

Investigating the Relationship Between Age and Kidney Failure in Adults With Category 4 Chronic Kidney Disease

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Huda Al-Wahsh¹ , Ngan N. Lam¹ , Ping Liu¹,
Robert R. Quinn¹, Marta Fiocco², Brenda Hemmelgarn³,
Navdeep Tangri⁴, Marcello Tonelli¹, and Pietro Ravani¹ 

Abstract

Background: In people with severe chronic kidney disease (CKD), there is an inverse relationship between age and kidney failure. If this relationship is the same at any age (linear), one effect (hazard ratio) will be sufficient for accurate risk prediction; if it is nonlinear, the effect will vary with age.

Objective: To investigate the relationship between age and kidney failure in adults with category G4 chronic kidney disease (G4 CKD).

Methods: We performed a population-based study using linked administrative databases in Alberta, Canada, to study adults with G4 CKD (estimated glomerular filtration rate [eGFR] = 15–30 mL/min/1.73 m²) and without previously documented eGFR < 15 mL/min/1.73 m² or renal replacement. We used cause-specific Cox regression to model the relationship between age and the hazard of kidney failure (the earlier of eGFR < 10 mL/min/1.73 m² or receipt of renal replacement) and death, incorporating spline terms to capture any nonlinear effect of age. We included sex, diabetes mellitus, cardiovascular disease, albuminuria, and eGFR in all models.

Results: Of the 27 823 participants (97 731 patient-years at risk; mean age = 76 years, ± 13), 19% developed kidney failure and 51% died. The decline in the hazard of kidney failure associated with a given increase in age was not constant but became progressively larger as people aged; that is, the hazard ratio became progressively smaller (closer to 0). Assuming an eGFR of 25 mL/min/1.73 m², for every 10-year increase in age, the hazard ratio declined from 0.76 (95% confidence interval = 0.73–0.79) at age 50 years to 0.43 (95% confidence interval = 0.34–0.56) at age 80 years in people without cardiovascular disease, and from 0.75 (95% confidence interval = 0.70–0.79) at age 50 years to 0.36 (95% confidence interval = 0.29–0.45) at age 80 years in people with cardiovascular disease.

Conclusions: The relationship between kidney failure and age varies with age. An age-dependent effect, rather than a constant effect, needs to be specified to accurately predict risk. These findings have implications for risk prediction and advanced care planning.

Abrégé

Contexte: Chez les personnes atteintes d'une forme grave d'insuffisance rénale chronique (IRC), on observe une corrélation inverse entre l'âge et le risque de néphropathie. Si la relation est linéaire (la même à tout âge), un seul effet (risque relatif) suffira pour prédire le risque de façon précise; si elle est non linéaire, l'effet variera avec l'âge.

Objectif: Examiner la relation entre l'âge et l'insuffisance rénale terminale chez les adultes atteints d'insuffisance rénale chronique de catégorie G4 (IRC G4).

Méthodologie: Nous avons procédé à une étude populationnelle à l'aide des bases de données couplées de l'Alberta (Canada). Nous avons inclus les adultes atteints d'IRC G4 (débit de filtration glomérulaire estimé [DFGe] entre 15 et 30 ml/min/1,73 m²) sans antécédents documentés de DFGe inférieur à 15 ml/min/1,73 m² ou de thérapie de remplacement rénal. Une régression de Cox par cause spécifique a servi à modéliser la relation entre l'âge et le risque d'insuffisance rénale terminale (la première situation survenant entre un DFGe inférieur à 10 ml/min/1,73 m² ou un remplacement rénal) et le décès. Les fonctions splines ont été incorporées pour capter tout effet non linéaire lié à l'âge. Nous avons inclus le diabète, les maladies cardiovasculaires, l'albuminurie, le DFGe et le sexe du patient dans tous les modèles.

Résultats: Des 27 823 patients inclus à l'étude (âge médian 76 ans ± 13 ans; total de 97 731 années-patients à risque), 19% ont évolué vers l'insuffisance rénale terminale et 51% sont décédés. Le déclin du risque d'insuffisance rénale associé à une hausse donnée de l'âge n'était pas constant, mais devenait progressivement plus important à mesure que le patient avançait



en âge; en ce sens que le risque relatif était devenu progressivement plus faible (se rapprochait de zéro). Pour chaque tranche de 10 ans d'âge, en supposant un DFGe de 25 ml/min/1,73 m², le risque relatif est passé de 0,76 à l'âge de 50 ans (intervalle de confiance à 95 %: 0,73-0,79) à 0,43 à 80 ans (IC 95 %: 34-56) pour les personnes sans maladies cardiovasculaires, et de 0,75 à l'âge de 50 ans (IC 95 %: 0,70-0,79) à 0,36 à l'âge de 80 ans (IC 95 %: 0,29-0,45) chez les personnes atteintes de maladies cardiovasculaires.

Conclusion: La relation entre l'âge et le risque d'insuffisance rénale terminale varie selon l'âge du patient. Un effet dépendant de l'âge, plutôt qu'un effet constant, doit être défini pour prédire le risque plus précisément. Ces résultats ont des implications pour la prévision des risques et la planification de soins avancés.

Keywords

chronic kidney disease, kidney failure, hazard, competing risks

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What was known before

In people with severe chronic kidney disease, there is an inverse relationship between age and kidney failure. This relationship is usually characterized as linear, implying the hazard ratio associated with a change in age is the same at any age.

What this adds

Older adults with category 4 chronic kidney disease (G4 CKD) are progressively less likely to develop kidney failure with every passing year and more likely to die. These findings could be used to improve prognostic tools and assist people with severe, nondialysis-dependent CKD to make treatment decisions aligned with their views and preferences.

