

Predicting timing of adverse events in CKD with severely decreased GFR

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ABSTRACT

People with chronic kidney disease and severely decreased glomerular filtration rate (GFR) are at high risk for kidney failure, but also cardiovascular disease (CVD) and death. Accurate estimates of risk and timing of adverse events could guide patient counseling and therapy. Source data included 264,296 participants with eGFR <30 ml/min/1.73m² from 29 cohorts in 30 countries. Median participant eGFR and urine albumin-to-creatinine ratio (ACR) were 24 ml/min/1.73m² and 168 mg/g, respectively. Using competing-risk regression, random-effect meta-analysis, and Markov processes with Monte Carlo simulations, we developed a 2- and 4-year model of the probability and timing of kidney failure requiring kidney replacement therapy (KRT), a non-fatal CVD event, and death according to age, sex, race, eGFR, ACR, systolic blood pressure, smoking status, diabetes mellitus, and history of CVD. Applied to a hypothetical scenario of a 60-year-old white man with a history of CVD, systolic blood pressure 140 mmHg, eGFR 25 ml/min/1.73m² and urine ACR 1000 mg/g, the 4-year model predicted a 17% chance of survival with KRT, 17% chance of survival after a CVD event, 4% chance of survival after both a CVD event and KRT, and a 28% chance of death (9% as a first event, and 19% after another CVD event or KRT). Risk predictions for KRT showed good overall agreement with the published Kidney Failure Risk Equation, and both models were well calibrated with observed risk. In conclusion, commonly-measured clinical characteristics can predict the timing and occurrence of clinical outcomes in patients with severely decreased GFR.

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INTRODUCTION

Chronic kidney disease (CKD) is an increasingly common global problem.¹ In the developing world, disease burden is shifting from communicable to non-communicable etiologies, and the prevalence of CKD has grown with the rise of hypertension, obesity, and diabetes.² In the developed world, the prevalence of CKD has increased with improvements in life expectancy.³ The implications of CKD include morbidity, mortality, and reduction in quality of life at the individual level and high costs at the societal level.⁴ Patients with severely decreased glomerular filtration rate (GFR) in particular are at high risk for adverse outcomes, including kidney failure, cardiovascular disease (CVD) events, and death.^{5,6} Accurate prediction of whether and when adverse events will occur in patients with severely decreased GFR (eGFR <30 ml/min/1.73 m²; subsequently designated as Stage G4+) will help target efforts to treat and prevent worsening of disease.

There are a few existing tools to predict the onset of kidney failure treated with KRT (also frequently referred to as end-stage kidney disease), one of the most costly outcomes of CKD.⁴ Tangri and colleagues developed an absolute risk prediction tool for patients with CKD stage G3-G5 (eGFR <60 ml/min/1.73 m²) in two Canadian cohorts,⁷ and this Kidney Failure Risk Equation (KFRE) was subsequently validated in 31 global cohorts.⁸ Other prediction tools exist but have not undergone robust validation.⁹⁻¹¹ None of these tools was developed specifically for a population with Stage G4+ CKD, nor do they predict other potentially more common events, such as pre-KRT death and non-fatal CVD events.

Using 29 cohorts of patients with Stage G4+ CKD participating in the international CKD Prognosis Consortium, we simultaneously assessed the risks of KRT, non-fatal CVD events, and death, applying competing risk, meta-analysis with random effects models, and Markov process methodology. The goal was to develop a 2- and 4-year calculator to predict both the probability and the order of clinical events according to nine demographic and clinical characteristics.

RESULTS

Baseline characteristics

In total, there were 264,296 participants with eGFR <30 ml/min/1.73 m² from 29 cohorts in 30 countries for use in model development (**Table 1; Supplemental Table 1**). Twenty cohorts had data on non-fatal CVD events, KRT, and death; nine had data on KRT and death only. Average age ranged from 47 years (Nanjing CKD, China) to 82 years (Parcours de Soins des Personnes Agées [PSPA], France). The distribution of eGFR and albuminuria varied by cohort, but was often skewed toward the higher end of eGFR <30 ml/min/1.73 m² and the lower end of urine albumin-to-creatinine ratio (ACR) (**Supplemental Figure 1-2**). Cause of CKD included

diabetes, hypertension, glomerulonephritis, polycystic kidney disease, and interstitial nephritis, but was unknown in the majority of cohorts (**Supplemental Table 2**).

Rates, risk factors, and adjusted absolute risk of adverse outcomes

Overall, there were 123,985 deaths, 31,541 events of kidney failure treated with KRT, and 70,394 CVD events identified over a mean follow-up of 3.5 years. Events were categorized not only by their occurrence but also by their timing relative to KRT and CVD events, and modeled as a function of age, sex, race, history of CVD, current smoking status, systolic blood pressure, diabetes mellitus, eGFR, and urine ACR (**Figure 1**). Strong risk factors for developing KRT as a first event included younger age, black race, higher systolic blood pressure, lower eGFR, and higher urine ACR (**Supplemental Table 3**). In contrast, strong risk factors for developing a CVD event prior to KRT included older age, previous history of CVD, and diabetes. Older age and smoking were the strongest risk factors for death prior to KRT or CVD. There was some quantitative heterogeneity across cohorts, but risk associations were qualitatively consistent (**Supplemental Figure 3-4**). The adjusted cumulative incidence of each event over time varied across cohorts, particularly by cohort type (**Figure 2**). The adjusted absolute risk of KRT as a first event was generally highest among the CKD research cohorts, whereas the risk of a CVD event or death prior to KRT was highest among the administrative cohorts. Second and third events were quantified in a similar manner (**Supplemental Table 4-6** and **Supplemental Figure 5-7**).

