Author's response to reviews

**Title:** Survival prognosis after the start of a renal replacement therapy in the Netherlands: a retrospective cohort study

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**Author's response to reviews:** see over
Dear editor,

Hereby I send you my revised manuscript (MS: 1162305659906239) with the title “Survival prognosis after the start of a renal replacement therapy in the Netherlands”. It is a revision to the earlier submitted version, based on the requested changes.

I want to thank you and the reviewers for the very useful comments on our manuscript. I hope the adjustments that we have made are to your satisfaction.

In this letter, I give a detailed response on every question/comment of the reviewers, including the original comment (in bold), and a detailed answer or description of how we handled each suggestion.

If you have any further questions regarding our revisions, you can contact me. I would like to inform you that I am not available to respond to eventual questions in the period July 15 – August 5, because of the summer holidays. In that period you might contact my colleague Martin Heemskerk (m.heemskerk@transplantatiestichting.nl).

I hope that you will find this manuscript suitable for publication in BMC Nephrology.

Yours sincerely,

Aline Hemke
Researcher Dutch Transplant Foundation
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Major revision 1 requested by reviewer 1 (LF):

The discussion (page 7) raises concerns as the study was build to define a prognosis in a therapeutic setting, not to compare each renal replacement therapy. The study did not allow comparing PD and HD survival. Anyway, it is very important to emphasize that new designs are currently emerging for this specific goal. Please see Beuscart Jean-Baptiste et al. Overestimation of the probability of death on peritoneal dialysis by the Kaplan-Meier method: advantages of a competing risks approach. BMC Nephrology 2012, 13:31.

This suggestion has been followed and we added this reference at the end of the discussion/limitations of the study (line numbers 242-244).

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Major revision 2 requested by reviewer 1 (LF):

Generalizability in other country is very doubtful, as countries differ in depth in dialysis and transplantation supplies and interactions. For instance, Netherlands are characterized by very high rates of peritoneal dialysis and living donor transplantation, and very low rate of elderly patients in dialysis. These 3 domains must impact survival prediction.

This doubt about the possibility to generalize the outcomes of the model to another country has been added to the discussion (second limitation, line numbers 229-231). In the future we would actually like to validate our model in populations of other countries. Considering the small variable-set in our model, this should be a feasible goal for further research.

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Minor revision 1 requested by reviewer 1 (LF):

How was defined primary renal disease? Did the investigators check the accuracy of this variable? 518 patients were excluded because of non registered PRD. Why these patients were not classified as unknown PRD?

The primary renal diseases are registered according to the ERA-EDTA coding system and grouped to 6 separate categories for our model. The unknown PRD is a specific category, as the nephrologist apparently was not able to define the original kidney disease. These are probably shrunken kidneys and, as this is a specific recognizable category of patients, it was decided to create a separate PRD-category ("unknown") for this group of patients. If the PRD is missing it could be any disease and therefore is, different from PRD “unknown”, not a specific type of PRD. We have now added the description of this difference between category “unknown” and missing PRD to the methods section of the document (line numbers 79-84).

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Minor revision 2 requested by reviewer 1 (LF):
The last sentence of the introduction looks like a conclusion of the manuscript. The last sentence of the background section (line numbers 67-69) is now changed into: “The objective of this study is to develop a prediction model that could be used by physicians to inform patients about their survival chances at the start of RRT, based on a few very easily obtainable variables.”

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Minor revision 3 requested by reviewer 1 (LF):


This reference has been added as a reference to the background section of this revision (line numbers 55-56). This indeed is a different kind of prediction model, which was not mentioned yet. It is different from our model, since this prediction of Couchoud has been built for a specific group of patients (of 65 years of age or older), which in fact is a subset of our adult patient group. Another difference with our model is that it focuses on short term survival. Because of their focus on short term survival the problem of differing outcomes as a consequence of different chances on kidney transplantation probably does not apply.

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Major compulsory revision 1 by reviewer 2 (DF):

The authors note the lack of external validation in the discussion (not entirely surprising as the random allocation of patients to a development and validation group results in 2 very similar groups which come from a similar health care system). This lack of external validation should be noted in the abstract too.

