Decline in glomerular filtration rate during pre-dialysis phase and survival on chronic renal replacement therapy

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Abstract

Background. Estimated glomerular filtration rate (eGFR) is widely used in follow-up and assessment of patients before start of chronic renal replacement therapy (RRT). Reported data on impact of eGFR decline pattern during pre-dialysis phase on consequent survival on RRT are, however, non-existent.

Methods. Using the database of the Finnish Registry for Kidney Diseases, we conducted a cohort study of all incident adult patients (n = 457) entering chronic RRT in Finland in 1998, with follow-up until 31 December 2008. We included those (n = 319) with three serum creatinine measurements (at ~12 and 3 months and 1 to 2 weeks prior to RRT start) and calculated their slopes of eGFR using the modification of diet in renal disease formula. According to eGFR slopes (in mL/min/1.73m²/year), patients were divided into tertiles: most rapid (>8.5, n = 107), intermediate (3.4–8.5, n = 107) and slowest decline (<3.4, n = 105).

Results. Median survival time was 5.6 (95% confidence interval 4.2–7.0) years. Compared to the patient group with the slowest eGFR decline, age- and gender-adjusted relative risk of death was 1.1 (0.8–1.5) in the intermediate group and 1.7 (1.2–2.4, P = 0.002) in the most rapid decline group. When further adjusting for kidney disease diagnosis, comorbidities, use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, body mass index, blood haemoglobin and serum albumin, the association was no longer significant.

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Conclusions. Rapid decline in eGFR before entering chronic RRT associates with increased mortality on RRT. The elevated mortality appears to be caused by known risk factors for death on RRT.

Keywords: end-stage renal disease; glomerular filtration rate; registry; renal replacement therapy; survival

Introduction

End-stage renal disease (ESRD) confers a devastating impact on patient survival. After entering chronic renal replacement therapy (RRT), the overall mortality is approximately 14–26% during the first year [1, 2] and 40–50% in 3 years [1, 3, 4], with significant variation related to age at RRT start, etiological disease causing ESRD and number of comorbidities [5, 6]. This has led to efforts to examine the association between factors present prior to RRT start and consequent patient survival.

Degree of renal insufficiency measured by estimated glomerular filtration rate (eGFR) is commonly used in patient monitoring during the pre-dialysis phase to assist in estimating prognosis of renal disease, introducing prophylactic therapy and in deciding when to start dialysis. The optimal timing of chronic RRT initiation has been subject to investigation in several studies, most of which have been observational and evaluated the association between eGFR at start of RRT and survival during RRT [5, 7–10]. Notably, the only randomized controlled trial to date showed no survival difference between early and late RRT start [11].

Uncertainty exists on how to interpret and best utilize the eGFR value of patients approaching onset of chronic RRT. eGFR calculation is based on serum creatinine, the level of which not only reflects residual renal function but is also influenced by gender, body composition and nutritional status [5, 12]. Moreover, our knowledge about the impact of pre-dialysis change in serum creatinine on mortality of RRT patients is very limited. To this end, we used multiple pre-dialysis measurements of serum creatinine to calculate eGFR slope, with the aim to explore the association between eGFR decline pattern and long-term survival on RRT.

Materials and methods

Cohort definition and data source

We conducted a cohort study of all incident patients ≥20 years who entered chronic RRT (haemodialysis, peritoneal dialysis or kidney transplantation) in Finland from 1 January 1998 to 31 December 1998 (n = 457). The patients were followed from the day of first dialysis treatment until death or end of the follow-up period on 31 December 2008 or until recovery of kidney function after 3 months from RRT start (n = 8). None of the patients moved abroad or was lost to follow-up. Mean follow-up time was 6.0 years. We used data from the Finnish Registry for Kidney Diseases, which has an estimated 97–99% coverage for all Finnish patients on chronic RRT since 1965. Kidney disease diagnoses have been stored as International Classification of Diseases -9 and later as -10 codes. The registry is maintained by the Finnish Kidney and Liver Association, which is fully financed by the Finnish government [13]. All patients provided written informed consent and permission to use the data anonymously in registry reports and for research purposes.

