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# **Translating chronic kidney disease epidemiology into patient care - the individual / public health risk paradox**

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## Abstract

**Background:** Applying the Kidney Disease Outcomes Quality Initiative definitions of chronic kidney disease (CKD), it appears that CKD is common. The increased recognition of CKD has brought with it the clinical challenge of translating into practice the implications for the patient and for service planning. To understand the clinical relevance and translate that into information to support individual patient care and service planning, we explored clinical outcomes in a large British community CKD cohort, identified through routine opportunistic testing, with 6 years follow-up (~13,000 patient-years).

**Methods:** A cohort had previously been identified with CKD - sustained reduced eGFR over at least 3 months and case-note review. Six year (13,339 patient-years) follow up for Renal Replacement Therapy (RRT) initiation and death was achieved through data-linkage. Age and sex specific mortality rates were compared to the general population.

**Results:** Of 3414 individuals (most stage 3b-5), median age 78.6 years, followed for 13,339 patient-years, 170 (5%) initiated RRT and 2024 (59%) died without initiating RRT. RRT initiation rates decreased with age from 14.33 to 0.65 per 100 patient-years amongst those 15-25 years and 75-85 years at baseline but the actual numbers initiating RRT increased from 6 to 34 respectively. RRT initiation rates were lower for female sex, absence of macroalbuminuria and less advanced CKD stage.

Mortality rates increased with age from 1.9 to 33.8 per 100 patient-years for those aged 15-45 and over 85 years at baseline, an excess of 2 and 17 per 100 patient-years over that of the general population respectively. However the increase in relative risk was 19 fold for those aged 15-45, and just two-fold in those over 85 years. These data have been converted into simple tools for considering individual patients' risk and informing service planning

**Conclusions:** The contrast between relative and absolute risk for both RRT initiation and mortality by age group illustrate the difficulties for planning services. The challenge that now faces clinicians is how to appropriately identify which elderly with CKD are at high risk of poor outcome.

### Keywords

Chronic kidney disease  
epidemiology and outcomes  
mortality  
renal progression  
risk communication

## Introduction

The principles of the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines(1), for the classification of chronic kidney disease (CKD) have been accepted internationally (2, 3) and have successfully highlighted the importance of CKD. By facilitating earlier diagnosis and management, the intention was to slow progression, improve outcomes and ultimately reduce the need for renal replacement therapy (RRT).

With application of this classification, it appears that CKD is common (between 3.8% and 11.1% of the population) (4) and, with an ageing population and increasing prevalence of diabetes, thought likely to increase. High cardiovascular morbidity and mortality, and all-cause mortality among people with CKD (5-7) have led to calls for CKD screening as a public health measure. However despite the excess mortality and morbidity, not all patients with CKD die prematurely or initiate RRT (8). The lack of clarity about prognosis in CKD has sparked debate regarding whether the definition truly identifies those at risk of poor outcome or merely 'label' many, particularly the elderly, with disease, without a clear prognostic role (9). The increased recognition of CKD has brought with it the clinical challenge of translating into practice the implications for the patient and for service planning.

To understand the clinical relevance of CKD and translate that into information to support individual patient care and service planning, we explored the relationship between RRT initiation, all-cause mortality rates and baseline characteristics in a large British community CKD cohort, identified through routine opportunistic testing, with 6 years follow-up (~13,000 patient-years).

## Methods

The National Health Service (NHS) Grampian administrative region provides medical services to a well-defined population (n= 433,109, over 15 years of age in 2003) in North-East Scotland, with little use of external health services due to geographical remoteness. All biochemistry services (in-patient, community and private) are provided through two linked National External Quality Assessment Service monitored laboratories. All renal services (except transplantation up to 10 days post-transplant) are provided from a single regional unit.

In 2003, all adults (aged over 15 years) resident in the region, with abnormal renal function tests (creatinine above 150  $\mu\text{mol/l}$  for men and 130  $\mu\text{mol/l}$  for women measured from January to June) were identified (n=5538). Those on RRT were excluded. Results of those with acute kidney injury and early follow-up on those with CKD are reported elsewhere (10, 11), only those with CKD are reported here.

### ***GLOMMS-I - the cohort***

The first Grampian Laboratory Outcomes Mortality and Morbidity Study (GLOMMS-I) comprised a cohort of 3426 individuals with CKD from the 2003 group. Individuals with CKD were identified by virtue of 3 either raised creatinine measurements (above the 150  $\mu\text{mol/l}$  or 130  $\mu\text{mol/l}$  threshold), or depressed estimated glomerular filtration rate (eGFR) values (median eGFR below 60  $\text{ml/min/1.73m}^2$ ) documented over at least 3 months either before or after the index creatinine. Case-note review provided baseline comorbidity. Regional health administration systems recorded all RRT provision, admissions, discharges, out-patient attendances and death registrations within the region. Data linkage between these systems and the cohort took place to allow full follow up to the 30<sup>th</sup> June 2009.

GLOMMS-I was approved by the University of Aberdeen Research Ethics Committee, the NHS Grampian Caldicott Guardian and discussed with the North of Scotland NHS Research Ethics Committee.

### **Biochemistry**

#### *Excretory renal function*

An individual's first creatinine value above the threshold during the period January 2003 to June 2003 inclusively, was taken as the "index" creatinine. Serum creatinine values were measured using the kinetic Jaffe method (Siemens automated analyser using Siemens reagents) and were traceable over time to the isotope dilution mass spectrometry (IDMS) method. Estimated glomerular filtration rate (eGFR) values were calculated using the modified 4 variable MDRD equation suitable for use with IDMS traceable creatinine values. eGFR at "index" was used to assign a CKD stage.

#### *Proteinuria/ Albuminuria*

In the clinical dataset urinary protein creatinine ratio (PCR) and albumin creatinine ratio (ACR) were used, these were automatically calculated as part of the measurement of these urinary values on a Siemens automated analyser using Siemens reagents. Patients were defined as "untested", "normoalbuminuric", "microalbuminuric" or "macroalbuminuric" based on the single most recent (between 1999 and "index") measurement of proteinuria or albuminuria. The thresholds for microalbuminuria were  $\geq 2.5\text{mg}/\text{mmol}$  ACR for men,  $\geq 3.5\text{mg}/\text{mmol}$  ACR for women; for macroalbuminuria  $\geq 30\text{mg}/\text{mmol}$  ACR for both men and women, or  $\geq 50\text{mg}/\text{mmol}$  PCR. No dipstick measurements were used.

### **Baseline comorbidity & smoking status**

Nephrology specialists reviewed all case notes for important comorbidities and smoking status (table 1), data was extracted and data transfer checked by another individual.

### **Clinical outcomes and follow-up**

The two outcomes of interest were:- initiation of renal replacement therapy (RRT) and all-cause mortality, with follow-up truncated at midnight 30<sup>th</sup> June 2009 (6 years from the end of the "index" period). Date and cause of death as registered as ICD-10 codes with the General Registrar Office Scotland were recorded, as was date of chronic renal replacement therapy initiation (defined as per UK Renal Registry definition, no recovery of renal function within 90 days). Use of other NHS Grampian services (laboratory, out-patient or in-patient) within a year of study end was checked to estimate possible loss to follow-up. Of the 3426 individuals in this CKD cohort, twelve died on the day of the index creatinine and were therefore excluded from the remainder of the analysis.

### **Analysis**

Baseline characteristics were tabulated by gender and differences tested for using Chi squared or Mann Whitney test as appropriate.

