Elevated relative mortality risk with mild-to-moderate chronic kidney disease decreases with age

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Abstract

Background. Renal disease is common in the general population and whilst few people progress to end-stage renal failure, mortality is increased. The aim of this study was to examine all-cause mortality risk in relation to chronic kidney disease (CKD) stages defined by estimated glomerular filtration rate (eGFR).

Methods. Data were extracted from a computerized central laboratory system for a defined geographical area over a 3-year study period. The eGFR was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) formula and aligned to the MDRD laboratory. Average annual mortality and relative risk (RR) of all-cause mortality was determined and compared for defined age and CKD bands.

Results. 106,366 participants (55.5% female; 85% White, 13% South Asian, 2% Black and others) were eligible and studied, representing 49% of the Coventry adult population. 12,540 (12%) of the sample had some evidence of decreased kidney function, with an eGFR < 60 ml/min/1.73 m². 7,611 (7%) participants died and there were significantly elevated risks of mortality with increasing renal dysfunction; RR = 4.0, 8.3, 16.2 and 43.5 for eGFR 45–59, 30–44, 15–29 and < 15 ml/min/1.73 m², respectively. Within age bands, RRs were statistically significantly raised with CKD progression and within CKD stage, RR of death decreased as age increased.

Conclusions. CKD prevalence increased with age and absolute and RR of mortality increased with progression of CKD. People aged over 75 years, with mild-to-moderate renal disease, representing 41% of this age group, have no increased RR of mortality. Further study of CKD and mortality, particularly progression over time and with respect to age is needed.

Keywords: all-cause mortality; chronic kidney disease; diabetes; South Asian ethnicity

Introduction

In recent years it has been recognized that renal impairment is very common in the general population and more so in the elderly, with a high prevalence of people with reduced kidney function [1]. Whilst only a minority of people progress to end-stage renal disease, renal impairment is associated with an increased risk of death, often from cardiovascular disease [2–9]. Chronic kidney disease (CKD) is now regarded as an independent and novel cardiovascular risk factor leading to premature death [10].

CKD has been classified by the National Kidney Federation (NKF) Kidney Disease Quality Outcomes Initiative (KDOQI) system, in five stages [11]. Epidemiological studies using this classification have indicated that as many as 10% of the adult population and 20–54% of the elderly population have CKD in stages 3–5 [11,12–16]. In the UK, with an ageing population and increasing prevalence of type-2 diabetes mellitus, CKD is a substantial public health problem requiring urgent development and evaluation of targeted interventions to improve clinical outcomes.

Importantly, the KDOQI CKD classification is not staged according to increasing age, meaning that a glomerular filtration rate (GFR) of 50 ml/min/1.73 m² is regarded as indicative of moderate CKD (stage 3) whatever the age of the subject, even though this GFR falls well within the normal range in the elderly [11].
It has been recognized for many years that GFR declines with age at a rate of ~1.0 ml/min/1.73 m²/year [1,17,18]. The significance of this decline is uncertain and it is possible that CKD stage 3 (GFR 30–59 ml/min/1.73 m²) could be normal in individuals at the extremes of age, in vegetarians or after unilateral nephrectomy [11].

The aim of this study was to explore the clinical significance of CKD stage in the population, by measuring its effect on mortality.

Subjects and methods

Setting

The study took place in the city of Coventry with an adult population of 218 990 (female 112 041, 51.2%) aged 20 years or older (Census 2001)[19]. Coventry has an ethnically diverse population with 87% White, 10% South Asian, 2% Black and 2% other ethnic groups, 2.5 times more South Asian than the UK average.

Participants

After local Ethical Committee approval, data were extracted from the computerized central laboratory system for Coventry. Participants were included if they were aged 20 years or older between 1 June 2000 and 31 May 2003, if they were Coventry residents and had one or more serum creatinine measurements. Demographic data were recorded (age, sex and ethnicity). Ethnicity was self-reported, combined with Nam Pehchan software to assign South Asian ethnicity on the basis of names [20]; this software has been reported to have a sensitivity of over 90% [21].

Death year was recorded, using the hospital patient management system and the National Strategic Tracing Service (NSTS) [22]. For reasons of confidentiality, patients identified solely through the Genito-urinary medicine department were excluded. Participants were excluded if they had neither a Coventry post code nor registration with a Coventry General Practitioner. Duplicated records were amalgamated as appropriate. Participants seen by a Coventry nephrologist were identified (nephrologists have supported acute general medicine and have admitted approximately 2000 patients/year). Prior to analysis, data were fully anonymized in the University Hospital Coventry and Warwickshire (UHCW) information department.

