The progression of chronic kidney disease: A 10-year population-based study of the effects of gender and age

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The increase in demand for renal replacement therapy makes it important to investigate the prognosis of the earlier stages of chronic kidney disease (CKD). We examined the change in glomerular filtration rate (GFR), and patient and renal survival in CKD stage 3 in the municipality of Tromsø, a well-defined European community with a population of 58 000. All patients with estimated GFR between 30 and 59 ml/min/1.73 m^2 for more than 3 months during a 10-year study period were identified from a complete database of all 248 560 measurements of serum creatinine made in the community in the study period. Change in GFR was estimated for each patient using a multilevel model. A complete follow-up with respect to patient and renal survival was obtained from hospital databases. A total of 3047 patients was included. The median number of measurements of creatinine for each patient was 9, and the median observation time was 44 months. Mean estimated change in GFR was −1.03 ml/min/1.73 m^2/year. Seventy-three percent of the patients experienced a decline in GFR. The 10-year cumulative incidence of renal failure was 0.04 (95% CI 0.03–0.06) and mortality 0.51 (95% CI 0.48–0.55). Female gender was associated with slower decline in GFR and better patient and renal survival. In this population-based study, the decline in GFR in CKD was slower than in previously studied selected patient groups. A high mortality pre-empted the development of renal failure in many patients. The prognosis of CKD depended strongly on gender.

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The need for renal replacement therapy (RRT), that is, dialysis or kidney transplantation, is increasing rapidly. In most countries, demand will exceed capacity for providing this kind of costly care in a few years.[1] One solution to the problem would be to prevent the progression of chronic kidney disease (CKD) to renal failure. Researchers are now focusing on the milder forms of CKD and therapy that may retard or even reverse its progression.

As a prerequisite for this research, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative to establish a consensus definition of the term 'chronic kidney disease' has met broad approval among nephrologists. The finding of a reduced glomerular filtration rate (GFR) and/or structural damage to the kidney of more than three months duration can now be used for categorizing CKD into five stages from chronic kidney damage with normal GFR (stage 1) to kidney failure with GFR less than 15 ml/min/1.73 m^2 body surface area (stage 5).[2] This classification is intended as a starting point both for research and for establishing clinical guidelines.

To serve these purposes, it would be useful if each stage was, to some extent, homogenous in clinical manifestations, especially with regard to progression to renal failure. Previous studies of the prognosis of CKD do not provide a clear answer to this issue. The largest epidemiological studies of CKD were not longitudinal,[3,4] the longitudinal ones did not provide estimates of change in GFR,[5–9] and some were based on selected populations.[6,7,9] Also, some recent studies did not verify that a reduced GFR persisted for 3 months or more, as required by the definition, thereby risking bias from including patients with reversible acute renal failure.[4,9]

The present longitudinal observation study was undertaken to investigate the long-term prognosis and change in GFR of a cohort of patients with CKD stage 3, which is the least advanced stage defined from GFR alone.[2] The cohort was identified from all serum creatinine measurements in a population within a well-defined geographic area being served by one provider of nephrological services in a health care system with universal coverage. There was complete follow-up of initiation of RRT and deaths. The aim of the study was to examine the effects of gender and age on the

rate of change in GFR, initiation of RRT, and all-cause mortality.

RESULTS

Of the 38 241 patients with measurements of creatinine, 6863 had one or more GFR estimate in the interval 30–59 ml/min/1.73 m^2. Of these, 88 had subsequent estimates lower than 30 and 2175 greater than 59 ml/min/1.73 m^2, which excluded them according to the 3-month requirement of the definition. A total of 1526 patients had no second measurement more than 3 months after the first. Thus, 3074 patients, who were all 20 years or older, satisfied the definition of CKD stage 3. After excluding 27 patients on RRT, 3047 patients were included in the study.

Of these, 30% were men and 70% women (Table 1). Median observation time was 44 months (mean 50 months) during which each patient was subjected to a median of nine analyses of creatinine (mean 14 analyses).

Survival analysis

In the study period, 959 (31%) of the patients died and 62 (2%) developed renal failure (CKD stage 5 or initiation of RRT) (Table 1). Of the 58 patients with CKD stage 5, 24 subsequently received RRT (19 dialysis, five kidney transplant), and of the rest 30 were dead and four alive at the end of the study period.