Introduction

Chronic kidney disease (CKD), defined as estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m², affects 10%-16% of the general population and is associated with increased risk of adverse health outcomes.^{1,2} CKD is classified into categories of increasing severity, primarily on the basis of eGFR.¹ All CKD categories are more common with advancing age, especially G4 CKD (eGFR = 15-30 mL/min per 1.73 m²),³⁻⁵ which affects 0.1% of people below 65 and 9% of those ≥85 years.⁶ In a population-based study, 75% of people newly diagnosed with G4 CKD are 70 years of age or

older.⁷ Although the risk of kidney failure is much smaller than the risk of death in this elderly population,⁷ existing guidelines place considerable emphasis on preparing all people with G4 CKD for renal replacement.^{1,2}

With increasing age, kidney function declines more slowly,⁸ and the rates of kidney failure and death among adults with comparable eGFRs vary considerably by age.⁹ In one study, kidney failure became progressively less common and death became progressively more common with advancing age, regardless of CKD severity.⁹ A more recent analysis based on data from the Chronic Kidney Disease Prognosis Consortium (CKD-PC) suggested that the hazard of kidney failure declined by approximately 20% for every 10-year increase in age.¹⁰⁻¹² Based on existing literature, prediction tools calculate the risk of kidney failure for a person assuming a constant change in the hazard of kidney failure for a given change in age,¹⁰⁻¹² which implies a linear relationship. However, such relationship may be nonlinear, and the hazard decline associated with the same increase in age may become smaller or larger as people age (Figure 1). Characterizing the true relationship between age and kidney failure, considering both its direction and shape, is important because age is a key risk predictor, and assuming a constant effect of age when in fact such effect varies by age will result in inaccurate predictions.

We designed a population-based study to investigate whether the relationship between age and kidney failure is the same at any age or varies across the age range in adults with G4 CKD. We also assessed whether the relationship

¹Departments of Medicine and Community Health Sciences, Cumming School of Medicine, University of Calgary, AB, Canada

²Department of Medical Statistics and Bioinformatics, Mathematical Institute, Leiden University, Leiden, The Netherlands

³Department of Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada

⁴Department of Internal Medicine, University of Manitoba, Winnipeg, Canada

Corresponding Author:

Pietro Ravani, Departments of Medicine and Community Health Sciences, Cumming School of Medicine, University of Calgary, 3230 Hospital Dr. NW, Calgary, AB, Canada T2N 4Z6.

Email: pravani@ucalgary.ca

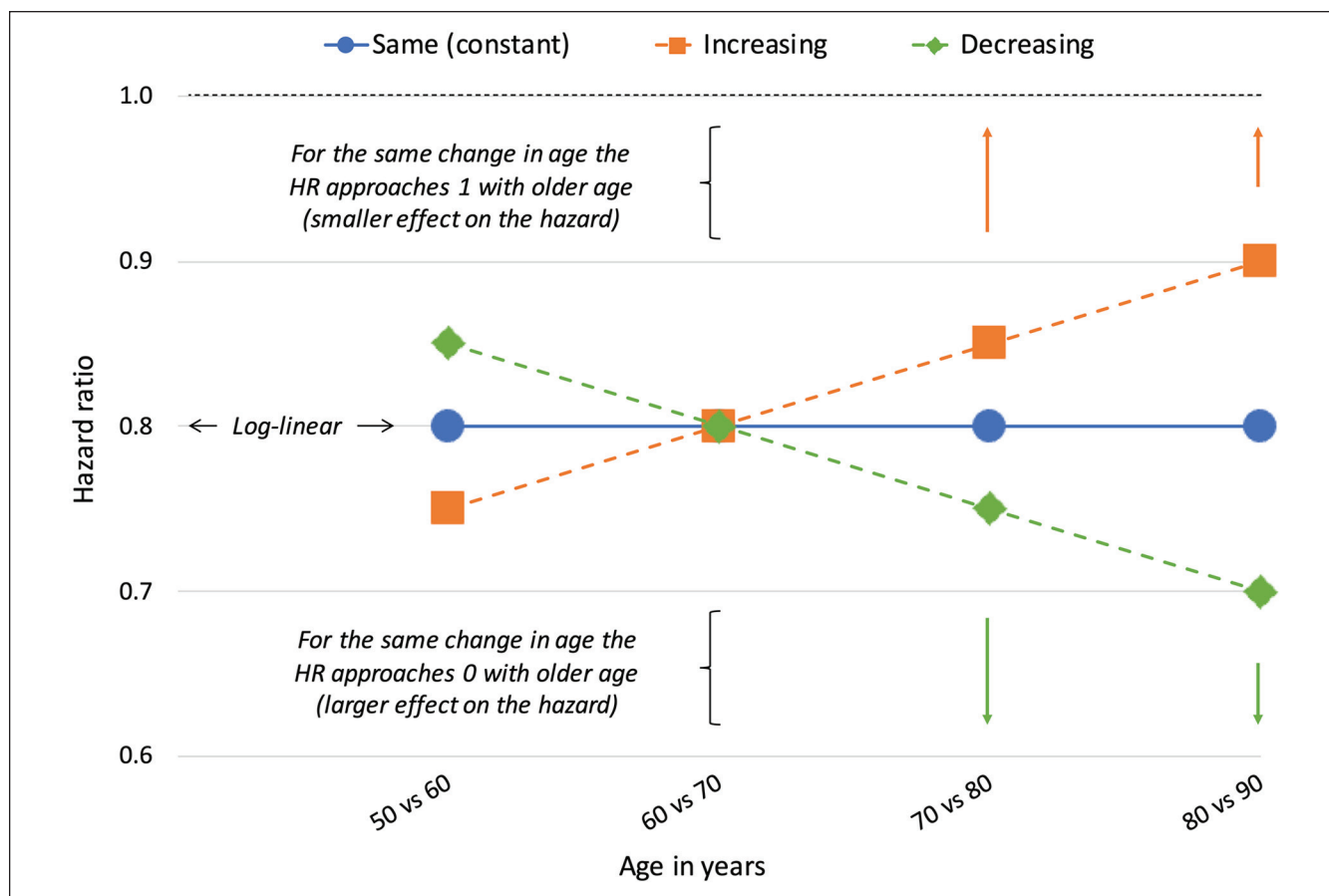


Figure 1. Direction and shape of the relationships between age and kidney failure.