Risk prediction model: 2- and 4-year outcomes

Risk factors and adjusted absolute risk were combined using a Markov process and simulations to create a prediction model for the probability and timing of clinical events, and approximated using a multinomial model (median $R^2=0.99$; **Supplemental Table 7**; temporary version until publication: <http://adityasurapaneni.com/morgan/pie2.html>). In hypothetical scenarios, the probability of adverse events increased with longer follow-up and higher albuminuria. For example, a 60-year-old white man with a history of CVD, systolic blood pressure of 140 mmHg, eGFR of 25 ml/min/1.73 m² and urine ACR of 30 mg/g but no current smoking or diabetes mellitus was predicted to have a 74% chance of remaining event-free at 2 years, along with a 9% chance of death and a 5% chance of KRT (**Figure 3A**). In contrast, a similar scenario but for urine ACR of 1000 mg/g and assessment at 4 years resulted in a prediction of event-free survival of 34%, with a 28% chance of death, a 17% chance of survival with KRT, a 17% chance of survival with CVD, and a 4% chance of both (**Figure 3B**). Other scenarios that dramatically affected the probability of adverse events included lower eGFR (higher risk of KRT), the presence of diabetes mellitus (higher risk of CVD events) and older age (higher risk of death) (**Supplemental Figures 8-13**).

Comparison with the KFRE and observed risk of kidney failure treated with KRT

We compared absolute risk projections from the developed risk prediction model with the previously developed, 2-year, 4-variable KFRE for a set of scenarios holding constant the overlapping risk characteristics (age, sex, eGFR, and albuminuria) but varying others that were included only in our model (race, systolic blood pressure, diabetes mellitus, smoking status, and history of CVD), demonstrating good agreement (within-cohort R^2 ranging from 0.89 to 0.97; median within-study C-statistic of 0.814 (range, 0.680 to 0.972) and 0.817 (range, 0.666 to 0.929) respectively; **Supplemental Figures 14-19**). Calibration to observed risk using clinically relevant categories was also good for both the developed risk prediction model as well as the KFRE (**Supplemental Figure 20**). Within cohorts, the prevalence of 2-year predicted KRT risk >40% (potentially an actionable threshold) was approximately 10% in most cohorts using the KFRE and slightly higher using our Markov model, but many participants had >50% predicted probability of remaining event-free at 4-years (**Supplemental Figure 21-22**).

Alternative risk prediction model: Assessment of variation by cohort type

Alternate versions of the risk model that incorporated adjusted absolute risk estimates from the three types of cohort (CKD research, administrative, and referred CKD) showed an approximately two-fold variation in the predicted risk of clinical events between models (**Supplemental Figure 23; Figure 4**). The predicted probability of KRT was higher and of death was lower in the CKD research cohort-based prediction model compared to the overall prediction model; the opposite was true in the administrative cohort-based prediction model (**Supplemental Figures 24-26**). Variation in adjusted absolute risk over time was less consistent by region or cause of disease (**Supplemental Figures 27-28**).

Alternative risk prediction model: Three-state Markov model

In sensitivity analysis, we compared the predicted probability of KRT and death from the 5-state Markov model derived from data from the 20 cohorts with all three outcomes to the predicted probability of KRT and death from a 3-state Markov model (CKD G4+, KRT, and death) derived from data from all 29 cohorts with available KRT and death (**Supplemental Figure 29**). Risk projections were similar (**Supplemental Figure 30**).

DISCUSSION

In this global consortium of 264,515 patients with eGFR <30 ml/min/1.73 m², we developed and tested a model to predict the absolute risk and relative order of KRT, non-fatal CVD events, and death in a 2- and 4-year period. The risk calculator has been made publicly available (temporary version until publication: <http://adityasurapaneni.com/morgan/pie2.html>) and may aid in patient counseling, including referral recommendations for transplantation or vascular access surgery. With the caveat that many of our cohorts represent incident CKD G4+ patients, we found that

occurrence of events (KRT, non-fatal CVD events, or death) was not uniformly high, with nearly 50% of the participants expected to be event-free at the end of four years.

Our study provides additional evidence that baseline risk factors have strong relationships with subsequent events, even in individuals with severely decreased GFR.¹² Both lower eGFR and higher albuminuria were strong risk factors for kidney failure treated with KRT. However, the absolute risks varied substantially according to age, with the predicted 4-year risk of KRT declining from 33% in a 35-year-old to 5% in an 85-year old in a scenario with baseline eGFR of 25 ml/min/1.73 m² and urine ACR of 100 mg/g. Not surprisingly, a history of CVD was an exceptionally strong risk factor for the occurrence of a CVD event among patients with Stage G4+ CKD, supporting the potential importance of cardiovascular risk factor reduction in these patients despite their advanced kidney disease. Interestingly, in the included cohorts, many of the participants were predicted to remain event-free in the subsequent four years. This may be in part due to selection: there was a significant subset of participants with relatively low albuminuria, which may or may not be generalizable to the greater population.

