Glomerular filtration rate estimation and mortality in an elderly population

Y. MAARAVI, M. BURSZTYN, R. HAMMERMAN-ROZENBERG, and J. STESSMAN

From the Departments of 1 Rehabilitation and Geriatric Medicine and 2 Medicine, Hadassah University Hospital, Jerusalem, Israel

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Summary

Background: Few studies have addressed the link between minor renal dysfunction and mortality in the elderly.

Aim: To compare three equations for estimated GFR (eGFR) in assessing renal dysfunction and predicting mortality in an elderly population.

Design: Longitudinal observational study.

Methods: We studied 441 people from the Jerusalem Seventy Year Olds Longitudinal Study who had measurements of serum creatinine, all of whom were aged 70 years at study initiation and were living in the community. GFR was estimated based on serum creatinine and using the Cockcroft-Gault (CG), the abbreviated Modification of Diet in Renal Disease (MDRD) and the Mayo Clinic equations. Twelve-year mortality was the main outcome measure.

Results: The prevalence of reduced eGFR was 51% using the CG, 34% using MDRD and 16% using the Mayo Clinic equation. eGFR dichotomized by the definition of CKD significantly predicted mortality only with the Mayo Clinic equation (hazard ratio 1.56, 95%CI 1.01–2.39). When eGFR was divided into quartiles and the lowest compared to the highest, all equations predicted mortality. Hazard ratios (95%CI) were 5.48 (1.27–23.65), 7.47 (2.74–20.3), and 7.375 (3.13–17.36), for CG, MDRD, and Mayo Clinic, respectively.

Discussion: Reduced eGFR was prevalent in this study group, and associated with mortality. This association was strongest using the Mayo Clinic equation.

Introduction

End-stage renal disease significantly increases the risk of death and cardiovascular disease, and recently, even minor renal dysfunction has been linked to increased cardiovascular risk. However, few studies address the question of moderate chronic kidney disease (CKD) and mortality in old age.

The early detection of CKD provides an alert to the need for evaluation and cardiovascular risk reduction. It is therefore of prime importance to accurately identify subjects with renal dysfunction as early as possible.

Current clinical guidelines published by the National Kidney Foundation’s Kidney Disease Quality Outcome Initiative (NKF-K/DQOI) define evaluation, classification and risk stratification in chronic kidney disease. These guidelines recommend using The Abbreviated Modification of Diet in Renal Disease (MDRD) or the Cockcroft-Gault (CG) equations to estimate GFR. The MDRD equation is superior to the CG equation and even to measured urinary creatinine clearance, but a publication from the Mayo Clinic found that the MDRD equation underestimated GFR by 29% in healthy

Address correspondence to Dr Y. Maaravi, Department of Rehabilitation and Geriatric Medicine, Hadassah University Hospital, Mount Scopus, PO Box 24035, Jerusalem 91240, Israel. email: maaravi@md2.huji.ac.il

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subjects, and offered an alternate equation to estimate GFR.

The different equations for GFR estimation were developed by using specific groups of subjects, but not elderly people. To the best of our knowledge, they have not yet all been compared in an elderly population. We therefore studied the estimation of GFR based on the CG, the abbreviated MDRD and the Mayo Clinic equations, in a community-dwelling elderly population as part of The Jerusalem Longitudinal Study, and compared their performance in assessing renal dysfunction and in predicting mortality over 12 years.

Methods

Subjects

The Jerusalem Longitudinal Study is an age-homogenous cohort study following a representative sample of Jerusalem residents all born in 1920–1921, all aged 70 years at study initiation. The study ran from June 1990 to May 1991. Of the 1859 residents living in Jerusalem at that time, born in 1920–1921, 759 were sampled, of whom 605 agreed to participate and 456 agreed to undergo physical examination and blood sampling (Figure 1). The sample was not different from the entire age stratum with respect to health resource use or mortality. Complete data for the calculation of the different GFR-estimation equations were available for 443 subjects for the CG equation and for 441 subjects for the abbreviated MDRD and the Mayo Clinic equations. These subjects represent the present study group. There were no exclusions criteria for the present study, and subjects with pre-existing renal disease were also recruited, but none had advanced renal disease or was being treated with dialysis.

In personal interviews, subjects responded to a questionnaire offering graded multiple-choice answers providing detailed demography, personal history, life style, health services use, function and cognitive status. They also underwent a thorough medical history and examination by experienced certified geriatric specialists. Standard clinical laboratory tests were also performed. All subjects gave informed consent, and the institutional review board approved the study.

