Association of eGFR and mortality with use of a joint model: results of a nationwide study in Iceland

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ABSTRACT

Objectives. Prior studies on the association of estimated glomerular filtration rate (eGFR) and mortality have failed to include methods to account for repeated eGFR determinations. The aim of this study was to estimate the association between eGFR and mortality in the general population in Iceland employing a joint model.

Methods. We obtained all serum creatinine and urine protein measurements from all clinical laboratories in Iceland in the years 2008–16. Clinical data were obtained from nationwide electronic medical records. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation and categorized as follows: 0–29, 30–44, 45–59, 60–74, 75–89, 90–104 and >104 mL/min/1.73 m². A multiple imputation method was used to account for missing urine protein data. A joint model was used to assess risk of all-cause mortality.

Results. We obtained 2 120 147 creatinine values for 218 437 individuals, of whom 84 364 (39%) had proteinuria measurements available. Median age was 46 (range 18–106) years and 47% were men. Proteinuria associated with increased risk of death for all eGFR categories in persons of all ages. In persons ≤65 years, the lowest risk was observed for eGFR of 75–89 mL/min/1.73 m² without proteinuria. For persons aged >65 years, the lowest risk was observed for eGFR of 60–74 mL/min/1.73 m² without proteinuria. eGFR of 45–59 mL/min/1.73 m² without proteinuria did not associate with increased mortality risk in this age group. eGFR >104 mL/min/1.73 m² associated with increased mortality.

Conclusions. These results lend further support to the use of age-adapted eGFR thresholds for defining chronic kidney disease. Very high eGFR needs to be studied in more detail with regard to mortality.

Keywords: chronic kidney disease, eGFR, KDIGO criteria, kidney failure, mortality

INTRODUCTION

Chronic kidney disease (CKD) is recognized as an increasingly common cause of morbidity and mortality worldwide and is associated with substantial healthcare costs resulting from both kidney replacement therapy (KRT) and pre-dialysis care [1]. The burden of CKD is expected to increase among the rapidly growing ageing population [2, 3] and, therefore, the need for greater healthcare resources has been predicted [4].

Current recommendations on definition and staging of CKD from the Kidney Disease: Improving Global Outcomes (KDIGO) are essential steps in standardizing the identification and diagnosis of the disorder [5]. The definition is supported by large meta-analyses from the CKD Prognosis Consortium that demonstrated an association of estimated glomerular filtration rate (eGFR) and albuminuria with clinical outcomes across various populations and age groups [6, 7]. Although the importance of these meta-analyses has been widely recognized, controversies still remain. Some authorities have criticized the interpretation of eGFR of 45–59 mL/min/1.73 m² in the absence of other kidney abnormalities in the elderly (CKD stage G3A1) [8]. While there was a statistically significant increase in adverse outcomes in the CKD Prognosis Consortium's meta-analyses, the clinical relevance has been questioned [8]. Reanalysis of the consortium's data with redefined reference eGFR for each age group support the use of age-adapted CKD thresholds as the risk of adverse outcomes in the elderly first became apparent at eGFR <45 mL/min/1.73 m² [8]. Furthermore, a recent study of a Canadian cohort revealed that 5-year risk of kidney failure or death in persons aged >65 years without proteinuria was similar in the groups with eGFR of 60–74 mL/min/1.73 m² and 45–59 mL/min/1.73 m² [9]. This is important since many epidemiological studies on the burden of CKD have shown stage 3A to be the most prevalent one [10], and that age-adapted eGFR threshold would substantially reduce the true prevalence of CKD [11].

KEY LEARNING POINTS

What is already known about this subject?

- Controversies exist regarding stage G3A1 of chronic kidney disease (CKD) in the elderly population as there are frequently no signs of kidney disease other than the mild reduction in estimated glomerular filtration rate (eGFR) which may be due to normal aging.
- Prior studies on the association of eGFR and mortality have failed to include methods that account for repeated eGFR determinations.

What this study adds?

- The study accounts for repeated eGFR determinations using a joint model. The eGFR category 45–59 mL/min/1.73 m^2 in persons aged >65 years who did not have proteinuria was not associated with increased risk of mortality, whereas in younger persons eGFR between 60 and 74 mL/min/1.73 m^2 may suggest CKD.
- Very high eGFR is associated with increased mortality in the elderly.

What impact this may have on practice or policy?

- The study lends further support to the use of age-adapted eGFR thresholds for the definition of CKD.
- More attention should be paid to elderly patients with very high GFR.

Changes in kidney function over time strongly affect the risk of mortality associated with a person's GFR [12, 13]. This is addressed in most analyses by defining eGFR as a time-varying variable [14]. However, this approach may lead to bias for several reasons, including assumption of error-free measurement [15], failure to reflect true trajectory over time and irregular measurement dates [16], as is often the case in observation studies. In addition, this method may be sensitive to informative dropout, as eGFR determinations of persons who experience an event are likely to differ from those in persons who do not [17]. Joint modeling has been introduced to overcome these flaws [17, 18] and has demonstrated less bias compared with Cox proportional hazard analysis [19]. This methodology has gained increasing attention in clinical research in recent years due to advancements in computational power and software [20–22]. In nephrology research, joint modeling has been employed for outcome analysis of CKD cohorts [22–25]. This method has not been incorporated in studies carried out in the general population.

The aim of this study was to estimate the association between eGFR and mortality in the general population in Iceland, using a joint model.

MATERIALS AND METHODS

Ethical approval

The study was approved by the National Bioethics Committee of Iceland (VSN 13-138).