Table 2 shows the cumulative 5- and 10-year incidence of the two end points. For all patients, the 10-year cumulative incidence of renal failure was 0.04, and that of death was 0.51. The cumulative incidences of both end points were higher for men, but increasing age led to higher mortality but lower cumulative incidence of renal failure. Cox proportional-hazards regression analyses found age, gender, and baseline GFR significant regressors for both endpoints and confirmed the opposite effects of age on renal failure and mortality (Table 3). Interactions between these three regressors were tested in both analyses, but none were found significant. Non-linear effects of age and GFR were tested by adding quadratic terms for these variables to both models, but none was statistically significant.

Table 2 | Cumulative 5- and 10-year incidence of the competing risks renal failure and death in patients with CKD stage 3 (*n*=3047)

Age	Men	Women	Total
<69 years			
No. (%)	279 (28)	704 (72)	983 (100)
Cumulative incidence (95% CI)[a]			
Renal failure[b]			
5-year	0.05 (0.03–0.09)	0.02 (0.01–0.03)	0.03 (0.02–0.04)
10-year	0.12 (0.08–0.20)	0.04 (0.02–0.08)	0.07 (0.05–0.11)
Death			
5-year	0.20 (0.16–0.27)	0.08 (0.06–0.11)	0.12 (0.10–0.15)
10-year	0.26 (0.20–0.35)	0.13 (0.09–0.17)	0.17 (0.14–0.21)
70–79 years			
No. (%)	404 (35)	759 (65)	1163 (100)
Cumulative incidence (95% CI)			
Renal failure			
5-year	0.02 (0.01–0.04)	0.01 (0.01–0.02)	0.01 (0.01–0.02)
10-year	0.06 (0.03–0.11)	0.03 (0.01–0.07)	0.04 (0.02–0.07)
Death			
5-year	0.41 (0.35–0.46)	0.21 (0.18–0.25)	0.28 (0.25–0.31)
10-year	0.65 (0.58–0.73)	0.40 (0.35–0.46)	0.49 (0.45–0.54)
>79 years			
No. (%)	245 (27)	656 (73)	901 (100)
Cumulative incidence (95% CI)			
Renal failure			
5-year	0.02 (0.01–0.05)	0.01 (0.00–0.02)	0.01 (0.00–0.02)
10-year	0.05 (0.03–0.11)	0.01 (0.00–0.03)	0.03 (0.01–0.05)
Death			
5-year	0.64 (0.57–0.71)	0.53 (0.49–0.57)	0.56 (0.52–0.60)
10-year	0.88 (0.81–0.95)	0.83 (0.77–0.89)	0.84 (0.80–0.89)
Total			
No. (%)	928 (30)	2119 (70)	3047 (100)
Cumulative incidence (95% CI)			
Renal failure			
5-year	0.03 (0.02–0.04)	0.01 (0.01–0.02)	0.02 (0.01–0.02)
10-year	0.08 (0.05–0.11)	0.03 (0.02–0.04)	0.04 (0.03–0.06)
Death			
5-year	0.41 (0.38–0.45)	0.28 (0.26–0.30)	0.32 (0.30–0.34)
10-year	0.61 (0.56–0.67)	0.47 (0.43–0.50)	0.51 (0.48–0.55)

[a]CI denotes confidence interval.
[b]Renal failure was defined as irreversible CKD stage 5 or initiation of RRT.

Table 1 | Baseline characteristics of cohort of patients with CKD stage 3

	Men	Women	Total
No. (%)	928 (100)	2119 (100)	3047 (100)
Median age (IQR)[a]	75.0 (67.7–80.4)	75.0 (66.3–81.5)	75.0 (67.0–81.2)
Median GFR at baseline (IQR) (ml/min/1.73 m^2)	54.7 (49.9–57.7)	55.3 (51.1–58.0)	55.1 (50.8–57.9)
Median observation time (IQR) (months)	39 (20–67)	47 (28–71)	44 (26–69)
Median number of creatinine analyses (IQR)	12 (6–22)	8 (4–15)	9 (4–17)
Patients with fewer than 3 analyses (%)	7	11	10
End points,no. (%)			
Renal failure			
Chronic kidney disease stage 5	33 (4)	25 (1)	58 (2)
Renal replacement therapy	2 (0.2)	2 (0.1)	4 (0.1)
Death	383 (41)	576 (27)	959 (31)
Censored	510 (55)	1516 (72)	2026 (66)

[a]IQR denotes interquartile range.