Patient selection and calculation of glomerular filtration rate slope

For each patient (n = 457) entering chronic RRT in 1998, an additional questionnaire was asked to be filled out by the treating nephrologists. The questionnaire included specific details on previous medication, laboratory results, length of nephrological care and comorbidities. Of the total 457 patients, for 431 (94%), a sufficiently filled out questionnaire was received, and of these, 8 regained kidney function and 23 died during the first 90 days of RRT. Data on creatinine were available for 329, 356 and 365 patients taken at ~12 months, 3 months and 1 to 2 weeks prior to RRT start, respectively, with exact dates of measurements reported. We had data on creatinine concentration at all three time points for 319 patients (69.8% of all that initially entered chronic RRT), which were included in the final analysis. We estimated GFR using the Modification of Diet in Renal Disease (MDRD) formula (eGFR = \(175 \times [\text{plasma crea in } \mu \text{mol/L/88.4}]^{-1.154} \times \text{age}^{-0.203} \times 0.742 \) for males and equation multiplied by 0.742 for females) [14]. Slope of eGFR for each patient was calculated using a linear regression formula: \(eGFR = a + b \times T\), where ‘a’ represents eGFR at start of RRT, ‘b’ (beta) stands for slope and ‘T’ the time (in years) from the first creatinine measurement to start of RRT. As a result, we obtained annual eGFR slopes (in mL/min/1.73m²).

Patient subdivisions

Patients (n = 319) were divided into tertiles according to eGFR slope (beta) based on the three creatinine measurements preceding start of RRT: those with the most rapid decline (over 8.5 mL/min/1.73m², n = 107), the intermediate group (decline 3.4–8.5 mL/min/1.73m², n = 107) and the ones with the slowest decline (<3.4 mL/min/1.73m², n = 105) per year. Patient group characteristics are shown in Tables 1 and 2.

Statistical methods

Comparisons between groups were performed using chi-square test for categorical variables and Kruskal–Wallis test for continuous variables. Binary logistic regression was used for studying age-adjusted associations between eGFR tertiles and comorbidities. We calculated survival probabilities using the Kaplan–Meier method, with death as the event, and patients were censored on 31 December 2008 or at the date of recovery of kidney function. Median survival times were estimated from the Kaplan–Meier curves. We used Cox proportional hazards regression to perform multivariable modelling of survival probabilities. When studying comorbidities in multivariable analysis, we used the assumption that missing data equals absence of comorbidity. Less than 4% of the patients lacked data on angina pectoris, myocardial infarction, cerebral infarction or cancer, while 13% did not have data on left ventricular hypertrophy. Two-sided P-values <0.05 were considered statistically significant. For statistical analyses, we used PASW Statistics 18 (SPSS Inc., Chicago, IL). All first and second-degree interactions between the explanatory variables considered relevant to the results were tested in the Cox model building.

Results

Factors associated with rapid eGFR decline

Division of the 319 patients into tertiles according to eGFR decline rate clearly separated the fastest decliners from the two other patient groups (Figure 1). Rapid eGFR decline correlated with male gender, younger age, lower body mass index, lower blood haemoglobin, lower serum albumin, use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, shorter nephrological follow-up and ESRD diagnosis other than polycystic disease or pyelonephritis (Tables 1 and 2). Patients with Type 1 diabetes as the cause of ESRD often had rapid eGFR decline, whereas those patients with pyelonephritis or polycystic degeneration had a relatively slow decline in eGFR during the year before RRT start. Patients with glomerulonephritis, Type 2 diabetes, amyloidosis or other or undefined diagnosis of kidney disease were fairly equally distributed in the tertiles of eGFR decline. The frequency of kidney
transplantation was not significantly different between the eGFR decline tertiles (P = 0.102); of all patients in our study, 43% received a kidney transplant during the follow-up period (Table 2). On the contrary, nephrological follow-up time was unevenly divided between eGFR tertiles; compared to the slow and intermediate eGFR decliners, the fast eGFR decliners had been followed by a nephrologist for a shorter time (P < 0.001) (Table 1). In a multivariable analysis comparing fast eGFR decliners with the others, low serum albumin, young age at RRT start, use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and male gender (in this order of statistical significance) remained independent predictors of rapid eGFR decline.

**Comorbidities and eGFR decline rate**

Without adjustment, there were no significant differences in the diagnoses nor the amount of comorbidities between the three eGFR decline rate groups. There was a mild tendency towards higher prevalence of angina pectoris and left ventricular hypertrophy and higher number of comorbidities among intermediate and fast eGFR decliners (Table 2). However, with age-adjustment, angina pectoris (P = 0.031) and left ventricular hypertrophy (P = 0.050) were significantly more frequent in the fast eGFR decline tertile, and similarly, having one or more comorbidities was more common (P = 0.011).

