Postprint Version	1.0
Journal website	http://ndt.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=21317411
Pubmed link	http://www.ncbi.nlm.nih.gov/pubmed/21317411
DOI	10.1093/ndt/gfq856

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Full loss of residual renal function causes higher mortality in dialysis patients; findings from a marginal structural model

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ABSTRACT

Background. Declining residual renal function, as indicated by the glomerular filtration rate (GFR), is associated with an increased mortality risk in patients with end-stage renal disease (ESRD) on dialysis.

Methods. We monitored GFR and mortality in 1800 haemodialysis (HD) and peritoneal dialysis (PD) patients in 1996–2006. We used a marginal structural model to estimate the causal effects both of GFR when it was not completely lost and of the subsequent full loss of GFR on mortality, avoiding the drawbacks of standard regression models that include covariates to adjust for confounding. Instead, effect estimates were adjusted for possible baseline and time-varying confounders using inverse probability weighting.

Results. We estimated a hazard ratio (HR) corresponding to the effect of the full loss of GFR on mortality, as compared to not having fully lost GFR, of 1.50 [95% confidence interval (CI) 1.09–2.07]. The HR corresponding to the effect of GFR when GFR is not (yet) fully lost on mortality was 0.97 (95% CI 0.92–1.02) (per mL/min/1.73m^2). We found no significant difference in the effect of GFR on mortality between patients starting on PD and HD.

Conclusions. Preventing or delaying the full loss of GFR can improve survival in dialysis patients. This supports the importance that is given to the effect of treatment options for patients with ESRD on the rate of decline of the residual renal function.

INTRODUCTION

One of the primary goals for nephrologists managing patients with CKD is the preservation of the residual renal function, as operationalized by the glomerular filtration rate (GFR). When dialysis treatment is initiated, preservation of GFR remains important. Previous studies have shown that the preservation of GFR contributes significantly to the overall health and well-being of dialysis patients [1] and is associated with

lower mortality [2–11]. This suggests that the association between GFR and mortality is at least partly causal. Therefore, it is of interest to quantify the causal effect of GFR on mortality to investigate if the preservation of GFR is indeed important for patient survival.

A randomized clinical trial is the standard design to quantify the causal effect of an intervention. However, the causal effect of GFR on mortality in dialysis patients cannot be estimated from a trial since GFR cannot be randomly assigned like a medical treatment. In order to estimate this effect from observational data, it is necessary to adjust not only for baseline covariates but also for possible time-varying confounders such as indicators of disease progression. Because disease progression indicators can be intermediate for the effect of GFR, the use of standard regression models including these time-varying confounders as covariates ('conditional' models) can lead to bias since part of the effect of GFR could be adjusted away [12, 13]. For example, serum albumin could be a confounder for the effect of GFR. Serum albumin could also be affected by the previous GFR status. By including serum albumin as a covariate in a regression model, which means that it will 'hold constant' mathematically, the indirect effect of GFR on mortality through serum albumin will be lost. Furthermore, the use of standard conditional models can lead to bias due to noncollapsibility, a mathematical inconvenience that occurs when using models that are not linear or log-linear. Noncollapsibility means that the effect estimate for GFR, as estimated from a Cox proportional hazards model such as in our study, changes by adding covariates that are completely independent from GFR [14]. The use of conditional models can also induce selection bias by including a covariate that is a consequence of the exposure but does itself not affect the outcome, when there exists an unmeasured variable that affects both the covariate and the outcome of interest [15]. Therefore, exposure effects as estimated from regression models that include covariates to adjust for confounding can be severely biased when trying to estimate an effect comparable to the causal effect as estimated from a trial.

Marginal structural models (MSMs) provide a way to overcome the drawbacks of standard conditional models [16]. MSMs estimate causal effects, defined as contrasts between the outcomes that would have been observed, when all patients would have received a specific exposure level ('counterfactual outcomes') [17]. For example, an MSM could compare mortality in hypothetical situations such as 'everyone always receives exposure A,' versus 'everyone always receives exposure B'.

We fitted an MSM, adjusting for confounding using inverse probability weighting (IPW) [17] as was previously applied, e.g. to estimate the effect of epoetin dose on haematocrit in patients with end-stage renal disease (ESRD) [18], to estimate the association between number of months below K/DOQI haemoglobin target and hospitalization or death [19] or to examine the relationship between epoetin alpha dose and mortality [20]. When fitting MSMs using IPW, it is necessary to make four assumptions [17], which are described and evaluated in the statistical methods section.

