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Original Investigation

A Dynamic Predictive Model for Progression of CKD

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Background: Predicting the progression of chronic kidney disease (CKD) is vital for clinical decision making and patient-provider communication. We previously developed an accurate static prediction model that used single-timepoint measurements of demographic and laboratory variables.

Study Design: Development of a dynamic predictive model using demographic, clinical, and time-dependent laboratory data from a cohort of patients with CKD stages 3 to 5.

Setting & Participants: We studied 3,004 patients seen April 1, 2001, to December 31, 2009, in the outpatient CKD clinic of Sunnybrook Hospital in Toronto, Canada.

Candidate Predictors: Age, sex, and urinary albumin-creatinine ratio at baseline. Estimated glomerular filtration rate (eGFR), serum albumin, phosphorus, calcium, and bicarbonate values as time-dependent predictors.

Outcomes: Treated kidney failure, defined by initiation of dialysis therapy or kidney transplantation.

Analytical Approach: We describe a dynamic (latest-available-measurement) prediction model using time-dependent laboratory values as predictors of outcome. Our static model included all 8 candidate predictors. The latest-available-measurement model includes age and the latter 5 variables as time-dependent predictors. We used Cox proportional hazards models for time to kidney failure and compared discrimination, calibration, model fit, and net reclassification for the models.

Results: We studied 3,004 patients, who had 344 kidney failure events over a median follow-up of 3 years and an average of 5 clinic visits. eGFR was more strongly associated with kidney failure in the latest-available-measurement model versus the baseline visit static model (HR, 0.44 vs 0.65). The association of calcium level was unchanged, but male sex and phosphorus, albumin, and bicarbonate levels were no longer significant. Discrimination and goodness of fit showed incremental improvement with inclusion of time-dependent covariates (integrated discrimination improvement, 0.73%; 95% CI, 0.56%-0.90%).

Limitations: Our data were derived from a nephrology clinic at a single center. We were unable to include time-dependent changes in albuminuria.

Conclusions: A latest-available-measurement predictive model with eGFR as a time-dependent predictor can incrementally improve risk prediction for kidney failure over a static model with only a single eGFR.
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INDEX WORDS: Risk prediction; predictive model; chronic kidney disease (CKD); disease progression; disease trajectory; kidney failure; estimated glomerular filtration rate (eGFR); eGFR slope; albuminuria; renal replacement therapy (RRT); time-dependent predictor; Kidney Failure Risk Equation (KFRE).

Editorial, p. 492

Chronic kidney disease (CKD) is a major public health issue with growing incidence and prevalence worldwide.[1] Recent estimates suggest that 24 million Americans have CKD. Such patients are at risk for cardiovascular disease, anemia, bone mineral metabolism abnormalities, and progression to kidney failure requiring treatment with dialysis or kidney transplantation.[2] Predicting progression to kidney failure in patients with CKD is difficult because of the heterogeneous population and competing risk for death.[3,4] Successful prediction is valuable for informing patient-provider interactions and renal replacement therapy planning, such as fistula insertion for hemodialysis and preemptive kidney transplantation.[5]

Recent guidelines suggest combining albuminuria with estimated glomerular filtration rate (eGFR) to risk-stratify patients with CKD.[6,7] In addition, guidelines also recommend the use of validated risk prediction instruments for the prediction of progression to kidney

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failure. In 2011, we developed and validated the Kidney Failure Risk Equations (KFREs), which are predictive models with electronically captured covariates that predict progression to kidney failure with accuracy. Our models can be easily applied at the bedside via smartphone/tablet applications and online calculators.[8]

One limitation of KFREs is that they are "static" and treat laboratory data derived from each provider encounter in isolation without consideration of prior values. A "dynamic" approach to risk prediction would incorporate changes in laboratory test results over time and would more closely simulate a nephrologist's clinical approach to evaluating the patient. We evaluated whether a dynamic predictive model for progression to kidney failure that incorporates changes in kidney function and other laboratory variables as time-dependent predictors can improve predictive performance compared to our static model, which uses data from a single baseline visit.

METHODS

Study Population

This study included patients seen April 1, 2001, to December 31, 2009, in the outpatient CKD clinic of Sunnybrook Hospital, a tertiary referral center serving the North York region of Toronto, Canada. The Sunnybrook Nephrology electronic health record, a point-of-care CKD management system, was used in determining the study sample.