**Survival of patients according to eGFR slope**

Of all patients (n = 319), 214 (67%) died during the 10 years of follow-up. The median survival time was 5.6 [95% confidence interval (CI) 4.2–7.0] years. The cause of death was cardiovascular in 44%, infection in 22% and other in 34% of all patients, with no difference between the three eGFR decline groups (P = 0.98). In unadjusted analysis, the risk of death was not statistically significantly different between the eGFR slope tertiles. When adjusted for age and gender, however, the patients with the steepest eGFR decline had a 73% higher risk of death than the patients with the slowest eGFR decline (Figure 2 and Figure 3, Models 1 and 2). We performed further adjustment (on top of age and gender) for variables that were significantly differently distributed between the tertiles of eGFR decline. With adjustment for body mass index, risk ratio (RR) of death for the fastest GFR decliners was unchanged as compared to the slowest decliners (1.73, 95% CI 1.22–2.45). Correspondingly, when adjusted for serum albumin, the RR was 1.44 (1.00–2.07), with additional inclusion of haemoglobin leaving the result unchanged, as did adjustment for use of angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist. If adjustment was done for ESRD diagnosis, the relative risk of death for the fast decliners was 1.43 (95% CI 1.00–2.05, P = 0.052) compared to the slow decliners. Adjustment for all comorbidities (angina pectoris, myocardial infarction, cerebral infarction, left ventricular hypertrophy and cancer) revealed a corresponding RR of death of 1.53 (95% CI 1.08–2.17) in patients with the steepest eGFR decline compared to the patient group with the most gradual sloping. Adjustment for length of nephrological follow-up, in addition to age and gender, correspondingly resulted in an RR of death of 1.54 (95% CI 1.07–2.22). Adding the eGFR value measured 12 months

**Fig. 1.** Patients (n = 319) divided according to the tertiles of eGFR decline rate during the year before commencement of chronic RRT. eGFR decline rate is expressed in mL/min/1.73m²/year.

**Table 1.** Characteristics (continuous variables) of patient groups according to pre-dialysis phase decline in eGFR expressed as per 1 yeara

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Slowest (n = 105)</th>
<th>Intermediate (n = 107)</th>
<th>Fastest (n = 107)</th>
<th>All (n = 319)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64 (53–72)</td>
<td>56 (46–70)</td>
<td>54 (41–65)</td>
<td>60 (47–69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>168 (161–172)</td>
<td>170 (162–177)</td>
<td>170 (166–175)</td>
<td>170 (163–175)</td>
<td>0.109</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73 (63–85)</td>
<td>72 (63–81)</td>
<td>73 (63–81)</td>
<td>72 (63–83)</td>
<td>0.598</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26 (23–30)</td>
<td>25 (22–27)</td>
<td>24 (22–27)</td>
<td>25 (22–28)</td>
<td>0.028</td>
</tr>
<tr>
<td>Haemoglobin, g/L</td>
<td>108 (97–120)</td>
<td>105 (94–118)</td>
<td>102 (92–111)</td>
<td>104 (94–117)</td>
<td>0.039</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>35 (32–38)</td>
<td>34 (30–38)</td>
<td>30 (26–35)</td>
<td>34 (29–37)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nephrological follow-up, months</td>
<td>47.5 (20.2–92.3)</td>
<td>49.9 (16.2–92.7)</td>
<td>16.3 (7.6–33.6)</td>
<td>32.7 (11.2–81.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>7.8 (4.2–10.0)</td>
<td>6.7 (5.3–8.2)</td>
<td>6.8 (5.2–8.5)</td>
<td>7.1 (5.6–8.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>eGFR –12 months prior to RRT start, mL/min/1.73m²</td>
<td>9.3 (7.6–12.1)</td>
<td>11.6 (10.5–14.2)</td>
<td>19.8 (15.8–29.5)</td>
<td>13.3 (9.7–18.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*aVariables are expressed as median (interquartile range). eGFR decline rate tertiles (mL/min/1.73m²): slowest = <3.4, intermediate = 3.4–8.5, fastest = >8.5.
prior to RRT start to the model lowered RR to 1.46 (95% CI 0.96–2.22) for the fast versus slow decliners, which was expected because eGFR value at this time point strongly correlated to subsequent eGFR decline (Figure 1). Finally, with adjustment for eGFR at RRT start, no significant change in RR of death between tertiles emerged.

