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Elucidating the present and future of individuals with kidney disease: a multifaceted epidemiological approach

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Chapter 07

Predicting kidney failure with the Kidney Failure Risk Equation: time to rethink probabilities

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Abstract

Chapter 07 discusses a study by Chu et al., the abstract of which is given here.

Rationale & Objective. The Kidney Failure Risk Equation (KFRE) predicts the 2-year risk of kidney failure for patients with chronic kidney disease (CKD). Translating KFRE-predicted risk or eGFR into time to kidney failure could inform decision-making for patients approaching kidney failure.

Study Design. Retrospective cohort.

Setting & Participants. CKD Outcomes and Practice Patterns Study (CKDOPPS) cohort of patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 from 34 US nephrology practices (2013-2021).

Exposure. 2-year KFRE risk or eGFR.

Outcome. Kidney failure defined as initiation of dialysis or kidney transplantation.

Analytical Approach. Accelerated failure time (Weibull) models used to estimate the median, 25th, and 75th percentile times to kidney failure starting from KFRE values of 20%, 40%, and 50%, and from eGFR values of 20, 15, and 10 mL/min/1.73m^2. We examined variability in time to kidney failure by age, sex, race, diabetes status, albuminuria, and blood pressure.

Results. Overall, 1,641 participants were included (mean age 69±13 years; median eGFR 28 mL/min/1.73m^2 [IQR 20-37 mL/min/1.73m^2]). Over a median follow-up of 19 months [IQR 12-30 months], 268 participants developed kidney failure and 180 died before reaching kidney failure. Median estimated time to kidney failure was widely variable across patient characteristics from an eGFR of 20 mL/min/1.73m^2 and was shorter for younger age, male sex, Black (versus non-Black), diabetes (versus no diabetes), higher albuminuria, and higher blood pressure. Estimated times to kidney failure were comparably less variable across these characteristics for KFRE thresholds and eGFR 15 or 10 mL/min/1.73m^2.

Limitations. Inability to account for competing risks when estimating time to kidney failure.

Conclusions. Among those with eGFR <15 ml/min/1.73 m^2 or KFRE risk >40%), both KFRE risk and eGFR showed similar relationships with time to kidney failure. Our results demonstrate that estimating time to kidney failure in advanced CKD can inform clinical decisions and patient counseling on prognosis, regardless of whether estimates are based on eGFR or the KFRE.

Source: Adapted from Chu CD, et al., "Utility of the Kidney Failure Risk Equation and Estimated GFR for Estimating Time to Kidney Failure in Advanced CKD" Am J Kidney Dis. 2023 Oct;82(4):386-394.e1. Licensed under CC-BY 4.0. Original copyright (2023) by the authors. Published by Elsevier Inc on behalf of the National Kidney Foundation, Inc.

The rate of disease progression highly varies between individuals with chronic kidney disease (CKD). To better elucidate individual risks for progression to kidney failure and improve personalized medicine, patients and physicians have access to a multitude of clinical prediction models (1), which combine multiple prognostic factors into a single individual risk for kidney failure. One of the most used kidney failure prediction models is the 4-variable Kidney Failure Risk Equation (KFRE), developed by Tangri et al. (2), which combines age, sex, urine-albumin creatinine ratio (uACR), and estimated glomerular filtration rate (eGFR) to calculate the 2-year and 5-year risks of kidney failure for an individual patient. The KFRE has been validated in and works well across many populations (3). However, both patients and physicians may struggle in understanding and communicating the estimated risks (4). A predicted risk between 0% and 100% is always an incorrect projection of the future on an individual level, as the individual either experiences the outcome or not. Comprehending the meaning of a 20% risk of kidney failure within 2 years for an individual patient is tricky and not intuitive; the intrinsic uncertainty is difficult to communicate and it is easier to grasp the concept of when a patient is expected to progress. For a physician, estimating time until kidney failure is an essential part of daily practice as important clinical interventions (e.g. nephrologist referral, preparing for transplantation, and planning vascular access) must be planned on time. Because these key interventions in a patient's CKD trajectory are primarily time-to-event dependent, not risk-of-event dependent, it seems long overdue to translate these time-frame dependent probabilities (e.g. 20% risk within 2-years) into an expected time-to-event (e.g. expected to develop kidney failure within 12-15 months).

In this issue of AJKD, Chu *et al.* make an important step in this direction (**Figure 1**). They converted risk estimates predicted by the 2-year KFRE to the median time until kidney failure in a cohort of 1,641 United States CKD patients and modelled the relationship between 2-year risks and time until kidney failure in months using accelerated failure time (AFT) models (5). They focused on the 20%, 40%, and 50% 2-year risk thresholds due to the relevance of these cut-offs for clinical decision making and the incorporation of these risks in various guidelines regarding kidney replacement therapy planning. Additionally, they converted different eGFR estimates to the median time until kidney failure, with a specific focus on 20, 15, and 10 mL/min/1.73m^2. Their main results are the median time until kidney failure based on the KFRE risk or eGFR. The authors also performed subgroup analyses to determine homogeneity of estimated times across various patient characteristics. They observed that the estimated time until kidney failure based on the KFRE compared to eGFR was both more consistent and less uncertain early in the disease trajectory. In advanced CKD there was little difference between the time estimations based on the KFRE or eGFR alone. This shows that the KFRE is especially useful in earlier stages of CKD, when time to kidney failure remains difficult to estimate based on eGFR alone. A noteworthy caveat, also mentioned by the authors, is the large competing risk of death when predicting kidney failure; many patients die of other causes before ever reaching kidney failure. Because this was not taken