The fact that the model was only internally validated and no external validation was performed, is explicitly noted in this revision in the methods section of the abstract (line numbers 36-37).

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Major compulsory revision 2 by reviewer 2 (DF):

**Authors should consider if a better approach would be to allocate patients on a geographical basis that would reduce similarity between the 2 groups. Another approach would be internal-external cross-validation (see Royston, Construction and validation of a prognostic model across several studies, with an application in superficial bladder cancer, STATISTICS IN MEDICINE, 2004, 23:907-926.**

In our study, we have randomly split the research group in 2, which did actually lead to two comparable groups, except for the sex distribution. We agree that dividing the research group in two geographically separate groups would indeed be an alternative approach. We decided to perform additional validity tests (sensitivity analyses) on two regional groups. We divided the Dutch population into two (an eastern and western) regions based on the ZIP-codes of the patients addresses. We excluded cases with missing values and created two comparable sized groups with a cut-off point at the ZIP-code of 4707-
The two regions differ in age-distribution, PRD-distribution, the starting period, primary therapies and transplantation rate. Only the sex-distribution was similar in both regions. We also compared the two regions with the development group of our research. The western region had most similarities with the development group; there was only a difference on PRD-distribution. The eastern region differed more from the development group, with significant differences in age-distribution, PRD-distribution, the therapy at 90 days and the transplantation rate in the follow-up. We did two sensitivity analyses. First we estimated a new model in one region and validated this model in the other region. This model differs from our original model, but is comparable with respect to the mutual relations. This model has a similar calibration in comparison with the original model, and an adequate discrimination of 0.71, which is slightly lower than the original model (C=0.72). Therefore we decided to keep the original as our final model. As a second sensitivity analysis we also validated our original/final model in both separate regions. The discrimination was similar in both regions (C=0.71) and the model calibration was also comparable in both regions (calibration slope for PI: 0.982 and 1.040). We mentioned the performance of these sensitivity analysis to the methods section of the abstract (line numbers 34-36) and the main document (line numbers 118-119) We added the outcomes of this sensitivity analyses to the results in the revised document (line numbers 161-173).

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Major compulsory revision 3 by reviewer 2 (DF):

In addition to evaluating discrimination by looking at the c-statistic, discrimination should also be evaluated and plotted in prognostic groups, for instance quartiles of predicted survival. Also provide the confidence intervals around the c-statistic.

We have calculated the discrimination for both the 10 year and 3 year survival for quartiles of predicted survival. For the 10 year survival the discriminative ability within different risk groups showed different results, with the best discriminative ability in the first quartile with lowest risk and worst discriminative ability in the last quartile with highest risk (C-index: Q1: 0.662, Q2: 0.586, Q3: 0.532, Q4: 0.521) and for the 3 year survival this ranges from 0.645-0.519. The C-index for the 4 quartiles is less than the overall C-index, as it is more difficult to discriminate within the different risk groups where patients are grouped based on more or less comparable risk profiles. We propose not to included above mentioned data in the manuscript, in the interest of space, and as we fear the results of the intra-group discrimination might confuse the readers. As a result of the second suggestion we used STATA to calculate the confidence intervals for discrimination for the 3, 5 and 10 year survival (line numbers 97, 107-108), which were quite acceptable and have been added to the results section of the revised document (line numbers 152-154).

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Major compulsory revision 4 by reviewer 2 (DF):

In addition to the calibration plot, calibration should also be evaluated by looking at survival curves at fixed time points by grouping patients in risk groups (for instance quartiles) and comparing and plotting observed survival with predicted survival from the prognostic model.
The calibration plot had only been shown in the first version of our document for the 10 years predicted versus observed survival. The stratification for this plot was by 10 risk groups (10 deciles of calculated prognostic index). As a result of the next suggestion (major compulsory revision 5 by reviewer 2) we also made the calibration plot for every prognostic group (deciles) for the 3- and 5-year survival (mentioned at line numbers 107-108 and results in figure 1).