Creatinine measurements and estimated GFR (eGFR)

Serum creatinine was measured with the Roche Modular P-Unit by the O’Leary modification of picrate method of Jaffe [23] (Synermed Europe Ltd, Sussex, UK). The between-day CVs were <2.0% at concentrations of 100 and 485 μmol/l. The reference range of serum creatinine is 70–120 μmol/l for men and 50–105 μmol/l for women.

The eGFR was estimated using the four-variable abbreviated Modification of Diet in Renal Disease (4vMDRD) formula [24]. Specifically, the modified MDRD study equation with serum creatinine concentration traceable to the isotope dilution mass spectrometry (ID-MS) reference method, as suggested by Levey et al. [25]:

\[\text{eGFR} = 175 \times \left( \frac{\text{serum creatinine in mg/dl}}{1.73} \right)^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if ethnic group = black}) .\]

Our serum creatinine values were corrected according to the Roche enzymatic method. This enzymatic assay method is traceable to the ID-MS reference method for serum creatinine measurement. Further, calibration to allow for drift in the assay was applied resulting in a new formula:

\[\text{eGFR} = 175 \times \left( \frac{1.1203(\text{serum creatinine} - \text{serum creatinine} \times 0.028) - 34.66}{88.4} \right)^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (female)} \times 1.212 \text{ (if ethnic group = black)} .\]

These serum creatinine adjustments align the results from this study with the creatinine assay used in the development of the modified 4vMDRD equation and allow direct comparison of our results with previous work [25]. We used a modified NKF classification of CKD [11] to classify eGFR in the following ranges: at least 60 ml/min/1.73 m² (stages 1 and 2), 45–59 ml/min/1.73 m² (stage 3A), 30–44 ml/min/1.73 m² (stage 3B), 15–29 ml/min/1.73 m² (stage 4) and <15 ml/min/1.73 m² (stage 5). Since proteinuria was not routinely measured, CKD stages 1 and 2 could not be separated. The reference group for risk estimation used in this study comprised all participants in CKD stages 1 and 2 and included all with eGFR ≥60 ml/min/1.73 m², including those with no CKD.

Definition of diabetes mellitus

Diabetes was defined as random serum glucose ≥11.1 mmol/l or glycosylated haemoglobin >6.8%.

Statistics

Analyses were performed using the SAS statistical analysis package. Estimates of period prevalence (3 years) of CKD stages for the age banded population were made based on eGFR calculated using the modified 4vMDRD, with the mean of all serum creatinine measurements available (1–3 measurements). Since the eGFR formula used includes a term for gender, 1998 people identified in the study with no recorded gender were excluded from all CKD stages prevalence and relative risk (RR) estimates, leaving a total of 106 366. For analysis of RR of death, a conservative approach was adopted, using the minimum creatinine measured for each subject during the 3-year study period to calculate eGFR and CKD stage. To eliminate confounding effects of age, an age band stratified analysis was performed. Within age bands, the RR of death for people in CKD stages 3(A and B), 4 and 5 was estimated using participants in CKD stages 1 and 2 (eGFR ≥60 ml/min/1.73 m²) as the reference group. Annual percent mortality was estimated by dividing deaths by population in age and CKD bands and further dividing by 3 years of study.

Results

Over the 3 years studied, a total of 108 364 participants with a mean age of 57.7 ± 19.1 years were identified, representing 49% of the Coventry population aged 20 years or older. Gender was missing for 1998 (2%) who were excluded from all analyses. With increasing age the proportion of the population identified as
participants increased; 31% at ages 20–44 rising to 100% of the age band 85+ years (Figure 1). Almost the entire population aged 65 years and older were included. Table 1 shows basic characteristics of the sample. Ethnic group distribution of the sample was similar for men and women separately. The age and CKD stage distribution: 1.9, 6.4, 11.1, 16.5 and 20.6% in CKD stages 1, 2, 3A, 3B, 4 and 5, respectively. In Figure 3, annual average mortality by age band and CKD stage-defined subgroups are shown. The age and CKD stage group distributions are illustrated clearly, with the youngest participants having lowest mortality which increased as CKD stage progression. Participants with diabetes experienced considerably higher prevalence of all CKD stages 3–5 (Table 2). Participants with diabetes had a serum creatinine >150 μmol/l in accordance with previous referral guidelines.