into account in the development of the KFRE or in the modelling strategies of Chu et al., predicted estimates may be overestimated. Therefore, these results should be interpreted as the expected time until kidney failure, conditional on the premise that the patient will not die. Lastly, the authors also externally validated the KFRE; a valuable analysis to undertake when using prediction models as the performance is highly dependent on characteristics of the validation population (6). During the validation, they did account for the competing risk of death, allowing us to assess the model performance in a more realistic clinical setting in which patients may die before experiencing kidney failure (7). The model was able to discriminate well in their population and was reasonably calibrated.

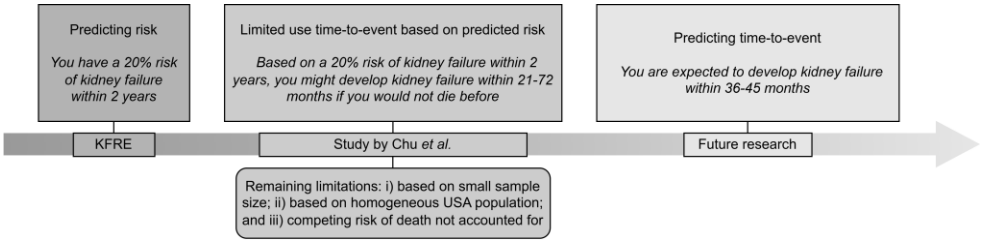
By being able to determine the patient's expected time until kidney failure, patients can be better informed and key interventions in a patient's disease trajectory may be more precisely tailored to the individual. However, when treatment interventions are based on predicted risks, the use of the KFRE becomes an intervention in itself. Given the widespread use of the KFRE, going forward impact trials for various KFRE based interventions (such as vascular access planning or risk communication) are necessary to evaluate whether using the KFRE actually benefits patient care. Such an impact trial was performed for the 5-year KFRE, where the primary outcome was performing recommended laboratory tests in the next 6 months and the secondary outcome was nephrologist referral (8). This trial found no advantage of the KFRE for these outcomes. Although there were some significant limitations in study design, this study exemplifies that model performance is not always related to model impact. After all, it may well be that physicians already take risk estimates into account sufficiently without the KFRE, or do not trust the KFRE enough to influence their decision making. Nevertheless, a single impact trial is not enough, as the KFRE might have a different impact for different applications. Outcomes of interest may also differ: one currently ongoing impact trial studies the effect of integration of KFRE into the healthcare system on markers of disease (albuminuria, eGFR), received care (patient management, medication usage), healthcare costs, and patients' trust in physician care (9). These impact trials form a crucial part in solidifying the role of the KFRE into clinical practice.

The study by Chu *et al.* is a meaningful contribution to translating predicted risk into predicted time-to-event. Nonetheless, their estimated median time-to-event may be further refined. Even though the KFRE risks underlying the time-to-event estimates were validated extensively, the newly estimated times until kidney failure based on these KFRE risks need to be validated too. The current estimated median times, derived from a relatively small population from the US, may not be readily applicable to other populations and the underlying assumptions of the modelling strategy may not hold in every population. Additionally, a model to directly estimate time-to-event instead of converting risk estimates might be more accurate and can include additional predictors to increase accuracy. These models should take competing risks into account.

Going into more technical detail, adaptations of the Cox proportional hazard PH models for competing risks can be used (e.g. Fine-Gray models). Although, in contrast to AFT models, Cox PH models and adaptations do not parametrically estimate the underlying hazard which prohibits direct prediction of individual survival times, indirectly, individual predicted time-to-event can be calculated by specifying the underlying distribution of the baseline hazard (10). Since the KFRE was originally developed as a Cox PH model, these times until kidney failure could even be derived directly from the KFRE itself. Because the KFRE has been shown to perform well across many populations, this might be the most pragmatic starting point for time to kidney failure estimation, predominantly for early stages of CKD where the competing risk of death remains low.

Individualized predictions of time until kidney failure can be of great value to patient-centered healthcare and it is time we rethink predicted probabilities. While we await further studies that provide validated predictions of time until kidney failure for different populations, that take competing risks into account, the study by Chu et al. offers a solution to estimating an individual's time until kidney failure based on their KFRE risk.

Figure 1. The timeline from kidney failure risk predictions to time to kidney failure predictions. The timeline shows the research progress of going from predicting kidney failure risk to predicting time to kidney failure. The upper boxes show the different research steps. The italics show how the results of these steps would allow clinicians to communicate kidney failure prognosis to a patient. The lower boxes show what study has realized these steps so far. The lowest box indicates limitations that remain after the study by Chu *et al*.



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