Variables

Subjects graded their performance of the activities of daily living and the instrumental activities of daily living. Because of the near universality of function without assistance, independence was defined as performance with ease, as previously described. Subjects were asked to define their health status as ‘healthy’ or not. Based on subjects’ answers about smoking habits, smoking was quantified in pack-years (one pack of cigarettes smoked daily for a year). Exercise was defined as light activity, such as walking, at least 4 h a week or sport at least twice weekly. Blood pressure was measured twice with a mercury sphygmomanometer. Hypertension was defined as at least one of the following: treatment with blood-pressure-lowering medications, systolic blood pressure \( \geq 140 \text{ mmHg} \), diastolic blood pressure \( \geq 90 \text{ mmHg} \) or above. All subjects had baseline serum creatinine measured as part of the laboratory profile.

Serum creatinine levels were assayed using the rate-Jaffe reaction on a Hitachi 747 autoanalyzer (Roche Diagnostics) calibrated with the uncompensated method. Serum creatinine was defined as elevated if measurement was \( > 106 \text{ mmol/l} \) (>1.2 mg/dl), based on the upper normal level used by most laboratories.

GFR was estimated based on each of the following equations: CG equation \( \text{CrCl} = \frac{((140-\text{age}) \times \text{weight})}{(72 \times \text{serum creatinine})} \times (0.85, \text{ if female}) \), abbreviated MDRD equation \( \text{GFR} = 186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 1.212 \) (if black) \( \times 0.742 \) (if female) and the Mayo Clinic equation \( \text{GFR} = \exp \times ((1.911 + (5.249/\text{serum creatinine}) – (2.114/\text{serum creatinine}^2) – 0.00686 \times \text{age} – 0.205 \text{ (if female)}) \) (if serum creatinine < 0.8 mg/dl, use 0.8 for serum creatinine). All equations were corrected for body surface area and results expressed as \( \text{ml/min/1.73 m}^2 \). Survival was determined for 12 years following the initial examination at age 70, from the national Interior Ministry registry of death certificates.

Statistical analysis

Data were analysed using SAS version 8.1. for PC. The dependent variable of the study was survival.
during 12 years follow up. Baseline characteristics at age 70 were compared using \( \chi^2 \) test, t test or Wilcoxon rank sum test, as appropriate. Difference in survival between subjects stratified by GFR was assessed with Kaplan-Meier curves, and statistical significance was evaluated using the log rank test.

We initially defined reduced eGFR as <60 ml/min per 1.73 m\(^2\), based on the NKF clinical practice guidelines\(^3\) and aimed at identifying the most accurate equation in predicting mortality at moderate renal dysfunction. As previous studies found increased mortality risk only for the lowest eGFR,\(^13\) we then divided the eGFR into quartiles according to CKD stage definition of the NKF: GFR (ml/min/1.73 m\(^2\)) <30; 30–59; 60–89; and \( \geq 90.\)^\(^3\)

Multivariable survival analysis using Cox proportional hazard model was used to determine the impact of reduced GFR at age 70 on mortality over the next 12 years. To account for confounding factors, demographic, functional, medical and other laboratory variables at age 70 were introduced into the regression as independent variables. These included sex, smoking, serum cholesterol level, hypertension, ischaemic heart disease, diabetes mellitus, malignant diseases, physical activity and eGFR, and were based on previous studies.\(^13,14\)

## Results

### Identification of renal dysfunction by the different equations

The results of GFR estimation for the study group using each equation are shown in Table 1. While the CG equation identified 51% of the group as having renal dysfunction, MDRD identified only 34% and the Mayo Clinic equation only 16%. Mean eGFR for the renal dysfunction group was the same for all equations, but that of the eGFR >60 group was much higher for the Mayo Clinic equation, as was the mean eGFR for the whole group by this equation. None of the subjects had an eGFR level <15 ml/min/1.73 m\(^2\) by any equation.

### Baseline characteristics

The baseline characteristics of the study group are shown in Table 2. Nearly all participants were independent in activities of daily living, and more than half engaged in regular physical activity. One in six had diabetes mellitus, one in four ischaemic heart disease, and more than 70% suffered from hypertension, of whom more than 60% received antihypertensive medications.