Note. All hazard ratios in the plot are below 1 (value of no effect—dotted line), indicating that the relationship between age and kidney failure is inverse. Knowing the direction (in which direction the outcome kidney failure changes as the predictor age changes) does not inform about the shape of the relationship, that is, whether the relationship is the same or varies across the age range. A constant hazard ratio or effect of age at any age implies a log-linear relationship between age and kidney failure (blue line). A decreasing hazard ratio with older age means that the effect of age on the hazard becomes larger with older age (green line). An increasing hazard ratio with older age implies that the effect of age on the hazard becomes smaller with older age (orange line).

between age and the competing risk of death varies with advancing age in this patient population.¹³

Materials and Methods

Study Design and Data Sources

In this population-based study, we linked administrative and laboratory data from the province of Alberta, Canada, using the Alberta Kidney Disease Network, which incorporates data from Alberta Health, the provincial health ministry (see “Methods” section in Online Appendix). More than 99% of Alberta residents (pop 4.4 million) are registered with Alberta Health and have universal access to hospital care, laboratory testing, and physician services. The institutional review boards at the Universities of Alberta (Pro00053469) and Calgary (REB16-1575) approved this study with a waiver of participant consent. We followed recommended reporting standards (RECORD checklist).¹⁴

Cohort

We used the CKD-EPI equation to calculate eGFR, with serum creatinine values standardized to isotope dilution mass spectrometry traceable methods.¹⁵ We assumed that all participants were white as data on race were not available. The consequences of race misclassification on eGFR estimation are expected to be minimal as only ~3% of Albertans are black. We included all Alberta residents aged ≥ 18 years with newly identified G4 CKD (eGFR = 15–30 mL/min/1.73 m²) between July 30, 2002, and March 31, 2014. To maximize the inclusion of incident cases and minimize the inclusion of people with unstable clinical conditions, we defined G4 CKD using a *moving average eGFR method* and considering only outpatient laboratory measures (see “Methods” section in Online Appendix).¹⁶ We used the date of the last eGFR measurement included in the calculation of the average (index eGFR) to define cohort entry (index date). We excluded people with previous receipt of renal replacement

or with an eGFR <15 mL/min/1.73 m² before the episode qualifying for study entry and those with missing information on albuminuria.

Follow-up

We followed participants from study entry until the earliest of emigration from the province, end of study (March 31, 2017), 10 years following cohort entry, or outcome of interest (kidney failure, death). To minimize bias in outcome ascertainment, we censored observations at 1.5 years from an eGFR measurement, if there was no subsequent measurement within 1.5 years of this eGFR.

Exposure

We assessed the relationship between age and the hazard ratio (HR) of kidney failure and death (ie, the change in magnitude of the hazard as age increases) considering categories of age in crude analyses (<65 , 65-74, 75-84, and ≥ 85 years)⁷ and age as a continuous variable in model-based analyses.

Independent Variables

We considered the following baseline covariates as potential confounders or modifiers: sex, index eGFR, albuminuria, diabetes mellitus, and cardiovascular disease. The latter was defined as one or more of congestive heart failure, myocardial infarction, stroke or transient ischemic attack, or peripheral vascular disease (amputation or peripheral revascularization). We used validated coding algorithms applied to physician claims and hospitalization data to define comorbidities based on *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* and *International Statistical Classification of Diseases, Tenth Revision (ICD-10)*; eTable 1).¹⁷ We used the most recent albuminuria values (on or within the 2 years preceding the index date), with the following types of measurement in descending order of preference: albumin-to-creatinine ratio, protein-to-creatinine ratio, and urine dipstick. We categorized albuminuria as normal, moderate, or severe with the following types of measurement in descending order of preference: albumin-to-creatinine ratio (<3 ; 3-30; >30 mg/mmol), protein-to-creatinine ratio (<15 ; 15-50; >50 mg/mmol), and urine dipstick (negative or trace; 1+; $\geq 2+$).¹⁸

Outcomes

We treated kidney failure as primary outcome and death without kidney failure as a competing event. We defined kidney failure as the earliest of initiation of renal replacement (dialysis or kidney transplantation) or an eGFR <10 mL/min/1.73 m². We defined dialysis initiation based on at least one inpatient or outpatient physician claim. The receipt of a kidney transplant was based on at least one physician claim

or hospitalization (eTable 2). For the eGFR criterion, we applied the *moving average method* to minimize the influence of a single or a few measurements above the threshold,¹⁶ with a threshold of <10 mL/min/1.73 m² and using the date of the last eGFR measured during the assessment period to define the event date (see “Methods” section in Online Appendix). We chose this threshold because most people start renal replacement or receive conservative care when eGFR <10 mL/min/1.73 m². In addition, this threshold allows for separation of the lowest value defining cohort entry and the value defining the outcome. We considered other definitions of kidney failure in sensitivity analyses. First, we defined kidney failure as initiation of renal replacement or occurrence of sustained eGFR <10 mL/min/1.73 m². We defined sustained eGFR <10 mL/min/1.73 m² by the occurrence of ≥ 2 consecutive eGFR values <10 mL/min/1.73 m² over a period of >90 days. We used the date of the last eGFR in the first episode of *sustained eGFR measurements* <10 mL/min/1.73 m² as the event date. Second, we defined kidney failure solely by initiation of renal replacement, defined as receipt of a kidney transplant or registration in the provincial database of chronic dialysis. Finally, we defined kidney failure as initiation of renal replacement or moving average eGFR <15 mL/min/1.73 m².