We estimated the effect of the full loss of residual renal function as indicated by a GFR of zero, as well as the effect of measured GFR when GFR was not yet fully lost. We chose to model these effects separately since observed GFR was approximately normally distributed (on the cube root scale), with distinctly separate from this distribution a large number of zeros (Figure 1). This is known as 'zero-inflation', and implies that the reaching of a GFR of zero is a distinct event, that could have an effect on mortality separate from the effect of GFR when the residual renal function is not yet fully lost [21]. A similar distinction was made by Wang et al. [5].

[FIGURE 1]

In a secondary analysis, we also estimated the overall effect of GFR on mortality without distinguishing between the effect of the full loss of GFR and the effect of GFR when it is not fully lost, for comparability with previous studies. We also performed a secondary analysis, estimating the effect of GFR for patients starting on peritoneal dialysis (PD) and haemodialysis (HD) separately. We estimated these effects using a cohort of patients with ESRD who were followed from the start of dialysis treatment.

MATERIALS AND METHODS

Study data

Netherlands Cooperative Study on the Adequacy of Dialysis is a large prospective cohort of renal patients [22]. From 1996 up to 2006, patients with ESRD were included at the start of PD or HD treatment. In 38 of

the 50 dialysis units in the Netherlands, all new ESRD patients were consecutively invited to participate in the study. To be eligible for the study, patients had to be ≥18 years and dialysis had to be their first renal replacement therapy. The study was approved by all local medical ethics committees and all patients gave informed consent before inclusion.

Measurements were taken at baseline and subsequently every 6 months, with an extra measurement at 3 months after the start of dialysis. To avoid problems associated with early events due to acute renal failure, we selected only those patients who survived the first 3 months of dialysis and used 3 months after the start of dialysis as time origin in our analysis. The total number of patients selected for the analysis was 1800.

Baseline variables include age, body mass index, sex, primary kidney disease, diabetes mellitus, cardiovascular disease, malignancy, smoking, having a partner, having children, education level and employment status. Time-varying variables include blood albumin, blood haemoglobin, nutritional status, comorbidity and dialysis treatment, in addition to GFR. Time-varying variables were all measured from the start of the follow-up onwards. GFR was calculated as the mean of creatinine and urea clearance adjusted for body surface area (mL/min/1.73m^2). Five hundred and ninety-eight patients reached a GFR of zero during the follow-up. Of these, for 494 patients, GFR remained zero after reaching zero. For the remaining 104 patients, GFR increased after reaching zero for the first time but was set to zero in the analysis for simplicity (during 145.9 person-years or 3.0% of the total follow-up). Patients were classified as having no, intermediate or severe comorbidity based on the number of comorbid conditions according to Davies' comorbidity index [23]. The nutritional status was scored on the standardized seven-point scale of the Subjective Global Assessment (SGA), based on the clinical judgment of the dialysis nurse [24]. A higher SGA score represents a better nutritional status. Subjects could switch dialysis treatment during the study.

Statistical methods

To estimate the causal effect of GFR on mortality, we fitted a Cox proportional hazards regression model for survival. The effect of GFR was included on a linear scale; full loss of GFR was included as a dummy variable (0 when GFR is not zero, 1 when a GFR of zero is reached). Both were included as time-varying variables. In the first secondary analysis, we fitted a Cox model containing only the overall effect of GFR, regardless of whether GFR was fully lost or not. In another secondary analysis, we fitted a Cox model for survival containing main effects for the full loss of GFR, the effect of GFR when it was not fully lost and baseline dialysis modality (indicator for PD or HD), as well as the interaction between loss of GFR and baseline dialysis modality and between GFR when it was not lost and baseline dialysis modality. We fitted this model only on observations of patients up to the first dialysis switch. The proportional hazards assumption for all three Cox models was checked by plotting the Schoenfeld residuals.

We used IPW to adjust for confounding as described by Hernán et al. [25]. Time-varying measurements of patients received a weight inversely proportional to the estimated probability of having the observed GFR history, given the measured baseline and time-varying covariates (Table 1). Similar to Cotter et al. [18], the inverse probability weights were estimated by fitting a mixture of two longitudinal models: a complementary log-log regression model to estimate the probability of reaching a GFR of zero and a linear regression model to estimate the distribution of the cube root of GFR among those who do not yet have a GFR of zero. Both models included the measured baseline and time-varying covariates as listed in Table 1. In addition, we included GFR at a previous time point, which is also a potential confounder for the effect of GFR on mortality.