A well-validated risk equation for kidney failure requiring KRT in CKD G3+ already exists.^{7,8} Our study adds to the literature by simultaneously accounting for and estimating rates of competing events, particularly death. We confirm the accuracy of the KFRE in a population with lower GFR than the cohorts in which it was originally developed and validated, and we compare the KFRE to our own model, finding similar results. We might suggest that health providers and systems use the KFRE in persons with GFR <60 ml/min/1.73 m², in whom kidney failure treated with KRT is the primary event of interest, and when a limited number of covariates are available. For patients with eGFR <30 ml/min/1.73m² in whom there is interest in incident CVD events or death, or the sequence of such events in relation to KRT, we would suggest our newly developed equation, which uses additional covariates to produce a more refined estimate.

Strengths of our study include a very large number of patients with CKD Stage G4+ from a broad range of countries. Models were developed and rigorously tested with many different sensitivity analyses. Prediction tools incorporated nine different clinical and demographic variables and explained approximately 40-fold of the variation in explained risk, but there remained approximately 5-fold variation between cohorts that was unexplained. Type of cohort did seem to be an important contributor in risk variation, with research cohorts having markedly higher KRT risk than others, even adjusted for baseline covariates. In those cohorts for which we had data, cause of CKD was not a major contributor to variation between cohorts. Although region has previously been found to play an important role in KRT risk, we did not see consistent differences between North America and non-North American regions, perhaps due to the relatively small number of cohorts from each region.⁸ We had limited data with which to evaluate whether differences in therapeutic interventions such as renin-angiotensin system inhibition or statin use might partially explain variation across cohorts.¹³

As with all models, there were certain assumptions. Relative risks were modeled as constant over time. The cumulative incidence of competing events was scaled to the cumulative incidence of the composite event derived from Cox regression. Initiation of KRT, which we and others used as an operational definition for the major adverse renal endpoint, is a treatment decision which may be influenced by factors other than kidney function. For example, our observation of older age conferring lower risk for KRT may reflect preferences for conservative care rather than a slower progression of CKD or fewer symptoms. Fatal CVD events were simply counted as death, and not CVD.

In conclusion, our model predicts the occurrence and order of non-fatal CVD events, kidney failure treated with KRT, and death in patients with eGFR <30 ml/min/1.73 m², based on parameters that are readily available in routine clinical practice. This tool may be a useful supplement to existing risk calculators when refined estimates that take into account competing events and patterns of events are required. Additional work is needed to further characterize sources of unexplained variation between cohorts, with the ultimate goal of identifying treatment strategies and practice patterns that can prevent or forestall adverse outcomes in patients with severely decreased GFR.

METHODS

Study population

Cohorts were identified from the CKD Prognosis Consortium as well as through an open call by the Kidney Disease: Improving Global Outcomes (KDIGO). The CKD-PC has been described previously and in more detail in **Appendices 1-2**.¹⁴⁻¹⁷ Cohorts were considered eligible for the current study if they contained at least 500 patients with eGFR <30 ml/min/1.73 m², data on albuminuria, and at least 50 events each of kidney failure requiring KRT and death. There were 29 cohorts included in analyses using a 3-state Markov model, and 20 cohorts using a 5-state Markov model. Thirteen cohorts were classified as CKD research cohorts (designed as a research study with planned study visits and active outcome ascertainment), five were classified as administrative cohorts (captured from a clinical or health system database covering an entire patient population), and 11 were classified as referred CKD cohorts (similar design as the administrative cohorts, but restricted to patients under the care of a nephrologist or in a CKD registry). This study was approved by the institutional review board at the Johns Hopkins Bloomberg School of Public Health (Baltimore, Maryland, USA).

Covariates & Outcomes

Serum creatinine was standardized to isotope dilution mass spectrometry and converted to eGFR using the CKD-EPI 2009 creatinine equation.¹⁸ Measures of albuminuria included the urine albumin-to-creatinine ratio, urine albumin excretion rate, urine protein-to-creatinine ratio, with

conversion to ACR as needed.⁷ In analyses, urine ACR was log-transformed and scaled to $\ln(10)$, so that coefficients were interpreted reflecting differences per 10-fold higher ACR. Diabetes was defined by individual cohorts as fasting glucose ≥ 7.0 mmol/L (126 mg/dL), non-fasting glucose ≥ 11.1 mmol/L (200 mg/dL), hemoglobin A1c $\geq 6.5\%$, use of glucose lowering drugs, or self-reported diabetes. History of CVD was defined as a history of myocardial infarction, coronary revascularization, heart failure, or stroke. Smoking was categorized as current smoker versus former/never smoker. Systolic blood pressure was reported by the cohorts and treated as a linear spline in regression models, with a knot at 140 mmHg. Cause of disease was classified by individual cohorts. Outcomes included KRT, cardiovascular events, and death, and were defined using cohort-specific definitions (**Appendix 1**). Missing covariates (except age, sex, race, and eGFR) were estimated using multiple imputation chained equations.¹⁹⁻²¹

Competing risk analyses

The associations between baseline covariates and first outcome were determined using competing risk regression using the method of Fine and Gray and treating first KRT, first non-fatal CVD event, and pre-KRT, pre-cardiovascular death as competing events.²² This was repeated for all participants who reached KRT first, treating post-KRT CVD events and death as competing events, and for all participants who had a CVD event first, treating post-CVD event KRT and death as competing events. Only the first non-fatal CVD event after the onset of eGFR < 30 ml/min/1.73 m² was captured. At each step, a composite endpoint was also evaluated in the same manner using Cox regression. For the first event, the composite endpoint consisted of first KRT, first CVD event or death pre-KRT and pre-CVD event. For the second event after KRT, the composite endpoint consisted of post-KRT CVD events or post-KRT death. For the second event after a CVD event, the composite endpoint consisted of post-CVD event KRT or post-CVD event death. For the outcome of death after a participant had developed both KRT and a CVD event, Cox regression was used to estimate associations, since there was no competing event.