Statistical Analysis

We used standard methods for qualitative (frequencies) and quantitative data (mean/standard deviation) to summarize baseline information and competing risk analysis to estimate risks. We used semi-parametric regression to model cause-specific hazard functions and estimate the HRs of each event associated with 10-year increase in age.¹⁹ We used subdistribution hazard regression to estimate the relationship between age and the cumulative incidence function for each event.²⁰ We removed the linear restriction on the log HR and the sub-HR by transforming age into a vector of fixed knot basis splines. This approach captures any kind of association between continuous exposure (age) and outcome (log hazard), including linear, quadratic, cubic functions, and their possible combinations. The motivation for using cause-specific and subdistribution hazard models in the presence of competing risks is described in the Online Appendix (see “Methods” section), along with the methods and packages we used for model building and checking.

Results

Cohort Description

We identified 27 823 adults who met the criteria for G4 CKD during the accrual period (eFigure 1). Participants were on average 76 years old (± 13), 45% were men and 47% had diabetes (Table 1). People excluded for incomplete data on albuminuria were 5 years older on average (81 vs 76) and

Table 1. Baseline Characteristics.

Characteristics	All (N = 27823)	Age <65 (n = 4837)	Age 65-74 (n = 5410)	Age 75-84 (n = 9990)	Age ≥ 85 (n = 7586)
Age, in years, mean (SD)	76.32 (13.4)	53.45 (10.2)	70.62 (2.9)	80.26 (2.8)	89.77 (3.6)
Men, No. (%)	12394 (44.5)	2640 (54.6)	2755 (50.9)	4474 (44.8)	2525 (33.3)
eGFR, in mL/min/1.73 m ² , mean (SD)	26.31 (3.4)	25.59 (3.8)	26.37 (3.4)	26.55 (3.2)	26.39 (3.2)
Albuminuria (normal), No. (%)	13318 (47.9)	1093 (22.6)	2190 (40.5)	5278 (52.8)	4757 (62.7)
Albuminuria (moderate), No. (%)	7091 (25.5)	1026 (21.2)	1464 (27.1)	2736 (27.4)	1865 (24.6)
Albuminuria (severe), No. (%)	7414 (26.6)	2718 (56.2)	1756 (32.5)	1976 (19.8)	964 (12.7)
Diabetes, No. (%)	13056 (46.9)	2654 (54.9)	3241 (59.9)	4693 (47.0)	2468 (32.5)
Cardiovascular disease, No. (%)	16048 (57.7)	1701 (35.2)	2933 (54.2)	6196 (62.0)	5218 (68.8)
Myocardial infarction, No. (%)	3299 (11.9)	340 (7)	632 (11.7)	1351 (13.5)	976 (12.9)
Congestive heart failure, No. (%)	11463 (41.2)	1051 (21.7)	2014 (37.2)	4413 (44.2)	3985 (52.5)
Stroke or transient ischemic attack, No. (%)	7050 (25.3)	689 (14.2)	1205 (22.3)	2728 (27.3)	2428 (32)
Peripheral vascular disease, No. (%)	2063 (7.4)	239 (4.9)	499 (9.2)	829 (8.3)	496 (6.5)

fewer were diabetics (30% vs 47%). In the study cohort, mean eGFR at baseline was similar across age categories, ranging from 25.6 (\pm 3.8) mL/min/1.73 m² in people aged <65 to 26.4 (\pm 3.2) mL/min in people aged \geq 85 years (eFigure 2). In older age categories, there were fewer men, fewer people with diabetes or severe albuminuria, and more people with cardiovascular disease or normal albuminuria (eFigure 3).

Cumulative Incidence Functions

During follow-up (97731 patient-years at risk), 5181 participants developed kidney failure (4477 received renal replacement) and 14247 died without kidney failure. In 99% of the participants, the time interval between the first and the last eGFR <10 mL/min/1.73 m² defining kidney failure was <1 year and all participants had an interval <2 years. Of the 7327 participants who were censored in this study, 2498 were censored at 1.5 years from the last available eGFR record. The 5-year probability of censoring for the absence of eGFR records increased with advancing age from 5.4% in people aged <65 years to 6.5%, 8.1%, and 9.5% in age groups 65 to 74, 75 to 84 and \geq 85 years, respectively. The risk of kidney failure decreased with advancing age, and the risk of death increased. Except for people aged <65 years, the risk of kidney failure was smaller than the risk of death by progressively larger amount with increasing age (Figure 2). The presence of cardiovascular disease and higher eGFR were associated with a lower risk of kidney failure (eFigures 4 and 5).

Relationship Between Age and the HR of Kidney Failure

The best model performance was achieved by specifying spline functions of age with knots at 60, 75, and 90 years and their interactions with cardiovascular disease and baseline eGFR (eTable 3; Akaike information criterion = 90369 vs 90611 of a linear model, likelihood ratio test $P < .01$).

According to this model, the hazard of kidney failure associated with older age declined in a nonlinear fashion across the age range. At an eGFR of 25 mL/min/1.73 m², the HR of kidney failure associated with a 10-year increase in age decreased from 0.76 (95% confidence interval = 0.73-0.79) at age 50 years to 0.43 (95% confidence interval = 0.34-0.56) at age 80 years in people without cardiovascular disease, and from 0.75 (95% confidence interval = 0.70-0.79) to 0.36 (95% confidence interval = 0.29-0.45) in people with cardiovascular disease (Figure 3). Except for people with eGFR as low as 15 mL/min/1.73 m², the HR of kidney failure for a 10-year increase in age decreased with advancing age, especially in the presence of cardiovascular disease and with higher eGFR (Figure 4). With eGFR between 25 and 30 mL/min/1.73 m², the HR decline associated with older age became steeper earlier in life.