Study design and data collection

The study population has previously been described in detail [26]. Briefly, data were collected retrospectively on all inhabitants of Iceland aged 18 years or older who had one or more serum creatinine (SCr) measurements available in the years 2008–16. We obtained all SCr values and urine protein and albumin determinations from all clinical laboratories in the country. We also retrieved all available glycated hemoglobin

(HbA1c) values. Data on age, sex, hospital admissions and discharges, and diagnoses of kidney disease and comorbid conditions based on International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10) codes were obtained from the nationwide electronic medical record system, as well as the date of death. Study entry for each person was defined as the date of his/her first SCr measurement. Persons receiving KRT with dialysis or transplanted kidney at any time during the study period were included in the study, the rationale being that outcome was all-cause mortality.

Definitions of comorbid conditions and outcomes and categorization of eGFR

We used the ICD-9 and ICD-10 diagnosis codes or biochemical markers to define comorbid conditions as previously described [26]. In addition, diabetes was categorized by levels of HbA1c and burden of comorbid diseases by the Elixhauser Comorbidity Index [27]. Hospital Frailty Risk Score was calculated from diagnosis codes and classified as outlined by Gilbert *et al.* [28]. The original Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR from SCr [29]. Initial eGFR was categorized in line with the KDIGO classification and staging of CKD to enable comparison with the current staging system. Measurements of SCr obtained during an episode of transient elevation consistent with acute kidney injury (AKI), as defined by the SCr component of the KDIGO criteria, were excluded from the analysis [30, 31]. Proteinuria was defined as urinary albumin excretion rate ≥30 mg/24 h, urinary protein excretion rate ≥150 mg/24 h, urine ACR ≥30 mg/g or urine dipstick value of 1+ or greater, in the absence of a urinary tract infection defined as a positive dipstick test for leukocyte esterase or nitrates. Data on death were acquired through the Iceland Causes of Death Register. In addition to all-cause mortality, the analysis was performed using major cardiovascular event (MACE) as an outcome. MACE was defined as a composite outcome of new ischemic heart diseases (ICD-10 codes I20-24), congestive

heart failure (ICD-10 code I50) and acute cerebrovascular disease (ICD-10 codes I64-65). The analysis was carried out in the imputed proteinuria cohort for persons without previously documented MACE before study entry and with censoring at death.

Statistical analysis

Comparison of groups was performed using Chi squared test and T-test. A Kaplan–Meier estimate was calculated to assess survival probability according to the initial eGFR category. A joint model was created for more detailed analysis. The joint model consisted of two submodels: a linear mixed-effect model for longitudinal outcome analysis and Cox regression model for mortality analysis. First, the longitudinal model was constructed to estimate the rate of change in eGFR in mL/min/1.73 m^2 over time, accounting for the number of SCr measurements, the time between measurements and the time each subject spent in the study. Time was defined as years from the first SCr measurement. Both random intercept and slope were used, representing variation in eGFR at study entry and change in eGFR over time. Second, we constructed a time-to-event outcome model using Cox regression with all-cause mortality as the primary outcome. The model was adjusted for age at study entry as a continuous variable and sex, hypertension, diabetes, coronary artery disease, congestive heart failure, malignancy and AKI as categorical variables defined as being present if observed during the study period. The Elixhauser Comorbidity Index and Hospital Frailty Risk Score were constructed as numerical variables and the worst score during the study period was recorded. The output of the model was hazard ratio according to initial eGFR category and the presence of proteinuria (dummy variable). Finally, a joint model was created, combining defined shared random effects. The survival analysis thus included change in eGFR over time as a time-varying covariate to account for its effect on mortality in the linear mixed-effect model. We constructed two joint models that were stratified for age ≤65 and >65 years, in addition to a subgroup analysis for persons aged 40–65 years, according to age at first SCr measurement. Reference eGFR category for each age group was determined based on the lowest mortality risk.

For persons with no available urine protein measurement, multiple imputation by chained equations was performed to determine the presence of proteinuria for the whole cohort. The presence of proteinuria was defined as binary categorical variable and imputed using logistic regression. A total of 60 imputations were made for 10 iterations as approximately 60% of the cohort had no documented urine protein measurement [32]. All variables and outcomes in the analytical model were included in the imputation procedure [33]. Missing values were assumed to be missing at random. The principal analysis was conducted using the imputed dataset. Additional sensitivity analysis was also performed using only individuals with complete data. All statistical analyses were performed using R version 4.0.2 (www.r-project.org) in R-Studio with the survival and JM packages for survival analysis and MICE for multiple imputation.

RESULTS

Characteristics of the cohort

A total of 2 120 147 SCr measurements were obtained for 218 437 inhabitants in Iceland who were aged ≥18 years in 2008–16. Table 1 demonstrates the baseline characteristics of the cohort according to the first documented eGFR. The majority had an initial eGFR ≥90 mL/min/1.73 m^2. Overall, advancing age and prevalence of comorbid conditions increased with declining eGFR. We obtained 306 531 urine protein measurements for 84 364 (39%) persons of which, 58 835 from 21 736 persons yielded a positive value after exclusion of concomitant urinary tract infection. The median time from study entry until first urine protein measurement was 0.5 years (interquartile range 0–2.4). Supplementary data, Table S1 shows the number and proportion of persons with missing urine protein measurement according to initial eGFR category and age. Those with available urine protein measurement were older, more likely to be women and had higher prevalence of comorbid conditions (Table 2). In Table 3, the characteristics of persons who entered the study at age >65 years are compared with persons entering at a younger age. Among persons aged >65 years, the median age was 75 years and their comorbidity burden was greater than that of younger persons (Table 3).