Renal survival was defined as not having initiated RRT, censoring at time of death, and was plotted using the Kaplan-Meier method. Outcomes (RRT initiation and all-cause mortality) were calculated as number of events and rates per person-years. Incidence rate ratios (IRRs) were used to compare outcome incidence between baseline exposure levels for age, sex, CKD stage, proteinuria status, comorbidity and smoking status categorised as shown in table 1. To allow for the potential non-linear increase in IRR with change in categories of age, and other categorical exposures, these exposures were analysed using indicator variables. Outcomes by combined age groups 15-44, 45-54, 55-64, 65-74, 75-84 and 85+ years were also calculated given the small numbers in the youngest age

bands and population mortality data only being available for the composite age 85+ years. Analyses, stratified separately by CKD stage, hypertension status and age were conducted to assess whether these modified the effect of other exposures e.g. gender. Poisson models were used to explore the effect of baseline characteristics on both outcomes separately. These were repeated with only those with a measurement of proteinuria to ensure there was no change in effect.

Mortality rates were compared with age, sex strata specific mortality estimates for the whole Grampian population (estimated from the number of deaths registered and mid-year population estimates for years 2003 through 2009 (12, 13)). These comparisons were expressed both as mortality rate excess and mortality rate ratios.

To translate the risk data into information useful for supporting patient care, the percentage with incident RRT at 5 years by baseline age, sex, CKD stage and proteinuria status was also calculated. Similarly, to translate the competing risk of death, the percentages of the cohort that were still alive and not on RRT at 5 years for these same categories were calculated.

All analysis was carried out with Stata 11.1.

## **Results**

### ***Baseline***

The 3414 individuals had a median age of 78.6 years (interquartile range 71.1 to 84.1 years), 44.2% were male (table 1). The majority (66.4%) had stage 3b CKD (figure 1). Reflecting clinical practice, in 70.5% there had been no laboratory quantification of urinary protein. Comorbidity was common – 40% had ischaemic heart disease and 25% diabetes at baseline.

### ***Outcomes***

At 6 years follow-up, 170 (5%) had initiated RRT (77 subsequently dying), 2024 (59%) died without initiating RRT, and 1220 (36%) were alive without initiating RRT (see supplemental table 1). Of these 1220 survivors, only 51 had no contact with NHS Grampian within a year of study end. The characteristics of those initiating RRT or dying, are shown in table 2. There were 12,919 and 13,339 patient-years of follow up for initiation of RRT and death respectively (420 patient-years after initiating RRT).

### ***Renal replacement therapy***

Overall the chronic RRT initiation rate was 1.3 per 100 patient years, males at 1.96 and females at 0.81 per 100 patient-years, respectively. Over the six years, the annual RRT initiation rates for reported risk factors were stable (results not shown). Initiation rates dropped with age from 14.33 to 0.65 per 100 patient-years amongst those 15-25 years and 75-85 years at baseline respectively, with no-one initiating chronic RRT who was above 85 years at baseline (figure 2), the actual numbers initiating RRT however increased from 6 to 34 in these age groups, and was 49 in those aged 65-74 years. Both CKD stage and the presence of proteinuria were associated with RRT initiation rates (renal survival is shown in figure 3 and Poisson regression derived incidence rate ratios adjusted as appropriate in table 2). There was no evidence of modification of the effects outlined in table 2 when stratified by CKD stage, hypertension status and age

(results not shown), nor when the analyses were repeated without those with no measure of proteinuria (see supplemental table 2).

#### *Mortality*

All cause mortality rates were 15.6 and 15.9 per 100 patient-years in males and females respectively. Circulatory system diseases were recorded as the main cause of death in 1030 (49% - ICD-10, I00-I99), specifically ischaemic heart disease in 576 (28%). Mortality rates in the CKD cohort increased with age, from 1.9 to 33.8 per 100 patient-years in those aged 15-45 years and over 85 years at baseline, compared to 0.1 and 16.5 per 100 patient-years in the general Grampian population. Mortality rates increased with worse CKD stage, most comorbidities, proteinuria and male sex (table 2).

#### *Translating into patient care*

The percentage of the cohort, stratified by sex, age band (<50, 50-69, ≥70 years), proteinuria status (presence of macroalbuminuria or not (normoalbuminuria, microalbuminuria and un-measured)) and CKD stage, that had initiated RRT by 5 years is presented (figure 4) as a simple illustrative risk communication tool. This shows the variability by age even within a given sex, CKD stage, or proteinuria status group.

The effect of age and sex on absolute and relative all-cause mortality rates in those with CKD is shown in figures 5 and 6. The 19-fold and 2-fold increase in mortality in those with CKD aged 15-45 years and 85 years and older respectively equates to 2 excess deaths per 100 patient-years amongst those aged 15-45, and 17 excess deaths per 100 patient-years amongst those aged 85 years and over (shown separately by sex in figures 6 and 5 respectively).

There were 1220 individuals in the GLOMMS-I cohort who neither died nor initiated RRT. The percentage of the cohort who were RRT-free and alive at 5 years are shown in figure 7.

## **Discussion**

In this large British community CKD cohort with ~13,000 patient-years of follow-up, the rate of RRT initiation was 1.3 per 100 patient-years. Young male individuals with macroalbuminuria, type 2 diabetes and advanced CKD (stage 5) were at highest risk of initiating RRT, but the numbers initiating RRT were highest in the older age groups. Overall mortality was high, particularly amongst the elderly. However the relative mortality risk, comparing those with CKD to the general population was highest amongst the young. A third of our cohort were still alive and not on RRT after six years despite being quite elderly. This survivor group illustrate that despite the competing risks of death and RRT initiation, many with CKD will not suffer these events and planning for care of these individuals is important.

Whether identified through opportunistic healthcare testing as part of routine clinical practice or through screening, the prognostic significance of CKD is a challenging message to communicate. Age, sex (14), CKD stage and proteinuria status are important predictors of outcome in CKD. The low rate of progression to ESRD and RRT (5, 6) creates a clinical challenge when faced with interpreting low eGFR results both at the individual patient level and the population level for planning services. Figure 4, showing the proportion initiating RRT after 5 years, by age, sex, CKD stage and the presence of macroalbuminuria, offers a template for a tool for clinicians for informing patients of risk (personalised by their physician in light of disease course and interventions). It is similar to the tables

outlined by Hallan (15) and Levey (16) using excretory function and albuminuria, but here we add age and gender as important additional factors when determining the risk of initiation of RRT.

In GLOMMS-I, we identified the cohort through routine laboratory data and thus patients were identified by opportunistic testing. Compared to key studies based on cohorts identified through population screening (5, 7), GLOMMS-I better reflects likely outcomes in clinical practice. However, the use of routine laboratory data introduced a potential source of bias with inclusion dependent on an indication for measuring renal function. Some with CKD will have been missed due to a lack of retesting to confirm chronicity; and the creatinine inclusion thresholds of 130  $\mu\text{mol/l}$  and 150  $\mu\text{mol/l}$ , limits the generalisability of the findings to those with more advanced CKD (stage 3b (eGFR 30-45 ml/min/1.73m<sup>2</sup>) or worse) particularly so amongst the elderly, however the insistence on at least 3 months of depressed renal function ensures that those with just acute kidney injury are excluded. Many had not had a measurement of proteinuria and this potentially weakens the discriminatory effect that microalbuminuria may have had over normoalbuminuria if more information had been available. However since this information is missing in a non-random way (presumably not thought to be clinically relevant), no attempt to impute the results have been made. Indeed the exclusion of these individuals made little difference to the overall results. The use of secondary care documentation for comorbidity is a potential source of ascertainment bias, however case-note review by clinicians for pre-specified diagnostic criteria is an acceptable standard for comorbidity ascertainment. Grampian is a predominantly northern European Caucasian population and thus limits the generalisability of our findings. This cohort is important, however, because it reflects current clinical practice and is therefore very relevant to patients in care settings where there is opportunistic detection of CKD. Information on medication at baseline would have been ideal but was not available and is unlikely to have a huge effect over those of age and stage of renal disease. Although we adjusted for potential confounders, there might be additional confounders for which we were unable to correct. The illustrative tool is just illustrative, and has not been validated in other populations. Due to the small numbers in each risk category the estimates are imprecise, and volatile - any one young individual's outcome has a large impact.