Relationship Between Age and the HR of Death

The increase in the HR of death associated with each 10-year increment in age was more pronounced in people without cardiovascular disease who had lower underlying risk of death (eFigure 5). The hazard of death increased in a nonlinear fashion with advancing age and varied by levels of eGFR and presence versus absence of cardiovascular disease (eFigure 6). eFigures 7 and 8 show the superior performance of the spline model, which assumes varying HRs with advancing age, as compared with the linear model, which assumes constant HRs as age varies.

Other Analyses

When we modeled the relationship between age and kidney failure or death using regression model of Fine and Gray, we found similar results (eFigure 9). These models included additional interaction terms to satisfy the proportionality assumption on the subhazard scale (eTable 4). We obtained

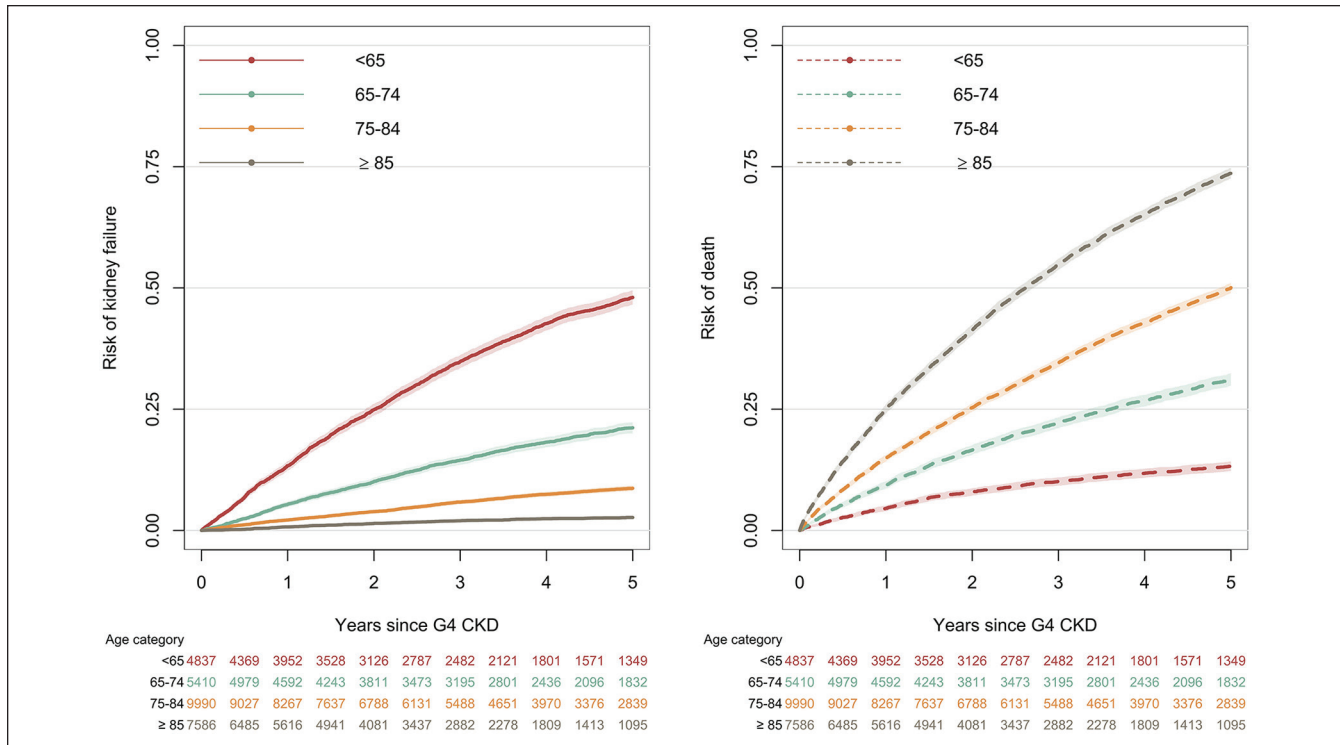


Figure 2. Cause-specific cumulative incidence functions by age.

Note. Unadjusted cumulative incidence functions of kidney failure (left; solid line) and death (right; dashed line) across age category in years (shaded areas represent the 95% confidence interval for the fitted curves). CKD = chronic kidney disease.

similar results when we defined kidney failure as initiation of renal replacement or occurrence of sustained $eGFR < 10 \text{ mL/min/1.73 m}^2$ (eFigure 10), receipt of a kidney transplant or registration in the provincial database of chronic dialysis (eFigure 11), or initiation of renal replacement or occurrence of moving average $eGFR < 15 \text{ mL/min/1.73 m}^2$ (eFigure 12). Although the form of the relationship between age and kidney failure remained nonlinear when kidney failure was defined as start of renal replacement, the decline in the hazard with older age was more pronounced. For example, when kidney failure was defined as initiation of renal replacement or $eGFR < 10$, the HR for an 85-year-old versus a 75-year-old was 0.5 and 0.7 in the presence and absence of cardiovascular disease, respectively, assuming an $eGFR$ of $20 \text{ mL/min/1.73 m}^2$. Corresponding HRs for renal replacement were 0.3 and 0.4, respectively. Model assumptions were met in all models (eFigures 13-16).