Association eGFR category and outcome

In total, 17 453 persons (8.0%) died during the study period, a finding that was comparable for men and women. Persons who died were older and had higher prevalence of CKD and other comorbid conditions (Table 4). Figure 1 demonstrates Kaplan–Meier curves for overall survival according to the initial eGFR category and age group. Results of mortality analysis using the joint model are presented in Tables 5 and 6. In the whole cohort that included imputed urine protein values, persons aged ≤65 years with eGFR of 75–89 mL/min/1.73 m^2 and without proteinuria had the lowest risk of mortality. When compared with this reference group, individuals in the lower eGFR categories were shown to have a continuous rise in mortality risk. Persons with eGFR >104 mL/min/1.73 m^2 also had an increased mortality risk. Those with proteinuria had greater risk of mortality in all eGFR categories compared with the reference eGFR category (Table 5). For persons aged >65 years, the lowest mortality risk was observed for those with eGFR of 60–74 mL/min/1.73 m^2. Compared with this reference group, persons with eGFR of 45–59 mL/min/1.73 m^2 without documented proteinuria did not show significantly increased mortality in the adjusted or unadjusted models, whereas all other eGFR categories associated with higher mortality risk, which was highest for eGFR >104 mL/min/1.73 m^2 (Table 5). Table 6 displays the results of the mortality analysis using the joint model in the cohort with available urine protein measurements (N = 84 364). Unlike in the imputed cohort, the eGFR category 60–74 mL/min/1.73 m^2 did not reveal a statistically significant increase in mortality risk for persons aged ≤65 years without proteinuria when compared with the reference group. In

Table 1: Baseline characteristics of the study population according to initial eGFR.

eGFR, mL/min/1.73 m^2	0–29, $N = 1429$	30–44, $N = 3898$	45–59, $N = 10\,635$	60–74, $N = 25\,698$	75–89, $N = 48\,095$	90–104, $N = 60\,607$	>104, $N = 68\,075$
Age at study entry	80 (18–106)	79 (18–106)	73 (18–104)	62 (18–104)	54 (18–100)	48 (18–91)	30 (18–102)
Age >65 years	1174 (82)	3418 (88)	7500 (71)	10 386 (40)	11 663 (24)	3719 (6)	77 (0.1)
Sex, women	791 (55)	2365 (61)	6294 (59)	13 659 (53)	24 154 (50)	30 199 (50)	38 481 (57)
Number of SCr measurements	24 (1–325)	19 (1–254)	14 (1–355)	8 (1–229)	6 (1–387)	4 (1–428)	1 (1–468)
CKD[a]	1188 (83)	3329 (85)	7353 (69)	6324 (25)	3951(8)	2065 (3)	1786 (3)
Urine protein measurement	1160 (81)	2984 (77)	6710 (63)	12 174 (47)	18 593 (39)	20 377 (34)	22 366 (33)
Proteinuria documented[b]	680 (48)	1326 (34)	2375 (22)	3411 (13)	4515 (9)	4554 (8)	4875 (7)
Proteinuria imputed	750 (52)	1436 (37)	2535 (24)	3600 (14)	4785 (10)	4764 (8)	5024 (7)
Hypertension	1109 (78)	2998 (77)	6981 (65)	12 582 (49)	17 949 (37)	16 959 (28)	7673 (11)
Diabetes mellitus[c]	404 (28)	1065 (27)	2538 (24)	4792 (19)	7429 (15)	8154 (13)	5053 (7)
Coronary artery disease	662 (46)	1706 (44)	3523 (33)	5474 (21)	6732 (14)	5136 (8)	1086 (2)
Congestive heart failure	595 (42)	1345 (35)	2143 (20)	2204 (9)	2328 (5)	1183 (2)	321 (0.4)
Cerebrovascular disease	317 (22)	797 (20)	1648 (15)	2280 (9)	2670 (6)	1717 (3)	640 (1)
Chronic lung disease	429 (30)	1108 (28)	2856 (27)	5742 (22)	9794 (20)	11 429 (19)	11 531 (17)
Malignancy	435 (30)	1244 (32)	2939 (28)	5505 (21)	8441 (18)	9156 (15)	12 518 (18)
Psychiatric disease	362 (25)	1012 (26)	2618 (25)	5466 (21)	9849 (20)	12 903 (21)	16 814 (25)
AKI[d]	835 (58)	1619 (42)	2770 (26)	3373 (13)	4164 (9)	3754 (6)	3439 (5)
Elixhauser Comorbidity Index	11 (–7 to 42)	7 (–7 to 44)	3 (–7 to 42)	–3 (–7 to 45)	–7 (–7 to 50)	–7 (–7 to 43)	–7 (–7 to 39)
Hospital Frailty Risk Score[e]							
Low	190 (13)	612 (16)	2770 (26)	10 806 (42)	24 437 (51)	33 989 (56)	38 975 (57)
Intermediate	622 (44)	1728 (44)	4819 (45)	11 100 (43)	19 249 (40)	23 783 (39)	27 045(40)
High	617 (43)	1558 (40)	3046 (29)	3792 (15)	4409 (9)	2835 (5)	2055 (3)
Death in the study period	982 (69)	2095 (54)	3358 (32)	3759 (15)	4249 (9)	2212 (4)	798 (1)

Data are presented as number (%) and median (range) unless otherwise stated. Values represent prevalent data in the study period.
[a]Identified according to the KDIGO criteria as eGFR <60 mL/min/1.73 m^2 and/or proteinuria persistent for >90 days and/or kidney damage based on kidney disease-specific diagnosis.
[b]Any positive urine protein measurement in the absence of established urinary tract infection.
[c]Diabetes defined by documented ICD codes or HbA1c $\geq$6.5%.
[d]AKI episodes were determined according to the SCr component of the KDIGO criteria.
[e]Hospital Frailty Risk Score categorization: low risk: <5; intermediate risk: 5–15; high risk: >15.

persons aged >65 years, the results were similar to the imputed cohort as those with eGFR of 45–59 mL/min/1.73 m^2 without proteinuria did not have a significantly increased mortality risk, and the observed risk was highest for the eGFR category >104 mL/min/1.73 m^2. A sub-analysis of persons aged 40–65 years at study entry in both cohorts yielded similar results as for persons aged $\leq$65 years, apart from eGFR category 60–74 mL/min/1.73 m^2 which carried increased risk in both cohorts (Supplementary data, Tables S2 and S3).

