Estimation of glomerular filtration rate: does haemoglobin discriminate between ageing and true CKD?

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Abstract

Aim. The aim of this study was to analyse the association between chronic kidney disease (CKD) defined by an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² and anaemia in older people.

Background. Guidelines focus on early identification and management of CKD to prevent CKD progression and cardiovascular disease. However, the significance of CKD classification using eGFR in older people is unclear.

Methods. Serum creatinine and haemoglobin from individuals attending non-nephrology outpatient clinics were extracted from the state pathology provider over a 4-month period. The associations between eGFR, gender, age and haemoglobin were explored.

Results. Serum creatinine in 9853 individual patients aged ≥15 years was available for analysis. Haemoglobin was simultaneously available in 8752 (88.8%) subjects. There was a negative relationship between age and median eGFR, and the slope of the regression line was −0.68 ml/min/year for males and −0.74 ml/min/year for females. Over 35% of individuals ≥65 years were classified as having CKD stage ≥3. Odds ratios for haemoglobin < 100 g/l for an eGFR < 15, 15–29 and 30–59 versus reference GFR ≥ 60 ml/min/1.73 m² in subjects 25–44 years were 3.42 (3.07–37.7), 23.4 (20.2–26.6) and 7.2 (5.3–9.1), respectively. In comparison, these were 8.9 (6.7–11.1), 5.6 (4.9–7.3) and 1.6 (1.1–2.1), respectively, in subjects ≥65 years. In subjects ≥65 years, odds ratios for haemoglobin < 100 g/l for an eGFR 30–44 and 45–59 ml/min/1.73 m² versus reference GFR ≥ 60 ml/min/1.73 m² were 1.9 (1.3–2.5) and 1.2 (0.7–1.7), respectively.

Conclusions. An eGFR < 60 ml/min/1.73 m² is very common in older people. Only an eGFR < 45 ml/min/1.73 m² identified a smaller subgroup of older people with an increased prevalence of significant anaemia suggesting a clinically relevant disease. The benefits of identifying older people with an eGFR ≥ 45 ml/min/1.73 m² need to be determined.

Keywords: age; anaemia; chronic kidney disease; eGFR; prevalence

Introduction

Early identification of patients with chronic kidney disease (CKD) offers the potential to delay progression, reduce their high cardiovascular morbidity and mortality and reduce the rate of patients commencing dialysis with < 3 months of pre-dialysis care due to late referral. Because serum creatinine is an insensitive measure of kidney dysfunction, guidelines have advocated routine use of estimated glomerular filtration rate (eGFR) to identify patients with CKD. The Australasian Creatinine Consensus Working Group [1] recommended in June 2005 that Australasian laboratories automatically report an eGFR using the Modification of Diet in Renal Disease (MDRD) formula each time a serum creatinine test was requested [2]. Although a non-targeted screening for CKD has not been recommended, reporting of an opportunistic eGFR < 60 ml/min/1.73 m² is often accompanied by a suggestion that referral to a nephrologist should be considered. A recent experience in the UK recognized that nephrology services can be readily overwhelmed unless eGFR reporting is introduced alongside an enhanced referral assessment service to ensure that the guidelines are achievable [3].

There are several issues in the use of the MDRD formula to estimate GFR. The two major inherent problems are its reliance on standardized serum creatinine assays and its age dependence. Due to the lack of standardization of serum creatinine assays, large differences in eGFR with different corrections for serum creatinine are observed, resulting in important CKD classification differences [4]. Ageing is characterized by a decline in renal function [5,6], but the prevalence and clinical significance of a reduced eGFR in older people is unclear [7,8]. Moreover, the MDRD formula is insufficiently accurate for routine clinical use to estimate GFR values > 60 ml/min/1.73 m² [9].

Therefore, it has been advised that the staging system needs to be modified to reflect the severity of the kidney disease, the degree of proteinuria and in particular the complications of CKD [10]. In younger people, as kidney function declines, additional physiological consequences such as anaemia, dyslipidaemia and disturbances in mineral
metabolism occur with increasing frequency. The relationship between these consequences and kidney function in older people is less studied and has not been investigated in an unselected population. A recent longitudinal study reported that anaemia was an independent predictor for subsequent decline in kidney function, suggesting that haemoglobin should be considered in the assessment of renal disease [11]. In general, age-related decision points have not been agreed on eGFR reporting. However, the revised recommendations of the Australasian Creatinine Consensus Working Group have indicated that in people aged over 70 years, eGFR values in the range 45–59 ml/min/1.73 m², if stable over time and unaccompanied by other evidence of kidney damage, may be interpreted as typical for this age group [12].