[TABLE 1]

Patients dropped out of the study when receiving a renal transplantation, possibly causing informative censoring. Therefore, we computed IPW weights to adjust for informative censoring [25], using a complementary log-log regression model. Similarly, when modelling survival conditional on dialysis modality, we used IPW to correct for informative censoring at a dialysis switch. All inverse probability weights were stabilized [17], using only follow-up time as a predictor, to estimate the numerators of the weights. Confidence intervals (CI) were computed using a robust standard error estimator. In the third model, we tested the significance of the interactions with dialysis modality using a multivariate Wald tests with a robust covariance matrix.

The Cox proportional hazards models, as described above, are equivalent to MSMs when making the following assumptions [12, 13, 16, 17]:

(1) There should be no unmeasured confounding. Based on the literature [1–11], we are confident that we have adjusted for all important confounders.
(2) 'Positivity' is the assumption that all levels of the exposure (GFR) occur within all subgroups that could be defined based on the confounding variables. For example, for all values of serum albumin, we should observe the same range of values of GFR as in the whole sample (but possibly with a different distribution). With continuous confounders and exposure, this assumption is never met exactly since both can attain an infinite range of values. This can be overcome by smoothing, through the use of regression models to estimate the IPW weights. Based on descriptive statistics (data not shown), we concluded that the range of confounding variables is similar enough for different values of GFR, to allow for smoothing through the use of regression models.
(3) We assume that we have correctly modelled the full loss of GFR and GFR when it was not completely lost, as a function of possible confounders. The regression models used to estimate the weights were specified beforehand. We included main effects of the possible confounders. The effect of follow-up time was modelled using natural splines with five degrees of freedom [26]. The fit of these models was assessed by making residual plots (Q-Q plot of residuals for the linear regression model, marginal model plots [27] for complementary log-log regression models). We concluded that adequate model fit was obtained.
(4) The assumption of 'consistency' means that we have estimated the effect of a clearly defined intervention. Similarly to Ishani et al. [19], we have estimated the effect of a variable, which is not a treatment, and cannot be directly manipulated. Therefore, we have not examined the effect of an intervention directly. However, our results are an estimate of the impact of the loss of residual renal function on mortality, adequately adjusted for confounding. Furthermore, our results can give an estimate of the effect on mortality of a certain treatment, when that treatment changes GFR.

RESULTS

Sample descriptives

Table 1 contains descriptive statistics for the 1800 included patients. The total number of person-years of follow-up was 4812. During follow-up, 745 deaths were observed. Censoring due to receiving a kidney transplant occurred in 514 individuals and 319 individuals were lost to follow-up. Of the 609 patients starting on PD, 143 switched to HD during follow-up, and of the 1191 patients starting on HD, 64 switched to PD during follow-up. Figure 1 contains histograms of GFR plotted on the cube root scale, within strata of time since the start of dialysis treatment. From Figure 1, it is apparent that the distribution of GFR is zero-inflated.

Distribution of the IPW weights

Table 2 gives descriptive statistics for the IPW weights that were used to adjust for confounding. Figure 2 displays boxplots of the weights, plotted on the logarithmic scale, within strata of follow-up time. The minimum (0.001) is small. However, both truncating the weights to the 1st and 99th percentile (0.051 and 10.94, respectively) or removing observations with a weight smaller than the 1st or bigger than the 99th percentile did not cause a change in the first two decimals of the parameter estimates from the main MSM. Therefore, we concluded that there are no 'extreme' observations that have a relatively high or low impact on the final effect estimates. Since truncating or removing observations as described above did not substantially affect the length of the CIs, we chose to use the weights without truncating and did not remove any observations. Note that the median of the weights decreases over follow-up time, while the mean increases (Figure 2). This indicates that the distribution of the weights is not symmetrical (on the log scale) at later time points. From previous simulation studies, we know that this is often the case when correcting for time-varying confounders.

[TABLE 2]

[FIGURE 2]

Effect of GFR on mortality

Table 3 contains estimated hazard ratios (HRs) with 95% CIs for the effect of the full loss of residual renal function, as well as the effect of measured GFR when GFR was not fully lost, both overall and conditional on baseline dialysis modality. The HR corresponding to the overall effect of the full loss GFR was 1.50 (95% CI 1.09–2.07). This indicates that the full loss of GFR causes higher mortality in dialysis patients. The HR corresponding to the overall effect of GFR when there was still some residual renal function (GFR > 0) was 0.97 (95% CI 0.92–1.02) (per mL/min/1.73m^2). Even though the latter effect estimate did not differ significantly from 1, this finding suggests that when GFR increases by 1 mL/min/1.73m^2, the mortality risk decreases by 3% in patients with ESRD. Vice versa, when the GFR decreases by 1 mL/min/1.73m^2, the mortality risk would increase by 3%.