Meta-analysis and estimation of baseline sub-hazards

Fine and Gray sub-hazard ratios derived in each cohort were pooled using random-effects meta-analysis. Heterogeneity was evaluated using forest plots and I^2 statistics.²³⁻²⁵ Cohort-specific adjusted baseline sub-hazards were estimated in each cohort using competing risk regression, holding sub-hazard ratios constant and equal to the meta-analyzed sub-hazard ratios, but allowing the baseline sub-hazard to vary between cohorts. The baseline sub-hazards were then used to calculate the adjusted cumulative incidence of each event over time. Baseline sub-hazards (i.e., the adjusted absolute risk over time) were displayed graphically to evaluate heterogeneity and summarized as the equal-weighted mean over cohorts and, for cohort type-specific analysis, the equal-weighted mean within cohort type. Note that, for the composite endpoints as well as event of death after KRT and a CVD event (where there is no competing event), Cox regression and baseline hazards were used, but the procedure was otherwise the

same. A Weibull model was then fit on the equal-weighted mean adjusted sub-hazard (or hazard), in order to allow a smooth, parametric estimate for use in the Markov process.

Markov process and simulations of absolute risks

The combination of parameters from the Weibull model and the meta-analyzed sub-hazard ratios were used to predict time-varying state transition probabilities (e.g., the probability of moving from CKD G4+ to first KRT) for a given set of baseline covariates (age, sex, race, history of CVD, smoking status, diabetes mellitus, systolic blood pressure, eGFR, and urine ACR). In order to ensure that the probabilities for each state summed to 1, we scaled the cumulative probability of the events (for the first state transition, first KRT, first CVD event, and first death) to the cumulative probability of a composite endpoint ascertained using Cox proportional hazards model, as done previously.²⁶ These state transition probabilities thus varied by time, age, and baseline covariates and were incorporated in a heterogeneous Markov process using a cycle length of 1 month and a time horizon of 2- and 4-years. Outcomes were estimated using 10,000 simulations for each scenario, where a scenario corresponds to a set of covariates. In other words, each iteration corresponds to one hypothetical person with the given set of covariates, and variation in the results of the iteration represent the stochastic natures in which persons traverse the Markov model. In order to assess the sensitivity of risk prediction to cohort type, we repeated the procedures using cohort-type specific parameters for the baseline sub-hazards. We also repeated analyses in a 3-state model (CKD G4+, KRT, and death; **Supplemental Figure 29**) to compare the results. To evaluate sources of unexplained variation, we examined the distribution of cumulative incidence of events by type of cohort, region, and prevalence of different causes of CKD.

Development of a web calculator

In order to implement the Markov process as a web tool, we developed an estimating equation on simulated estimates for 3,702 baseline scenarios (every combination of age (35, 45, 55, 60, 65, 75, 80 and 85 years), sex, race (black and non-black), diabetes status, history of CVD status, smoking status (current smoker and never/former smoker), systolic blood pressure (180 and 140 mmHg), eGFR (15 and 25 ml/min/1.73 m²), and ACR (30, 100 and 1000 mg/g)). To do this, we fit multinomial models and weighted by the inverse probability of each outcome from simulations (e.g., KRT only, CVD only, death only, KRT followed by CVD, CVD followed by KRT, etc.). Multinomial models incorporated all the available covariates and two-way interactions significant for any of the outcomes. Calibration of the multinomial model to the simulated outcomes was assessed using R² and root-mean-squared errors for each outcome. Functional forms of covariates were the same as those used in the competing risk regression. For the purposes of this manuscript, predicted probabilities in the figures and text stem from the multinomial model.

Comparison of our developed risk model with the KFRE and observed risk

We compared absolute risk estimates of the probability of KRT from our newly developed risk model to that calculated in the absence of competing events using the previously published KFRE.^{7,8} To do this, we held shared variables constant (age, sex, eGFR, and ACR) and varied the covariates unique to our model (race, systolic blood pressure, diabetes mellitus, smoking status, and history of CVD), and we assessed R^2 within cohorts. We also compared risk predictions from our developed risk model as well as the KFRE to observed KRT risk. To do this, we classified predicted risk categories into <20% 20-40%, >40% probability of KRT in the subsequent two years (clinically meaningful thresholds) using our developed risk model and the KFRE, and then we plotted the mean risk estimate against the observed risk within each category by cohort. Discrimination was assessed using the C-statistic.

All analyses were done in Stata 14 MP (College Station, TX).

