Past Decline Versus Current eGFR and Subsequent ESRD Risk

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ABSTRACT

eGFR is a robust predictor of ESRD risk. However, the prognostic information gained from the past trajectory (slope) beyond that of the current eGFR is unclear. We examined 22 cohorts to determine the association of past slopes and current eGFR level with subsequent ESRD. We modeled hazard ratios as a spline function of slopes, adjusting for demographic variables, eGFR, and comorbidities. We used random effects meta-analyses to combine results across studies stratified by cohort type. We calculated the absolute risk of ESRD at 5 years after the last eGFR using the weighted average baseline risk. Overall, 1,080,223 participants experienced 5163 ESRD events during a mean follow-up of 2.0 years. In CKD cohorts, a slope of $-\frac{26}{4}$ versus $0 \text{ ml/min per } \text{ m}^2$ per year over the previous 3 years (an decline of $18 \text{ ml/min per } \text{ m}^2$ versus no decline) associated with an adjusted hazard ratio of ESRD of 2.28 (95% confidence interval, 1.88 to 2.76). In contrast, a current eGFR of 30 versus 50 ml/min per 1.73 m² (a difference of 20 ml/min per 1.73 m²) associated with an adjusted hazard ratio of 19.9 (95% confidence interval, 13.6 to 29.1). Past decline contributed more to the absolute risk of ESRD at lower than higher levels of current eGFR. In conclusion, during a follow-up of 2 years, current eGFR associates more strongly with future ESRD risk than the magnitude of past eGFR decline, but both contribute substantially to the risk of ESRD, especially at eGFR<30 ml/min per 1.73 m².


CKD is characterized by poor outcomes and high costs, and its increasing worldwide prevalence represents a significant public health challenge.1 Although the vast majority of patients with CKD have early-stage disease,2–4 patients with late-stage disease and especially, those with ESRD suffer from an especially high burden of comorbid conditions, have extremely poor outcomes, and consume a disproportionate amount of health care resources.5 It

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is, thus, important to focus interventions, such as efforts to slow kidney progression and preparation for the transition to ESRD, on patients who are most prone to experience a progressive disease course. Recent studies have emphasized the importance of eGFR and albuminuria as measures of kidney disease severity, which can be assessed at the point of clinical contact, used to classify patients into various stages of CKD and form the basis of clinical interventions.\(^2\) However, many other factors influence the rate of progression, including age,\(^6,7\) comorbid conditions, such as diabetes mellitus or hypertension,\(^7-9\) race-ethnicity,\(^10\) and genetic mutations.\(^11\)

Nonetheless, these factors do not account for the observed variability in kidney disease progression.\(^12\)

A seminal study almost 40 years ago proposed that the trajectory of kidney disease progression could be predicted from the past rate of decline in kidney function.\(^13\) Current clinical practice guidelines continue to recommend assessing the future risk of kidney disease progression from the past slope of eGFR over time.\(^2\) Despite the widespread acceptance of this practice, relatively few studies have evaluated the past eGFR decline as a predictor of ESRD after taking into account the current level of eGFR.\(^14\) In clinical practice, both the level of eGFR at the point of assessment and its past trajectory over time are readily available for assessment, but the relative contribution of each to the risk of subsequent ESRD is not clear. We, thus, examined the magnitudes of associations of past decline in eGFR over 3 years versus current level of eGFR at the end of the slope evaluation period with subsequent progression to ESRD in 22 large and diverse cohort studies from across the globe to investigate the usefulness of both measures as predictors of CKD progression in clinical practice.