[Table 3]

The HR for the effect of GFR on mortality, as estimated from a model containing only a main effect of GFR without distinguishing between the effect of the full loss of GFR and the effect of GFR when it is not fully lost, is 0.94 (95% CI 0.91–0.97) (per mL/min/1.73m^2).

In the secondary analysis conditional on baseline dialysis type, the multivariate Wald test did not detect a significant interaction between GFR and dialysis modality (P = 0.29). We present the estimates for the two subgroups from this model in Table 3 as an illustration. These suggest that the effect of the loss of GFR on mortality is somewhat higher in patients starting on PD (HR = 2.15) compared to patients starting on HD (HR = 1.35).

DISCUSSION

We found that retaining GFR, as compared to the full loss of GFR, is associated with better survival, in patients with ESRD on dialysis. We give a causal explanation to this association, under the assumptions listed in the methods section. We found no significant difference in the effect of GFR on mortality between patients starting on PD and HD. Our study is the first to avoid the problems associated with the use of standard conditional models. Therefore, our results are an important addition to the literature investigating the effect of GFR on mortality.

The positive effect of retaining GFR on survival that we have found is in line with the associations found in previous studies, both for patients on PD and HD [2–11]. For example, for patients on PD, Wang et al. [5] found an unadjusted HR for the effect of the full loss of GFR on mortality of 2.17 (95% CI 1.34–3.50). Szeto et al. [9] found an adjusted HR for the effect of the full loss of GFR on mortality of 1.54 (95% CI 1.06–2.22) for patients on PD. Termorshuizen et al. [10] found an adjusted HR for the overall effect of GFR (without estimating a separate effect for the full loss of GFR) on mortality in PD patients of 0.88 (95% CI 0.79–0.99), using partly the same data as used in our study. For patients on HD, Shemin et al. [7] estimated an adjusted HR for the effect of the full loss of GFR on mortality of 0.35 (95% CI 0.18–0.68). However, the results of these four studies could suffer from biases that do not occur in our study since in these previous studies (i) fewer possible confounders were adjusted for and/or (ii) only baseline versions of some possible confounders were adjusted for and (iii) all studies used standard regression models, including covariates to correct for confounding, which suffers from the drawbacks that were listed in the introduction.

The MSM methodology that we used provides an estimate of the effect of an exposure, without including additional covariates, while still adjusting for confounding through IPW. This means that we have only obtained estimates of the causal effect of GFR on mortality. Estimating the causal effect of other variables would require different models, e.g. as used with the same data as a previous study to estimate the effect of dialysis modality on mortality [28].

The effect of GFR conditional on dialysis modality, as estimated in a secondary analysis, should be interpreted as being conditional on the received dialysis modality up to the first dialysis switch since we have fitted this model on observations censored at the first dialysis switch. To estimate the effect of GFR conditional on time-varying dialysis modality (even after a switch) cannot be done using a standard MSM. Conditioning on a time-varying covariate in an MSM could induce bias due to adjusting away the effect

[12, 13] and collider stratification [15], as described in the introduction. Such an analysis can be performed, e.g. by using recently developed methodology for history adjusted-marginal structural models [29, 30].

Our results implicate that delaying or preventing the full loss of residual renal function could lead to lower mortality in patients with ESRD. This gives support to the importance that is given to the effect of treatment options for patients with ESRD on the rate of decline of the residual renal function. The literature suggests that the decline of residual renal function is slower in patients who receive PD as compared to HD [31–33]. Therefore, our study could give indirect support to the preference of PD over HD, when possible.

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TABLES AND FIGURES

[Figure 1]

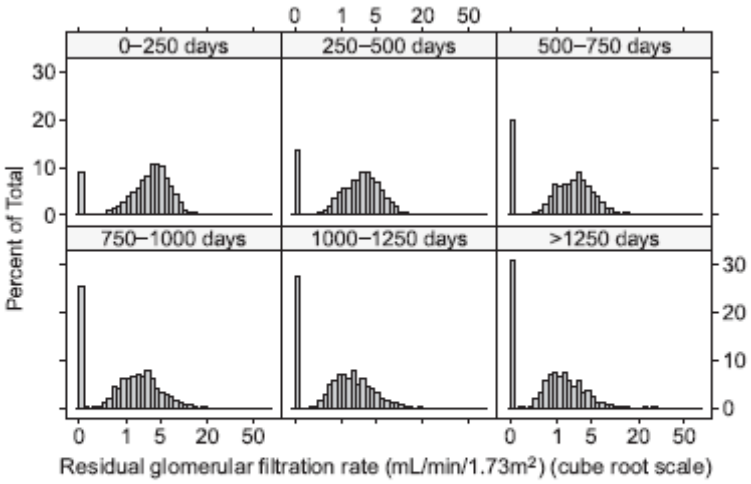

Fig. 1. Histograms of residual GFR (mL/min/1.73m^2), plotted on the cube root scale, within strata of time since the start of dialysis treatment. Note that there is a peak at the value zero (zero-inflation).