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Table 1. Outcomes and baseline characteristics of included cohorts

study	N	Death	Kidney failure treated with KRT	CVD event after baseline	Mean follow-up, yrs	Age, yrs	Systolic blood pressure, mmHg	eGFR, ml/min/1.73 m ²	Urine ACR, mg/g	Male sex	Black race	History of CVD	Diabetes mellitus
AASK (USA)	622	135	286	38	4 (3)	56 (12)	135 (21)	25 (4)	130 (34, 488)	60%	100%	53%	1%
BC CKD (Canada)	9672	4717	3036	NA	5 (3)	71 (13)	137 (23)	24 (5)	225 (42, 1233)	55%	0.41%	16%	50%
CanPREDDICT (Canada)	1739	452	435	334	3 (2)	69 (13)	134 (20)	23 (5)	188 (37, 929)	62%	1.6%	38%	52%
CCF (USA)	9256	3000	1115	NA	2 (1)	73 (13)	130 (22)	24 (5)	51 (13, 346)	46%	17%	24%	30%
CRIB (UK)	315	133	185	NA	6 (3)	62 (14)	152 (23)	18 (7)	589 (118, 1345)	61%	5.1%	45%	17%
CRIC (USA)	1764	473	834	475	5 (3)	60 (11)	131 (24)	25 (4)	267 (48, 1066)	54%	45%	45%	60%
CRISIS (UK)	1717	710	461	NA	3 (3)	66 (14)	140 (22)	20 (6)	150 (55, 466)	62%	0.64%	48%	36%
GCKD (Germany)	504	34	33	34	2 (0)	64 (11)	140 (22)	26 (4)	130 (23, 877)	61%	0%	43%	44%
Geisinger (USA)	19293	10039	1802	6292	4 (4)	73 (14)	127 (22)	24 (5)	48 (15, 232)	41%	0.99%	56%	43%
GLOMMS2 (UK)	6384	3283	265	NA	3 (2)	79 (11)		25 (5)	44 (10, 189)	38%	<5%†	26%	12%
Gonryo (Japan)	729	57	354	48	2 (2)	67 (13)	135 (17)	19 (7)	666 (318, 1401)	59%	0%	27%	38%
Hong Kong CKD (China)	502	191	270	NA	6 (3)	61 (12)	138 (19)	17 (7)	60 (21, 150)	56%	0%	27%	46%
ICES-KDT (Canada)	79272	42006	9240	25993	4 (3)	76 (13)		25 (5)	53 (13, 360)	43%	<5%†	34%	48%
Maccabi (Israel)	12576	7531	1693	3480	4 (3)	76 (13)	135 (22)	25 (5)	70 (10, 301)	49%	0%	64%	46%
MASTERPLAN (Netherlands)	437	93	142	32	4 (1)	61 (12)	138 (22)	24 (5)	185 (53, 666)	69%	0%	32%	32%
MDRD (USA)	851	474	724	NA	14 (7)	51 (13)	134 (19)	22 (6)	335 (64, 1002)	60%	10%	17%	9%
Nanjing CKD (China)	1584	116	1003	108	4 (3)	47 (14)	141 (22)	21 (6)	1008 (550, 1839)	54%	0%	12%	21%
NephroTest (France)	740	213	372	NA	6 (4)	61 (14)	139 (22)	22 (6)	277 (69, 820)	67%	11%	24%	36%
NRHP-URU (Uruguay)	2090	658	512	385	3 (2)	72 (13)	135 (22)	21 (5)	83 (0, 655)	49%	0.14%	36%	32%
NZDCS (New Zealand)	1372	919	438	620	6 (3)	71 (12)	138 (21)	23 (6)	13 (2, 93)	43%	0.073%	47%	100%
PSP CKD (UK)	3522	1251	141	688	2 (1)	80 (12)	131 (19)	24 (5)	48 (18, 151)	43%	0.51%	47%	30%
PSPA (France)	573	437	294	NA	3 (2)	82 (5)	145 (22)	13 (4)	463 (174, 1015)	57%	0%	55%	39%
RCAV (USA)	78114	30012	4148	21672	3 (2)	69 (11)	125 (24)	24 (5)	38 (10, 220)	97%	21.6%	61%	58%
RENAAL (Multi*)	1078	234	327	400	3 (1)	60 (7)	151 (21)	26 (3)	1604 (690, 3133)	59%	12.5%	28%	100%
SCREAM (Sweden)	18486	12370	1132	7882	3 (2)	70 (12)		25 (5)	112 (27, 787)	45%	<5%†	54%	25%
SMART (Netherlands)	137	79	31	29	6 (4)	65 (11)	152 (25)	21 (8)	187 (47, 523)	70%	0%	52%	29%

SRR CKD (Sweden)	2555	778	770	932	3 (2)	69 (14)	142 (23)	21 (6)	211 (43, 953)	66%	<5%†	33%	38%
Sunnybrook (Canada)	1592	636	362	533	3 (2)	72 (14)	136 (22)	23 (6)	236 (62, 807)	54%	0%	17%	41%
West of Scotland CKD (UK)	6820	2954	1136	419	5 (3)	68 (13)	143 (24)	24 (6)	151 (34, 800)	49%	0.088%†	25%	21%
Total	264296	123985	31541	70394									