Table 3 | Cox proportional-hazards regression analyses of the effects of age, gender, and GFR at baseline on the competing risks renal failure and death (*n*=3047)

	Renal failure			Death		
Baseline variables	Hazard ratio	95% confidence interval	*P*-value	Hazard ratio	95% confidence interval	*P*-value
Female gender	0.35	0.21–0.59	<0.0001	0.55	0.48–0.62	<0.0001
Age (10 year increment)	0.75	0.63–0.89	0.0009	2.28	2.11–2.46	<0.0001
GFR at baseline (10 ml/min/1.73 m^2 decrement)	2.50	1.89–3.31	<0.0001	1.25	1.14–1.37	<0.0001

Table 4 | Standardized incidence rate ratios for death and renal failure for patients with CKD stage 3 (*n*=3047) relative to the general population of Tromsø

	Men		Women		Total	
Age (years)	Ratio	95% confidence interval	Ratio	95% confidence interval	Ratio	95% confidence interval
<69						
Renal failure[a]	48.0	(22.7–101.5)	27.0	(11.9-61.2)	36.6	(21.2-63.2)
Death	3.6	(2.6–5.0)	2.7	(2.0–3.7)	3.1	(2.5–3.9)
70–79						
Renal failure	4.2	(1.8–9.6)	3.8	(1.8-8.3)	3.1	4.0 (2.3–7.0)
Death	2.4	(2.0–2.9)	1.8	(1.5–2.1)	2.0	(1.8–2.3)
>79						
Renal failure	4.6	(2.4–8.9)	2.6	(1.1-6.2)	3.7	(2.2-6.2)
Death	2.3	(2.0–2.6)	2.1	(1.9–2.3)	2.2	(2.0–2.3)
Total						
Renal failure	6.5	(4.3–9.9)	4.3	(2.7-6.9)	5.3	(3.9–7.3)
Death	2.4	(2.2–2.7)	2.1	(1.9–2.3)	2.2	(2.1–2.4)

[a]Renal failure was defined as irreversible CKD stage 5 or initiation of RRT.

Table 5 | Multilevel multivariate linear regression analysis of the effects of age and gender on GFR in CKD stage 3 (*n*=3047)

	Baseline GFR (ml/min/1.73 m^2)			Change in GFR per year (ml/min/1.73 m^2/year[a])		
Baseline variables	Regression coefficient (ml/min/1.73 m^2)	95% confidence interval	*P*-value	Regression coefficient (ml/min/1.73 m^2/year)	95% confidence interval	*P*-value
Estimate for 60-year-old male	53.70	53.13 to 54.27	<0.0001	−0.88	−1.18 to −0.59	<0.0001
Female gender	1.21	0.62 to 1.80	<0.0001	0.50	0.20 to 0.81	0.001
Age, 10 year increment	−0.72	−0.95 to −0.49	<0.0001	−0.38	−0.51 to −0.26	<0.0001

[a]This translates to a mean change in GFR per year at ages 30, 40, 50, 60, 70, 80 years of 0.26, −0.12, −0.50, −0.88, −1.26, −1.64 ml/min/1.73 m^2/year for men, and 0.76, 0.38, 0.00, −0.38, −0.76, −1.14 ml/min/1.73 m^2/year for women. A positive change signifies an increase in GFR with time, a negative change a decreasing GFR.

The possibility of bias because renal failure was not detected in patients who died was examined by estimating expected GFR at the time of death from a linear model for disease progression for each patient. Patients falling below a GFR of 15 ml/min/1.73 m^2 before death were then considered to have experienced CKD stage 5 and the Cox proportional-hazards regression analyses repeated. The results were not materially different from those presented above.