#### Table 1 Estimated GFR according to the various equations

<table>
<thead>
<tr>
<th>Equation</th>
<th>Higher n</th>
<th>Mean ± SD</th>
<th>Reduced n</th>
<th>Mean ± SD</th>
<th>All subjects n</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault</td>
<td>214</td>
<td>72.2 ± 9.8</td>
<td>229</td>
<td>49.8 ± 8.0</td>
<td>443</td>
<td>60.6 ± 14.3</td>
</tr>
<tr>
<td>Abbreviated MDRD</td>
<td>290</td>
<td>78.2 ± 14.4</td>
<td>151</td>
<td>49.5 ± 9.2</td>
<td>441</td>
<td>68.3 ± 18.7</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>370</td>
<td>87.6 ± 13.6</td>
<td>71</td>
<td>48.0 ± 12.4</td>
<td>441</td>
<td>81.2 ± 19.8</td>
</tr>
<tr>
<td>‘Refit MDRD’</td>
<td>351</td>
<td>82.9 ± 16.2</td>
<td>90</td>
<td>49.8 ± 10.0</td>
<td>441</td>
<td>76.1 ± 20.1</td>
</tr>
</tbody>
</table>

Higher, eGFR \( \geq 60 \) ml/min/1.73 m\(^2\); Reduced, eGFR <60 ml/min/1.73 m\(^2\).

The mean serum creatinine level of the study group was 95.5 \( \mu \)mol/l (1.08 mg/dl), with a standard deviation of 30 \( \mu \)mol/l (0.34 mg/dl).

Figure 2 shows the distribution of the subjects with reduced eGFR according to each equation and, in parentheses, those who died during the 12 years of follow-up. The identification of reduced eGFR was shared by the CG and MDRD for 131 subjects, by the MDRD and the Mayo Clinic equation for 71 subjects and by the Mayo Clinic equation and the CG for 69 subjects. All subjects identified as having reduced eGFR by the Mayo Clinic equation were also identified by the other two equations.
Baseline serum creatinine at age 70 was in the normal range for the majority of subjects (mean ± SD 94.6 ± 30.1 μmol/l). None of the subjects was being treated with lipid-lowering medications at study initiation.

**Cockcroft-Gault equation**

Subjects with reduced eGFR and those with an eGFR of at least 60 ml/min per 1.73 m² were similar in terms of representation of women, independence in activities of daily living, physical activity, self-rated health and frequencies of diabetes mellitus, ischemic heart disease, hypertension and smoking. Body mass index was lower and serum cholesterol level higher in the group with reduced eGFR (Table 3).

**MDRD equation**

In the group with reduced eGFR there were fewer women, a higher prevalence of hypertension, and higher body mass index and serum cholesterol levels (Table 3).

**Mayo Clinic equation**

Lower female representation in the group with reduced eGFR was significantly more pronounced, as was the higher frequency of hypertension and smoking (Table 3).

**Mortality according to estimated GFR**

Kaplan-Meier survival probability curves during the 12-year follow-up, for eGFR below and above 60 ml/min/1.73 m², based on each equation, are shown in Figure 3, a–c. Renal function as measured by the CG or the MDRD equation did not significantly predict survival whereas only 52% of subjects classified with reduced eGFR by the Mayo Clinic equation survived at 12 years follow-up, compared to 71% of those classified as GFR ≥ 60 ml/min per 1.73 m² (p = 0.0002).

Cox proportional hazard analysis was performed for each equation, using the following independent variables at age 70: sex, smoking, serum cholesterol level.

### Table 2 Baseline characteristics of the study group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>199 (45.1%)</td>
</tr>
<tr>
<td>Independent in ADL</td>
<td>383 (88.9%)</td>
</tr>
<tr>
<td>Active physically</td>
<td>238 (54.1%)</td>
</tr>
<tr>
<td>Feels healthy</td>
<td>316 (72.1%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>71 (16.1%)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>115 (26.1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>317 (72.2%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>17 (3.8%)</td>
</tr>
<tr>
<td>On antihypertensive medics</td>
<td>198 (44.9%)</td>
</tr>
<tr>
<td>On anti-diabetes medics</td>
<td>36 (7.7%)</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>15.3 ± 22.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.1 ± 3.9</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>5.9 ± 1.1</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>94.6 ± 30.1</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>84.8 ± 10.2</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>142.8 ± 20.6</td>
</tr>
</tbody>
</table>

Data are numbers (%) or means ± SD, as appropriate. ADL, activities of daily living.