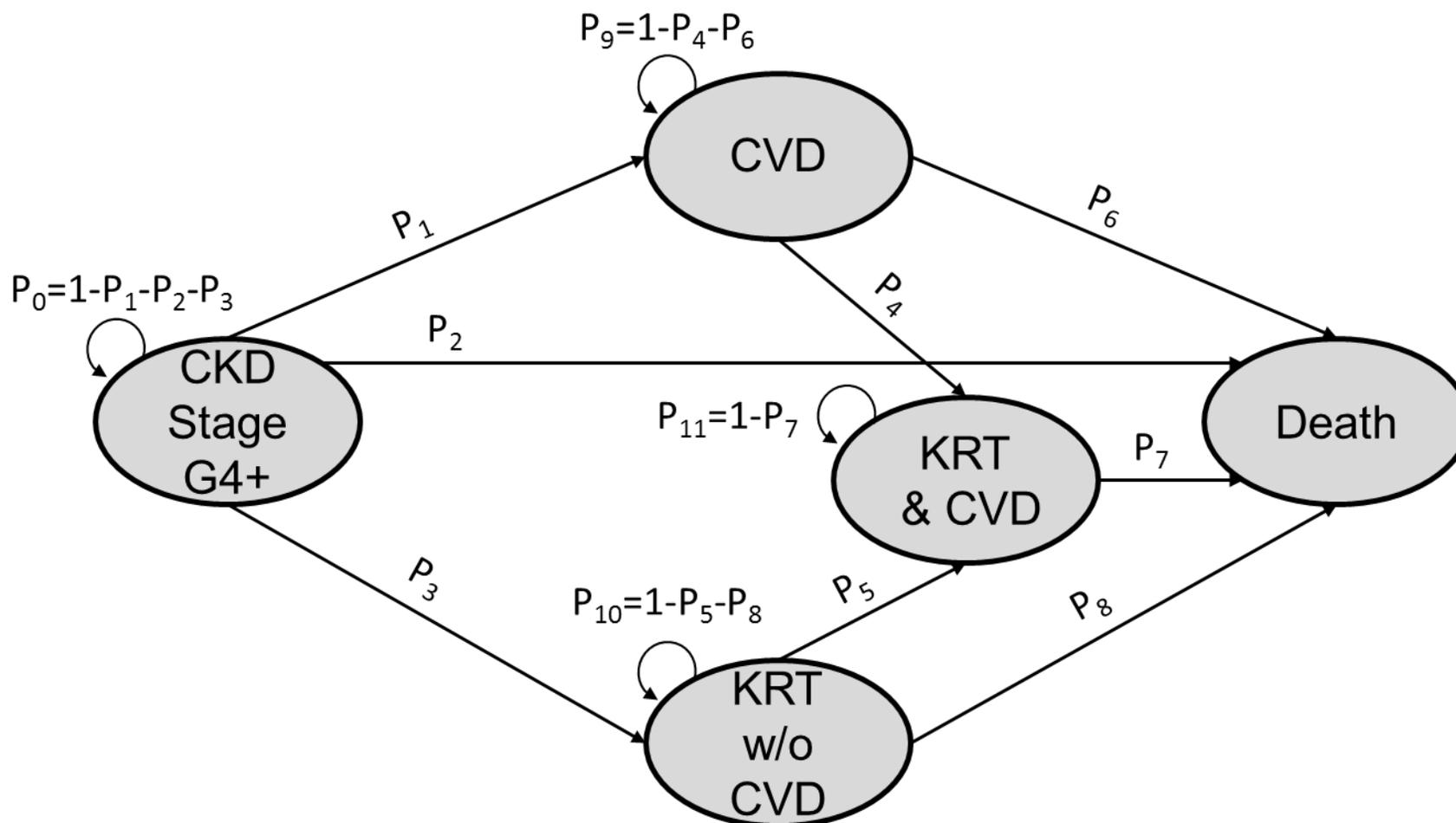
Blue color indicates administrative cohort (general population cohort from a clinical or health system database; covariates and outcomes generally from ICD codes); green color indicates referred CKD cohort (similar design to Administrative, but restricted to patients under the care of a nephrologist or in a CKD registry); red color indicates CKD research cohort (designed as a research study with planned study visits and active outcome ascertainment – patients may be similar to those in the referred CKD type).

*RENAAL contains participants from 28 countries; Argentina, Austria, Brazil, Canada, Chile, China, Costa Rica, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, New Zealand, Peru, Portugal, Russia, Singapore, Spain, Slovakia, United Kingdom, United States of America, Venezuela

†See analytic notes in Appendix 1 for the cohort in regards to the race variable.

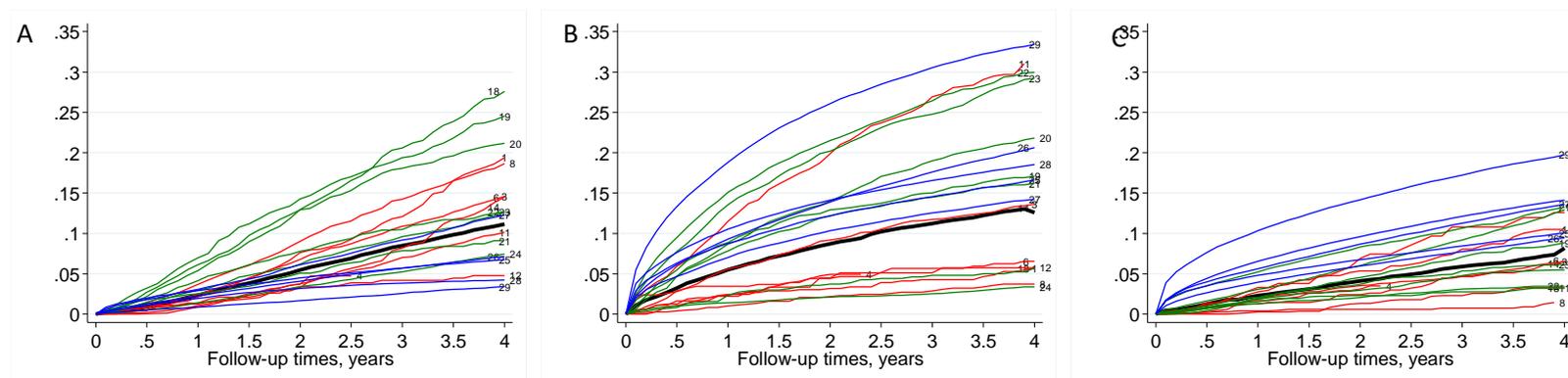
Abbreviations: N, number of participants; KRT, kidney replacement therapy; CVD, cardiovascular disease; yrs, years; eGFR, estimated glomerular filtration rate; ACR: urine albumin-to-creatinine ratio. Numbers represent mean (standard deviation) or median (1st quartile, 3rd quartile).