Standardized incidence rate ratios for death and renal failure relative to the Tromsø population were estimated (Table 4). For both death and renal failure, the ratios demonstrated increased incidence rates for CKD stage 3, especially for the youngest age group. There were higher renal failure ratios for men than for women, but the differences were not statistically significant.

Change in GFR

In the multi-level model, gender and age were significant regressors of both baseline GFR and change in GFR (Table 5). Both dependent variables decreased with increasing age and for male gender. Interactions between age and gender in both equations (2) and (3) were tested. While this demonstrated that the gender difference in baseline GFR was the highest for the younger age groups ($P=0.002$), there was no interaction between age and gender for change in GFR ($P=0.53$). When including a quadratic term for age in equation (3), a weak effect on change in GFR was also significant ($P=0.02$), but was found non-significant when the nine patients in the age group 20–29 years were excluded from the analysis.

In Table 6, estimates of change in GFR under the model conditional on the observed GFRs are tabulated according to age and gender. The mean overall change in GFR was

Table 6 | Estimated mean change in GFR in patients with CKD stage 3 according to gender and age (*n*=3047)

Age	Men	Women	Total
<69 years			
No. (%)	279 (28)	704 (72)	983 (100)
Mean ΔGFR (ml/min/1.73 m^2/year)[a]	−0.94	−0.33	−0.50
Patients with ΔGFR <0 ml/min/1.73 m^2/year (%)	69	58	61
Patients with ΔGFR <−5 ml/min/1.73 m^2/year (%)	9	3	5
70–79 years			
No. (%)	404 (35)	759 (65)	1163 (100)
Mean ΔGFR (ml/min/1.73 m^2/year)	−1.29	−0.91	−1.04
Patients with ΔGFR <0 ml/min/1.73 m^2/year (%)	76	75	75
Patients with ΔGFR <−5 ml/min/1.73 m^2/year (%)	7	4	5
>79 years			
No. (%)	245 (27)	656 (73)	901 (100)
Mean ΔGFR (ml/min/1.73 m^2/year)	−2.07	−1.43	−1.60
Patients with ΔGFR <0 ml/min/1.73 m^2/year (%)	87	82	83
Patients with ΔGFR <−5 ml/min/1.73 m^2/year (%)	9	6	7
Total			
No. (%)	928 (30)	2119 (70)	3047 (100)
Mean ΔGFR (ml/min/1.73 m^2/year)	−1.39	−0.88	−1.03
Patients with ΔGFR <0 ml/min/1.73 m^2/year (%)	77	71	73
Patients with ΔGFR <−5 ml/min/1.73 m^2/year (%)	8	4	6

[a]ΔGFR denotes change in GFR. Estimates of the underlying change in GFR for each patient under the statistical model conditional on the observed GFRs was used (see text).

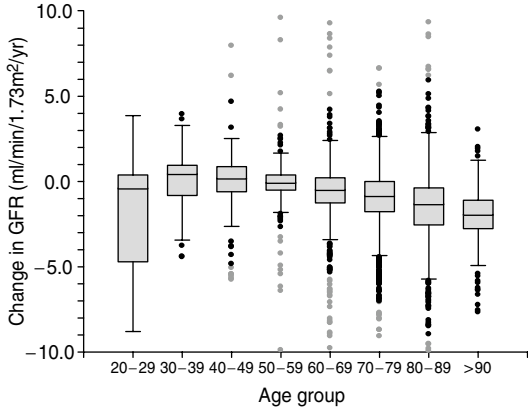

Figure 1 | Box-plot of distribution of estimated change in GFR in patients with CKD stage 3 according to age group (*n* = 3047). Boxes indicate interquartile range with middle line representing median. Whiskers indicate largest observation that is less than or equal to the 75th percentile plus 1.5 times interquartile range and smallest observation that is greater than or equal to the 25th percentile minus 1.5 times interquartile range. Values that are less than three interquartile ranges from the 25th and 75th percentiles are shown as black dots, and those outside three interquartile ranges as gray dots.

−1.03 ml/min/1.73 m^2/year. Seventy-three percent of the patients had a change in GFR less than 0 and 6% less than −5 ml/min/1.73 m^2/year (Figure 1).