We further constructed a large multivariable model with 13 variables (Figure 3, Model 3). The model included 294 of the total 319 patients, of which 198 (67%) died during the follow-up. Of all the variables included in the model, age at start of RRT, the comorbidities cancer and myocardial infarction, serum albumin and diagnosis of ESRD emerged as statistically significant predictors of survival. Of the ESRD diagnoses, Type 1 diabetes and amyloidosis were connected to the worst prognosis with relative risks of death of >2 as compared to glomerulonephritis. Decline rate of eGFR was not a statistically significant predictor of death in the multivariable model.

**Discussion**

We found that the rate of eGFR decline during the year preceding initiation of chronic RRT is associated with subsequent survival on RRT and the association appears to be jointly explained by a number of confounding factors. To our knowledge, this is the first study to report pre-dialysis phase change in eGFR and subsequent survival on chronic RRT.
Our results are to some extent in line with those of Rifkin et al. who studied creatinine and serum cystatin C in a cohort of 4380 patients aged 65 years. The study revealed an association with the slope of annual eGFR decline over 3 mL/min/1.73m² and increased risk of cardiovascular and all-cause mortality [15]. However, their timeframe focus was not on the pre-dialysis phase (i.e. near entering chronic RRT) but instead earlier during mild renal insufficiency. Wu et al. evaluated 573 patients with chronic kidney disease Stages 3–5, and in a 12-month follow-up compared the effect of multidisciplinary pre-dialysis patient education on risk of developing ESRD or death. The patients who received enhanced education had slower eGFR decline and therefore decreased risk of entering RRT, and furthermore, decreased risk of all-cause death [16]. Survival on chronic RRT was not analysed.

Chen et al. investigated survival from the time point of a pre-dialysis eGFR level of 15 mL/min/1.73m² (a point chosen from a regression line calculated from at least three eGFR measurements) and found that the patients with early nephrological referral (over 6 months prior to RRT start) had a better survival than those with later referral. In concordance with the results of our study, the eGFR decline was faster for the later referred (1.06 versus 0.57 mL/min/1.73m²/month, P = 0.002), and these patients also had higher mortality [17]. In a very recent randomized controlled trial comparing early dialysis start to late defined as eGFR 10–14 versus 5–7 mL/min/1.73m² at RRT start, planned early initiation was not associated with improved survival or outcomes [11]. The study included 828 adult patients, and the median time from randomization to RRT
start was 1.8 months in the early-start group and 7.4 months in the late-start group. Noteworthy, at RRT start, the difference in mean eGFR (MDRD) values between the two groups was fairly small (9.0 versus 7.2 mL/min/1.73m²), and in the late-start group ~76% of patients started RRT with eGFR over 7 mL/min/1.73m². In this first and only randomized trial on timing of RRT start, no significant mortality difference between the groups was found.

To date, despite the efforts for optimal patient outcome on chronic RRT, we still do not know many of the pre-dialysis patient-level factors and their impact on survival after start of RRT. During the pre-dialysis phase, serum creatinine measurement-based estimation of GFR is widely used to assist in foreseeing the moment of approaching dialysis. Unfortunately, knowing whether eGFR at start of chronic dialysis is high or low has not resulted in our ability to predict patient survival on RRT. Moreover, based on present knowledge, we are unaware of the optimal timing of RRT start. The most employed serum creatinine-based formulae for estimation of GFR, Cockroft-Gault and MDRD, are not optimal. Although inexpensive and readily available in most countries, some investigators have questioned their reliability [18–20]. But, compared to serum creatinine measurement alone, these formulae substantially increase accuracy of renal function assessment in chronic and moderate or more severe insufficiency [21]. Furthermore, these formulae mostly correct for the effects of increasing age but cannot sufficiently correct for diminishing muscle mass and poor nutritional status [22]. Therefore, combining measurement of creatinine and urea clearance or using other renal function markers, for instance cystatin C, has been suggested [23–25]. Nevertheless, the MDRD formula, which is considered more reliable than Cockroft-Gault, is at present the most applicable and favoured for routine clinical work in pre-dialysis patients [19, 26].