After excluding persons with a documented MACE before study entry ($N = 14\,435$), 204 002 persons remained at risk, of whom 13 113 (6.4%) were identified with a new MACE in the study period. Supplementary data, Tables S4 and S5 show the proportion of MACE at baseline and incident MACE, stratified by initial eGFR category and proteinuria. Supplementary data, Table S6 shows the characteristics of persons who were identified with MACE in the study period compared with those who were not. Table 7 demonstrates the risk of MACE derived from the joint model, according to initial eGFR category and proteinuria in the imputed cohort. For persons $\leq$65 years at study entry, the presence of proteinuria was associated with incident MACE across all eGFR categories in Model 1, whereas among those without proteinuria only the eGFR category $\geq$90 mL/min/1.73 m^2 was associated with MACE. In Model 2, these associations of proteinuria with MACE were attenuated and only remained significant for eGFR $\geq$75 mL/min/1.73 m^2. A similar trend was

observed for persons >65 years, whereas in Model 2 the risk of MACE in persons with proteinuria remained significant for eGFR $\geq$45 mL/min/1.73 m^2.

DISCUSSION

In this nationwide study that included the majority of the Icelandic population, we found that mortality risk across eGFR categories differed according to age, demonstrating a J-shaped pattern. In persons aged $\leq$65 years, a stronger association was observed for the lower eGFR categories, whereas in persons aged >65 years the risk was highest for those with eGFR >104 mL/min/1.73 m^2. Increased mortality risk was observed for all eGFR categories among persons with proteinuria. Importantly, the study did not demonstrate an increased mortality risk for eGFR ranging from 45 to 59 mL/min/1.73 m^2 without evidence of proteinuria in persons aged >65 years. To our knowledge, this is the first study to apply joint modeling to assess the risk of mortality according to eGFR in the general population.

The work of the CKD Prognosis Consortium provided the foundation for currently accepted CKD definition and clinical practice guidelines, by establishing the association of eGFR with adverse outcomes such as all-cause mortality, cardiovascular mortality and the need for KRT [34]. As opposed to the results of the meta-analysis by Hallan et al., which described a significant risk of kidney failure and death in accordance to

Table 2: Baseline characteristics of persons with available urine protein measurement compared with those without urine protein measurement.

	Urine protein measurement, $N = 84\,364$	No urine protein measurement, $N = 134\,073$	P-value
Age at study entry	52 (18–106)	43 (18–104)	<.001
Sex, women	49 770 (59)	66 173 (49)	<.001
First eGFR, mean (SD)	90 (24)	97 (20)	<.001
Number of SCr measurements	10 (1–468)	3 (1–267)	<.001
CKD[a]	19 345 (23)	6651 (5)	<.001
Proteinuria[b]	21 736 (25)	0	
Hypertension	35 636 (42)	30 615 (23)	<.001
Diabetes mellitus[c]	17 624 (21)	11 811 (9)	<.001
Coronary artery disease	15 302 (18)	9017 (7)	<.001
Congestive heart failure	7943 (9)	2176 (2)	<.001
Cerebrovascular disease	6908 (8)	3161 (2)	<.001
Chronic lung disease	20 914 (25)	21 975 (16)	<.001
Malignancy	22 047 (26)	18 191 (14)	<.001
Psychiatric disease	23 489 (28)	25 535 (19)	<.001
AKI[d]	15 402 (18)	4552 (3)	<.001
Elixhauser Comorbidity Index	–1 (–7 to 50)	–7 (–7 to 36)	<.001
Hospital Frailty Risk Score[e]			
Low	28 195 (34)	83 584 (62)	<.001
Intermediate	41 555 (49)	46 791 (35)	<.001
High	14 614 (17)	3698 (3)	<.001
Death in the study period	12 788 (15)	4665 (3)	<.001

Data are presented as number (%) and median (range) unless otherwise stated. Values represent prevalent data in the study period.
[a]Identified according to the KDIGO criteria as eGFR <60 mL/min/1.73 m^2 and/or proteinuria persistent for >90 days and/or kidney damage based on kidney disease-specific diagnosis.
[b]Any positive urine protein measurement in the absence of established urinary tract infection.
[c]Diabetes defined by documented ICD codes or HbA1c $\geq$6.5%.
[d]AKI episodes were determined according to the serum creatinine component of the KDIGO criteria.
[e]Hospital Frailty Risk Score categorization: low risk: <5; intermediate risk: 5–15; high risk: >15.

baseline eGFR and proteinuria across all age groups [7], we found that eGFR of 45–59 mL/min/1.73 m^2 in persons aged >65 years did not associate with increased risk of mortality. Several factors can explain this finding. First, our reference eGFR category for persons aged >65 years was defined as 60–74 mL/min/1.73 m^2 because persons with this eGFR range carried the lowest risk of mortality in our cohort. This eGFR range is lower than that used by Hallan *et al.*, who arbitrarily defined the reference eGFR level as 80 mL/min/1.73 m^2. Interpretation of hazard ratios depend on the reference level, and our findings are in agreement with analysis by Delanaye *et al.*, demonstrating that by altering the reference eGFR in persons aged >65 years, the risk of mortality did not increase until the eGFR had declined to <45 mL/min/1.73 m^2 [8]. Furthermore, reported meta-analyses have used single values for estimating the association of eGFR and albuminuria with outcome [7, 34, 35]. In the current study, we included eGFR as an endogenous time-dependent variable in the analysis. Both increase and decrease in eGFR from baseline has been shown to affect the risk of mortality [12, 36, 37]. It is therefore vital to account for eGFR as a continuous time-dependent variable in the assessment of the association between eGFR and mortality. Since separate analysis of mortality and repeated eGFR levels can lead to bias, joint modeling has been proposed as an optimal method for detailed analysis of such data [25, 38].