Figure 1. Diagram of states and transitions included in the 5-state Markov model



States are shown in gray ovals and include CKD Stage G4+, CVD, KRT without CVD, KRT & CVD, and death. The state transition probabilities are denoted by P_1 through P_8 , where P is a function of age, x , and time, where x is a vector of covariates. This vector includes baseline sex, race, history of cardiovascular disease, current smoking, systolic blood pressure, diabetes status, albuminuria (P_1 - P_4 and P_6), eGFR (baseline for P_1 - P_3 , time-updated for P_4 and P_6), and transplantation status (for P_5 , P_7 , and P_8). The probabilities of remaining in a state are denoted by P_0 , and P_9 - P_{11} .

Figure 2. Adjusted* cumulative incidence of (A) kidney failure requiring kidney replacement therapy, (B) cardiovascular event, and (C) death as first event from Markov model. Color coding of the lines is described in panel D. The black bold line indicates the equal weighted mean.



D

CKD Research Cohort	AASK	CRIB	CRIC	GCKD	Hong Kong-CKD	MASTERPLAN	MDRD	Nanjing-CKD	NephroTest	PSPA	RENAAL	SMART
	1	2	3	4	5	6	7	8	9	10	11	12
Referred CKD	BC2016	CanPREDDICT	CCF	CRISIS	GLOMMS2	Gonryo	NRHP-URU	NZDCS	PSP-CKD	SRR-CKD	Sunnybrook	WestScot-CKD
	13	14	15	16	17	18	19	20	21	22	23	24
Administrative Cohorts	Geisinger			ICES-KDT			Maccabi		RCAV		SCREAM	
	25			26			27		28		29	

*Adjusted to age 60 years, half male, non-black, half history of CVD, half smoker, systolic blood pressure 140 mmHg, half diabetes, eGFR 25 ml/min/1.73 m² and urine ACR 100 mg/g. Grey shaded cohorts in panel D do not have cardiovascular events and are not included in panels A-C.

Figure 3. The probability and timing of adverse events at 2 and 4 years with increasing level of albuminuria. Top panel shows 2 years and urine ACR 30 mg/g, bottom panel shows 4 years and urine ACR 1000 mg/g. In these models, the scenario was set at age 60 years, male, white, with a history of cardiovascular disease, not a current smoker, systolic blood pressure of 140 mmHg, no diabetes, and an eGFR of 25 ml/min/1.73m².