### Table 3 Baseline characteristics by eGFR using each equation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cockcroft-Gault</th>
<th>MDRD</th>
<th>Mayo Clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Higher</td>
<td>Reduced</td>
<td>Higher</td>
</tr>
<tr>
<td>Females</td>
<td>107 (45.3%)</td>
<td>92 (45.4%)</td>
<td>146 (50.3%)</td>
</tr>
<tr>
<td>Independent in ADL</td>
<td>206 (89.4%)</td>
<td>175 (87.6%)</td>
<td>255 (89.8%)</td>
</tr>
<tr>
<td>Active physically</td>
<td>124 (52.3%)</td>
<td>112 (55.3%)</td>
<td>153 (52.9%)</td>
</tr>
<tr>
<td>Feels healthy</td>
<td>172 (73.5%)</td>
<td>142 (70.3%)</td>
<td>204 (71.1%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>39 (16.4%)</td>
<td>32 (15.7%)</td>
<td>46 (15.9%)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>57 (23.8%)</td>
<td>58 (28.4%)</td>
<td>69 (23.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>171 (72.3%)</td>
<td>145 (71.9%)</td>
<td>196 (68.1%)</td>
</tr>
<tr>
<td>Smoking (pack-years)</td>
<td>13.9 ± 22.0</td>
<td>16.6 ± 23.5</td>
<td>14.5 ± 22.6</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.5 ± 3.9</td>
<td>25.8 ± 3.6*</td>
<td>26.7 ± 4.0</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.8 ± 1.1</td>
<td>6.1 ± 1.1*</td>
<td>5.9 ± 1.1</td>
</tr>
</tbody>
</table>

Data are numbers (%) or means ± SD, as appropriate. Higher, eGFR ≥ 60 ml/min/1.73 m²; Reduced, eGFR <60 ml/min/1.73 m². ADL, activities of daily living. *p < 0.05, by χ² test, Wilcoxon rank-sum test or student t-test, as appropriate.
level, hypertension, ischaemic heart disease, diabetes mellitus, malignant diseases, physical activity and eGFR (Table 4). Based on this analysis, reduced eGFR as identified by either the CG or MDRD equations did not predict mortality (hazard ratios 1.23, 95%CI 0.87–1.73, *p* = 0.23 and 1.19, 95%CI 0.83–1.71, *p* = 0.33, respectively) but eGFR estimated by the Mayo Clinic equation did predict mortality (hazard ratio 1.56, 95%CI 1.01–2.39, *p*=0.04). Another analysis was performed using eGFR derived from the ‘Refit MDRD equation’. This equation was presented by the authors of the Mayo Clinic equation to account for serum creatinine calibration. It was developed using all CKD patients like the original MDRD, but using the same serum creatinine assay as the Mayo Clinic equation. The results (Table 4) are closer to the Mayo Clinic than to the MDRD equation (hazard ratio 1.49, 95%CI 1.02–2.19, *p*=0.041).

Mortality hazard ratios were adjusted for the following baseline variables: sex, smoking, serum cholesterol level, hypertension, ischaemic heart disease, diabetes mellitus, malignant diseases, physical activity and eGFR.

![Graph](image)

**Figure 3.** Survival probability for reduced and normal eGFR at age 70, according to the different equations (using log-rank test). a Cockcroft-Gault, b MDRD, c Mayo Clinic.

<table>
<thead>
<tr>
<th>Equation</th>
<th>Hazard ratio</th>
<th>Value</th>
<th>95%CI</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault</td>
<td>Adjusted</td>
<td>1.23</td>
<td>0.87–1.73</td>
<td>0.23</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.31</td>
<td>0.94–1.82</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>MDRD</td>
<td>Adjusted</td>
<td>1.19</td>
<td>0.83–1.71</td>
<td>0.33</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.33</td>
<td>0.94–1.86</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>Adjusted</td>
<td>1.56</td>
<td>1.01–2.39</td>
<td>0.04</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.05</td>
<td>1.39–3.01</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>‘Refit MDRD’</td>
<td>Adjusted</td>
<td>1.49</td>
<td>1.02–2.19</td>
<td>0.041</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.63</td>
<td>1.13–2.35</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4** Cox proportional hazard ratios for 12-year mortality with reduced eGFR (<60 ml/min/1.73 m²) by different equations.