For each patient, the start of observation (origin) was the date of the earliest clinic visit. Patients were followed up until the start of treated kidney failure, defined as the date of dialysis therapy initiation or of kidney transplantation up to December 31, 2009 (end date). For patients who did not initiate renal replacement therapy before December 31, 2009, the end date was the earliest of death or the latest record of either a clinic visit, medication change, or laboratory test requisition. The observation time for each patient was computed as the number of days between the origin and end dates. A clinic visit was considered unique if it occurred more than 28 days after the preceding clinic visit. Participants were excluded from analysis if there were insufficient data to compute an origin date (eg, patient was referred to but not seen at the nephrology clinic) and end date, if information regarding the date of birth or sex were missing, or if eGFR at presentation was ≥60 mL/min/1.73 m^2. A total of 3,004 patients had eGFRs < 60 mL/min/1.73 m^2 and were therefore suitable for inclusion in the analysis. Variables with >30% missing values were not included. All other missing data for albuminuria and serum phosphate, calcium, bicarbonate, and albumin were imputed using the multiple imputation technique with 5 imputations based on PROC MI, SAS version 9.1 (SAS Institute Inc). Multiple imputation was performed using PROC MI in SAS on the data set using only variables included in predictive models. Most variables imputed had a very low percentage of missing values (<1%), and 3 variables had slightly higher rates of missing values (<5%).

Informed consent for individual participants was waived by the Sunnybrook Hospital Research Ethics Board because this was a retrospective review of deidentified patient records (REB #430-2008, 302-2010).

Candidate Variables

We used covariates from our previously published 8-variable KFRE developed in the same study population—age at first clinic visit (origin date), sex, eGFR, log-transformed albuminuria (urinary albumin-creatinine ratio [ACR]), and serum calcium, phosphate, bicarbonate, and albumin values and derived new coefficients. Baseline laboratory values were defined as the first value within 365 days of the origin date and were used in the static model. Sex was treated as a time-independent variable in both the static and dynamic models. Age and laboratory variables (except for albuminuria) were evaluated as time-dependent predictors in the dynamic model. Albuminuria was treated as a time-independent variable in the dynamic model because <50% of patients had 3 or more quantifiable/distinct measurements. ACR was the preferred measure of albuminuria and was log-transformed due to its skewed distribution. Twenty-four–hour urinary protein excretion was transformed to an ACR using a formula from the CKD Prognosis Consortium.[9]

Primary Outcome

The outcome of interest was treated kidney failure, defined as initiation of dialysis therapy or kidney transplantation. Patients were censored at the earliest of death or the latest record of a clinic visit, medication change, or laboratory test requisition.

Statistical Analysis

Construction of Prediction Models

In this study, the static model was a baseline visit static model using demographic and laboratory data from the first clinic visit, while the dynamic model was a latest-available-measurement model that used time-dependent covariates in a survival analysis framework. In the baseline visit static model, we included all covariates as time-independent variables in a Cox proportional hazard model using the baseline value for all covariates. In the latest-available-measurement model, we included sex and urinary ACR as time-independent covariates using their baseline value and included age and other laboratory variables as time-dependent covariates using their values from all visits. Both models used a counting process style of data input to perform proportional hazard modeling and facilitate appropriate comparisons.[10] Baseline hazard of developing kidney failure was calculated for each 90-day period starting from a patient's first nephrology clinic visit until the maximum follow-up time. Then for each 90-day period that a patient was observed, a unique hazard estimate was calculated for the patient by multiplying the baseline hazard by the inverse logarithm of the patient's calculated β predictor value closest to the start of the 90-day period. Cumulative hazard function was calculated for each patient by summing the hazard estimates across all of the patient's 90-day periods. The inverse logarithm of the negative cumulative hazard function was calculated to develop survival probabilities for each patient at the end of follow-up. For the static model, the same covariate values were used to calculate the β predictor value for each 90-day period. For the dynamic (latest-available-measurement) model, values for the time-dependent covariates were updated at each clinic visit (Item S1, available as online supplementary material). Values from the previous period were carried forward if updated values were unavailable.

Prediction Model Performance

We used a series of methods to evaluate the characteristics and performance of the 2 models.