Although other British studies have reported on mortality (19, 24, 29) and RRT initiation (19) in those with CKD, we believe that this is the largest British cohort to date reporting on both outcomes, with the longest follow-up time; however there are larger studies from elsewhere (6, 8, 18, 23, 26). The use of linked data, collected as part of routine care, provides an efficient methodology for the establishment and follow-up of a community cohort that reflects clinical practice. GLOMMS-I was carefully characterised at baseline with confirmation of chronicity, and case-note review for comorbidity. Because of the remoteness of the population there were few losses to follow-up; only 1.5% of the cohort had no documentation of initiating RRT, dying or having contact with NHS Grampian within a year of study end. Using all creatinine measurements to determine inclusion in the cohort ensured a community perspective of CKD, rather than focussing on those referred to secondary care. The accepted risk factors for progressive renal disease, type 2 diabetes and proteinuria, were associated with initiation of RRT.

Routine eGFR reporting and the international acceptance of the principles of the KDOQI CKD definitions, has focused clinical attention on CKD. CKD's importance lies with its association with progression to end stage renal disease (ESRD), RRT initiation, increased mortality and cardiovascular disease. Reduced eGFR is common in the adult population, particularly the elderly, and some scepticism has

arisen about the appropriateness of labelling so many individuals with a disease (9). Although the rate and relative risk of RRT initiation is highest amongst the young, absolute numbers are higher amongst the older population. Registry data (17) shows that RRT incidence increases with age, however the risk of initiating RRT for those with CKD decreases (14, 18, 19). This reflects the increasing prevalence of CKD with increasing age (20-22), possibly differing renal pathology i.e. younger people with CKD may progress faster than elderly individuals, and probably more use of conservative care amongst those greater numbers of elderly with CKD. Whether this decreasing rate of initiation is due to progression rate, mortality, or differing acceptance rates (due to comorbidity and expected survival) with age is unclear. The association of worse CKD stage (18, 19) and proteinuria status (5, 6, 19, 23) with higher RRT initiation rates is clear. The association between comorbidity and RRT initiation rates is complex and open to ascertainment bias. Another study has illustrated that even for diabetes, the association with increased RRT initiation rates disappears after correction for eGFR and proteinuria (23). We also found this, so although models adjusting for comorbidity were developed, they were dropped since they made little difference to model performance.

Mortality in those with CKD is a far more common outcome than the initiation of RRT (6, 19), although in Nephrology clinics this may not be so (8). The relative importance of CKD for all-cause mortality, by age is less often illustrated (24, 25). We found the relative risk of death in those with CKD compared to the general population was highest in the young; this may be due to a greater contribution to mortality from premature cardiovascular disease and non-traditional cardiovascular risk factors in the young than the elderly, where cardiovascular disease is more widespread. However the absolute numbers dying were far higher in the elderly with CKD, with many more excess deaths per 100 patient-years, a finding supported by Hallan et al (26) for cardiovascular mortality.

The increase in mortality with worsening levels of excretory function (CKD stage) is a consistent finding (6, 7, 27-29) and in tandem with proteinuria status has been the focus of a recent patient level meta-analysis (30). This found, as did we, that increasing albuminuria and worsening eGFR is associated with increasing mortality risk, even amongst those with microalbuminuria.

The contrast between relative and absolute risk for both RRT initiation and mortality by age group illustrate the challenge in planning CKD services to meet the individual (clinical) and population (public health) needs. A young person with CKD has a very high personal risk for both initiating RRT and death. However the societal costs for the small numbers involved is low. Whereas an elderly person with CKD has a very low risk of initiating RRT, and mortality risk just twice that of the general population, however the societal costs in terms of the numbers initiating RRT and dying are substantial. This study provides some simple illustrative tools as a template for clinicians for informing patients of risk and to inform service planning. The challenge that now faces clinicians is how to identify appropriately those amongst the elderly (the majority with CKD) who will benefit from intervention, and to investigate the non-fatal, non-RRT healthcare costs of CKD, the high rates of comorbidity complicate this further. It seems clear that all young people with CKD are at high risk and should be monitored carefully. Simple tools, aimed at supporting clinical care and service planning are an important element in translating the epidemiological understanding of CKD into practice.

**Conflicts of interest**

This work has previously been accepted in abstract form for the ERA-EDTA congress 2010, Scottish Renal Association meeting November 2010, World Congress of Epidemiology 2011 and Renal Association conference 2011.