Discussion

In this population-based study, we found that in people with G4 CKD, the relationship between age and kidney failure was not constant but varied depending on age. While the direction of the relationship we found is consistent with existing studies, that is, there is an inverse association between age and kidney failure, our data do not support the linear relationship existing studies assume. The magnitude of

the decline in the hazard of kidney failure for a given increment in age was larger with advancing age, regardless of other clinical characteristics. Similarly, the relationship between age and death was nonlinear as people aged. The magnitude of the increase in the hazard of death for a given increment in age was larger with advancing age. We also found that levels of $eGFR$ and history of cardiovascular disease modify these relationships. At higher $eGFR$ or in the presence of cardiovascular disease, age-dependent changes in the HR were larger than at lower $eGFR$ levels or in the absence of cardiovascular disease. These findings have implications for accurate risk prediction given the large representation of older adults with severe CKD.

Recent studies have suggested that the inverse association between age and kidney failure is partly explained by the competing risk for death.^{4,10} Consistent with this interpretation, we found that the inverse relationship was more pronounced according to the Fine and Gray model as compared with the cause-specific Cox model. This happens because the associations of age with kidney failure and death have opposite direction, and the subdistribution HRs (as opposed to the HRs) have direct interpretation in terms of cumulative incidence function (see “Methods” section in Online Appendix).²¹ For example, at an $eGFR$ of $25 \text{ mL/min/1.73 m}^2$, the HRs associated with 10-year increase in age ranged from 0.75 to 0.35 in cause-specific Cox regression and from 0.70 to 0.20 in Fine and Gray regression. Yet, we found the same pattern

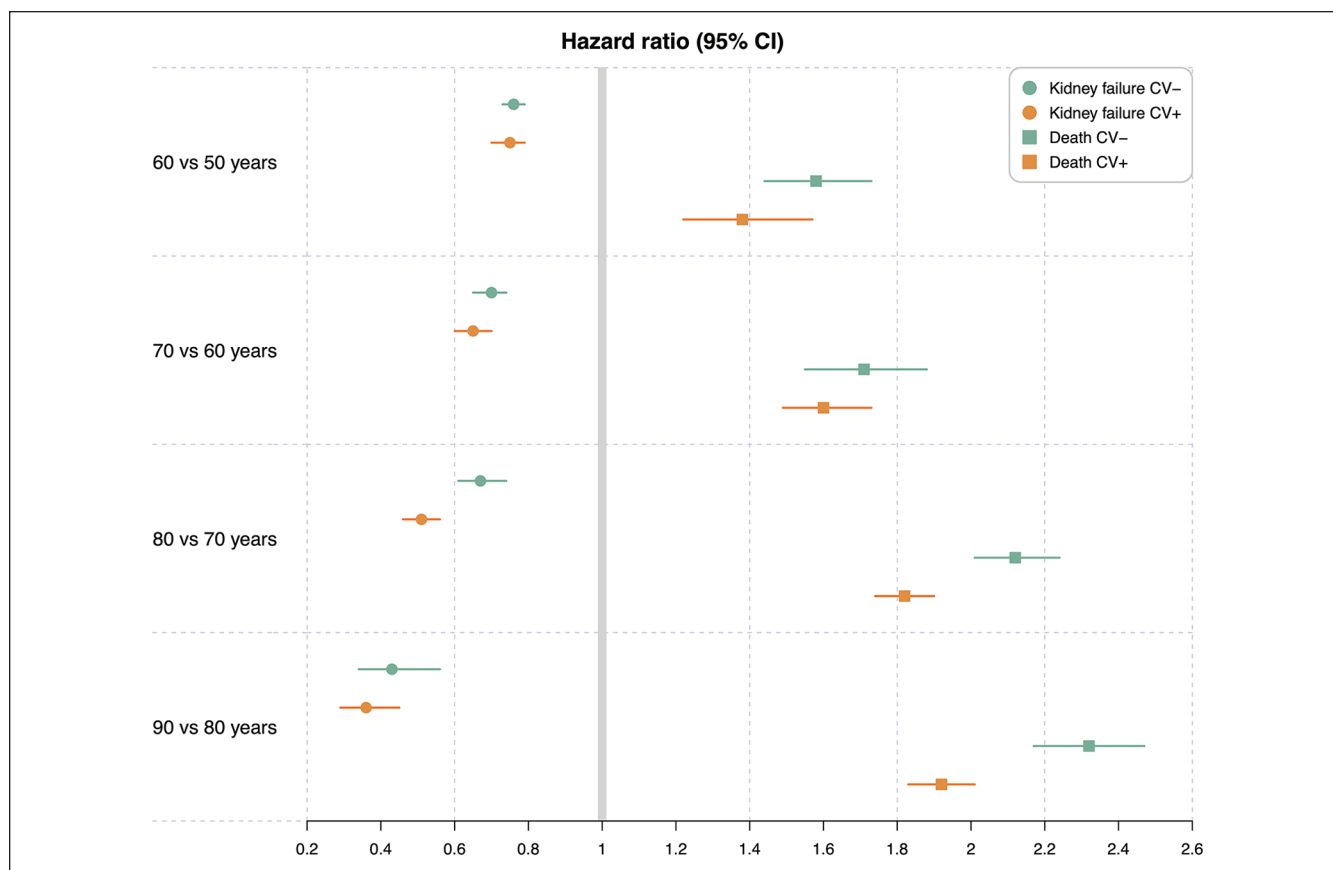


Figure 3. Association between older age and outcomes at 4 prespecified ages.

Note. Adjusted hazard ratios of kidney failure and death (eTable 3) associated with 10-year increment at ages 50, 60, 70, and 80 years, by the presence and absence of cardiovascular disease assuming an estimated glomerular filtration rate of 25 mL/min/1.73 m². 95% CI indicates 95% confidence interval; CV+/CV- indicates with/without cardiovascular disease.

of association or shape of the relationship between age and kidney failure on both the hazard and subhazard scales. These findings are consistent with studies in CKD populations showing that eGFR declines more slowly with older age independent of other risk factors.^{8,21} The mechanisms underlying this phenomenon and its prognostic significance are still a matter of debate, and some argue that eGFR decline in the elderly is a part of the normal aging process as opposed to a disease condition.²² Larger effects of age on the hazard of kidney failure in the presence of higher eGFR and cardiovascular disease are consistent with this interpretation.