In order to evaluate the significance of eGFR decline with age, we assessed the frequency of different severities of CKD and their association with the common and clinically important complication of anaemia using pathological test data from a single state provider of pathology (PathWest Laboratory) in outpatients not referred to or attending nephrology outpatients.

Methods

Pathological test data from outpatient attendances at adult public hospitals in metropolitan WA from March to June 2007 were provided by PathWest, Western Australia. Blood samples from inpatients were not considered in this analysis. The dataset contained patient unique identifier (medical record number—MRN), sex, age, serum creatinine, haemoglobin and other variables of possible relevance to kidney disease. In total, 24741 records were extracted. These records were for 15757 individual persons identified by MRN. Individuals who were known to state renal services (dialysis, transplant and general outpatient clinic) and haematology or oncology patients were excluded (N=5904). Thus, data on 9853 individual patients from the metropolitan area aged 15 years or older and not previously known to nephrologists were available for analysis. This study specifically did not set out to screen the population, relying instead on those patients who were tested as part of their routine care. In patients with multiple samples, only the one with the lowest serum creatinine reading was used for the analysis.

Serum creatinine was measured using a kinetic colorimetric assay (Jaffe method) analysed on the Roche Hitachi 917 analyser (Roche Diagnostic GmbH, Mannheim Germany) in all PathWest laboratories involved. The assay was IDMS-aligned to justify the use of the Modification of Diet in Renal Disease (MDRD) to estimate GFR [2]. The coefficients of variation for this assay are 6.6% at 70 μmol/l and 4.1% at 485 μmol/l. The simplified MDRD equation (eGFR = 175 × [Cr/88.4]−1.154 × [Age]−0.203×0.742 if female) was used to estimate GFR (in ml/min/1.73 m²). Stages of CKD were created using eGFR, with the following definitions: no definite CKD when the eGFR was ≥60 ml/min/1.73 m², stage 1 CKD when the eGFR was 30–59 ml/min/1.73 m², stage 2 CKD when the eGFR was 15–29 ml/min/1.73 m² and stage 5 CKD when the eGFR was <15 ml/min/1.73 m². Age was categorized in four groups: 15–24, 25–44, 45–64 and ≥65 years of age.

Statistical analysis

Pearson χ² tests were used to examine the difference in CKD patient distributions by gender and age. Age-specific CKD prevalence rates were estimated by multiplying four monthly prevalence rates by 3. The 2007 WA metropolitan resident population was estimated by using a linear project method based on the 2002–2006 population figures sourced from the Australian Bureau of Statistics. Linear regression analysis was adopted to evaluate the relationship between age and eGFR. Analysis of variance (ANOVA) was used to assess the effect of age or CKD stages on haemoglobin. Odds ratios and their 95% confidence intervals were derived to compare prevalence rates of significant anaemia among subjects with an eGFR <15, 15–29 and 30–59 in relation to a reference eGFR >60 ml/min/1.73 m². Significant anaemia was defined as having haemoglobin <100 g/l. This level was chosen because it represents the threshold for Medicare reimbursement of erythropoietic stimulating agents in Australia, when anaemia in patients with an eGFR <60 ml/min/1.73 m² is certified by a nephrologist as being of renal origin. The relationship between anaemia, eGFR and age was also analysed using WHO definitions of haemoglobin <120 g/l for women and <130 g/l for men [13].

Results

Study population

Serum creatinine and eGFR were available from 9853 individual patients (2.1% indigenous). The eGFR was calculated in all subjects without correction for race, where race is not censored to estimate GFR. A simultaneous haemoglobin reading was available in 8752 (88.8%) subjects, while blood glucose, microalbuminuria and other parameters of relevance for kidney diseases were requested in <5% of cases. The mean (±SD) age was 58.8 ± 17.2 years and 49% were females. The majority of subjects were 45 years of age or older (N = 7669, 77.8%), with 4099 (41.6%) older than 65 years, and only 329 (3.3%) were younger than 25 years.