Model characteristics and fit. Overall model fit was compared using Akaike information criterion, which takes into account the statistical goodness of fit and number of parameters required to achieve this particular degree of fit by imposing a penalty for increasing the number of parameters.[11] We compared the hazard ratio (HR) for both the static and dynamic models for the association between the predictors and progression to kidney failure.

Discrimination. Discrimination refers to the ability of a model to correctly distinguish between 2 classes of outcomes (eg, kidney failure vs no kidney failure). Concordance statistics (C statistics) and integrated discrimination improvement (IDI) statistics were computed as measures of discrimination; IDIs were used to compare discrimination between models.

Calibration. Calibration describes how closely the predicted probabilities agree numerically with the observed outcomes. We compared observed versus predicted risk for kidney failure for each decile of predicted risk and determined the magnitude of the deviation using the D'Agostino and Nam[12] χ^2 statistic.

Reclassification. Reclassification refers to the movement of patients from one class to another based on changes in assignment to risk categories. Risk categories to guide treatment decisions regarding CKD progression have not been extensively used in clinical practice. As such, a category-free reclassification improvement was quantified using the net reclassification improvement statistic.[13]

Both discrimination and reclassification were calculated using 200-fold bootstrapping and cross-validation.[11,13-15] All statistical analyses were performed using SAS, version 9.2.

RESULTS

Study Population

We included 3,004 patients with CKD stages 3 to 5 in our analysis (Table 1). A majority of patients were older than 65 years and 42% were women. Patients with more advanced stages of CKD had higher urine ACR, phosphorus, and potassium levels and lower serum albumin, calcium, and bicarbonate levels. More than two-thirds of patients had CKD stage 3 at the time of referral, but only 3% of those patients progressed to kidney failure by the end of follow-up. Six percent of patients had CKD stage 5 at referral, and 60% of those patients had progressed to kidney failure.

Median duration of follow-up was 1.7 (interquartile range, 0.6-3.6) years. Median number of visits per patient was 6 (range, 1-36), with an average of 4 months between clinic visits. Mean time to event from the baseline visit creatinine level to the outcome was 893 days in the static model, and from the most recent serum creatinine level to the outcome was 182 days for the latest-available-measurement (dynamic) model. Median eGFR at visit 1 was 36 mL/min/1.73 m^2 and it decreased to 31 mL/min/1.73 m^2 by visit 6. The number of patients available for analysis was 3,004 at the first visit, and it decreased to 1,512 by visit 6. Patients who had 6 or more visits were similar in age, sex, eGFR, and ACR to those with fewer than 6 visits (Table S1).

Characteristics of Prediction Models

In the baseline visit static model, similar to our previous work, lower eGFR, younger age, and male sex were associated with higher risk for progression to kidney failure. Higher urine ACR; lower serum calcium, albumin, or bicarbonate level; and higher phosphorus level were also associated with the outcome of interest (Table 2). In the latest-available-measurement model incorporating all available data, eGFR was a more potent predictor of progression to kidney failure than in the static model (for each 5–mL/min/1.73 m^2 greater eGFR, the HR for kidney failure was 0.44 [95% confidence interval (CI), 0.41-0.48] vs 0.65 [95% CI, 0.62-0.69]). Conversely, the HR for urine ACR was attenuated significantly (for each 1-log greater urine ACR, values were 1.30 [95% CI, 1.19-1.43] and 1.45

Table 1. Study Population Baseline Characteristics and Follow-up Events by CKD Stage