Our aim was to examine whether estimated GFR (MDRD) decline during pre-dialysis phase correlates with mortality on RRT. Based on our findings, an annual eGFR decline over 8.5 mL/min/1.73m² imparts increased risk of death later on chronic RRT. Moreover, we observed that patients with Type 1 diabetes usually had a rapid decline in eGFR, while patients with primary renal disorders such as polycystic disease or pyelonephritis lost their kidney function slowly. Patients with Type 1 diabetes, Type 2 diabetes or amyloidosis had worse prognosis than those with a primary renal disease, which is already known from earlier studies on RRT patients [27, 28]. However, the association between rapid eGFR decline and worse survival cannot be explained by the diagnoses alone because association only slightly weakened when adjusting for ESRD diagnoses.

Regarding independent predictors of rapid eGFR decline other than ESRD diagnosis found in our study, low serum albumin is generally considered a marker of poor nutritional status, chronic infection or inflammation and possibly of a more severe nephrological disease (with proteinuria causing hypoalbuminaemia) and thus logically relating to faster eGFR decline. Furthermore, as faster eGFR decline correlates to higher mortality in our study results, low serum albumin could partly explain the survival difference between eGFR decline tertiles. In our study, male gender was an independent predictor of rapid eGFR decline, but like in earlier studies on RRT patients, male gender did not associate with increased mortality. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are often prescribed to slow progression of renal disease, and it is likely that in our study population, these regimens were started for patients presenting with a more aggressive renal disease, and hence the more frequent use of these drugs correlated with a more rapid eGFR decline. But, this correlation was partly a result of the higher percentage of patients with diabetes (who more frequently use these drugs) among the rapid decliners. Finally, comorbidities seem to play an important and possibly etiological role in eGFR decline rate: with age-adjustment, the fast eGFR decliners showed higher frequency of comorbidities, especially angina pectoris and left ventricular hypertrophy. Furthermore, as comorbidities are known to increase risk of death—as shown also by our multivariable model—they may well explain part of the association between eGFR decline rate and mortality.

To further analyse potentially important factors of progression in our study population, kidney transplantation, causes of death and length of nephrological follow-up were investigated. Frequency of kidney transplantation did not differ between the eGFR decline tertiles. The distribution of causes of death was also very similar between the groups. With regard to the length of nephrological follow-up, the fast eGFR decliners had been followed for a shorter time than the other patients. This may indicate a disadvantage caused by shorter nephrological care but was most probably caused by the fact that a more rapidly progressing renal disease brings patients to the attention of nephrologists late.

Based on our study results, fast eGFR decline rate exhibits itself as a predictor of increased mortality but not as an etiological factor behind the impaired survival. In fact, there appears to be multiple factors that confound the association between rapid eGFR decrease and increased mortality. In our large multivariable model, consisting of 12 variables in addition to the eGFR tertiles, the correlation of fast eGFR decline to increased mortality became statistically insignificant. This reflects the importance of these factors on eGFR, and further, on increasing the mortality risk. We also evaluated the role of the confounders by studying them one by one (in addition to age and gender); especially ESRD diagnosis, serum albumin and comorbidities weakened the association between eGFR decline tertiles and mortality. These factors are known risk factors of death among patients on RRT and appear to at least partially lie behind the observed association between eGFR and survival outcome.

There are some limitations of our study that merit discussion. First, the number of patients is moderately small. This is, however, the first study exploring the correlation between pre-dialysis eGFR decline and survival on RRT and thus the largest study so far. The cohort is also multi-centred and nationally representative with virtually complete follow-up of all included patients. Second, the well-known confounders of serum creatinine measurement-based estimation of GFR are relevant also in our study and might have influenced the results. Nonetheless, we think that as estimation of GFR is highly preferred in everyday nephrological work, the more important it is to examine the association of the method to patient outcomes.
Third, we acknowledge the limitation of having based the eGFR decline rate calculations on only three eGFR measurement points, as more measurements could have increased the reliability of eGFR slope calculation. Fourth, being an observational study, many variables (e.g. comorbidities) could potentially have confounded the results. The large amount of comprehensive data and use of multivariable methods in our study, however, enabled us to control for these confounders.

To conclude, a rapid decline in estimated GFR before entering chronic RRT associates with increased mortality on RRT when adjusting for age. The association mainly appears to be explained by the confounding effect of ESRD diagnosis, comorbidities and serum albumin.

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Mikko Haapio and Patrik Finne had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest statement. None declared.

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