Prevalence of CKD

The mean (and 95% CI) eGFR was 76.8 ml/min/1.73 m² (76.1–77.5) in males and 76.9 ml/min/1.73 m² (76.1–77.6) in females. There was a negative relationship between age and median eGFR, and the slope of the regression line was 0.68 ml/min/year for males and 0.74 ml/min/year for females (Figure 1). The age-specific prevalence of CKD stage 3 or higher derived from eGFR in this population is summarized in Table 1. Regardless of age, the prevalence of CKD was 20.3% (95% CI 19.2–21.3) for an eGFR 30–59, 3.3% for an eGFR 15–30 (95% CI 2.9–3.8) and 1.1% (95% CI 0.8–1.3) for eGFR <15 ml/min/1.73 m². Figure 2 shows the prevalence of CKD stage 3 or higher by gender and age group. The prevalence of an eGFR < 60 ml/min/1.73 m² was higher in women than in men (χ² = 4.22, P = 0.038) in the age group 45–64 years. Based on eGFR calculations, CKD stage 3 or higher affected more than every one in three individuals older than 65 years. Estimates from available data indicate that in subjects ≥75 years, the prevalence of CKD was 40.9% (95% CI 38.2–43.6) for an eGFR 30–59, 6.7% (95% CI 5.3–8.2) for an eGFR 15–30 and 1.8% (95% CI 1.2–2.7) for an eGFR <15 ml/min/1.73 m². Using age- and sex-specific prevalence figures, we estimated that in Western Australia ~32 800 people would have CKD stage 3, 5500 CKD stage 4 and 1870 CKD stage 5.

eGFR and haemoglobin

The mean (±SD) haemoglobin concentration was similar in the age groups 15–24 (139 ± 19 g/l), 25–44 (139 ± 18 g/l) and 45–64 (139 ± 18 g/l), but decreased in subjects ≥65 years (132 ± 18 g/l, F = 102.1, P < 0.0001). The haemoglobin concentration decreased with the increasing CKD stage (Figure 3), but the effect of stage 4 and 5 CKD
was stronger in the younger age group compared to the older age group. The relationship between age, eGFR and haemoglobin as a continuous covariate demonstrated a significant effect of both age (coefficient $-0.122$, $P < 0.0001$) and eGFR (coefficient $0.110$, $P < 0.0001$), and the combination of age and CKD stage was found to be a strong predictor of haemoglobin by general linear model analysis ($F = 3.12$, $P < 0.001$). The relationship between age group, CKD stage and haemoglobin $< 100$ g/l is shown in Figure 4. In subjects aged $25–44$ years and in $20\%$ of those aged $15–24$ years. Table 2 shows the odds ratios for haemoglobin $< 100$ g/l for the different eGFR and age group categories with the reference category being eGFR $\geq 60$ ml/min/1.73 m$^2$. The age group $15–24$ years was excluded from the analysis due to small samples. In subjects $\geq 65$ years, odds ratios for haemoglobin $< 100$ g/l for an eGFR $30–44$ and $45–59$ ml/min/1.73 m$^2$ versus reference GFR $\geq 60$ ml/min/1.73 m$^2$ were $1.9$ ($1.3–2.5$) and $1.2$ ($0.7–1.7$), respectively. For each eGFR category, the older the subject the smaller was the OR. Also for each age group, the higher the CKD stage the greater the OR. In most cases, the ORs for stages 4 and 5 were overlapped in $95\%$ confidence intervals except for the age group $25–44$ years. When significant anaemia, defined as [14], was analysed in relationship to eGFR and age, only the eGFR ($F = 23.14$, $P < 0.0001$), but not age ($F = 2.17$, $P = 0.09$), was found to be a significant predictor of anaemia (Figure 4).

### Discussion

With the introduction of automated GFR reporting and CKD staging, renal disease has become a health issue

### Table 1. Age-specific prevalence (%) of CKD in a non-nephrological outpatient cohort in metropolitan Western Australia, 2007