**Transparency declaration**

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## Tables

**Table 1 - Baseline characteristics of GLOMMS-I CKD cohort**

|                                                                                                      | All             | Male            |        | Female          |        | P value § |
|------------------------------------------------------------------------------------------------------|-----------------|-----------------|--------|-----------------|--------|-----------|
| Grampian population (15 years and over)^<br>(2003 estimate from 2001 census)                         | 433,109         | 212,621         | (49.1) | 220,488         | (50.9) |           |
| Tested population (January to June 2003, 15+ years)                                                  | 82,530          | 36,526          | (44.3) | 46,004          | (55.7) |           |
| Population with creatinine ≥ 150µmol/l (males) or<br>≥ 130µmol/l (females)<br>(January to June 2003) | 5,538           | 2,616           | (47.2) | 2,922           | (52.8) |           |
| Cohort identified with CKD*                                                                          | 3,426           | 1,514           | (44.2) | 1,912           | (55.8) | <0.001    |
| COHORT WITH CKD AND FOLLOW-UP > 1 DAY                                                                | 3,414           | 1,510           | (44.2) | 1,904           | (55.8) | <0.001    |
| Excretory renal function at baseline*                                                                |                 |                 |        |                 |        |           |
| Creatinine, median and (range)                                                                       | 158 (130 - 942) | 170 (150 - 696) |        | 146 (130 - 942) |        | <0.001    |
| eGFR, median and (range)                                                                             | 33 (3 - 50)     | 36 (7 - 50)     |        | 32 (3 - 45)     |        | <0.001    |
| CKD stage                                                                                            |                 |                 |        |                 |        |           |
| Stage 3 #                                                                                            | 2,286 (67.0)    | 1,118 (74.0)    |        | 1,168 (61.3)    |        | <0.001    |
| Stage 4                                                                                              | 1,036 (30.3)    | 355 (23.5)      |        | 681 (35.8)      |        |           |
| Stage 5                                                                                              | 92 (2.7)        | 37 (2.5)        |        | 55 (2.9)        |        |           |
| Proteinuria at baseline*                                                                             |                 |                 |        |                 |        |           |
| Not measured                                                                                         | 2,406 (70.5)    | 1,001 (66.3)    |        | 1,405 (73.8)    |        | <0.001    |
| Normoalbuminuric                                                                                     | 509 (14.9)      | 252 (16.7)      |        | 257 (13.5)      |        |           |
| Microalbuminuric                                                                                     | 181 (5.3)       | 78 (5.2)        |        | 103 (5.4)       |        |           |
| Macroalbuminuric                                                                                     | 318 (9.3)       | 179 (11.9)      |        | 139 (7.3)       |        |           |
| Age (years)*                                                                                         |                 |                 |        |                 |        |           |
| 15-24                                                                                                | 9 (0.3)         | 5 (0.3)         |        | 4 (0.2)         |        | <0.001    |
| 25-34                                                                                                | 31 (0.9)        | 16 (1.1)        |        | 15 (0.8)        |        |           |
| 35-44                                                                                                | 49 (1.4)        | 27 (1.8)        |        | 22 (1.2)        |        |           |
| 45-54                                                                                                | 112 (3.3)       | 66 (4.4)        |        | 46 (2.4)        |        |           |
| 55-64                                                                                                | 280 (8.2)       | 165 (10.9)      |        | 115 (6.0)       |        |           |
| 65-74                                                                                                | 758 (22.2)      | 363 (24.0)      |        | 395 (20.7)      |        |           |
| 75-84                                                                                                | 1,418 (41.5)    | 642 (42.5)      |        | 776 (40.8)      |        |           |
| 85-94                                                                                                | 695 (20.4)      | 215 (14.2)      |        | 480 (25.2)      |        |           |
| 95-104                                                                                               | 62 (1.8)        | 11 (0.7)        |        | 51 (2.7)        |        |           |
| Comorbidity at baseline (present)*†                                                                  |                 |                 |        |                 |        |           |
| Ischaemic heart disease                                                                              | 1,361 (39.9)    | 669 (44.3)      |        | 692 (36.3)      |        | <0.001    |
| Congestive cardiac failure                                                                           | 584 (17.1)      | 301 (19.9)      |        | 283 (14.9)      |        | <0.001    |
| Peripheral vascular disease                                                                          | 399 (11.7)      | 202 (13.4)      |        | 197 (10.3)      |        | 0.006     |
| Cerebrovascular disease                                                                              | 515 (15.1)      | 236 (15.6)      |        | 279 (14.7)      |        | 0.429     |
| Hypertension                                                                                         | 1,811 (53.0)    | 793 (52.5)      |        | 1,018 (53.5)    |        | 0.581     |
| Haematological malignancy                                                                            | 79 (2.3)        | 41 (2.7)        |        | 38 (2.0)        |        | 0.165     |
| Non haematological malignancy                                                                        | 488 (14.3)      | 241 (16.0)      |        | 247 (13.0)      |        | 0.013     |
| Dementia                                                                                             | 201 (5.9)       | 60 (4.0)        |        | 141 (7.4)       |        | <0.001    |
| Chronic obstructive pulmonary disease                                                                | 290 (8.5)       | 139 (9.2)       |        | 151 (7.9)       |        | 0.185     |
| Connective tissue disease                                                                            | 164 (4.8)       | 44 (2.9)        |        | 120 (6.3)       |        | <0.001    |
| Type 1 diabetes                                                                                      | 59 (1.7)        | 26 (1.7)        |        | 33 (1.7)        |        | 0.980     |
| Type 2 diabetes                                                                                      | 787 (23.1)      | 370 (24.5)      |        | 417 (21.9)      |        | 0.073     |
| Chronic liver disease                                                                                | 35 (1.0)        | 16 (1.1)        |        | 19 (1.0)        |        | 0.859     |
| No comorbidity at baseline                                                                           | 55 (1.6)        | 16 (1.1)        |        | 39 (2.0)        |        | 0.023     |
| Smoking status at baseline*‡                                                                         |                 |                 |        |                 |        |           |
| Current smoker                                                                                       | 351 (10.3)      | 187 (12.4)      |        | 164 (8.6)       |        | <0.001    |
| Ex-smoker                                                                                            | 1,307 (38.3)    | 760 (50.3)      |        | 547 (28.7)      |        |           |
| Non-smoker                                                                                           | 1,472 (43.1)    | 448 (29.7)      |        | 1,024 (53.8)    |        |           |
| Unknown                                                                                              | 284 (8.3)       | 115 (7.6)       |        | 169 (8.9)       |        |           |

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; stage3=eGFR30-59ml/min/1.73m<sup>2</sup>; stage 4 = eGFR15-29 ml/min/1.73m<sup>2</sup>; stage 5 = eGFR<15ml/min/1.73m<sup>2</sup>.

§ P value calculated for proportions using Chi squared test statistic, and distributions using Mann Whitney test

^ General Register Office for Scotland (13)

\*Unless otherwise stated table is of the format N in group and (%)

# Only 17 males and 1 female had stage 3a disease.

†Criteria for ascribing comorbidities:- Ischaemic heart disease (IHD) = A history of angina, myocardial infarction, abnormal coronary angiogram, coronary angioplasty or coronary artery bypass grafting; Congestive cardiac failure (CCF)= Record of New York Heart Association criteria symptoms; peripheral vascular disease = a history of claudication, suggestive angiogram or tissue loss due to vascular disease; Cerebrovascular disease (CVD) = a diagnosis of transient ischaemic attack, stroke (with or without full recovery) or an abnormal CT scan in keeping with cerebrovascular disease; hypertension = either an in-patient or general practitioner (GP) diagnosis; dementia = a hospital consultant or GP diagnoses of dementia; Chronic obstructive pulmonary disease (COPD) = either a respiratory physician diagnosis, or supportive evidence such as pulmonary function tests and a non-respiratory physician diagnosis; Connective tissue disease = A diagnosis of rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease or similar, made by physicians used to managing these conditions (e.g. nephrologists, rheumatologists, respiratory physicians); Type 1 diabetes (DM type I)= diagnosis made by a diabetes clinic; Type 2 diabetes (DM type II) = diagnosis made by a diabetes clinic, or by a non-diabetes physician and treated initially with diet or oral hypoglycaemic agents; Chronic liver disease = a diagnosis of cirrhosis or chronic active hepatitis by a hepatologist, or by a non-hepatologist with supportive hepatic imaging or biopsy; non-haematological malignancy = Any diagnosis of non-haematological malignancy; Haematological malignancy = A diagnosis of haematological malignancy.

‡Smoking status:- "Non-smoker" and "ex-smoker" status were defined based on record of these in the case notes up to the time of "index". "Current smoker" status was assigned if there was a record of this up to 12 months post-index (if no earlier status was available). If none of these were recorded in the notes the smoking status was recorded as unknown.

**Table 2 – Numbers, rates and incidence rate ratios for characteristics of those initiating RRT and for mortality in the GLOMMS-I cohort after 6 years follow-up**