The association of eGFR with MACE was stronger in the presence of proteinuria both in those aged ≤65 and >65 years. These associations were however reduced when adjusted for comorbidity, although they remained significant for higher eGFR categories in both age groups. The lack of association in the adjusted model for the lower eGFR categories might be explained by incomplete recording of diagnosis codes or the competing risk of death.

This study expands our previous work on the epidemiology of CKD, applying the chronicity criterion and age-adapted GFR thresholds in addition to the KDIGO definition of CKD [26]. Using age-adapted eGFR thresholds in the definition of CKD yields a marked reduction in the prevalence of the disorder, especially in the elderly population [26]. To further support this finding, a recent report has demonstrated a similar 5-year risk of death or progression to end-stage kidney disease for persons aged ≥65 years with eGFR of 45–60 mL/min/1.73 m^2 and their peers with eGFR of 60–74 mL/min/1.73 m^2 [28]. Moreover, the probability of CKD regression or death exceeds the risk of end-stage kidney disease in elderly people [39, 40]. Hence, our results add further evidence supporting the notion that current age-independent definition of CKD based on GFR needs to be re-evaluated. Our study indicates that eGFR >60 mL/min/1.73 m^2 may be relevant when defining CKD in young people. As the age group ≤65 years spans a diverse population with respect to comorbid conditions, an analysis stratified by age in a more detailed manner in a larger sample might further elucidate to which age group such an approach might apply. Events in participants below age 40 years were too few to allow for separate analysis of this age group.

Existing definitions of very high GFR vary from 90 to 175 mL/min/1.73 m^2, making comparison between studies

Table 3: Baseline characteristics of persons who entered the study according to age below or above 65 years.

	Age ≤65 years, N = 180 500	Age >65 years, N = 37 937	P-value
Age at study entry	41 (18–65)	75 (66–106)	<.001
Sex, women	95 415 (53)	20 528 (54)	<.001
First eGFR, mean (SD)	99 (19)	70 (18)	<.001
Number of SCr measurements	4 (1–468)	14 (1–334)	<.001
CKD[a]	9363 (5)	16 633 (44)	<.001
Proteinuria[b]	13 758 (8)	7978 (21)	<.001
Hypertension	41 221 (23)	25 030 (66)	<.001
Diabetes mellitus[c]	19 887 (11)	9548 (25)	<.001
Coronary artery disease	10 490 (6)	13 829 (36)	<.001
Congestive heart failure	2144 (1)	7975 (21)	<.001
Cerebrovascular disease	3649 (2)	6420 (17)	<.001
Chronic lung disease	32 213 (18)	10 676 (28)	<.001
Malignancy	28 578 (16)	11 660 (31)	<.001
Psychiatric disease	40 531 (22)	8493 (22)	<.001
AKI[d]	10 121 (6)	9833 (26)	<.001
Elixhauser Comorbidity Index	−7 (−7 to 50)	4 (−7 to 44)	<.001
Hospital Frailty Risk Score[e]			
Low	102 960 (57)	8819 (23)	<.001
Intermediate	70 812 (39)	17 534 (46)	<.001
High	6728 (4)	11 584 (31)	<.001
Death in the study period	3818 (2)	13 635 (36)	<.001

Data are presented as number (%) and median (range) unless otherwise stated. Values represent prevalent data in the study period.
[a]Identified according to the KDIGO criteria as eGFR <60 mL/min/1.73 m^2 and/or proteinuria persistent for >90 days and/or kidney damage based on kidney disease-specific diagnosis.
[b]Any positive urine protein measurement in the absence of established urinary tract infection.
[c]Diabetes defined by documented ICD codes or HbA1c ≥6.5%.
[d]AKI episodes were determined according to the serum creatinine component of the KDIGO criteria.
[e]Hospital Frailty Risk Score categorization: low risk: <5; intermediate risk: 5–15; high risk: >15.

Table 4: Baseline characteristics of persons who died in the study period compared with those who survived.

	Died, N = 17 453	Survived, N = 200 984	P-value
Age at study entry	78 (18–106)	44 (18–102)	<.001
Sex, women	8644 (50)	107 299 (53)	<.001
First eGFR, mean (SD)	69 (24)	96 (20)	<.001
Number of SCr measurements	18 (1–387)	4 (1–486)	<.001
CKD[a]	7511 (43)	18 485 (9)	<.001
Proteinuria[b]	5347 (30)	16 389 (8)	<.001
Hypertension	10 358 (60)	55 893 (28)	<.001
Diabetes mellitus[c]	3579 (21)	25 856 (13)	<.001
Coronary artery disease	6862 (39)	17 457 (9)	<.001
Congestive heart failure	5244 (30)	4875 (2)	<.001
Cerebrovascular disease	3868 (2)	6201 (3)	<.001
Chronic lung disease	5328 (31)	37 561 (19)	<.001
Malignancy	8014 (46)	32 224 (16)	<.001
Psychiatric disease	5042 (29)	43 982 (22)	<.001
AKI[d]	7065 (41)	12 889 (6)	<.001
Elixhauser Comorbidity Index	7 (−7 to 50)	−7 (−7 to 44)	<.001
Hospital Frailty Risk Score[e]			
Low	3170 (18)	108 609 (54)	<.001
Intermediate	8007 (46)	80 339 (40)	<.001
High	6276 (36)	12 036 (6)	<.001