<table>
<thead>
<tr>
<th>Age group</th>
<th>GFR (ml/min/1.73 m$^2$)</th>
<th>30–59</th>
<th>15–29</th>
<th>&lt;15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>N</td>
<td>No. of patients</td>
<td>%</td>
<td>No. of patients</td>
</tr>
<tr>
<td>15–24 years</td>
<td>329</td>
<td>7</td>
<td>2.1</td>
<td>1</td>
</tr>
<tr>
<td>25–44 years</td>
<td>1855</td>
<td>99</td>
<td>5.3</td>
<td>29</td>
</tr>
<tr>
<td>45–64 years</td>
<td>3570</td>
<td>486</td>
<td>13.6</td>
<td>76</td>
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<tr>
<td>&gt;65 years</td>
<td>4099</td>
<td>1401</td>
<td>34.2</td>
<td>219</td>
</tr>
<tr>
<td>Total</td>
<td>9853</td>
<td>1993</td>
<td>20.3</td>
<td>325</td>
</tr>
</tbody>
</table>
Fig. 3. Haemoglobin concentrations by age group and CKD stage. For each age group, an eGFR > 60 ml/min/1.73 m² is considered the reference (shaded bars) versus eGFR 30–59, 15–29 and <15 (open bars left to right). P-values by ANOVA with Bonferroni adjustment are shown for the comparison among reference groups and among different stages within the same age group.

Affecting up to 10% of the population [5,6]. Categorization of a continuous variable into CKD stages risks the classification of otherwise healthy individuals with an arbitrary definition of disease implicates CKD as a progressive condition. In reality, in the absence of other signs of kidney disease, especially proteinuria and hypertension or disorders such as diabetes that are associated with progression, the clinical relevance of a moderately reduced GFR, particularly in older people, is not proven [14]. We therefore investigated the prevalence of CKD and its association with anaemia, a pathologically established causal consequence of CKD, in a cohort of nearly 9000 individuals attending outpatient clinics and not under the care of a renal service. In this cohort, the prevalence of CKD stage 3 was 20.3%, which is higher than that previously reported from population studies in Australia [15], because elderly people were overrepresented and possibly with higher blood pressure and other risk factors for CKD. The data show that the prevalence of an eGFR < 60 ml/min/1.73 m² rose significantly with increasing age. In the older population, only a minority had significant anaemia that would require erythropoietin, and this finding was uncommon until the eGFR was < 30 ml/min/1.73 m².

There are limitations to the assessment of kidney function in cross-sectional studies. A single measure of serum creatinine may misclassify some patients who have an acute deterioration as having CKD. Because only data from outpatient attendances were collected in this study, it is unlikely that those with a significant acute illness were included. However, it is possible that some patients with acute illness, anaemia or renal impairment were over-represented because attendance at outpatient clinics implies ascertainment bias by referral for presumed or actual illness. Hence, we cannot exclude that these data are an overestimate of the true population prevalence. PathWest is the major provider of pathology services in the public sector. Individuals who were already under the care of a renal unit were removed from extracted data.

The majority of definitions of CKD stage require two readings at least 3 months apart. Although this study relied on a single opportunistic eGFR measurement, it reflects some of the current practices, where referrals from general practitioners are frequently based on the results of a single

<table>
<thead>
<tr>
<th>Age group</th>
<th>GFR (ml/min/1.73 m²)</th>
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<tbody>
<tr>
<td></td>
<td>45–59</td>
</tr>
<tr>
<td>25–44 years</td>
<td>4.9 (3.3–6.5)</td>
</tr>
<tr>
<td>45–64 years</td>
<td>2.2 (1.4–3.0)</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>1.2 (0.7–1.7)</td>
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opportunistic serum creatinine measurement. Thus, within the limitations described above, these data are likely to represent a good cross-sectional sample of an opportunistic population in Western Australia. Although this study did not set out to screen the population, these data are consistent with population-based data from Australia. In the AusDiab study, the prevalence of an eGFR <60 ml/min/1.73 m² and an eGFR <30 ml/min/1.73 m² in subjects aged >65 was 55% and 1.7%, respectively [6]. Using age- and sex-specific prevalence figures, we estimated that ~53 000 people in Western Australia would have an eGFR <60 ml/min/1.73 m² and ~12 000 would have an eGFR <30 ml/min/1.73 m². This is an enormous number, and it raises the question whether these figures are biased by the arbitrary limit imposed on a roughly normal distribution of eGFR that shifts to the left with age.