|                                       |                                               | Numbers                 |              |                                  |                                | Renal replacement therapy         |                                                                              |                  |               |                 |                                   | All cause mortality*                                                         |                 |               |                 |               |  |
|---------------------------------------|-----------------------------------------------|-------------------------|--------------|----------------------------------|--------------------------------|-----------------------------------|------------------------------------------------------------------------------|------------------|---------------|-----------------|-----------------------------------|------------------------------------------------------------------------------|-----------------|---------------|-----------------|---------------|--|
|                                       |                                               | Whole cohort            | Initiate RRT | Suffer death (include after RRT) | Survive without RRT to 30 June | Rate /100 patient years follow-up | Adjusted as appropriate for sex, age, CKD and proteinuria status at baseline |                  |               |                 | Rate /100 patient years follow-up | Adjusted as appropriate for sex, age, CKD and proteinuria status at baseline |                 |               |                 |               |  |
|                                       |                                               |                         |              |                                  |                                |                                   | Crude                                                                        |                  |               |                 |                                   | Crude                                                                        |                 |               |                 |               |  |
|                                       |                                               |                         |              |                                  |                                |                                   | IRR                                                                          | 95%CI            | IRR           | 95%CI           |                                   | IRR                                                                          | 95%CI           | IRR           | 95%CI           |               |  |
| Gender                                | Males                                         | 1510                    | 111          | 925                              | 525                            | 1.96                              | 1.00                                                                         | Reference        | 1.00          | Reference       | 15.61                             | 1.00                                                                         | Reference       | 1.00          | Reference       |               |  |
|                                       | Females                                       | 1904                    | 59           | 1176                             | 695                            | 0.81                              | 0.42                                                                         | (0.30 - 0.57)    | 0.42          | (0.30 - 0.59)   | 15.87                             | 1.02                                                                         | (0.93 - 1.11)   | 0.79          | (0.72 - 0.86)   |               |  |
| Excretory renal function at baseline  |                                               |                         |              |                                  |                                |                                   |                                                                              |                  |               |                 |                                   |                                                                              |                 |               |                 |               |  |
| CKD stage                             | Stage 3                                       | 2,286                   | 43           | 1315                             | 951                            | 0.46                              | 1.00                                                                         | Reference        | 1.00          | Reference       | 14.01                             | 1.00                                                                         | Reference       | 1.00          |                 |               |  |
|                                       | Stage 4                                       | 1,036                   | 81           | 721                              | 266                            | 2.34                              | 5.05                                                                         | (3.49 - 7.32)    | 5.60          | (3.86 - 8.15)   | 19.74                             | 1.41                                                                         | (1.29 - 1.54)   | 1.27          | (1.16 - 1.40)   |               |  |
|                                       | Stage 5                                       | 92                      | 46           | 65                               | 3                              | 33.53                             | 72.61                                                                        | (47.91 - 110.04) | 38.10         | (24.33 - 59.65) | 21.67                             | 1.55                                                                         | (1.21 - 1.98)   | 1.95          | (1.51 - 2.54)   |               |  |
| Proteinuria at baseline               |                                               |                         |              |                                  |                                |                                   |                                                                              |                  |               |                 |                                   |                                                                              |                 |               |                 |               |  |
|                                       | Not measured                                  | 2,406                   | 58           | 1526                             | 846                            | 0.64                              | 0.87                                                                         | (0.50 - 1.52)    | 1.28          | (0.74 - 2.24)   | 16.71                             | 1.35                                                                         | (1.19 - 1.54)   | 1.05          | (0.92 - 1.20)   |               |  |
|                                       | Normoalbuminuric                              | 509                     | 16           | 270                              | 231                            | 0.74                              | 1.00                                                                         | Reference        | 1.00          | Reference       | 12.33                             | 1.00                                                                         | Reference       | 1.00          |                 |               |  |
|                                       | Microalbuminuric                              | 181                     | 7            | 117                              | 61                             | 1.01                              | 1.35                                                                         | (0.56 - 3.29)    | 1.82          | (0.75 - 4.44)   | 16.41                             | 1.33                                                                         | (1.07 - 1.65)   | 1.34          | (1.08 - 1.66)   |               |  |
|                                       | Macroalbuminuric                              | 318                     | 89           | 188                              | 82                             | 8.46                              | 11.44                                                                        | (6.72 - 19.47)   | 4.90          | (2.83 - 8.49)   | 14.45                             | 1.17                                                                         | (0.97 - 1.41)   | 1.39          | (1.15 - 1.69)   |               |  |
| Age                                   |                                               |                         |              |                                  |                                |                                   |                                                                              |                  |               |                 |                                   |                                                                              |                 |               |                 |               |  |
| 15-24                                 | 15-24                                         | 9                       | 6            | 0                                | 3                              | 14.33                             | 3.24                                                                         | (1.33 - 7.90)    | 1.73          | (0.70 - 4.26)   | 0.00                              | -                                                                            |                 | -             |                 |               |  |
|                                       | 25-34                                         | 31                      | 11           | 3                                | 19                             | 7.72                              | 1.75                                                                         | (0.86 - 3.55)    | 1.63          | (0.80 - 3.33)   | 1.64                              | 0.43                                                                         | (0.13 - 1.42)   | 0.39          | (0.12 - 1.30)   |               |  |
|                                       | 35-44                                         | 49                      | 15           | 7                                | 32                             | 6.28                              | 1.42                                                                         | (0.75 - 2.69)    | 1.40          | (0.73 - 2.68)   | 2.51                              | 0.66                                                                         | (0.28 - 1.52)   | 0.61          | (0.26 - 1.42)   |               |  |
|                                       | 45-54                                         | 112                     | 25           | 24                               | 72                             | 4.42                              | 1.00                                                                         | Reference        | 1.00          | Reference       | 3.83                              | 1.00                                                                         | Reference       | 1.00          |                 |               |  |
|                                       | 55-64                                         | 280                     | 30           | 84                               | 174                            | 2.16                              | 0.49                                                                         | (0.29 - 0.83)    | 0.69          | (0.40 - 1.18)   | 5.70                              | 1.49                                                                         | (0.95 - 2.34)   | 1.51          | (0.96 - 2.37)   |               |  |
|                                       | 65-74                                         | 758                     | 49           | 359                              | 379                            | 1.46                              | 0.33                                                                         | (0.20 - 0.53)    | 0.59          | (0.36 - 0.98)   | 10.39                             | 2.71                                                                         | (1.80 - 4.10)   | 2.97          | (1.96 - 4.49)   |               |  |