Data are presented as number (%) and median (range) unless otherwise stated. Values represents prevalent data in the study period.
[a]Identified according to the KDIGO criteria as eGFR <60 mL/min/1.73 m^2 and/or proteinuria persistent for >90 days and/or kidney damage based on kidney disease-specific diagnosis.
[b]Any positive urine protein measurement in the absence of established urinary tract infection.
[c]Diabetes defined by documented ICD codes or HbA1c ≥6.5%.
[d]AKI episodes were determined according to the serum creatinine component of the KDIGO criteria.
[e]Hospital Frailty Risk Score categorization: low risk: <5; intermediate risk: 5–15; high risk: >15.

difficult [41, 42]. In the present study, eGFR ≥90 mL/min/1.73 m^2 was associated with increased mortality risk, particularly in older persons. Very high GFR has been linked to risk of adverse cardiovascular outcomes and mortality, and has been proposed as a marker of vascular dysfunction associated with conditions such as diabetes, hypertension and cardiovascular disease [43–46]. Notably, it has been argued that very high GFR defined based on eGFR derived from SCr in older persons is imprecise due to an overestimation of true GFR resulting from muscle wasting in individuals suffering from multimorbidity

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Table 5: Hazard ratios (95% confidence intervals) for death according to initial eGFR category and proteinuria for the whole cohort using multiple imputation for urine protein measurements.

eGFR (mL/min/1.73 m²)	Age ≤65 years						Age >65 years							
	Model 1[a]				Model 2[b]		Model 1[a]				Model 2[b]			
	N	Events	No proteinuria	Proteinuria	No proteinuria	Proteinuria	N	Events	No proteinuria	Proteinuria	N	Events	No proteinuria	Proteinuria
>104	62 992	520	1.45 (1.26–1.67)	5.05 (4.25–6.00)	1.20 (1.04–1.39)	2.97 (2.49–3.54)	59	34	4.80 (3.22–7.17)	5.31 (2.56–11.0)	18	10	4.28 (2.88–6.36)	4.47 (2.15–9.31)
90–104	52 753	939	1.08 (0.96–1.20)	4.27 (3.75–4.87)	1.07 (0.96–1.19)	2.47 (2.16–2.83)	3090	582	1.66 (1.50–1.85)	2.55 (2.20–2.97)	629	244	1.55 (1.40–1.73)	2.23 (1.92–2.60)
75–89	33 805	547	Ref	5.51 (4.78–6.36)	Ref	2.66 (2.29–3.09)	9505	2393	1.12 (1.05–1.19)	1.77 (1.64–1.91)	2158	1011	1.08 (1.02–1.15)	1.62 (1.50–1.75)
60–74	13 756	326	1.41 (1.22–1.62)	5.36 (4.50–6.39)	1.25 (1.08–1.43)	2.71 (2.27–3.25)	8342	2293	Ref	1.56 (1.44–1.68)	2044	970	Ref	1.42 (1.32–1.54)
45–59	2504	122	2.89 (2.35–3.55)	6.76 (5.22–8.76)	2.35 (1.91–2.87)	2.73 (2.09–3.55)	5596	2099	1.06 (0.99–1.13)	1.58 (1.46–1.71)	1904	1068	1.05 (0.99–1.12)	1.46 (1.35–1.57)
30–44	247	38	10.9 (7.62–15.5)	17.1 (12.3–23.7)	5.81 (4.06–8.32)	5.15 (3.68–7.21)	2215	1240	1.35 (1.25–1.46)	1.55 (1.41–1.70)	1203	773	1.33 (1.23–1.44)	1.41 (1.28–1.55)
0–29	70	21	29.7 (18.0–48.9)	46.4 (33.6–64.2)	7.77 (4.72–12.8)	6.53 (4.66–9.15)	609	483	2.17 (1.93–2.44)	2.45 (2.16–2.77)	565	435	1.97 (1.75–2.21)	2.09 (1.84–2.37)

[a] Adjusted for age and sex. The model is based on a multiple imputation dataset.
[b] Adjusted for age, sex, hypertension, diabetes, coronary artery disease, congestive heart failure, malignancy, AKI, Elixhauser Comorbidity Index and Hospital Frailty Risk Score. The model is based on multiple imputation dataset.
N is the same for Model 1 and Model 2.

Table 6: Hazard ratios (95% confidence intervals) for death according to initial eGFR category and proteinuria for persons with available urine protein measurement.

eGFR (mL/min/1.73 m²)	Age ≤65 years						Age >65 years							
	Model 1[a]				Model 2[b]		Model 1[a]				Model 2[b]			
	N	Events	No proteinuria	Proteinuria	No proteinuria	Proteinuria	N	Events	No proteinuria	Proteinuria	N	Events	No proteinuria	Proteinuria
>104	17 460	263	1.26 (1.03–1.54)	2.96 (2.39–3.67)	1.13 (0.92–1.40)	2.31 (1.85–2.90)	31	21	8.24 (5.33–12.73)	4.98 (2.70–9.20)	17	9	6.91 (4.46–10.7)	4.43 (2.41–8.17)
90–104	14 444	525	1.02 (0.86–1.21)	2.49 (2.08–2.99)	0.97 (0.81–1.16)	1.90 (1.57–2.30)	1379	358	1.47 (1.30–1.66)	2.16 (1.88–2.50)	605	231	1.35 (1.19–1.52)	1.91 (1.65–2.21)
75–89	9445	296	Ref	3.30 (2.71–4.02)	Ref	2.26 (1.83–2.79)	4633	1524	1.07 (0.99–1.15)	1.57 (1.45–1.71)	2038	944	1.04 (0.97–1.12)	1.46 (1.35–1.59)
60–74	4600	198	1.27 (1.02–1.59)	3.28 (2.57–4.18)	1.22 (0.97–1.53)	1.88 (1.45–2.46)	4163	1495	Ref	1.41 (1.30–1.53)	1938	916	Ref	1.32 (1.22–1.43)
45–59	1101	85	3.01 (2.22–4.08)	4.43 (3.12–6.31)	2.48 (1.80–3.40)	1.92 (1.28–2.87)	3234	1391	1.00 (0.93–1.08)	1.44 (1.33–1.57)	1771	979	1.04 (0.96–1.12)	1.39 (1.27–1.51)
30–44	161	29	6.78 (3.88–11.9)	11.0 (7.06–17.2)	4.80 (2.70–8.54)	4.79 (2.93–7.82)	1497	899	1.30 (1.18–1.42)	1.44 (1.30–1.59)	1101	695	1.35 (1.23–1.48)	1.42 (1.28–1.57)
0–29	51	17	14.6 (6.64–32.1)	24.4 (15.5–38.5)	4.42 (1.99–9.79)	5.63 (3.41–9.27)	429	340	1.98 (1.72–2.27)	2.24 (1.96–2.56)	508	385	1.93 (1.68–2.21)	2.13 (1.86–2.44)

