As patients with chronic kidney disease are followed up longitudinally, can accumulating information that becomes available over time be used to improve prediction of the risk for end-stage kidney disease? In this issue of AJKD, Dr Tangri and coauthors address this question by comparing the performance of static risk prediction based on demographic, clinical, and laboratory covariates available at a single baseline time point with the performance that could in principle be achieved by a time-updated approach if it were possible to incorporate future information for changes in the covariates after baseline.

The static risk prediction approach based on Cox proportional hazards regression has been used in numerous settings, including previous work by Tangri et al to produce widely cited prognostic models for end-stage renal disease (ESRD) risk over 1, 3, or 5 years for patients with chronic kidney disease. This static risk prediction approach has 4 core elements. First, a single baseline time point is designated as time 0 for each patient. Time 0 may be defined by a clinical transition, such as the initial diagnosis of a particular clinical condition, or by the occurrence of a medical procedure such as kidney transplantation. Alternatively, as in the context considered by the authors, it may be a time of convenience, such as the occurrence of an arbitrary clinic visit. Second, a set of baseline covariates measured at or before time 0 are designated for use in predicting events that occur after time 0. Third, event times during the evaluation period after time 0 are related to the baseline covariates under a Cox regression model with 2 components: (1) a baseline hazard function, which defines the risk for the event at each time during the evaluation period for one arbitrary set of values for the baseline covariates, and (2) a multiplying factor, which proportionally modifies the baseline hazard depending on the actual values of each patient’s baseline covariates. Fourth, the fitted Cox regression is applied to a new patient’s baseline covariates at time 0 to predict the probability that the patient will experience the event over designated time periods, such as 1, 3, or 5 years (Fig 1, top panel).

The time-updated approach considered by Tangri et al has a time-dependent Cox model at its core. The time-dependent Cox model retains several features of the static model, but updates the multiplying factor, which is applied to the baseline hazard function as new covariate measurements become available after time 0. Thus, time-dependent Cox regression relates the instantaneous risk for the event at each follow-up time to the most current measurements of the time-dependent covariates. As a result, the time-dependent Cox model is best viewed as a model for the association of the patient’s instantaneous risk with the patient’s most recently measured covariates and not as a tool for prognostication of events over some time horizon extending into the future (Fig 1, middle panel). This contrasts with the static Cox model, in which prediction of events from variables measured at time 0 extends over the full evaluation period. Thus, the static Cox model and the Cox model with time-dependent covariates address different questions. One expects the time-dependent model to obtain numerically better performance than the static model because the time-dependent model has an easier task; it is less difficult to estimate present risk than it is to predict future risk.

The questions posed by Tangri et al provide an excellent segue to emerging research in the statistical literature on predicting risk for clinical events from longitudinal data. This literature addresses prediction of the risk for a clinical event over a future time horizon, denoted \( \Delta \), from longitudinal data accumulated though the prediction time, denoted \( t \), in which both \( \Delta \) and \( t \) can range over all possible values compatible with the data. When \( t = 0 \), dynamic prediction can be reduced to the conventional static prediction problem. When \( \Delta \) is close to 0, dynamic prediction addresses a similar problem to classic time-dependent Cox regression (Fig 1, bottom panel).

In contrast to the static modeling approach, the dynamic approach is able to incorporate information from the relationship of future events with time-dependent covariates assessed throughout the follow-up period while accounting for changes in the population of patients who remain under follow-up as time evolves. And in contrast to time-dependent Cox regression, the dynamic approach can be used to predict future events over any time horizon compatible with the data. In addition to addressing a wider range of questions, dynamic modeling approaches seek to improve on the static prediction and time-dependent Cox modeling approaches by...
Figure 1. The left-hand tail of each blue arrow represents the time point from which predictions are made (denoted in text as $t_0$), and the arrow length represents the time horizon over which the event probability is calculated (denoted in text as $\Delta$). The dashed orange lines represent the time interval over which past data are available, which can be used in the prediction of future event probabilities. (Top panel) The static Cox model allows prediction of event probabilities over any time horizon from a fixed baseline defined by time 0. (Middle panel) The time-dependent Cox model allows estimation of the current risk (or future risk over a short time horizon) using information available at any time point. (Bottom panel) The dynamic regression approach allows prediction of event probabilities over any time horizon using information available at any time point.

more fully incorporating the information available in the data by relating the clinical event to time-updated covariates for all combinations of $t$ and $\Delta$.