Variable	Overall (N = 3,004)	CKD Stage 3 (n = 2,014)	CKD Stage 4 (n = 826)	CKD Stage 5 (n = 164)
Age, y	69 ± 14	68 ± 14	74 ± 14	72 ± 14
Male sex	58	60	52	53
Systolic BP, mm Hg	129 ± 22	128 ± 21	131 ± 22	140 ± 21
Diastolic BP, mm Hg	71 ± 12	71 ± 12	68 ± 12	73 ± 13
Diabetes	38	38	40	38
Hypertension	87	84	92	95
Vascular disease	42	39	48	43
Immune disease	25	25	26	23
eGFR, mL/min/1.73 m^2	36 ± 13	45 ± 11	23 ± 4	11 ± 3
ACR, mg/g	69 ± 115	41 ± 105	84 ± 156	151 ± 198
Albumin, g/dL	3.98 ± 0.5	4.0 ± 0.5	3.88 ± 0.5	3.2 ± 0.5
Calcium, mg/dL	9.34 ± 0.65	9.48 ± 0.60	9.22 ± 0.72	8.88 ± 0.92
Phosphate, mg/dL	3.93 ± 0.91	3.57 ± 0.78	4.05 ± 0.96	5.01 ± 1.35
Bicarbonate, mEq/L	26 ± 4	26 ± 3	25 ± 4	23 ± 4
Duration of follow-up, y	2.5 ± 2.3	2.5 ± 2.4	2.5 ± 2.2	1.6 ± 2.0
No. of visits	7.9 ± 7.3	7.6 ± 7.0	9.0 ± 7.7	7.1 ± 7.1
Kidney failure	11	3	22	60

Note: Values for categorical variables are given as percentages; for continuous variables, as mean ± standard deviation. Conversion factor for calcium in mg/dL to mmol/L, ×0.2495.

Abbreviations: ACR, albumin-creatinine ratio; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 2. Hazard Ratios for Kidney Failure for Variables in the Baseline Visit Static and Latest-Available-Measurement Models

Variable	Baseline Visit Static Model	Latest-Available-Measurement Model
eGFR, per 5 mL/min/1.73 m^2 greater	0.65 (0.62-0.69)	0.44 (0.41-0.48)
Urine ACR, per 1 log greater	1.45 (1.32-1.58)	1.30 (1.19-1.43)
Age, per 10 y older	0.86 (0.80-0.92)	0.86 (0.80-0.93)
Male sex	1.29 (1.03-1.61)	1.09 (0.87-1.36)
Albumin, per 5 g/L greater	0.87 (0.78-0.98)	0.98 (0.87-1.10)
Phosphate, per 1.0 mg/dL greater	2.03 (1.52-2.72)	1.05 (0.78-1.42)
Bicarbonate, per 1.0 mEq/L greater	0.95 (0.92-0.98)	0.98 (0.95-1.01)
Calcium, per 1.0 mg/dL greater	0.86 (0.76-0.97)	0.88 (0.77-1.00)
C statistic[a]	0.90 (0.88-0.92)	0.91 (0.89-0.93)
AIC[a]	4,091.68	3,795.31
IDI[a]	NA	1.39% (1.23%-1.56%)
NRI[a]	NA	18.29% (12.64%-23.93%)

Note: Unless otherwise indicated, values are given as hazard ratio (95% CI). Conversion factor for calcium in mg/dL to mmol/L, ×0.2495.

Abbreviations: ACR, albumin-creatinine ratio; AIC, Akaike information criterion; CI, confidence interval; eGFR, estimated glomerular filtration rate; IDI, integrated discrimination improvement; NA, not applicable; NRI, net reclassification improvement.

[a]AIC row gives AIC value; C statistic, IDI, and NRI rows give C statistic (95% CI), IDI (95% CI), and NRI (95% CI), respectively.

[95% CI, 1.32-1.58], respectively). The HRs for age and serum calcium level were relatively unchanged, but male sex and serum phosphorus, albumin, and bicarbonate levels were no longer independently associated with the outcome in the latest-available-measurement model.

Performance of Prediction Models

Performance measures comparing the baseline visit static and latest-available-measurement models are described in Table 2 and Fig 1. Compared to the baseline visit static model, the latest-available-measurement model had modestly better discrimination, as evidenced by the C statistic (0.91 [95% CI, 0.89-0.93] vs 0.90 [95% CI, 0.88-0.92]) and IDI statistic (absolute IDI, 1.39%; 95% CI, 1.23%-1.56%). Calibration was adequate for both models (Hosmer-Lemeshow χ^2 statistic < 20), with similar values for the mean absolute difference between observed and predicted values in the risk deciles. However, the latest-available-measurement model showed greater dispersion between risk deciles and better agreement between the observed and predicted probabilities (the highest risk decile had an observed probability of event of 72% for the latest-available-measurement model vs 58% for the baseline visit static model). Goodness of fit was also significantly improved in the latest-available-measurement model (Akaike information criterion of 3,795 vs 4,092; $P < 0.01$). Similarly, an improvement in the category-free net reclassification improvement of 18.3% (95% CI, 12.6%-23.9%) was observed with the latest-available-measurement model versus the baseline visit static model.