Figure 2 shows the relationship between age and CKD; deteriorating renal function is shown by the shift of eGFR into stages 3 and 4 with increasing age.
There were significantly elevated RRs of mortality with deteriorating renal function as compared with CKD stages 1 and 2 combined. RRs within age bands increased as CKD stage progressed, and within CKD stage decreased as age increased (Table 3). RR increased substantially with deteriorating kidney function as indicated by progression from stages 1 and 2 through to 5, with statistically significant differences in mortality compared with the reference group. At ages 75+ in CKD stage 3A, RRs were not significantly elevated compared with the reference group; RR (95% CI) for age band 75–84 was 1.2 (1.0–1.3) and 0.9 for ages 85+ (0.8–1.0). These groups with no significant increase in RR comprised 41% of the study population with eGFR <60 ml/min/1.73 m² and 14% of all participants aged 75+.

Figure 4 shows mean eGFR as determined for the study sample, plus mean eGFR ±1 and ±2 SDs. These are based on the first creatinine measurement for the whole study sample and illustrate clearly decreasing eGFR with advancing age. The overlaid reference lines show upper eGFR bounds for CKD stages 3–5. The intersections of the reference lines and eGFR slopes indicate that older population groups classified as having mild/moderate renal dysfunction using the 4vMDRD and KDOQI CKD stages; have mean eGFR well within 1 and 2 SDs from the mean.

Discussion

Participants were included in this study on the basis of serum creatinine measurement alone using routinely collected laboratory data to capture the sample with no need to obtain consent to enter a cohort study. The clear advantages of this method were the lack of refusals and the inclusion of all data in the study; on the other hand only limited clinical data were available. Almost 50% of the entire Coventry adult population and higher proportions of the elderly were included in the study. This is substantially higher
than recent primary care-based data reported in the NeoErica Study [26] but similar to a study of US Veterans [27] and probably reflects our inclusion of cases from both primary and secondary care sources.

The sample studied reflected variation in GP referral patterns, with fewer young and more older people included. The estimates of CKD prevalence may be inflated at younger ages as healthy individuals are unlikely to be tested, but the proportion of those aged 60 and older tested was over 80%, sufficient for us to feel confident in the estimates and risks evaluated. In contrast to other studies with insured populations [2,5,6,27], our study included a whole community population, in effect a cohort defined by their exposure to serum creatinine measurement. We excluded 1998 people with no gender recorded, but these did not differ markedly from the included group and an overall missing data rate of 2% for gender from combined primary and secondary care referrals seems acceptable and unlikely to have much impact on CKD stage or mortality risk estimation.

We found an overall period prevalence of CKD among the adult Coventry population of 6%, on the basis of decreased kidney function (eGFR < 60 ml/min/1.73 m^2, CKD stages 3–5) calculated using mean creatinine measurement during the study period. This estimate is conservative, since it assumes that no cases of CKD were missed. Whilst we had access to all data recorded, there are likely to be some missed cases. However, our population coverage was extremely high in the older age bands; those at highest risk of CKD.

After alignment to the MDRD laboratory, the NHANES III survey found a CKD prevalence of 4.7% in the adult American population [1]. Without alignment to the MDRD laboratory, or using the Cockroft–Gault GFR estimation method, prevalence rates between 4.9% and 13% have been reported [14–16,26]. In comparing these data it is important to remember that our estimates are based on 3-year period prevalence rather than a point prevalence.

There are no reported prevalence data for CKD within the South Asian community. Our overall CKD prevalence of 3.9% in those of South Asian ethnicity was lower than the 6.2% for the White population. This may in part be explained by a 10 years younger mean age for the South Asian group compared with the studied White population. The South Asian ethnicity group did have a slightly higher CKD stage 5 proportion, probably reflecting previously reported over-representation of dialysis treatment within this community [28]. It is important to be aware that the MDRD formula has not been validated for those of South Asian ethnicity.

It has been recognized that the physiological ageing process of the kidney leads to a deterioration of kidney function of about 1 ml/min/1.73 m^2 per year [1,17,18]. Our study appears to confirm this, although our eGFR estimates for age bands are based on a cross-section of groups of patients rather than coming from a longitudinal study following a cohort over time (Figure 4). Since our sample includes only those referred for creatinine measurement rather than a random population-based sample, the actual mean eGFR shown may be lower than for the total adult population. However, at ages 60 years and older our sample includes 80% of the total population, making the estimated mean eGFR more accurate in the older age groups in whom we are particularly interested.