[a] Adjusted for age and sex. The model is based on persons with available urine protein measurement.
[b] Adjusted for age, sex, hypertension, diabetes, coronary artery disease, congestive heart failure, malignancy, AKI, Elixhauser Comorbidity Index and Hospital Frailty Risk Score. The model is based on persons with available urine protein measurement.
N is the same for Model 1 and Model 2.

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Table 7: Hazard ratios (95% confidence intervals) for MACE according to initial eGFR category and proteinuria for the whole cohort using multiple imputation for urine protein measurements.

eGFR (mL/min/ 1.73 m²)	Age ≤65 years								Age >65 years							
	Model 1[a]						Model 2[b]		Model 1[a]						Model 2[b]	
	N	Events	No proteinuria	N	Events	Proteinuria	No proteinuria	Proteinuria	N	Events	No proteinuria	N	Events	Proteinuria	No proteinuria	Proteinuria
>104	62 561	685	1.28 (1.13–1.45)	4899	197	3.42 (2.9–4.03)	1.06 (0.93–1.20)	1.37 (1.16–1.62)	49	8	1.98 (0.90–4.24)	12	3	4.44 (1.75–11.2)	1.35 (0.63–2.88)	3.07 (1.21–7.79)
90–104	51 248	1890	1.11 (1.03–1.21)	3798	469	2.71 (2.43–3.03)	1.05 (0.97–1.14)	1.28 (1.15–1.44)	2665	428	1.28 (1.12–1.45)	484	168	2.64 (2.23–3.12)	1.14 (1.00–1.30)	1.57 (1.33–1.86)
75–89	32 767	1363	Reference	2408	291	2.57 (2.27–2.91)	Reference	1.26 (1.11–1.43)	7660	1524	1.16 (1.07–1.26)	1521	543	2.03 (1.82–2.24)	1.10 (1.01–1.27)	1.40 (1.26–1.55)
60–74	13 141	715	1.03 (0.93–1.15)	1388	197	2.41 (2.08–2.79)	1.02 (0.92–1.13)	1.02 (0.88–1.20)	6551	1352	Reference	1384	547	1.87 (1.69–2.07)	Reference	1.32 (1.19–1.46)
45–59	2331	169	1.13 (0.93–1.36)	514	84	2.32 (1.81–2.98)	0.94 (0.78–1.13)	0.88 (0.69–1.13)	4122	989	0.96 (0.87–1.05)	1174	479	1.62 (1.45–1.81)	0.95 (0.87–1.06)	1.13 (1.01–1.28)
30–44	218	14	0.59 (0.27–1.30)	187	24	1.88 (1.20–2.96)	0.42 (0.19–0.89)	0.66 (0.43–1.04)	1400	407	1.00 (0.87–1.14)	688	306	1.48 (1.28–1.72)	0.92 (0.80–1.05)	1.03 (0.89–1.19)
0–29	62	3	NA[c]	161	35	4.86 (3.15–7.48)	NA[c]	1.15 (0.75–1.75)	317	90	1.11 (0.86–1.42)	292	133	1.77 (1.43–2.18)	0.93 (0.72–1.19)	1.12 (0.91–1.38)