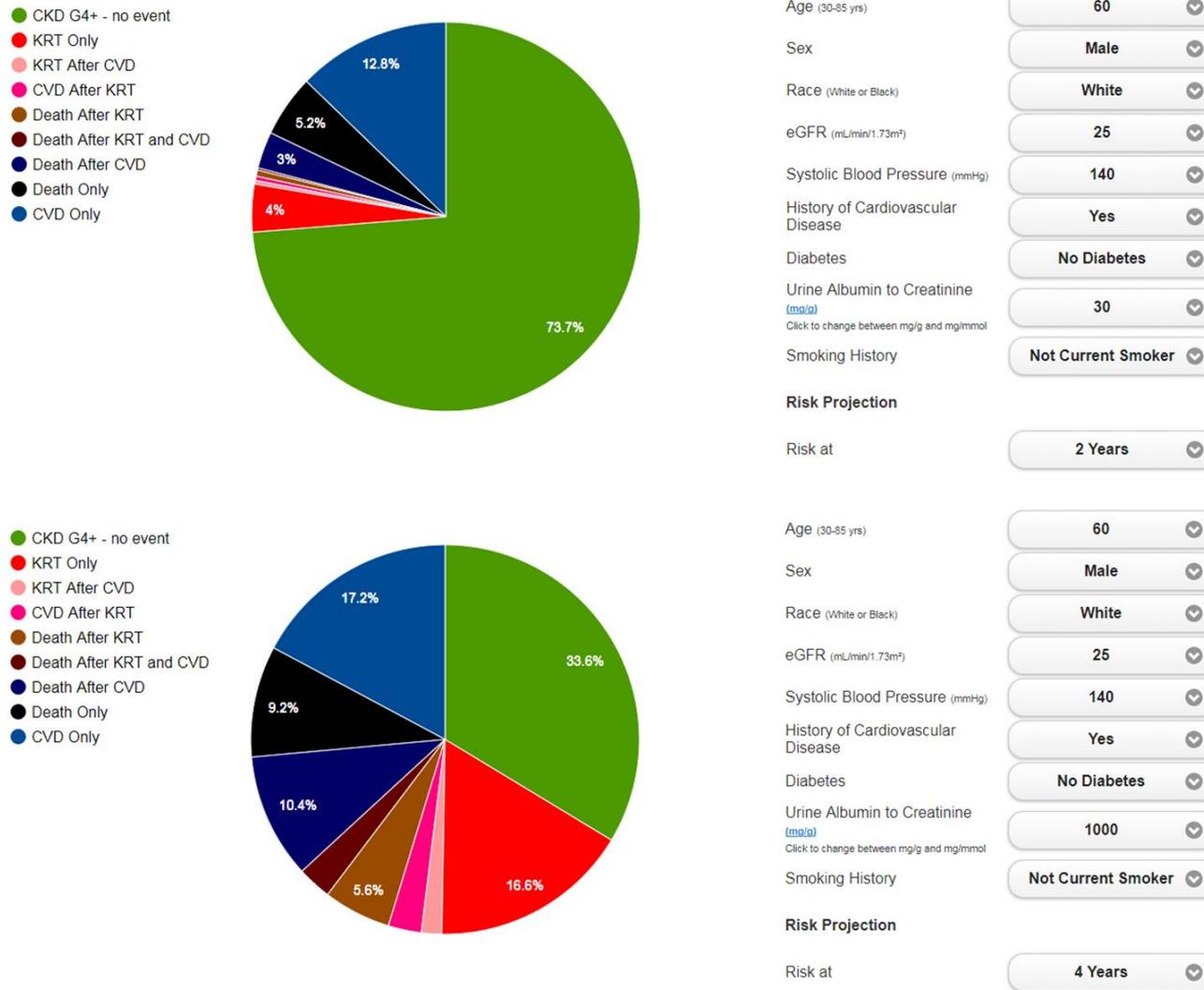
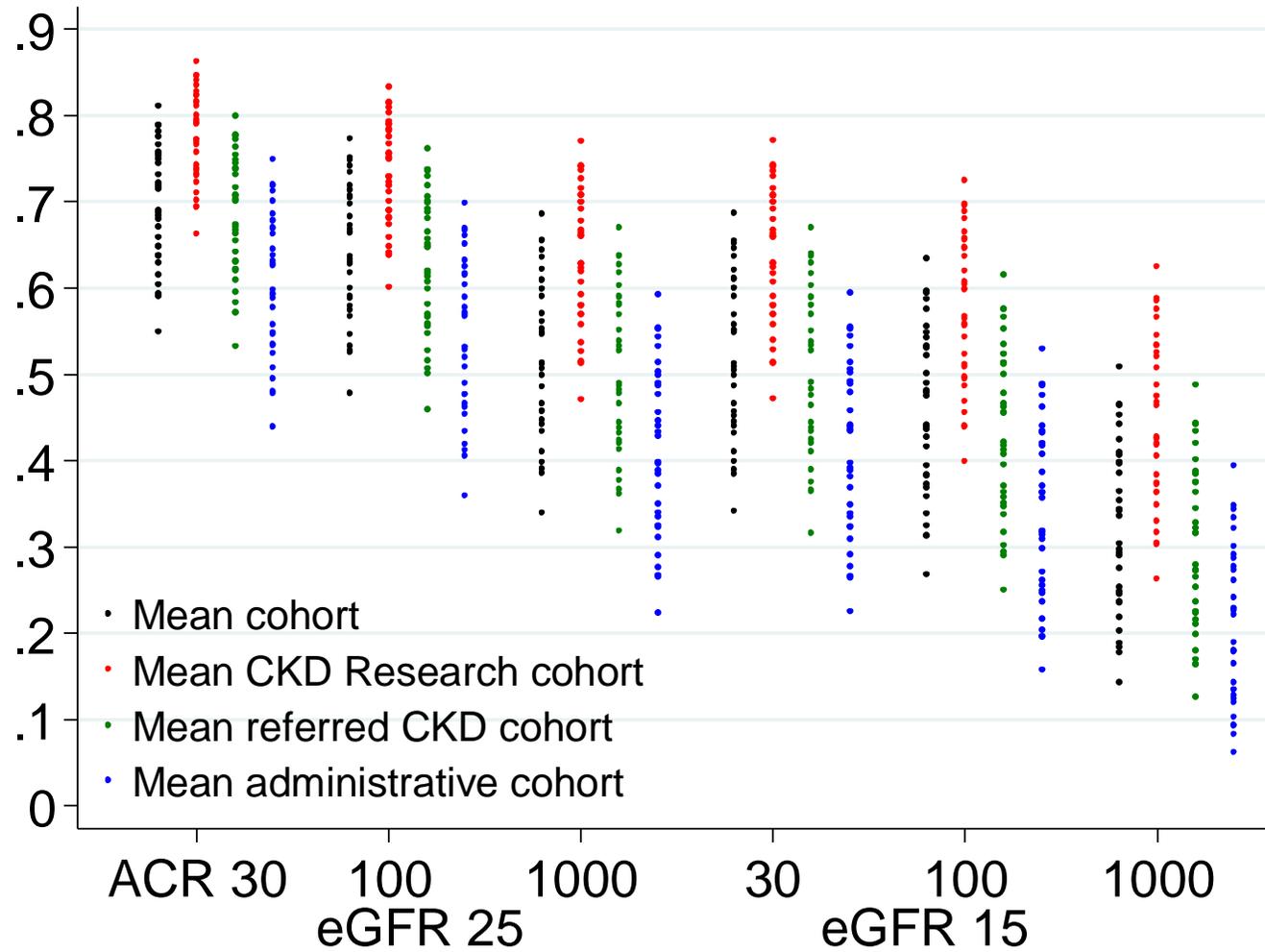


Figure 4. Markov model predicted 2-year survival without kidney failure treated with kidney replacement therapy or cardiovascular events for a range of scenarios (varying systolic blood pressure, race, diabetes, history of cardiovascular disease, and smoking status) for a 60-year old man, comparing estimates using overall mean with cohort type-specific means for the baseline hazards and sub-hazards.



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