RESULTS

We primarily provide results on the 3-year slope evaluation period and the absolute risk of ESRD at 5 years of follow-up in the CKD cohorts, and we present results for other baseline (1- and 2-year slopes) and follow-up periods (1, 3, and 10 years) and the other (general population and high risk) cohorts in the Supplemental Material. Twenty of 22 participating cohorts (11 CKD and nine other cohorts) provided data on change in eGFR for a slope evaluation period of 3 years. Among 1,080,223 participants (232,250 in CKD cohorts and 847,973 in other cohorts), approximately 10% and 5% had rapid decline (slope < -5 ml/min per 1.73 m\(^2\) per year) or rapid increase (slope > 5 ml/min per 1.73 m\(^2\) per year), respectively, with the remaining 85% having less rapid changes (slope \(\geq -5\) to \(\leq 5\) ml/min per 1.73 m\(^2\) per year) (Supplemental Table 1, Table 1). Individuals with rapid decline tended to have a poorer risk profile (higher prevalence of albuminuria, diabetes, and history of CVD) compared with those with rapid increase and less rapid changes, regardless of cohort types (Supplemental Tables 1–5, Table 1).
We observed a total of 5163 ESRD events (3256 in CKD cohorts and 1907 in other cohorts) during a mean subsequent follow-up period of 2.0 years after the 3-year baseline period (Supplemental Tables 2 and 6, Table 2). In CKD cohorts, the subsequent risk of ESRD showed overall higher adjusted hazard ratios (HRs) at both greater negative and positive slopes of eGFR compared with stable eGFR (slope of 0 ml/min per 1.73 m² per year) (Figure 1). This finding was most pronounced for 3-year slopes, being slightly weaker for slopes assessed over shorter (1 and 2 years) baseline periods (Supplemental Figure 1). Slopes of −6 and −3 ml/min per 1.73 m² per year over 3 years (−18 and −9 ml/min per 1.73 m² per year over 3 years) were associated with adjusted HRs of ESRD of 2.28 (95% confidence interval [95% CI], 1.88 to 2.76) and 1.73 (95% CI, 1.50 to 2.00), respectively. Other cohorts displayed similar trends (Supplemental Figure 2). Additional adjustment for albuminuria did not alter the results substantially (Supplemental Figures 3 and 4). Furthermore, results were largely consistent across individual cohorts (Figure 2, Supplemental Figure 5). Associations were similar in CKD cohorts for patients exposed to renin-angiotensin-aldosterone system (RAAS) inhibitors and those not exposed to such agents. In other cohorts, the association of slope with ESRD was significant in patients who received RAAS inhibitors but not in patients who were not exposed to such agents (Supplemental Figure 6). Participants with a rapid rise in eGFR also had an elevated ESRD risk, but the number of events in this group was small (n=18).

In analyses stratified by level of last eGFR, the risk of ESRD was always significantly associated with more rapid declines, but the magnitude of the excess risk was much less than that imparted by lower versus higher levels of last recorded eGFR (Figure 3A). The HRs of ESRD associated with eGFR levels of 20, 30, and 40 ml/min per 1.73 m² (compared with 50 ml/min per 1.73 m² and a slope of 0 ml/min per 1.73 m² per year) were 216.8 (95% CI, 124.8 to 376.7), 46.4 (95% CI, 31.9 to 67.6), and 9.99 (95% CI, 8.03 to 12.44) in those with a slope of −6 ml/min per 1.73 m² per year, respectively; 178.3 (95% CI, 92.9 to 342.2), 38.4 (95% CI, 23.8 to 61.9), and 8.11 (95% CI, 5.98 to 11.00) in participants with a slope of −3 ml/min per 1.73 m² per year, respectively; and 88.7 (95% CI, 50.0 to 157.3), 19.9 (95% CI, 13.6 to 29.1), and 4.46 (95% CI, 3.69 to 5.40) in participants with a slope of 0 ml/min per 1.73 m² per year, respectively (overall P for interaction between eGFR slope and last eGFR was 0.26). Consequently, both the slopes and the eGFR levels were independently associated with higher 5-year estimated absolute risk of ESRD (Figure 3B, Supplemental Table 7). The higher estimated absolute risk of ESRD associated with steeper declines in eGFR seemed to be more pronounced at lower levels of eGFR. Of note, at eGFR<30 ml/min per 1.73 m², the estimated absolute risk of ESRD was substantial, even at a slope of 0 ml/min per 1.73 m² per year. Results displayed similar trends when assessing 1- and 2-year slopes and when examining other cohorts (Supplemental Figures 7–11).
absolute risk of ESRD, especially in individuals with very low eGFR level. An additional finding in our study was that approximately 5% of participants had experienced a past rapid eGFR rise (>5 ml/min per 1.73 m² per year) and that a more rapid past rise in eGFR was associated significantly and independently with a higher ESRD risk. The results are consistent with the current body of evidence indicating that point estimates of eGFR are one of the most robust predictors of ESRD, but they also provide new evidence that the past trajectory of eGFR slopes could be used in addition to contemporarily evaluated other risk factors to assess future risk of ESRD.