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Major compulsory revision 5 by reviewer 2 (DF):

In calibrating the model mortality risk was split & investigated across 10 risk strata. Results are shown for 10 year survival. Please provide plots for 3 & 5 year survival which have greater utility given the overall annual mortality.

As a result of this suggestion we also made the calibration plot for every prognostic group (deciles) for 3- and 5-year survival (mentioned at line numbers 107-108 and results in figure 1). In addition, we also calculated the discrimination for the 3 and 5 years survival as well, and the outcomes have been described in the results section of the revised document (line numbers 150-154).

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Major compulsory revision 6 by reviewer 2 (DF):

The authors should comment on whether non-linearity of continuous variables was investigated during the variable selection process.

The only continuous variable used in the model was age. Linearity was tested by Kaplan Meier and Cox regression survival analysis, by dividing the population in 16 strata based on age at the start of renal replacement therapy (each stratum 5 years of age). The youngest patients had the best survival and survival chances decreased evenly with increasing age. We added the linearity-test to the statistical analysis section of this revision (line numbers 98-99) and the outcome of the test to the results (line number 128).

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Major compulsory revision 7 by reviewer 2 (DF):

The authors need to comment on whether interactions between prognostic risk factors were considered in the variable selection process.

As we had only a few variables in our dataset, there was no initial variable selection process. All four available variables for our research population have been used in our Cox regression analysis. To avoid over-fitting, we did not want to include all interactions in the model. Based on our clinical knowledge we did not suspect interactions between the 4 variables, and for that reason we did not include specific interaction terms in our analysis.
Major compulsory revision 8 by reviewer 2 (DF):

**Numbers of patients at risk per year should be included in a table to enable interpretation of the Cox model results and to ensure that there are adequate patient numbers past 5 years of follow-up. Provide information on whether the Cox proportional hazards model was tested for proportionality and describe the method used for testing the proportionality assumption.**

The numbers of patients at risk at 4 time points are now described at the results section of the manuscripts (line numbers 129-131). The proportionality assumption has been tested by visual inspection of the Schoenfeld residual plots (line numbers 99-100, results: 127-128).

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Major compulsory revision 9 by reviewer 2 (DF):

**Provide information on: censoring in the survival analysis, follow-up time (mean, median, minimum and maximum) and number of events (deaths).**

This information has been added to the results section of the revised document (line numbers 121-124).

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Major compulsory revision 10 by reviewer 2 (DF):

**The sensitivity analysis regarding listed status for transplantation should be mentioned in the abstract too.**

We added this in the abstract in the “methods” (line numbers 31-32).

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Minor essential revision 1 by reviewer 2 (DF):

**We appreciate that comorbidity is not always available but can the authors provide some analysis or comments on why this is not the case. If this is further work in progress please state as such. This would be valuable and thus would support (or not) their use of a simpler model.**

The research has been done on the complete cohort of patients starting renal replacement therapy in the period 1995-2005 and registered in the Dutch Renal Replacement Registry. This registry is based on a large registration of a few essential data, and only has information on PRD and therapies, and no comorbidities can be registered in this database. The advantage of our dataset was that we have information of many patients (incident patients in a 10-year period), but the disadvantage was that we do not have many variables. As stated in the discussion it would be desirable if an additional study would be performed to see whether it is possible to further improve the discriminative power of the model with use of additional clinical information. This might be possible with data from NECOSAD. NECOSAD stands for Netherlands cooperative study on the Adequacy of Dialysis treatment and has many extra items that could possibly improve the prediction of survival.
Previous work from the UK and elsewhere should be compared in the discussion. In the case of the UK data (Wagner 2011) the C statistic rose from 0.69 to 0.75 by adding comorbid condition data and laboratory measurements mainly because of the latter.
In the discussion we already did mention the work of Wagner, but we did not state the figures for discrimination. We added these figures to the discussion section in the revised document (line number 220), to give more information about the discriminative power we have reached in our model compared to that of others, as suggested by the reviewer.

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Discretionary revisions

**Delete use of ‘nowadays’ on page 3.** This has been changed into “in recent years” (line number 49)

**Spelling mistake on p6, paragraph3: de instead of the.** This has been corrected (line number 157).