Level, hypertension, ischaemic heart disease, diabetes mellitus, malignant diseases, physical activity and eGFR (Table 4). Based on this analysis, reduced eGFR as identified by either the CG or MDRD equations did not predict mortality (hazard ratios 1.23, 95%CI 0.87–1.73, *p* = 0.23 and 1.19, 95%CI 0.83–1.71, *p* = 0.33, respectively) but eGFR estimated by the Mayo Clinic equation did predict mortality (hazard ratio 1.56, 95%CI 1.01–2.39, *p*=0.04). Another analysis was performed using eGFR derived from the ‘Refit MDRD equation’. This equation was presented by the authors of the Mayo Clinic equation to account for serum creatinine calibration. It was developed using all CKD patients like the original MDRD, but using the same serum creatinine assay as the Mayo Clinic equation. The results (Table 4) are closer to the Mayo Clinic than to the MDRD equation (hazard ratio 1.49, 95%CI 1.02–2.19, *p*=0.04).

Serum creatinine was analysed in the same model, comparing levels below and above 106 μmol/l (1.2 mg/dl), but did not predict mortality (hazard ratio 1.25, 95%CI 0.85–1.85, *p* = 0.26).

**eGFR quartiles**

When using the same analysis but dividing the eGFR into quartiles, as described above, all equations predicted mortality significantly but only when the lowest quartile (eGFR <30 ml/min/1.73 m²) was compared to the highest (eGFR ≥90 ml/min/1.73 m²) (Table 5), possibly due to the limited stratification of subjects in the lower eGFR quartiles.
Discussion

The present study shows that in community-dwelling elderly people, a moderate reduction in eGFR, with associated increased mortality, is best identified by the Mayo Clinic equation.

Generalizability of study findings

The Jerusalem Longitudinal Study group is similar to other studied groups of similar age in terms of functional independence, physical activity, major morbidity, laboratory indices and mortality. The only other Israeli study reporting longitudinal mortality data in the elderly, the CALAS study, examined older subjects from different ages and reported higher 12-year mortality rates. The eGFR of the present study group (as calculated by the Mayo Clinic equation) is similar to the inulin clearance rate at the same age reported as early as 1950 (81 ± 19.9 ml/min/1.73 m²). The mortality associated with moderately reduced eGFR was also similar to that reported recently by Hallan et al.

Using different GFR estimation equations

eGFR <60 ml/min per 1.73 m² was a risk factor for mortality but this risk differed among the three equations studied, reaching statistical significance only for the Mayo Clinic equation (and the related ‘Refit MDRD’). When dividing the eGFR levels into quartiles, representing the CKD stages defined by the NKF, all three equations were again similar in predicting mortality but the risk was limited to the lowest quartile (eGFR <30 ml/min/1.73 m²).

Why does the use of the same variables produce such different results with different equations? Currently recommended estimation equations of GFR have been criticized for inaccuracy. The CG equation overestimates GFR, and the MDRD equation was developed in prospective kidney donors with the intention of improving on these shortcomings, but it too was not developed from a general population sample, and the group used notably lacked representation of elderly subjects.

Other sources of error are related to the measurement of serum creatinine. First, a systematic bias originates from calibration differences between measurement procedures. For instance, the method used in this study was the uncompensated rate-Jaffe method using the Hitachi-Roche auto-analyzer, a similar method to that used to develop the Mayo Clinic equation, but different from the MDRD study using the Beckman auto-analyzer. Second, a random measurement bias originates from random variability between laboratories in day-to-day calibration and from specimen-specific effects, such as endogenous and exogenous interfering substances. Comparing our data with the ‘refit MDRD equation’ derives a hazard ratio closer to the Mayo Clinic equation, and not to the MDRD, when the difference between these equations is the method for measurement and calibration of serum creatinine, offering some support for the systematic bias explanation.

Various studies have reported increased mortality only at lower cut-off levels of eGFR. In a recent report by O’Hare et al., mortality in elderly subjects increased only below 50 ml/min. It is possible that these findings result from using the MDRD equation with its limitations, and that using the Mayo Clinic equation (as in the present study) will more accurately identify moderately reduced GFR. A recent report by Rigalleau and colleagues demonstrated the superiority of the Mayo Clinic equation over the MDRD in diabetic subjects. The importance of identifying reduced GFR at the earliest increase in mortality risk cannot be underestimated. The Mayo Clinic equation appears to have an advantage in the present elderly group, being better able to predict mortality.