The level of eGFR is a well-established predictor of ESRD, but the role of past eGFR trajectories (slopes) in the assessment of patients with kidney disease has been less clear. Most previous studies have evaluated the association between slopes of eGFR and mortality,15-21 and a few assessed the role of future slopes (i.e., after the point of assessment adjusted for the initial level of eGFR) in predicting ESRD.22,23 The association of future slopes or percentage changes in eGFR with ESRD relates to their role as surrogate end points in clinical trials.24 In contrast, past slopes of eGFR are helpful to clinicians, who need information readily available at the point of contact for clinical decision making and future projection, and their association with ESRD events has not been previously extensively evaluated. Past slopes of eGFR provide an empirical measure of the disease process for an individual, which represents the aggregate effect of all known and unknown predictors of kidney disease progression for each patient. A prior community-based study found that the association between past slopes of eGFR and ESRD was attenuated and became nonsignificant after adjusting for the level of the last eGFR.14 Our study confirms the major association between eGFR level and the risk of ESRD but suggests that past slopes may also have an independent, albeit weaker association with this end point. Our study may have been better suited than the previous study for a detailed evaluation of the role of past eGFR trajectories because of the much higher statistical power imparted by the large number of outcomes, the availability of longer evaluation periods for slope estimations, and the diversity of patient populations with representation of higher-risk patient groups.

The finding of substantial risk of ESRD associated with very low eGFR in the absence of eGFR decline in the past 1–3 years suggests possible difficulty in accurate ascertainment of eGFR trajectory over a short interval, especially in patients with slowly progressive or nonlinear eGFR declines.25 The much stronger relative risk of ESRD associated with lower levels of eGFR versus steeper slopes may also be related to the fact that the studied end point (ESRD) is directly dependent on a very low eGFR but less dependent on rapid eGFR decline; hence, during the relatively short follow-up period of our study, it is much more likely for ESRD to be observed in patients who start follow-up with lower eGFR levels, and it is possible that more rapid declines in eGFR could have been stronger predictors of ESRD if patients were followed for a longer period of time. Nevertheless, in clinical practice, prediction of ESRD is

In this international meta-analysis of 1,080,223 participants in 22 diverse cohorts, approximately 10% of participants had experienced past rapid eGFR declines (slopes) of <−5 ml/min per 1.73 m² per year over 1–3 years before the current eGFR assessment. We observed a significant and independent association of both a lower current level of eGFR and a more rapid past decline in eGFR (slope) with higher subsequent risk of ESRD in CKD cohorts, especially when slopes were calculated from creatinine levels measured over 3 years. For example, a slope of −6–versus 0-ml/min per 1.73 m² per year change over 3 years (an 18-ml/min per 1.73 m² per year decline in total) was associated with adjusted HR of subsequent ESRD of 2.28 (95% CI, 1.88 to 2.76), whereas a current eGFR of 30 versus 50 ml/min per 1.73 m² (a 20-ml/min per 1.73 m² difference in final eGFR) was associated with an adjusted HR of subsequent ESRD of 19.9 (95% CI, 13.6 to 29.1) if the previous slope was 0 ml/min per 1.73 m². Other cohorts displayed similar trends but with substantially higher heterogeneity and lack of statistical significance, indicating that our conclusions primarily refer to patients with CKD. The current level of eGFR seemed to be associated with a larger risk of ESRD, especially at very low eGFR, where the ESRD risk was substantial, even with past slopes of 0 ml/min per 1.73 m² per year. However, more rapid past declines contributed substantially to significantly higher risk patient groups.

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DISCUSSION

Figure 1. Adjusted HR of ESRD associated with slope of eGFR during a 3-year baseline period and a histogram of the slope of eGFR in CKD cohorts. Values were trimmed at a −15-ml slope (0.3%) and a 10-ml slope (1.1%). Black dots indicate statistical significance compared with the reference (diamond) slope of eGFR=0 ml/min per 1.73 m² per year. Open circles show slope of eGFR=−0 and −3 ml/min per 1.73 m² per year.
most important for the immediately foreseeable future, because clinicians need to implement preparations, such as vascular access planning and referral for transplantation, during the 6–12 months preceding ESRD. These results suggest that interventions that slow kidney disease progression and preparations for ESRD should be continuously implemented in patients with CKD stages 4 and 5, even in the absence of demonstrable eGFR decline in the past 1–3 years.

Figure 2. Adjusted relative HRs of ESRD for a 6-ml/min per 1.73 m² per year decline and a 3-ml/min per 1.73 m² per year decline in eGFR (compared with a decline of 0 ml/min per 1.73 m² per year) during a 3-year baseline period in CKD cohorts. The left panel shows adjusted relative HRs for a 6-ml/min per 1.73 m² per year decline and the right panel shows adjusted relative HRs for a 3-ml/min per 1.73 m² per year decline. AASK, African American Study of Kidney Disease and Hypertension; BC CKD, British Columbia CKD Study; CCF, Cleveland Clinic CKD Registry Study; Geisinger, Geisinger CKD Study; GLOMMS1, Grampian Laboratory Outcomes, Morbidity and Mortality Studies 1; MASTERPLAN, Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner; MDRD, Modification of Diet in Renal Disease Study; NephroTest, NephroTest Study; Sunnybrook, Sunnybrook Cohort; VA CKD, Veterans Administration CKD Study.