DISCUSSION

CKD has traditionally been regarded as unremittingly progressive when GFR falls below a hypothesized point of no return. However, in the Modification of Diet in Renal Disease study, as many as 19% of patients with GFR between 25 and 55 ml/min/1.73 m^2 experienced improvement or stabilization of their renal function during the 2-year study period.[10] The results of the present study show that an even higher percentage of CKD patients in clinical practice may have favorable renal prognoses, as 27% did not experience a decline in GFR during a mean observation time of more than four years (Table 6).

The mean decline in GFR of about 1 ml/min/1.73 m^2/year was also markedly lower than in the Modification of Diet in Renal Disease study (4 ml/min/1.73 m^2/year).[10] Still, a significant percentage of CKD stage 3 patients (6%) experienced a rapid progression towards renal failure (change in GFR <−5 ml/min/1.73 m^2/year), although few actually reached the end point. However, mortality at 10 years was more than 50%. The same pattern was found by Keith *et al.*[7] in their study of members of Health Maintenance Organization (HMO) in Oregon. Although a formal survival analysis was not performed, 24% of patients with CKD stage 3 died during a 51-month observation period, whereas only 1.3% started on RRT.

To investigate the possibility of bias due to undetected renal failure at death, all analyses in the present study were repeated with GFR estimated at the time of death, with similar results. Thus, patients died from other causes before they developed renal failure. This relation between the competing risks of death and renal failure was particularly pronounced for older patients and was also found by Collins *et al.*[11] in their study of Medicare patients with CKD in the US. Whereas increasing age was associated with a faster GFR decline, older patients had a lower cumulative incidence of renal failure. The high prevalence of ESRD at high ages observed in renal registries must therefore be explained by the high prevalence of CKD in these age groups.[4]

CKD stage 3 was associated with increased incidence rates of both renal failure and death compared to the general population, particularly for those younger than 70 years (Table 4). Other investigations have found CKD an independent risk factor for both all-cause and cardiovascular mortalities.[9,12] Accordingly, for most CKD patients the risk of cardiovascular disease far outweighs the risk of renal failure. This has important consequences for the clinical management of this patient group. Intervention against cardiovascular risk factors, as for example, hypercholesterolemia, may be more important than preparing patients for RRT. A recent meta-analysis of randomized controlled trials found that statins were effective in reducing cardiovascular events in patients with CKD stage 3.[13]

In the present study, the prognosis of CKD depended on gender. Male gender had a negative effect on both decline of GFR and hazard of renal failure. The finding of twice as many women as men with CKD stage 3 raises the possibility that this could have been caused by selection bias from a failure to detect men with a good prognosis. Table 7 shows that there were fewer measurements of creatinine per person year for men than for women in the younger age groups. However, the proportion of men with CKD stage 3 among those who were tested was low as well, whereas the opposite would be typical if men were underdiagnosed. Also, the gender effects were uniform across age for both mortality, renal failure and rate of change in GFR, even though the gender differences in number of measurements varied widely across age. Finally, the prevalence of CKD stage 3 for men has been found lower than for women in other studies, as for example, in the third National Health and Nutrition Examination Survey, where the prevalence for men was 3.4% and for women 5.1%.[4] It is therefore unlikely that selection bias was the only explanation for the gender differences found in this study.

The effect of gender on the progression of CKD has been a matter of debate, where most of the evidence seems to point towards a negative effect of male gender.[14,15] In a recent study from Washington county, Haroun *et al.*[6] found a relative risk of developing a need for RRT of 1.7 for men, when adjusting for blood pressure, diabetes, and smoking. In contrast, Jafar *et al.*[16] found that the gender difference was reversed when correcting for baseline covariates in a meta-analysis of randomized controlled trials, indicating that the adjusted effect of male gender might be protective. The results of the present study indicate that preventive measures may be particularly important in men, and even more so if their adverse prognosis is caused by modifiable risk factors.