|                                       | 75-84                                         | 1,418                   | 34           | 962                              | 446                            | 0.65                              | 0.15                                                                         | (0.09 - 0.25)    | 0.29          | (0.17 - 0.49)   | 18.13                             | 4.73                                                                         | (3.16 - 7.10)   | 5.28          | (3.52 - 7.93)   |               |  |
|                                       | 85-94                                         | 695                     | 0            | 601                              | 94                             | 0.00                              | -                                                                            |                  | -             |                 | 32.26                             | 8.43                                                                         | (5.60 - 12.67)  | 9.76          | (6.47 - 14.73)  |               |  |
|                                       | 95-104                                        | 62                      | 0            | 61                               | 1                              | 0.00                              | -                                                                            |                  | -             |                 | 64.90                             | 16.95                                                                        | (10.57 - 27.18) | 19.79         | (12.28 - 31.89) |               |  |
|                                       | Comorbidity at baseline (presence vs absence) |                         |              |                                  |                                |                                   |                                                                              |                  |               |                 |                                   |                                                                              |                 |               |                 |               |  |
|                                       | Ischaemic heart disease                       | Ischaemic heart disease | 1,361        | 40                               | 922                            | 425                               | 0.83                                                                         | 0.52             | (0.36 - 0.74) | 0.87            | (0.60 - 1.28)                     | 18.81                                                                        | 1.35            | (1.24 - 1.47) | 1.23            | (1.13 - 1.35) |  |
| Congestive cardiac failure            |                                               | 584                     | 7            | 458                              | 125                            | 0.41                              | 0.28                                                                         | (0.13 - 0.60)    | 0.43          | (0.20 - 0.92)   | 26.64                             | 1.88                                                                         | (1.70 - 2.09)   | 1.71          | (1.54 - 1.90)   |               |  |
| Peripheral vascular disease           |                                               | 399                     | 18           | 292                              | 99                             | 1.38                              | 1.05                                                                         | (0.65 - 1.72)    | 1.48          | (0.89 - 2.47)   | 21.68                             | 1.44                                                                         | (1.27 - 1.63)   | 1.35          | (1.19 - 1.53)   |               |  |
| Cerebrovascular disease               |                                               | 515                     | 18           | 384                              | 124                            | 1.11                              | 0.82                                                                         | (0.51 - 1.34)    | 1.28          | (0.77 - 2.12)   | 23.10                             | 1.57                                                                         | (1.41 - 1.76)   | 1.30          | (1.16 - 1.45)   |               |  |
| Hypertension                          |                                               | 1,811                   | 128          | 996                              | 740                            | 1.74                              | 2.32                                                                         | (1.64 - 3.28)    | 1.41          | (0.99 - 2.03)   | 13.00                             | 0.67                                                                         | (0.61 - 0.73)   | 0.75          | (0.69 - 0.82)   |               |  |
| Haematological malignancy             |                                               | 79                      | 5            | 62                               | 16                             | 2.26                              | 1.74                                                                         | (0.71 - 4.22)    | 1.53          | (0.62 - 3.79)   | 26.93                             | 1.73                                                                         | (1.35 - 2.23)   | 1.84          | (1.43 - 2.38)   |               |  |
| Non haematological malignancy         |                                               | 488                     | 8            | 352                              | 133                            | 0.51                              | 0.35                                                                         | (0.17 - 0.72)    | 0.45          | (0.22 - 0.93)   | 22.03                             | 1.48                                                                         | (1.32 - 1.66)   | 1.34          | (1.20 - 1.51)   |               |  |
| Dementia                              |                                               | 201                     | 1            | 190                              | 10                             | 0.26                              | 0.20                                                                         | (0.03 - 1.39)    | 0.49          | (0.07 - 3.57)   | 49.29                             | 3.34                                                                         | (2.88 - 3.88)   | 2.06          | (1.77 - 2.41)   |               |  |
| Chronic obstructive pulmonary disease |                                               | 290                     | 4            | 219                              | 69                             | 0.46                              | 0.33                                                                         | (0.12 - 0.90)    | 0.65          | (0.24 - 1.78)   | 24.71                             | 1.64                                                                         | (1.42 - 1.88)   | 1.58          | (1.38 - 1.82)   |               |  |
| Connective tissue disease             |                                               | 164                     | 6            | 103                              | 59                             | 1.01                              | 0.76                                                                         | (0.34 - 1.72)    | 1.45          | (0.63 - 3.32)   | 17.05                             | 1.09                                                                         | (0.89 - 1.33)   | 1.27          | (1.04 - 1.56)   |               |  |
| Type 1 diabetes                       |                                               | 59                      | 16           | 26                               | 25                             | 6.26                              | 5.15                                                                         | (3.08 - 8.61)    | 1.36          | (0.76 - 2.41)   | 8.78                              | 0.55                                                                         | (0.38 - 0.81)   | 1.31          | (0.88 - 1.96)   |               |  |
| Type 2 diabetes                       |                                               | 787                     | 50           | 493                              | 276                            | 1.68                              | 1.39                                                                         | (1.00 - 1.94)    | 1.57          | (1.08 - 2.29)   | 15.93                             | 1.02                                                                         | (0.92 - 1.12)   | 1.17          | (1.04 - 1.32)   |               |  |
| Chronic liver disease                 |                                               | 35                      | 1            | 24                               | 11                             | 0.89                              | 0.68                                                                         | (0.10 - 4.83)    | 0.25          | (0.03 - 1.83)   | 21.21                             | 1.35                                                                         | (0.90 - 2.02)   | 2.37          | (1.58 - 3.57)   |               |  |
| No comorbidity at baseline            |                                               | 55                      | 0            | 27                               | 28                             | 0.00                              | -                                                                            |                  | -             |                 | 11.14                             | 0.70                                                                         | (0.48 - 1.02)   | 0.65          | (0.44 - 0.94)   |               |  |
| Smoking status at baseline            |                                               |                         |              |                                  |                                |                                   |                                                                              |                  |               |                 |                                   |                                                                              |                 |               |                 |               |  |
| Current smoker                        |                                               | Current smoker          | 351          | 26                               | 221                            | 118                               | 1.97                                                                         | 2.59             | (1.59 - 4.21) | 1.62            | (0.98 - 2.67)                     | 16.18                                                                        | 1.03            | (0.89 - 1.20) | 1.45            | (1.25 - 1.70) |  |
|                                       | Ex-smoker                                     | 1,307                   | 53           | 844                              | 439                            | 1.10                              | 1.44                                                                         | (0.97 - 2.16)    | 1.64          | (1.07 - 2.50)   | 17.09                             | 1.09                                                                         | (0.99 - 1.20)   | 1.17          | (1.06 - 1.29)   |               |  |
|                                       | Non-smoker                                    | 1,472                   | 43           | 896                              | 550                            | 0.76                              | 1.00                                                                         | Reference        | 1.00          | Reference       | 15.66                             | 1.00                                                                         | Reference       | 1.00          |                 |               |  |
|                                       | Unknown                                       | 284                     | 48           | 140                              | 113                            | 4.19                              | 5.49                                                                         | (3.64 - 8.28)    | 3.25          | (2.12 - 4.99)   | 10.67                             | 0.68                                                                         | (0.57 - 0.81)   | 0.75          | (0.62 - 0.89)   |               |  |