Figure 3. Adjusted HRs (95% CIs; reference: patients with eGFR=50 ml/min per 1.73 m² and slope of 0 ml/min per 1.73 m² per year) and absolute risks of ESRD associated with slope of eGFR and different levels of last eGFR during a 3-year baseline period in CKD cohorts. Panel A shows the adjusted HRs and panel B shows the absolute risks.
The finding that a more rapid past eGFR rise is associated with higher ESRD risk is reminiscent of associations between positive slopes and higher mortality in previous studies.\textsuperscript{16,18} The explanation for these seemingly counterintuitive associations is unclear but could be because of confounding by loss of muscle mass, volume overload, presence of severe illness with an underlying heightened propensity for faster kidney disease progression, or recovery from previous AKI events. In our study, patients with positive slopes represented a minority of the study population (7\% of patients) and experienced only a tiny fraction (n=18; 0.5\%) of the total ESRD events, thereby limiting our ability to distinguish among these potential explanations. The demographic and comorbidity characteristics of those with positive eGFR slopes were similar to those seen in patients with stable eGFR, and significantly fewer of them had albuminuria, making it less likely that a heightened propensity for progressive CKD existed in this group. Recovery from a prior AKI might be associated with an increased risk for and subsequent development of ESRD, perhaps as a result of another AKI event. Many of our cohorts included unselected patients, and even the cohorts that included stable patients provided follow-up creatinine measurements during a subsequent time period when acute events could have occurred. We did not have detailed information about the cause of ESRD, characteristics, such as body composition and muscle mass, or other filtration markers, such as cystatin C, that would be necessary to evaluate these possibilities.

Our study is notable for its large size, international representation, and a diverse patient population. Despite its advantages, this study also has a number of limitations. Standardization of serum creatinine values may have varied across time and studies. The assumption that slopes of eGFR are uniform over time may be flawed. The least squares regression method for the calculation of slopes provides an average linear trajectory over the evaluation period but cannot account for nonlinear trajectories, and its results may be influenced by transient reversible changes in kidney function (e.g., episodes of AKI). Variation in design across cohorts introduces heterogeneity, but the consistency of our results across cohorts, despite the marked variation in design and populations, inspires confidence in them. The added benefit of using slopes over longer durations than 3 years, more frequent serum creatinine measurements, or measurement of other filtration markers, such as cystatin C, was not studied.

In summary, although the last eGFR level seems to be a robust predictor of future ESRD, past trajectory of eGFR over time is also independently associated with ESRD and adds significantly to the information provided by the single last eGFR level, especially in patients with lower eGFR in whom risk of progression to ESRD in the near future is greatest. The ubiquity of electronic medical records makes the evaluation of both single eGFR levels and past slopes of eGFR readily available to increasing numbers of physicians, and their incorporation in everyday clinical practice could improve risk prediction and allow for better strategic resource allocation. The result could be the delivery of better care for later stages of CKD with potential downstream advantages, such as lower ESRD incidence or a more seamless transition to ESRD.

**CONCISE METHODS**

**Study Selection Criteria**
The Chronic Kidney Disease Prognosis Consortium (CKD-PC) has been described previously and is also described in Supplemental Appendices 1 and 2.\textsuperscript{26–30} Briefly, the CKD-PC incorporates cohorts with at least 1000 participants (not applied to cohorts predominantly enrolling persons with CKD [CKD cohorts]) with data on serum creatinine, albuminuria, and ≥50 events of outcomes of interest (mortality or kidney outcomes).\textsuperscript{26–30} This study included 22 cohorts (13 cohorts in which the presence of CKD was required for cohort entry [CKD cohorts] and nine cohorts in which entry was determined by factors other than CKD [general population and high–cardiovascular disease (CVD) risk cohorts; i.e., other cohorts]) with repeated measures of serum creatinine during baseline evaluation periods of 0.5–3.5 years to determine change in eGFR and data on subsequent ESRD. Meta-analyses were restricted to cohorts with a minimum of 10 ESRD events and participants ages ≥18 years old. This study was approved by the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health.