The different prognoses of CKD stage 3 in identifiable subgroups make it difficult to establish guidelines with a uniform approach to these patients. A patient with stable GFR may need more attention to an increased risk of cardiovascular disease, whereas patients with progressive disease must also be prepared for RRT. Old patients may benefit less from intensive diagnostic and therapeutic efforts than younger patients. The different risk profiles of men and women may require different approaches. The present National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines do not incorporate different approaches to subgroups of the CKD population, presumably because the evidence base has been lacking. More research is needed. The most important issue is to establish risk factors for predicting which patients will progress and which have a stable disease. Such risk factors should be included in the staging of CKD. The most obvious candidate is proteinuria, which is known to be associated with progressive disease.[2] Although included in the definition of stages 1 and 2, definitions of the more advanced stages have been made without taking proteinuria into account. This needs to be reconsidered.

The most important limitation of the present study was that measurements of creatinine were made for clinical purposes. This may have selected patients with a more serious disease and biased our estimates towards a faster rate of decline in GFR and higher incidences of the endpoints. However, this strengthens our conclusion that CKD is less progressive and has a lower risk of RRT than previously

Table 7 | Number of included patients with CKD stage 3 and creatinine measurements per person year in the Tromsø population

	Number of patients with CKD stage 3		CKD stage 3 patients per 1000 measurements		Total number of creatinine measurements		Measurements per person year		Total number of person years in study period	
Age group (years)	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
0–9					3 227	2 631	0.07	0.06	46 543	42 515
10–19					3 525	4 215	0.10	0.13	34 769	32 985
20–29	9	6	1.2	0.5	7 365	11 537	0.16	0.24	46 031	48 594
30–39	5	21	0.5	1.4	10 526	15 161	0.20	0.29	52 437	51 883
40–49	31	81	2.1	4.7	14 503	17 157	0.33	0.40	44 224	42 412
50–59	57	216	3.0	10.5	18 794	20 529	0.59	0.69	32 056	29 887
60–69	177	380	8.8	21.2	20 173	17 965	1.16	1.00	17 439	18 025
70–79	404	759	16.2	30.4	24 865	25 000	2.12	1.61	11 746	15 560
80–89	204	571	19.0	34.0	10 762	16 788	2.82	2.04	3 810	8 224
>90	41	85	29.9	34.4	1 369	2 468	3.15	1.91	434	1 289
Total	928	2119	8.1	15.9	115 109	133 451	0.40	0.46	289 489	291 374

estimated. In contrast, a possibility, that a significant number of patients with manifest CKD should not have been represented in the creatinine database seems unlikely. In fact, virtually all patients who actually developed a need for RRT in the study period were included in the study population. In Tromsø, routine creatinine analyses were made as a part of most consultations in both primary care and outpatient clinics, and the resulting number of measurements relative to the population size was very high (Table 7). The ideal study design would have been a random sample survey with prescheduled repeated measurements for the same follow-up period. However, even the estimates from a survey would not have been entirely unbiased, as elderly and diseased patients would have been less likely to attend.

Another problem in using routine analyses of creatinine for estimating changes in GFR over a long time period is to ensure stability of the assay. Although rigorous quality control routines are a safeguard against larger fluctuations, long-term drift cannot be completely excluded. To explore this issue, we repeated the multilevel regression analysis with covariates for measurement year, which did not materially alter the results. Variations in the calibration of serum creatinine assays relative to the laboratory used in the Modification of Diet in Renal Disease study have also been observed with corresponding variations in estimated GFR from the abbreviated Modification of Diet in Renal Disease formula.[17] However, this problem would affect absolute values most and is of less importance for change in GFR, which was the main focus of the present study.

The clinical manifestations of CKD are known to depend on ethnic and socioeconomic factors. The predominantly Caucasian population of Tromsø includes a small minority with Sámi background, but there are no studies of kidney disease in this group, and the creatinine database did not include information on ethnicity. The socioeconomic status of Norway is somewhat above the average for developed countries.[18] This may have contributed to lower the incidence of CKD, whereas little is known about how it might have affected prognosis.[5,19] Altogether, Tromsø is probably fairly representative of populations in the developed world.

We conclude that the tendency of CKD stage 3 to progress to renal failure is less than estimated from studies of selected patient groups, and that high mortality forestalls the development of renal failure in many patients. Both high age and male gender are independent predictors of poor prognosis. The present staging system for CKD focuses on level of GFR rather than on rate of progression. It should be improved to accommodate the need for different approaches to subgroups of patients by placing more emphasis on prognostic factors.