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; stage3=eGFR30-59ml/min/1.73m<sup>2</sup>; stage 4 = eGFR15-29 ml/min/1.73m<sup>2</sup>; stage 5 = eGFR<15ml/min/1.73m<sup>2</sup>; IRR=incidence rate ratio; CI=confidence interval. \* Including after initiating RRT Poisson regression used to derive incidence rate ratios (IRRs)

## Legends to figures and Figures

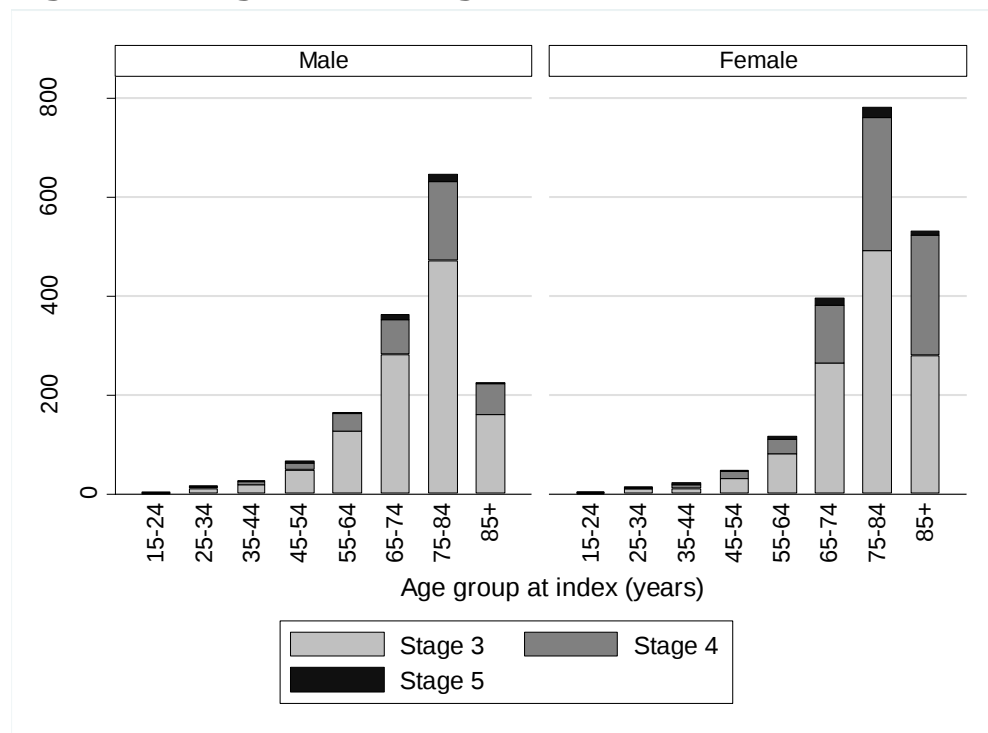


Figure 1 – Number of patients in GLOMMS-I cohort by CKD stage at baseline

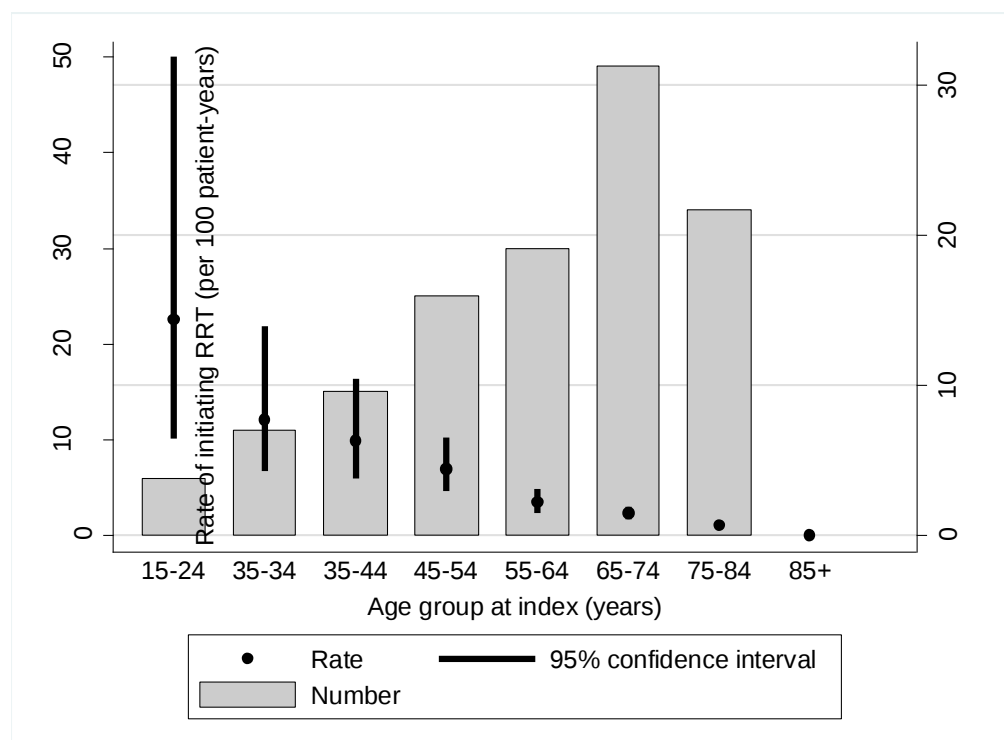
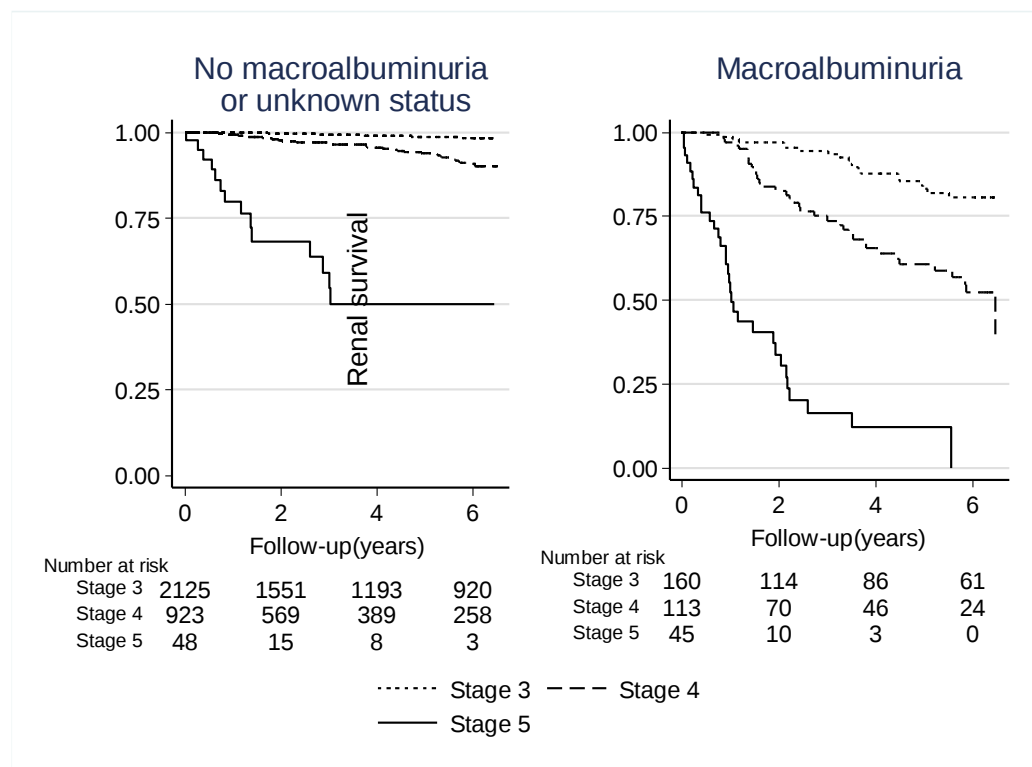


Figure 2 - Numbers and rates of patients initiating renal replacement therapy in GLOMMS-I cohort

CKD=chronic kidney disease; RRT=renal replacement therapy.



**Figure 3 – Renal survival by CKD stage and level of albuminuria**

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; stage3=eGFR30-59ml/min/1.73m<sup>2</sup>; stage 4=eGFR15-29 ml/min/1.73m<sup>2</sup>; stage 5=eGFR<15ml/min/1.73m<sup>2</sup>; no macroalbuminuria=albumin creatinine ratio (ACR)<30mg/mmol, or protein creatinine ratio (PCR)<50mg/mmol, or urine not tested; macroalbuminuria=ACR≥30mg/mmol, or PCR≥50mg/mmol.

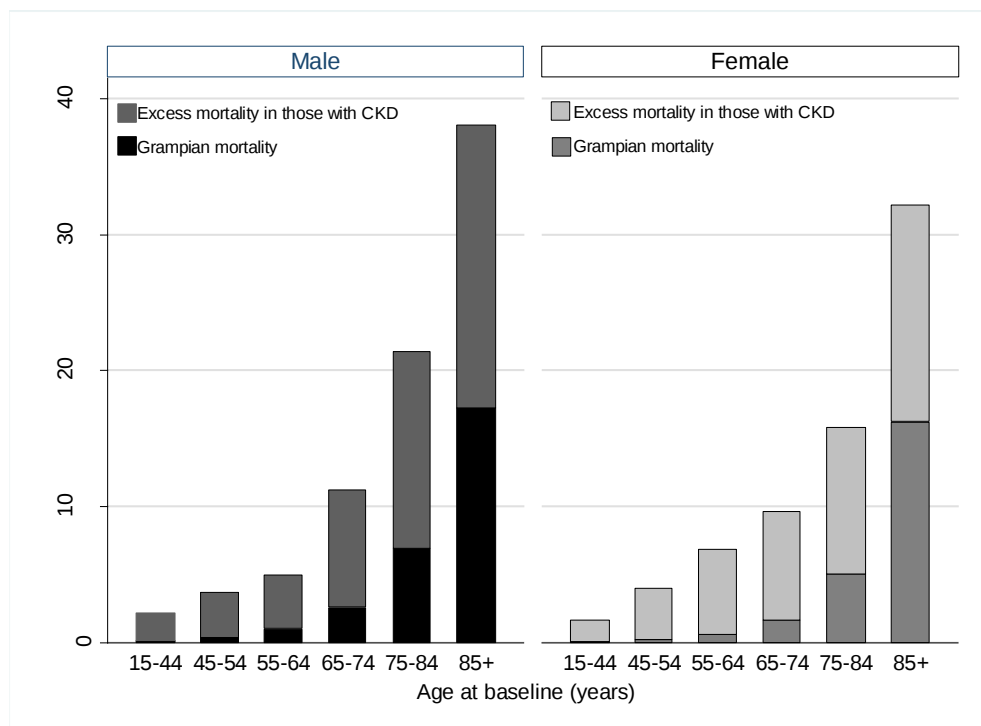
**Figure 4 – Percentage initiating renal replacement therapy by 5 years for age, gender, CKD stage, and proteinuria level specific subgroups**