Previous large studies modeled the association between age and kidney failure using age as a categorical rather than continuous variable, which masks important details about the shape of the relationship^{4,5,9} or assumed a linear relationship.¹⁰⁻¹² Our approach is novel as it expands on the relationship between age and kidney failure across the whole age range and other important factors, including levels of kidney function and comorbidity. We excluded people with category 5 CKD (eGFR <15 mL/min/1.73 m²) who were included in previous studies, although they already have kidney failure by definition in the guidelines¹⁰⁻¹² and defined kidney failure

based on the receipt of renal replacement therapy and eGFR criteria. As a result, findings from our study may be less sensitive to subjective decisions about treatments, an important consideration given that many older people opt for conservative kidney care.

Our findings have implications for clinical practice. Older adults with G4 CKD are progressively less likely to develop kidney failure with every passing year, especially if they have higher levels of eGFR and cardiovascular disease. They are also less likely to start renal replacement, if they develop kidney failure. Considering that mortality increases in parallel with age, this information is important for disease management and advanced care planning. Our study has also implications for research, including the development of risk calculators and decision aids. The performance of risk calculators may be improved by considering a more accurate relationship between age and kidney failure, and the effect modification of baseline eGFR and comorbidity.

Our study has other strengths, including the use of population-based data from Alberta, a province in Canada served by a universal health care system; a relatively large sample size with adequate follow-up; the use of validated algorithms to

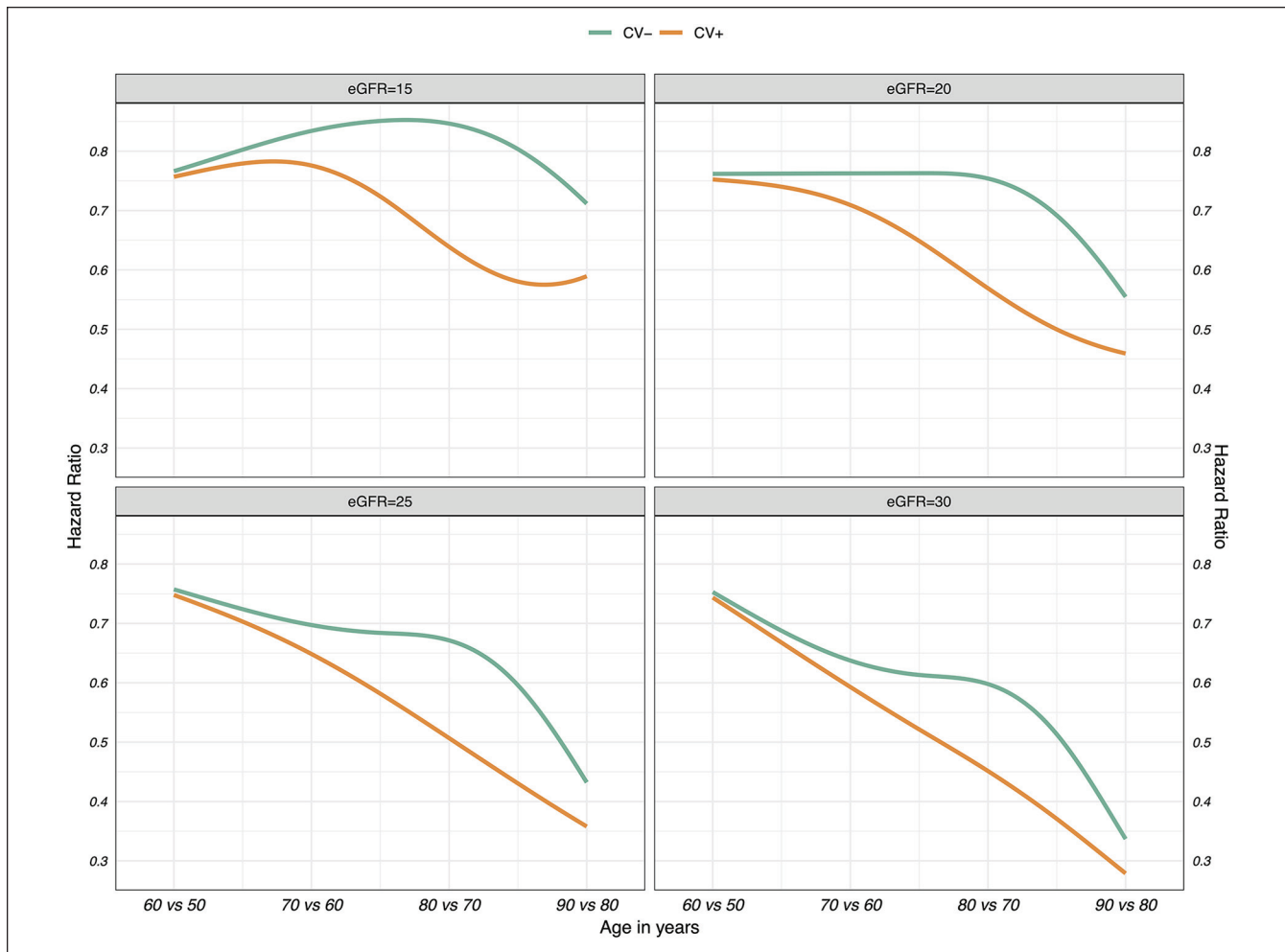


Figure 4. Association between older age and kidney failure across the age range.