Not surprisingly, more severe CKD, indicated by reduced eGFR, was associated with significantly increased RR of death, with higher RRs at advanced CKD stages in all age bands. Within CKD stage bands, the RR decreased with increasing age band, with younger adults in CKD stages 3–5 having higher RRs than older adults. Indeed adults aged 75+ years, in CKD stage 3A had elevated RRs which were not statistically significant. The RRs of death observed were clearly dependent on renal function and confirm previous large population and cohort studies [2,3,5,6,8]. A new and potentially important finding is that within the CKD stages a clear age effect was observed. In all CKD stages, the magnitude of elevated RRs declined as age increased and there was some suggestion that at older ages, moderate-to-mild declines in renal function may confer little or no excess mortality risk [27]. A similar observation has been made for end-stage renal disease patients [29]. In interpreting these data it is important to consider possible selection and survivorship biases. Those at older ages appear to be tested almost routinely. Since we had no clinical data we were unable to investigate possible influences of hypertension or other comorbidities which are likely to have more effect at older ages with longer duration of exposure. Similarly we were unable to investigate possible differential dialysis and transplantation rate effects within age bands. It would be expected that younger patients undergoing transplantation would be fitter and our estimates of RR in the eGFR<15 band might therefore be elevated at younger ages. The higher absolute mortality of older patients is in no doubt and gradients in average annual mortality reflect this, but our data do indicate that risk associated with mild renal dysfunction varies by age.

Previous investigations of impaired renal function at CKD stage 3 and all-cause mortality have found conflicting results [30]. Some studies that reported increased mortality analysed together both CKD stage 3 and more severe renal disease; all GFR <59 ml/min [3], all patients coded as chronic kidney disease [31], the top decile of serum creatinine levels [32] or all serum creatinine >133 μmol/l [33]. Analysis of all those aged 65 years plus as a single group tends to bias results in favour of an effect of CKD, as renal function deteriorates with age [31]. In a Framingham study, where those with severe renal failure were excluded, no increased mortality with moderate renal impairment was shown [34]. Conversely, in the Cardiovascular Health study [3] and in a pooled analysis of several trials [9], excluding patients with eGFR<15 ml/min/1.73 m^2 and taking account of age, increased mortality with eGFR levels of 15–60 ml/min/1.73 m^2
was reported. A more recent cohort study using eGFR and age bands observed an age-related attenuation of the association of eGFR with RR of death [27].

Equations based on serum creatinine level, age, sex and other variables, such as the MDRD formula perform much better at predicting GFR than serum creatinine level alone [24]. However, any equation used is critically dependent on the calibration and reproducibility of the serum creatinine assay [35,36]. Inter- and intra-laboratory agreement deteriorate as serum creatinine concentration nears the reference interval; imprecision at lower creatinine concentration contributes to greater error in GFR estimation than imprecision at higher creatinine concentration. In the current study we attempted to minimize errors introduced by imprecision and bias of creatinine measurements. Study samples were measured in one laboratory over the entire 3 years, using the same assay method and instrument. The Roche Enzymatic assay, shown to be very close to the gold standard ID-MS method of measuring serum creatinine was used to estimate the correction needed and to provide the adjustment to the MDRD laboratory [25]. The eGFR from the resulting formula allows direct comparison with previously published results and may be used as a starting point in establishing an international standard for the calibration of serum creatinine as previously suggested [25,36].

In the UK, new recommendations promote the disclosure of eGFR to General Practitioners rather than simply serum creatinine; the effects of this change in practice are still to be observed and monitoring referrals to nephrology departments should be a high priority. Our data demonstrate that a substantial proportion of the population may be in CKD stages 3A and 3B, particularly at older ages. We used the 4vMDRD equation with recalibration and allowing for assay drift. If some similar correction is not used in other UK laboratories, the proportions of people in CKD stage 3 with no evidence for increased RR of mortality are likely to be significantly higher. This has been acknowledged and the UK National Quality Assessment Scheme (UKNEQAS) have been working to produce method-specific correction factors to minimize the problem of bias.

Early identification of individuals and the prevention of progressive CKD are key factors in reducing CKD-associated mortality and alleviating the future burden of ESRD. More research is required to investigate the relationship between CKD, its progression over time and mortality, especially in the elderly.

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Conflict of interest statement. None declared.

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