**Procedures**
eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.\textsuperscript{31} In cohorts where the creatinine measurement was not standardized to isotope dilution mass spectrometry, creatinine concentrations were reduced by 5\%.\textsuperscript{32}

Our primary measure of change in eGFR was the annual change (slope), because this is the conventional approach to assess past trajectory in clinical practice. An average annual change in eGFR was estimated from a least squares regression model using all eGFR measurements during baseline periods of 1–3 years. For each baseline period, a 0.5 year of margin before and after the end of the period was allowed for determining the last available eGFR to calculate the change (e.g., eGFR between 0.5 and 1.5 years after the first available eGFR could be used for the 1-year baseline period analysis), but the eGFR closest to the baseline period of interest was selected for each participant. All covariates were assessed at the time of last eGFR (Supplemental Appendix 2 shows details for specific cohorts).

We defined diabetes as fasting glucose ≥7.0 mmol/L (126 mg/dl), nonfasting glucose ≥11.1 mmol/L (200 mg/dl), hemoglobin A1c ≥6.5\%, use of glucose-lowering drugs, or self-reported diabetes. Participants with a history of myocardial infarction, coronary revascularization, heart failure, or stroke were considered to have a history of CVD. Albuminuria was not available in all cohorts at the time of last eGFR, and hence, we adjusted for its severity only in sensitivity analyses. Our primary measure of albuminuria was the urine albumin-to-creatinine ratio, but we also included studies with urine albumin excretion rate, urine protein-to-creatinine ratio, or semiquantitative dipstick protein.\textsuperscript{33}
The primary outcome of interest was ESRD after the end of the baseline period. We defined ESRD as initiation of RRT or death caused by kidney disease other than AKI. Patients with ESRD before the baseline period were excluded from the analyses.

**Statistical Analyses**

We applied a two-stage meta-analysis, with each study first analyzed separately followed by a random effects meta-analysis. The overview of the analysis and analytic notes for individual studies are provided in Supplemental Appendix 2. We imputed missing values of covariates but not the main exposure (change in eGFR) using cohort-specific mean values. We quantified heterogeneity with the $I^2$ statistic and Cochran Q test and explored sources of heterogeneity with random effects meta-regression analysis. Because the absolute risk of ESRD and the implication of change in eGFR vary substantially depending on the type of patient population, analyses were first stratified by type of cohort (CKD versus other).

We modeled the adjusted HRs of subsequent ESRD as a spline function of eGFR slopes. In each study, we fitted piecewise linear splines for eGFR slopes (knots were placed at $-10$, $-5$, $-3$, $-1$, and $3$ ml/min per 1.73 m$^2$ per year). Cox models were adjusted for age, sex, race/ethnicity (black versus nonblack), systolic BP, total cholesterol, diabetes, history of CVD, and last eGFR used to calculate slopes for each evaluation period. Potential effect modifiers with change in eGFR were assessed by incorporating interaction terms. To assess the association of the past slope of eGFR with ESRD in the context of the level of the last eGFR, we present HRs according to eGFR slopes by prespecified levels of the last eGFR ($20$, $30$, $40$, and $50$ ml/min per 1.73 m$^2$) using no change in eGFR with last eGFR of $50$ ml/min per 1.73 m$^2$ as the reference. We selected these eGFR levels because of their relevance to progression to ESRD in the near future.

We translated meta-analyzed adjusted HRs for eGFR slopes stratified by level of last eGFR to absolute risk of ESRD at 1, 3, 5, and 10 years after the baseline period using the weighted average baseline risk; 1-year baseline risk in each cohort was calculated for the following combination of covariates: 60 years old, nonblack, men, no change in eGFR, last eGFR of $50$ ml/min per 1.73 m$^2$, systolic BP of $130$ mmHg, total cholesterol of $5$ mmol/L, and no history of diabetes or CVD. Risk was scaled for longer follow-up and pooled across cohorts using a weighted average (Supplemental Appendix 2). In sensitivity analyses, we applied the adjusted sub-HRs from competing risk models accounting for death as a competing end point. In additional sensitivity analyses, we examined the association between eGFR slopes and ESRD in subgroups of patients divided by exposure to RAAS inhibitor medications during the slope evaluation period.

Analyses were performed using Stata/SE 12 software (StataCorp., College Station, TX; www.stata.com). We considered $P$ values $<0.05$ statistically significant.

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The funders had no role in the design, analysis, or interpretation of this study and did not contribute to the writing of this report or the decision to submit the article for publication. Some of the data reported here have been supplied by the US Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US Government.

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DISCLOSURES

None.

REFERENCES


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