have revised the text to reflect this and stressed that the distribution of causes of death changes because those who die of CV or infectious causes die earlier.

11. Minor: spelling throughout should be checked (Mantle and Kaplin instead of Mantel and Kaplan, for example). There are also a few sentence fragments.

We have changed the spelling to Mantel and Kaplan where there were errors in the abstract and text and corrected various sentence fragments.

We hope the above-listed alterations render this document acceptable for publication.

Kind regards
In anticipation

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