[Table 1]

Table 1. Descriptive statistics for the sample of patients with ESRD selected from the NECOSAD cohort; IQR, interquartile range

Total number of patients	1800	
Total number of person-years	4811.8	
Number of deaths during follow-up	745	
Number of renal transplants	514	
Number lost to follow-up other than because of renal transplant	319	
Residual GFR (mL/min/1.73m^2)		
Mean at baseline	4.6 (SD = 3.2)	
At baseline	Median = 4.3, IQR = 2.4–6.4	
Baseline covariates	Descriptive statistics	
	Mean	SD
Age (years)	59.7	15.1
Body mass index (kg/m^2)	25.0	4.3
	n	Total (%)
Sex		
Male	1113	61.8
Primary kidney disease		
Diabetes mellitus	278	15.4
Glomerulonephritis	236	13.1
Renal vascular disease	322	17.9
Other	964	53.6
Diabetes mellitus	382	21.2
Cardiovascular disease	711	39.5
Malignancy	164	9.1
Smoking	382	21.2
Not with partner	627	34.8
Having children	1295	71.9
Higher education (beyond secondary level)	462	25.7
Unemployed/disabled/retired	1291	71.7
(+Baseline measurements of time dependent covariates)		
Time-varying covariates	Descriptive statistics (at baseline)	
	Mean	SD
Serum albumin (g/dL)	3.6	0.6
Haemoglobin (g/dL)	11.1	1.6
Nutritional status (SGA)	5.9	1.1
	n	Total (%)
Davies comorbidity score		
Low	857	47.6
Moderate	774	43.0
High	169	9.4
Peritoneal dialysis treatment at baseline	609	33.8
Switching to haemodialysis during follow-up	143	7.9
Haemodialysis treatment at baseline	1191	66.2
Switching to peritoneal dialysis during follow-up	64	3.6

[Table 2]

Table 2. Descriptives of the IPW weights that were used to adjust for confounding

Minimum	1st Quartile	Median	Mean	3rd Quartile	Maximum
0.001	0.605	0.864	1.091	1.063	11.000

[Figure 2]

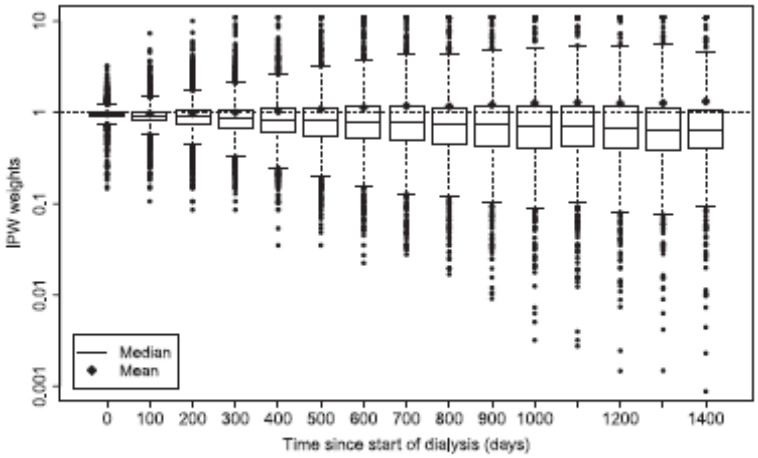

Fig. 2. Boxplots showing the distribution of IPW weights (plotted on the logarithmic scale) over time since the start of dialysis treatment.

[Table 3]

Table 3. Estimated HRs for the effect of the full loss of residual renal function, as indicated by a GFR (mL/min/1.73m^2) of zero (GFR = 0), as well as the effect of measured GFR when GFR was not fully lost (GFR, when GFR ≠ 0)[a]

	Overall		Patients starting on PD		Patients starting on HD	
Effect	HR	95% CI	HR	95% CI	HR	95% CI
GFR = 0 versus GFR ≠ 0	1.50	1.09–2.07	2.15	1.21–3.80	1.35	1.03–1.76
GFR, when GFR ≠ 0 (per mL/min/1.73m^2)	0.97	0.92–1.02	1.02	0.94–1.10	0.96	0.92–1.01

[a]Overall estimates and separate estimates for patients starting on PD and HD. Effect estimates were adjusted for baseline and time-varying covariates listed in Table 1 and GFR at a previous time point.