Secondary analyses were also performed. Baseline eGFR was limited to those with at least moderate CKD (eGFR < 45 mL/min/1.73 m^2); compared with the main analyses, no meaningful differences in HRs or model performance were detected. In addition, a subgroup analysis censoring all patients at 12 months of follow-up was performed; results obtained were similar to those from the main analyses.

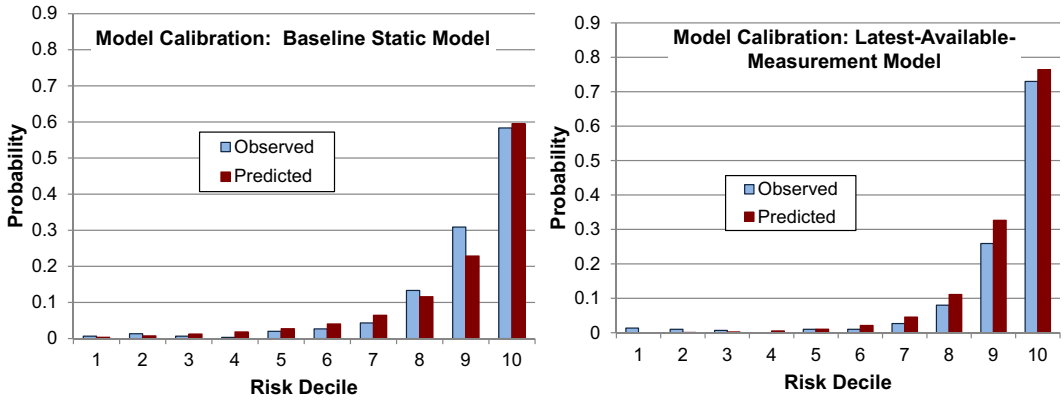

Figure 1. Observed versus predicted probabilities for the baseline visit static and the latest-available-measurement models.

DISCUSSION

We developed prediction models for progression of CKD to kidney failure and found that a dynamic predictive model that included time-varying measures of laboratory variables (the latest-available-measurement model) incrementally outperformed a static model that included only data from the baseline study visit. The most important time-varying measure was eGFR, and it attenuated the associations of most other laboratory variables and male sex. Our laboratory-based dynamic model represents a modest improvement over conventional models that ignore changes in patient characteristics over time.

The importance of change in eGFR as an important risk factor for subsequent kidney failure and all-cause mortality was demonstrated in a large meta-analysis by the CKD Prognosis Consortium.[16-19] The meta-analysis highlighted the greater importance of the most recent eGFR versus the change from baseline eGFR in predicting both outcomes. Results from this current study are consistent with these findings because there was less improvement with the latest-available-measurement model when the baseline visit static model used more recent clinical information. However, the previous studies did not examine eGFR as a time-dependent predictor and therefore did not take the entire trajectory of kidney function into account.

Previous studies examining changes in other laboratory measures of CKD progression are limited. One small study demonstrated a strong association between visit level changes and slopes of proteinuria in patients with immunoglobulin A nephropathy, and another larger study in Pima Indians with diabetic nephropathy did not show a benefit of sequential proteinuria measurements in predicting outcomes.[20-22] However, more recently, a large meta-analysis suggested that early reductions in proteinuria are associated with subsequent development of kidney failure, but it did not examine proteinuria as a risk factor in a time-dependent model.[23] Lack of longitudinal data for proteinuria prohibited this analysis in this study, but it could be updated in the future as additional data are acquired. To our current knowledge, no studies have examined the change in other serum laboratory variables and CKD outcomes. Recent analysis from the CRIC (Chronic Renal Insufficiency Cohort) Study has shown that time-dependent systolic blood pressure is more strongly associated with progression to kidney failure, but it did not evaluate its effect on risk prediction of kidney failure events. Baseline blood pressure did not significantly improve discrimination or calibration in our original KFRE, so we did not evaluate blood pressure as a predictor in this analysis.