Note. Adjusted hazard ratios of kidney failure associated with 10-year age increment across continuous age values (eTable 3). Curves are estimated at prespecified eGFR (eGFR in mL/min/1.73 m²). CV+/CV- indicates with/without cardiovascular disease. eGFR = estimated glomerular filtration rate.

verify the presence or absence of comorbidity; and the use of statistical methods recommended for competing risks. Our study also has limitations. First, administrative data do not contain information on the severity of each comorbid condition, which may introduce bias. Second, our study population consisted of data collected from people who accessed medical services. Only prospective studies can provide reliable estimates of the population burden of severe nondialysis-dependent CKD. Third, data are from a single province with a universal healthcare system and may not apply to other world regions. Fourth, we included people with G4 CKD who had complete data on albuminuria. Generalizations of our findings should consider the higher prevalence of diabetes of our study population, likely related to our eligibility criteria. Studies are needed to investigate the relationship between age and kidney failure in people with less severe CKD, who are younger and have lower competing risk of death. Fifth, although censoring

for lack of eGFR records did not affect the relationship between age and hazards, increasing probabilities of lack of eGFR records with advancing age need to be accounted for in prognostic studies of severe nondialysis-dependent CKD. Finally, the observational nature of the study allows inference about association and not causation. While our findings will require validation in other settings, we do not believe that these limitations had a substantial impact on the validity of our conclusions.

In summary, in people with G4 CKD, we found an inverse relationship between age and kidney failure, which became stronger with advancing age. Older adults with G4 CKD are progressively less likely to develop kidney failure with every passing year and more likely to die. These findings could be used to improve prognostic tools and assist people with severe, nondialysis-dependent CKD to make treatment decisions aligned with their views and preferences.

Ethics Approval and Consent to Participate

This study was approved by the Conjoint Health Research Ethics Board of the University of Calgary, with a waiver of patient consent.

Consent for Publication

All co-authors reviewed this final manuscript and consent to its publication.

Availability of Data and Materials

We are not able to make our data set available to other researchers due to our contractual arrangements with the provincial health ministry (Alberta Health), who is the data custodian. Researchers may make requests to obtain a similar data set at <https://sporresources.researchalberta.ca>.

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Author Contributions

H.A.-W. and P.R. had full access to all the data in the study, took responsibility for the integrity of the data and the accuracy of the data analyses, contributed to concept and design, and were involved in drafting the manuscript. All authors were involved in acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content. P.R. obtained funding and provided administrative, technical, or material support and supervision.




Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: This study is based in part by data provided by Alberta Health and Alberta Health Services. The interpretation and conclusions contained herein are those of the researchers and do not represent the views of the Government of Alberta or Alberta Health Services. Neither the Government of Alberta, Alberta Health, nor Alberta Health Services express any opinion in relation to this study.

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ORCID iDs

Huda Al-Wahsh  <https://orcid.org/0000-0002-8576-686X>
 Ngan N. Lam  <https://orcid.org/0000-0002-0129-7091>
 Pietro Ravani  <https://orcid.org/0000-0001-6973-8570>

Supplemental Material

Supplemental material for this article is available online.

References

1. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med.* 2013;158:825-830.
2. Akbari A, Clase CM, Acott P, et al. Canadian Society of Nephrology commentary on the KDIGO clinical practice guideline for CKD evaluation and management. *Am J Kidney Dis.* 2015;65(2):177-205.
3. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. *JAMA.* 2007;298:2038-2047.
4. Hallan SI, Matsushita K, Sang Y, et al. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA.* 2012;308:2349-2360.
5. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. *JAMA.* 2010;303:423-429.
6. Hemmelgarn BR, James MT, Manns BJ, et al. Rates of treated and untreated kidney failure in older vs younger adults. *JAMA.* 2012;307:2507-2515.
7. Ravani P, Fiocco M, Liu P, et al. Influence of mortality on estimating the risk of kidney failure in people with stage 4 CKD. *J Am Soc Nephrol.* 2019;30(11):2219-2227.
8. Hemmelgarn BR, Zhang J, Manns BJ, et al. Progression of kidney dysfunction in the community-dwelling elderly. *Kidney Int.* 2006;69(12):2155-2161.
9. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol.* 2007;18(10):2758-2765.
10. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. *JAMA.* 2011;305:1553-1559.
11. Grams ME, Sang Y, Ballew SH, et al. Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. *Kidney Int.* 2018;93:1442-1451.
12. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. *JAMA.* 2016;315:164-174.
13. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation.* 2016;133:601-609.
14. Benchimol EI, Smeeth L, Guttman A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Med.* 2015;12:e1001885.
15. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604-612.
16. Ishani A, Nelson D, Clothier B, et al. The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. *Arch Intern Med.* 2011;171:226-233.

17. Tonelli M, Wiebe N, Fortin M, et al. Methods for identifying 30 chronic conditions: application to administrative data Healthcare Information Systems. *BMC Med Inform Decis Mak.* 2015;15:31.
18. Stevens P, Levin A. KDIGO: Improving Global Outcomes (KDIGO CKD-Work-Group) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl.* 2013;3:1-150.
19. Putter H, Fiocco MGR. Tutorial in biostatistics competing risks and multi-state models. *Stat Med.* 2007;26:2389-2430.
20. Fine JP, Gray RJ. A proportional hazards model for the sub-distribution of a competing risk. *J Am Stat Assoc.* 1999;94:496-509.
21. Arora P, Jalal K, Gupta A, Carter RL, Lohr JW. Progression of kidney disease in elderly stage 3 and 4 chronic kidney disease patients. *Int Urol Nephrol.* 2017;49(6):1033-1040.
22. Glasscock R, Delanaye P, El Nahas M. An age-calibrated classification of chronic kidney disease. *JAMA.* 2015;314:559-560.