|                                          |           | Male        |       |      |           |     | Female      |       |      |
|------------------------------------------|-----------|-------------|-------|------|-----------|-----|-------------|-------|------|
|                                          |           | Age (years) |       |      |           |     | Age (years) |       |      |
|                                          |           | <50         | 50-69 | ≥70  |           |     | <50         | 50-69 | ≥70  |
| Macroalbuminuria                         | CKD stage |             |       |      | CKD stage |     |             |       |      |
|                                          | 5         | 100.0       | 83.3  | 60.0 |           | 5   | 100.0       | 60.0  | 46.2 |
|                                          | 4         | 66.7        | 50.0  | 16.7 |           | 4   | 42.9        | 36.4  | 10.0 |
|                                          | 3b*       | 18.2        | 19.0  | 4.2  |           | 3b* | 28.6        | 4.8   | 3.8  |
|                                          |           | Age (years) |       |      |           |     | Age (years) |       |      |
|                                          |           | <50         | 50-69 | ≥70  |           |     | <50         | 50-69 | ≥70  |
| No macroalbuminuria<br>or unknown status | CKD stage |             |       |      | CKD stage |     |             |       |      |
|                                          | 5         | 100.0       | 75.0  | 33.3 |           | 5   | ^           | 66.7  | 11.5 |
|                                          | 4         | 25.0        | 13.5  | 5.0  |           | 4   | 22.2        | 6.2   | 0.9  |
|                                          | 3b*       | 8.0         | 1.9   | 0.7  |           | 3b* | 9.5         | 0.0   | 0.4  |

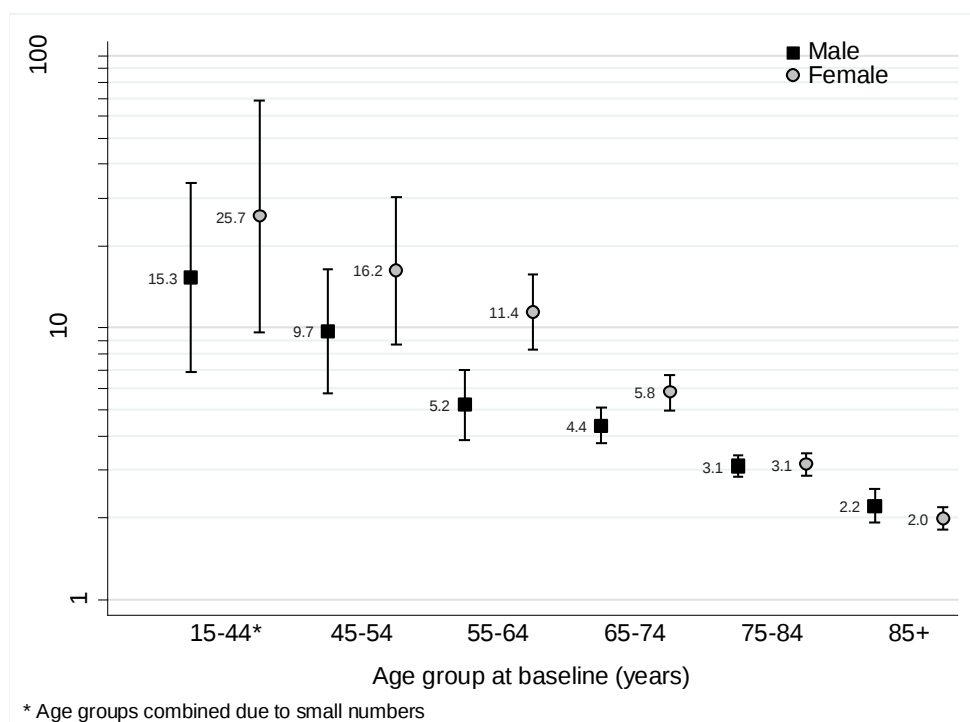
CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; stage3=eGFR30-59ml/min/1.73m<sup>2</sup> (divided in the UK into stage 3a (45-69 ml/min/1.73m<sup>2</sup>) and stage 3b (30-45 ml/min/1.73m<sup>2</sup>)); stage 4=eGFR15-29 ml/min/1.73m<sup>2</sup>; stage 5=eGFR<15ml/min/1.73m<sup>2</sup>; no macroalbuminuria=albumin creatinine ratio (ACR)<30mg/mmol, or protein creatinine ratio (PCR)<50mg/mmol, or urine not tested; macroalbuminuria=ACR≥30mg/mmol, or PCR≥50mg/mmol. For comparison, the percentage of the whole population that could be expected to have initiated RRT after 5 years (given an RRT initiation rate of 100 per million population) is estimated as 0.05%.

\* There were only 18 patients with stage 3a CKD (45-69 ml/min/1.73m<sup>2</sup>) therefore results not presented.

^ There were no individuals in this group. Numbers for macroalbuminuria subgroups: - male<50, 23; male50-69, 70; male>70, 82; female<50, 22; female 50-69, 37; female >70, 79. Numbers for those without macroalbuminuria or where it had not been measured at baseline: - male<50, 35; male50-69, 266; male>70, 1017; female<50, 30; female 50-69, 259; female >70, 1476.



**Figure 5 - GLOMMS-I mortality rate in excess of background population by age and sex**



**Figure 6 - Relative mortality risk in the GLOMMS-I cohort compared to the background population by age and sex**

**Figure 7 - Percentage of GLOMMS-I cohort alive and not on RRT by 5 years for age, gender, CKD stage, and proteinuria level specific subgroups**

|                                          |           | Male        |       |      | Female      |           |     |       |      |      |      |
|------------------------------------------|-----------|-------------|-------|------|-------------|-----------|-----|-------|------|------|------|
|                                          |           | Age (years) |       |      | Age (years) |           |     |       |      |      |      |
|                                          |           | <50         | 50-69 | ≥70  |             |           | <50 | 50-69 | ≥70  |      |      |
| Macroalbuminuria                         | CKD stage | 5           | 0.0   | 0.0  | 0.0         | CKD stage | 5   | 0.0   | 20.0 | 0.0  |      |
|                                          |           | 4           | 22.2  | 40.9 | 16.7        |           |     | 4     | 57.1 | 36.4 | 27.5 |
|                                          |           | 3b*         | 81.8  | 61.9 | 25.0        |           |     | 3b*   | 42.9 | 47.6 | 26.9 |
|                                          |           | Age (years) |       |      | Age (years) |           |     |       |      |      |      |
|                                          |           | <50         | 50-69 | ≥70  |             |           | <50 | 50-69 | ≥70  |      |      |
| No macroalbuminuria<br>or unknown status | CKD stage | 5           | 0.0   | 0.0  | 8.3         | CKD stage | 5   | ^     | 0.0  | 7.7  |      |
|                                          |           | 4           | 62.5  | 69.2 | 20.8        |           |     | 4     | 77.8 | 64.6 | 32.8 |
|                                          |           | 3b*         | 84.0  | 69.0 | 39.0        |           |     | 3b*   | 90.5 | 74.9 | 44.7 |

CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; stage3=eGFR30-59ml/min/1.73m<sup>2</sup> (divided in the UK into stage 3a (45-69 ml/min/1.73m<sup>2</sup>) and stage 3b (30-45 ml/min/1.73m<sup>2</sup>)); stage 4=eGFR15-29 ml/min/1.73m<sup>2</sup>; stage 5=eGFR<15ml/min/1.73m<sup>2</sup>; no macroalbuminuria=albumin creatinine ratio (ACR)<30mg/mmol, or protein creatinine ratio (PCR)<50mg/mmol, or urine not tested; macroalbuminuria=ACR≥30mg/mmol, or PCR≥50mg/mmol.

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