MATERIALS AND METHODS

Subjects and data

In the 10-year study period from 1 January 1994 to 31 December 2003, the annual mean population of Tromsø, a municipality in Northern Norway, was 58 086. The University Hospital of North Norway, which is located in the municipality, is its sole provider of nephrology and laboratory services.

In the hospital's database of serum creatinine analyses, persons are uniquely identified by date of birth and person number. The subjects of the study are the 38 241 persons identified by postcode analysis as living in the municipality of Tromsø. In total, these subjects had had 248 560 measurements of creatinine performed by the hospital's laboratory as a part of routine clinical activities in the study period. This included all health care in the municipality, both primary care and hospital in- and outpatients. Table 7 shows the number of creatinine measurements and person years in the total population. Population data were obtained from the website of Statistics Norway.[20]

As the aerial distance to the next hospital and laboratory is 150 km and by road 300 km, it seems reasonable to assume that the number of creatinine measurements carried out by other laboratories must have been negligible. To check this assumption, the only provider of clinical chemistry services at the national level was contacted. It was confirmed that the number of analyses of creatinine performed in patients from Tromsø was very low: fewer than 100 for the last 5 years of the study period. Accordingly, the database contained the results of virtually all analyses of creatinine performed on inhabitants of Tromsø in the study period.

GFR was estimated for all measurements of creatinine in the database from the Modification of Diet in Renal Disease abbreviated formula. Only measurements before initiation of first time RRT were included. The formula estimates GFR from creatinine, gender and age as $186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times 0.742$ for women $\times$ 1.21 if African American (Levey AS *et al. J Am Soc Nephrol* 2000; **11**: A0828, abstract).[21] The database included date of birth and a person number encoding gender. Age at the time of measurement was used for each estimate. The number of inhabitants of African descent in Tromsø was negligible, and the last factor was ignored.

Patients having GFR less than 60 ml/min/1.73 m^2 for 3 months or more have CKD according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative definition.[2] GFR from 30–59 ml/min/1.73 m^2 is classified as CKD stage 3. All GFR estimates in the study period in this interval were identified. When the identified measurements were followed by a second measurement in the same interval 90 days or more after the first, the patient was classified as having CKD stage 3 if there were no measurements outside the interval between the two. The observation time of each patient was defined to start 3 months after the date of the first registered measurement satisfying these criteria. Persons younger than 20 years were not included.

Measurements

Serum creatinine analyses were performed with instruments from Roche Diagnostics (GmbH, 68 298 Mannheim, Germany). The model Hitachi 917 was used from 1994 to 2002 and from 2002 the Modular model from Hitachi was used. A Jaffe method with reagents and calibrators purchased from the same company was used. Control samples with three levels of creatinine were analyzed for every 100 patient samples. An analytical coefficient of variation of 2% was used in the internal quality control system. The occurrence of two consecutive control observations exceeding the same mean $\pm$ 2 s.d. was used as rejection rule. Calibrations were performed when necessary. The laboratory participated in an External Quality Assessment Program provided by Labquality, Helsinki, FI, USA.

Outcomes

Death and renal failure were considered competing risks. Renal failure was defined as either initiation of RRT or CKD stage 5, and the date of the event that occurred first was registered. CKD stage 5 is defined as GFR less than 15 ml/min/1.73 m^2 and was ascertained from the database as the first date of a GFR below this level with no subsequent values of 15 or greater before RRT, death, or censoring.[2] Patients were censored at the end of the study period.

All initiations of RRT for inhabitants of the municipality are administered by the University Hospital of North Norway, and the date of initiation was recorded from hospital databases. Initiation of RRT in patients who had moved from the municipality was assumed to be negligible, as migration in persons over 40 years of age to and from the municipality was very low in the period.[20] To check the completeness of the creatinine database, it was matched with all patients from Tromsø having initiated RRT in the study period. Only four of 55 patients did not have any creatinine measurement previous to 3 months before start of RRT. In two of these, RRT was started within 3 months of the beginning of the study period.

Date of death was registered from the hospital's database, which is regularly updated against the Norwegian Central Population Register.