[a] Adjusted for age and sex. The model is based on multiple imputation dataset.
[b] Adjusted for age, sex, hypertension, diabetes, malignancy, acute kidney injury, Elixhauser Comorbidity Index and Hospital Frailty Risk Score. The model is based on multiple imputation dataset.
N is the same for Model 1 and Model 2.
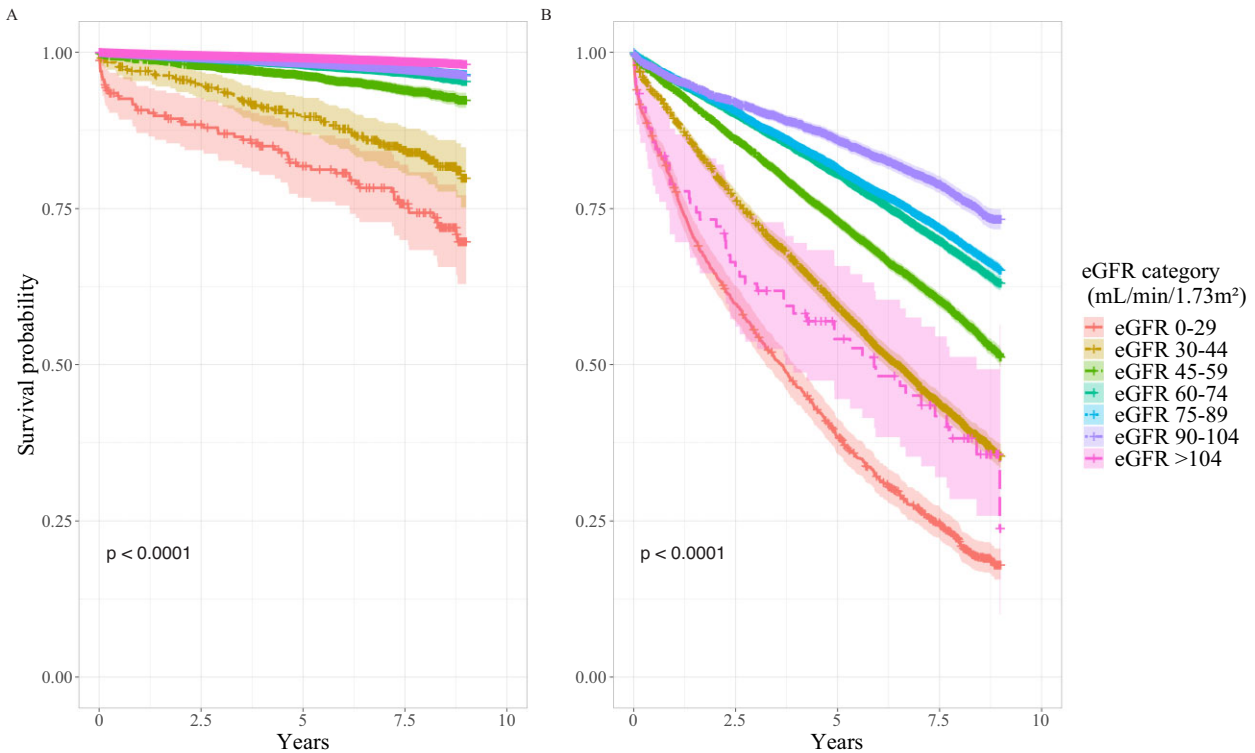[c] Unreliable estimates. NA, not applicable.

Figure 1: Kaplan–Meier estimate of survival according to initial eGFR category for persons ≤65 years (**A**) and persons aged >65 years (**B**).

[47]. This argument is based on an observation that association between very high GFR and outcome is weaker in younger age groups [7], and also when markers other than SCr are used to estimate GFR [48]. However, Park *et al.* reported an increase in mortality among apparently healthy, middle-aged persons with very high GFR after controlling for muscle mass [49]. Although we cannot exclude that eGFR might be overestimated in this group due to muscle wasting or other factors that lower the SCr concentration, we adjusted for major comorbidities associated with low muscle mass such as malignancy and frailty. Another possible explanation is a state of resolving AKI [36]. We identified the occurrence of AKI and excluded SCr measurements during such episodes, making this an unlikely explanation. Future research using direct measurement of GFR is needed in this population to establish a more reliable association between very high GFR and mortality.

An important strength of the study is our large sample size which includes the majority of the Icelandic population, estimated to be 330 737 on 31 December 2016, and robust information on comorbidity obtained through the electronic medical record system in Iceland. Another strength is the use of joint modeling to assess mortality which corrects for change in eGFR over time and errors in eGFR determinations [25]. The highly reliable information on deaths obtained from the Causes of Death Register in Iceland is an additional strength of the current study.

Our study also has several limitations, including the use of SCr measurements by clinical indications rather than in a randomly selected cohort. While this is important for prevalence and incidence calculations, it may be less of a limitation in the current study of mortality risk. Also, a high proportion of persons did not have urine protein measurement available. While this would be expected in a population-based study, it might nevertheless lead to bias in the current analysis. Comparison of persons with and without available urine protein measurements revealed a higher comorbidity in former group. Although we performed multiple imputations according to current standards, this approach might have resulted in bias, limiting the interpretation of predictive capabilities of proteinuria on the study outcome. This also makes the analysis vulnerable to immortality bias and therefore the effect size of proteinuria might be underestimated. However, as a high proportion of persons with available urine protein measurement did not have proteinuria, the effects of possible immortality bias are diluted. This is also expected to have a greater effect on the age group ≤65 years as persons with eGFR >60 mL/min/1.73 m^2 had the highest proportion of unavailable urine protein measurements. Notably, the overall trends in risk were similar when only those with available proteinuria measurement were analyzed. Another limitation is that we did not have access to information on the cause of death and thus were unable to assess the association of eGFR with death from cardiovascular causes. Furthermore, our dataset did not include medical therapies which could influence patients' outcomes. Likewise, lack of information on body weight and height precluded us from being able to partially account for variation in muscle mass. Other potential confounders, such as smoking and cholesterol levels, could not be adjusted for. Finally, it cannot be excluded that the sample size of some eGFR categories might have been too small and the analyses therefore vulnerable to type 2 error.

In conclusion, the results of the current study lend further support to the use of age-adapted eGFR thresholds in the definition of CKD. In particular, eGFR 45–59 mL/min/1.73 m^2 in the absence of proteinuria should not be classified as disease in the elderly. Very high GFR requires further study with respect to mortality.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

All authors have contributed to the study, A.J.J., B.O.E., O.S.I. and R.P. to the design, and A.J.J., O.S.I. and R.P. to collection of data. A.J.J., S.H.L. and O.S.I. performed the analysis. A.J.J. wrote the initial draft and all authors have contributed to the final manuscript. The results presented in this article have not been published previously in whole or in part, except in abstract form. Part of this work was presented at the Biennial Congress of the Nordic Society of Nephrology in May of 2022.

DATA AVAILABILITY STATEMENT

Data available upon request conditional on National Bioethics Committee approval.

CONFLICT OF INTEREST STATEMENT

None declared.

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