Two approaches to dynamic prediction have recently received considerable attention in the statistical literature. The first approach involves a joint model of the time-dependent longitudinal data and the time-to-event outcome.\(^5\) In the context of the research question tackled by Tangri et al, this joint model would typically consist of a model for the longitudinal trajectories of time-dependent biomarkers (eg, estimated glomerular filtration rate [eGFR] and other laboratory measures) and a Cox regression model relating time to ESRD to baseline and time-dependent covariates that characterize the longitudinal trajectories. The model for the longitudinal trajectories includes random effects to account for the uncertainty in future trajectories after the prediction time $t$. Given the estimated model, the predicted probability of kidney failure for any combination of $t$ and $\Delta$ can be calculated based on the observed longitudinal data history through time $t$.

The second approach uses the landmark Cox model,\(^6,7\) which consists of a series of related Cox models, each defined at a distinct prediction time. Each model is fitted to the individuals at risk at that time (ie, who remain in the study and have not yet had kidney failure). In our setting, the covariates are again eGFR and other laboratory, clinical, and demographic factors available at prediction time $t$. The outcome is the time from the prediction time to ESRD. Within each model, the covariates are fixed, but they are updated from one model to another. The parameters of these Cox models, including the baseline hazard function and hazard ratios, are allowed to change with time across the different models.

The time-updated approach considered by Tangri et al differs from the joint modeling and landmark approaches in that the risk score at a given time point (Item S1 in the Supplementary Material of their article) is the hazard function at that time, which quantifies the “current” risk instead of the predicted risk over a future time horizon. Because the time scale was discretized into 90-day intervals, the risk score can be transformed to provide updated estimates of the predicted probability of ESRD within the next 90 days (ie, $\Delta = 90$ days). However, whereas the static prediction, joint modeling, and landmarking approaches can directly generate predicted probabilities over any time horizon compatible with the data, the time horizon of the direct application of this approach considered by Tangri et al is restricted to 90 days. If one wishes to apply time-dependent Cox regression to estimate the predicted probability over substantially longer time horizons, it would be necessary to model the variation in the “future” longitudinal trajectories in the covariates beyond the prediction time $t$, as is done in the joint modeling approach.\(^5\)

Although the practical application of the time-updated approach considered by Tangri et al involves risk prediction over 90 days, the authors evaluated the performance of this approach by summing the time-dependent hazard to provide predicted event probabilities over the full evaluation period, which they then compared to the occurrence of actual events. In this way, they addressed an interesting hypothetical question: if at baseline we already knew the future covariate trajectories through the evaluation period, would this information improve risk prediction over the same period beyond what can be achieved in practice using a static model? Within this framework, the time-updated model was found to provide relatively small improvements. Although somewhat sobering, it is possible that the small size of the improvements resulted in part from attributes unique to the current study. These include the absence of follow-up proteinuria measurements, as noted by the authors, and the relatively short median study follow-up of 1.7 years. It is possible that updates to eGFR and other laboratory parameters provide a small advantage over 1.7 years but a greater improvement over a longer time. Improvements might also be achieved by incorporating trajectories or averages of biomarker measurements prior to prediction time $t$ in the time-updated projections.

We congratulate Tangri et al on an insightful article that introduces the idea of dynamic risk prediction to
the renal literature and expect that the methods being developed in the statistical dynamic prediction literature will provide additional fruitful applications to nephrology in the coming years.

Tom Greene, PhD
University of Utah School of Medicine
Salt Lake City, Utah

Liang Li, PhD
University of Texas MD Anderson Cancer Center
Houston, Texas

ACKNOWLEDGEMENTS

Support: None.

Financial Disclosure: Dr Greene receives consulting support from Jansen Pharmaceuticals, Durect Corporation, AstraZeneca, and Sanofi. Dr Li reports that he has no relevant financial interests.

Peer Review: Evaluated by a Statistics/Methods Editor and Editor-in-Chief Feldman.

REFERENCES