In our latest-available-measurement model, the association between eGFR and the outcome was stronger, but associations between other serum laboratory variables (albumin, bicarbonate, and phosphate) and the outcome were attenuated and no longer statistically significant. Despite this, the latest-available-measurement model had a better overall fit (lower Akaike information criterion) and improved discrimination. We hypothesize that changes in the magnitude of associations and the model fit are due to 2 possible reasons. First, updated eGFR measurements may track more closely with GFR changes over time, resulting in a stronger association for the eGFR variable. At the baseline visit, the remaining serum laboratory variables may reduce some of this error, but when eGFR is repeated and modeled over time, these variables may no longer be necessary. As GFR estimating equations become more precise, these hypotheses can be retested. Second, it is also possible that the association between the covariates and the outcome is truly different at every visit and that combining the β coefficients results in a more accurate representation of the true association. We believe that the former is more likely because referral to a nephrologist does not occur at incident CKD, but at variable times during the course of the disease for different patients.

It is important to note that the magnitude of the improvement in predictive ability for the latest-available-measurement model was modest and its clinical importance is uncertain. We believe that this finding is novel because it counters conventional wisdom about the importance of longitudinal measurements of laboratory variables, including eGFR, in predicting progression to kidney failure. Although it is possible that the magnitude of these improvements may have been limited by the already high C statistic of our static model, as well as the lack of longer term follow-up in our study population, we believe that other factors, including nonlinear trajectories of progression, bias and variability in eGFR and albuminuria measurements, and lack of an external validation data set, further limit the ability of the latest-available-measurement model for long-term risk prediction beyond the highly accurate static model that uses data from the recent visit.[24-26]

Our model has several strengths. First, it represents the first predictive model for progression of kidney failure that incorporates eGFR as a dynamic time-dependent variable and updates risk predictions for individual patients by accounting for the best available estimate of the patient's condition, rather than solely relying on baseline data. For short-term predictions, that is, less than 90 days, this time-dependent approach can be particularly useful. Second, it improves

discrimination, calibration, and goodness of fit over a static model built using the same covariates as our previously validated KFRE. Finally, it builds on the strength of electronic medical records by using variables that can be collected and updated automatically. This can lead to automatic reporting of risk prediction as well, which may be beneficial for patient care.

There are some limitations to our analysis. First, our data were derived from a nephrology clinic at a single center in Ontario. As a result, the improvement in risk prediction with the latest-available-measurement model seen in our analysis will need to be reproduced in other longitudinal data sets. Second, we were unable to include time-dependent changes in albuminuria in our model due to a lack of longitudinal data in our study population. As albuminuria testing becomes more routine for patients with CKD, these findings should be updated in the Sunnybrook cohort and others. Third, the time between laboratory measurements, particularly eGFR, was inconsistent between visits and driven by clinical indication. It is possible that regularly scheduled visits and measurements, such as those performed in longitudinal cohort studies such as CRIC, may enhance the ability of the latest-available-measurement model.[27] Fourth, we and others have recognized the importance of competing-risk survival analyses in examining risk factors and progression of CKD. Unfortunately, no methods currently exist to evaluate time-dependent covariates in a predictive model using competing-risk analyses and as such, we were unable to overcome this limitation. Fifth, there may be a small bias in the multiple imputation applied because it was based on an imputation model that included only the predictor variables. The outcome variable was not included because it is technically difficult to perform in the setting of Cox regression and missing data was not a major issue in this study. Finally, results of this study may not be generalizable to other settings in which the frequency of laboratory value measurements differs from that of the present study.

We present a dynamic predictive model for progression to kidney failure that modestly improves risk prediction over a static model for progression of kidney disease. Our model using electronically obtained covariates can lead to automatic risk calculation and reporting in the context of an electronic medical record and may enhance risk prediction of short-term events. Further studies comparing dynamic with static predictive models for kidney failure and competing outcomes of mortality and cardiovascular disease are needed.

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Contributions: Research idea and study design: NT, LAI, DN, DK, ASL; data analysis/interpretation: NT, LAI, DN, DK, ASL; statistical analysis: BH, JW. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. NT takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Peer Review: Evaluated by 3 external peer reviewers, a statistician, and an Acting Editor-in-Chief.

SUPPLEMENTARY MATERIAL

Table S1: Characteristics of patients stratified by duration of follow-up.

Item S1: Calculation of hazard of kidney failure at each visit from a time-dependent Cox model.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2016.07.030) is available at www.ajkd.org

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