What is the relevance of a decreasing GFR with age? Although guidelines do not recommend population screening for CKD [12], there seem to be high rates of routine and opportunistic testing for serum creatinine in older people as shown by this and other studies [16]. A decline in kidney function with age is well recognized, although the clinical significance of a reduced eGFR in older people is unclear and the age-dependent GFR decrease may not necessarily be a benign phenomenon. Lindeman et al. observed a more rapid decline in GFR with age in patients with mean blood pressure 114–120 mmHg than in those with values <107 mmHg [7]. On the other hand, the same authors reported a mean decrease in creatinine clearance of 0.75 ml/min/year when subjects with possible renal or urinary tract disease and subjects on diuretics and antihypertensives were removed from the study [8]. In our study, we were unable to evaluate the patients for associated markers of disease, such as blood pressure and proteinuria, and correlate this with the measures of CKD described here. This would be important, because some classification systems are now advocating the subdivision of CKD 3 into high and low risk groups based on the eGFR and the presence or absence of proteinuria [17]. However, as expected, proteinuria is rarely requested in conjunction to an opportunistic serum creatinine measurement.

One approach to assess the relevance of age-specific GFR would be to ascertain the relationship between eGFR and a known quantifiable complication of CKD. A reduced GFR is associated with several adverse pathophysiological consequences including anaemia, hyperphosphataemia, hyperkalaemia and hypertension. Because of the design of our study, blood pressure measurements were not included. While rising serum phosphate and potassium levels may be affected not only by the rate of clearance but also by increased uptake through diet, the haemoglobin concentration is largely dependent on endogenous erythropoietin, which is a function of renal parenchymal integrity. We therefore used haemoglobin as a biological indicator of significant renal functional loss in order to further assess the age-specific relevance of eGFR calculations. Mean haemoglobin was comparable in subjects aged 15–64 years, but was significantly lower in those ≥65 years. In the latter group, a significantly increased prevalence of haemoglobin <100 g/l, which would qualify for treatment with erythropoietic-stimulating agents to be reimbursed by Medicare, did not occur until the eGFR was <45 and increased further in those with an eGFR <30. A significant effect of both age and eGFR on haemoglobin levels remained when analyses were performed with haemoglobin levels used as a continuous covariate and the models corrected for age and gender. This dependence of haemoglobin on GFR in people aged 70 or over has been previously shown [18]. However, to our knowledge this is the first analysis demonstrating the reported dose-response relationship between age, GFR and significant anaemia. Our figures are also consistent with data from the CREATE trial, in which the mean eGFR was 25 ± 6 ml/min/1.73 m² in CKD patients treated with erythropoietin to correct mild-to-moderate anaemia (haemoglobin 110–125 g/l) [19].

It is worth noting that this study focused primarily on the prevalence of anaemia in the older subjects with CKD, but it did not look at the relationship with outcomes. Indeed, a few longitudinal studies reported increased renal and cardiovascular outcomes in subjects with different CKD stages with anaemia compared to subjects without anaemia [11,20]. Weiner et al. showed that a U-shaped relationship between haemoglobin and a composite of stroke myocardial infarction and all-cause mortality existed in a cohort of 1678 subjects with an eGFR<60 ml/min/1.73 m² [20]. On the other hand, Lee et al. showed that the prevalence of CKD increases only in subjects with baseline haemoglobin concentrations of <140 g/l [11].

Finally, one other aspect of the present study deserves consideration. In 2006, there were 937 women and 1441 men commencing dialysis in Australia (http://www.anzdata.org.au/). This 1.5-fold higher incidence of new end-stage kidney disease (ESKD) in men than in women is in apparent contrast with our data, which show a similar prevalence of stage 4 and 5 CKD in women and men and reversed relationship for ESKD consistent with previous studies [3,5,21,22], but interestingly not in the AusDiab study [6]. The relatively higher prevalence of CKD versus ESKD in females may indicate that the gender adjustment in the MDRD equation is too great in females, although there is no evidence of any significant bias in the validation studies [9].

In conclusion, our analysis of the relationship between age, eGFR and haemoglobin suggests that only an eGFR <45 ml/min/1.73 m² identifies a smaller subgroup of older people with a significant risk of anaemia. Other authors have shown that an eGFR 45–60 ml/min/1.73 m² in the absence of proteinuria is not associated with renal disease progression or increased cardiovascular risk in subjects without hypertension or diabetes [14]. Taken together, these observations support the recommendations that in people aged >65 years, eGFR values in the range 45–59 ml/min/1.73 m² should be interpreted with caution [12]. With the automated eGFR reporting a warning should alert physicians that the benefits of identifying older people with an eGFR >45 ml/min/1.73 m² need to be determined.
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