Statistical analysis

The association between estimated GFR and the predictor variables gender, age at inclusion and time was studied with a multilevel model.[22] At the first level, GFR was assumed to follow a linear regression on time for each patient:

$$\mathrm{GFR}_{ij} = \mathrm{GFR}_{0i} + \pi_{1i}\mathrm{time}_{ij} + \varepsilon_{ij} \quad (1)$$

where GFR_{ij} is the jth GFR estimate for the ith patient, GFR_{0i} is the true GFR at inclusion for the ith patient, π_{1i} the true rate of change in GFR for the ith patient, and ε_{ij} the residual variation. At the second level, GFR_{0i} and π_{1i} were modelled in linear models with age at inclusion and gender as independent variables:

$$\mathrm{GFR}_{0i} = \mathrm{GFR}_{00} + \beta_{01}\mathrm{age}_i + \beta_{02}\mathrm{gender}_i + \zeta_{0i} \quad (2)$$

$$\pi_{1i} = \beta_{10} + \beta_{11}\mathrm{age}_i + \beta_{12}\mathrm{gender}_i + \zeta_{1i} \quad (3)$$

where GFR_{00} represents the population true mean GFR at inclusion for a 60-year-old male, β_{01} and β_{02} the population true effects of age and gender on GFR at inclusion, respectively, β_{10} the population true mean change in GFR for a 60-year-old male and β_{11} and β_{12} the population true effects of age and gender on change in GFR, respectively. ζ_{0i} and ζ_{1i} represent residual variation. Age was entered as age in years minus 60 (to center the intercept at age 60 years) and gender as a dichotomous variable with 0 coding for male and 1 for female.

Substituting for GFR_{0i} and π_{1i} in equation (1) and rearranging terms gives

$$\begin{aligned}\mathrm{GFR}_{ij} =& (\mathrm{GFR}_{00} + \beta_{01}\mathrm{age}_i + \beta_{02}\mathrm{gender}_i \\ &+ \beta_{10}\mathrm{time}_{ij} + \beta_{11}\mathrm{age}_i \times \mathrm{time}_{ij} \\ &+ \beta_{12}\mathrm{gender}_i \times \mathrm{time}_{ij}) + (\zeta_{0i} + \zeta_{1i}\mathrm{time}_{ij} + \varepsilon_{ij})\end{aligned}$$

In this equation, the first parenthesis includes the fixed and the second the stochastic effects of the model. PROC MIXED in SAS (SAS Institute, Cary, NC, USA) was used for estimating parameters and confidence intervals. The model used all GFR estimates from the start of observation till death, initiation of RRT, or censoring. Interactions between age and gender were tested by including product terms in (2) and (3).

The possibility of bias because this model gives less weight to patients with few GFR estimates and a rapid decline in GFR has been a concern in some studies, and models incorporating informative censoring have been used.[23,24] In the present study, a high proportion of the study subjects died before the end of the study period. For these patients, Pearson's correlation coefficient between observation time and an ordinary least-squares estimate of change in GFR for each patient was only 0.03, which does not indicate that this type of bias was a problem. Accordingly, we chose a model without informative censoring.

For tabular and graphical presentations of the distribution of change in GFR, estimates of π_{1i} for each patient under the model conditional on the observed GFR estimates were used. Compared to using ordinary least-squares estimates of change in GFR for each individual patient, this method avoids high variability in estimates for patients with short follow-up.

Survival analysis of the competing risks of death and renal failure was performed by estimating non-parametric, maximum-likelihood estimates of the cumulative incidence of each endpoint in the presence of the other, as suggested by Kalbfleisch and Prentice.[25] The effects on the competing risks of age, gender, and GFR at baseline were analyzed with Cox proportional-hazards regression of each endpoint separately, as outlined by the same authors.[25] Nonlinear effects of age and GFR were tested by including quadratic terms in the models. These analyses were performed with Number Cruncher Statistical Systems (Kaysville, UT, USA).

Incidence rate ratios for death and renal failure relative to the general population of Tromsø standardized to the age and gender distribution of the CKD stage 3 cohort were estimated as described by Rothman and Greenland.[26] Mortality data were obtained from the website of Statistics Norway.[20]

Statistical significance was set at P less than 0.05.

This study was approved by the Norwegian Data Inspectorate and the Regional Ethics Committee of North Norway.

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