However, even with these known limitations of the available estimation equations, there is currently no better method of estimating GFR. The National Kidney Foundation’s Kidney Disease Quality Outcome Initiative (NKF-K/DQOI) recently published clinical practice guidelines recommending the use of estimation equations as the best method of diagnosing CKD in clinical practice. These guidelines acknowledge the limitations of these equations, but find them superior to serum creatinine concentration and measured creatinine clearance. Indeed, elevated serum creatinine (used exclusively in everyday life by most physicians) did not predict mortality in the present study. An estimated GFR within 30% of a measured

### Table 5

<table>
<thead>
<tr>
<th>Equation</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft-Gault</td>
<td>5.48</td>
<td>1.27–23.65</td>
<td>0.022</td>
</tr>
<tr>
<td>MDRD</td>
<td>7.47</td>
<td>2.74–20.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>7.37</td>
<td>3.13–17.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>‘Refit MDRD’</td>
<td>7.01</td>
<td>2.47–19.9</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

was developed in prospective kidney donors with the intention of improving on these shortcomings, but it too was not developed from a general population sample, and the group used notably lacked representation of elderly subjects.
GFR was considered acceptable by the KDQOI. A recent study demonstrated the use of serum cystatin C as a measure of renal function and a predictor of mortality, yet when previously compared with creatinine-based GFR estimates, there was no advantage to using cystatin C.

eGFR and mortality in the elderly

The association between eGFR and mortality has been shown in a number of studies over the last 5 years, but most of these studies evaluated risks among subjects with established clinical factors, including heart failure and hypertension, and may not pertain to the general community-dwelling elderly population. A recent report from the Cardiovascular Health Study related cystatin C to the elevated risk of mortality in community-dwelling older adults with CKD, although as mentioned above, cystatin C as an index of kidney function appears to have no advantage over creatinine-based GFR estimation and is less widely available worldwide.

The correlation demonstrated here between moderate renal insufficiency and mortality suggests that earlier recognition of reduced eGFR may possibly lead to intervention to improve this mortality risk. There are as yet no studies on the mechanism of such increased mortality: such studies will be greatly influenced by the method used to calculate eGFR below the NKF/DOQI threshold.

One possible link between CKD and increased mortality is cardiovascular disease. The putative mechanism might involve inflammation, as well as the metabolic and hormonal abnormalities associated with CKD. Elevated serum concentrations of phosphorus, calcium and parathyroid hormone are independently associated with cardiovascular morbidity and mortality.

Several studies have demonstrated improved outcome in patients with end-stage renal disease and CKD referred earlier to specialist care. Furthermore, evidence is emerging of ability to prevent cardiovascular risk. In the HOPE study, angiotensin-converting enzyme (ACE) inhibition with ramipril reduced the high cardiovascular risk in subjects with minor renal dysfunction. Treatment with statins also reduced cardiovascular morbidity and mortality in patients with minor renal dysfunction, as demonstrated in the ALERT and CARE trials using fluvastatin and pravastatin respectively, and in the ASCOT trial using atorvastatin.

Early detection of CKD may benefit subjects by delaying disease progression and reducing cardiovascular morbidity and mortality.

Study limitations

A limitation of our study is the relatively small sample size of elderly people all of the same age, but this group appears representative of the whole elderly population of the same age in Jerusalem. Moreover, the demonstration of a powerful predictor of mortality in such a small sample size emphasizes specificity without compromising sensitivity of the estimation equation, with even greater expected power in a larger sample size.

A second limitation may be that the study group comes from a single city, Jerusalem. However this group consists of subjects born in five continents and not less than 40 different countries, and as stated above, shows similarities with other populations and studies worldwide.

We did not measure GFR directly. Such a measurement is unlikely to be realistically available in a community-based elderly population study. Furthermore, since clinical indicators for diagnosis of CKD were not assessed, ‘normal’ GFR may overlook kidney diseases, such as polycystic kidney disease or incipient diabetic nephropathy.

The lack of analyses on cause-specific mortality precludes us from fully discussing mechanisms of increased mortality in CKD, but data in death certificates is frequently inaccurate, especially in older patients, mostly dying from a combination of factors and co-morbidities.

Strengths of the present study include its prospective nature, age homogeneity, an unusually long follow-up, and inclusion of prognostically important variables often missing from other analyses, such as functional independence, self-reported health status, smoking status and physical activity.

Conclusions

In our group of community-dwelling older adults, moderate CKD was prevalent and independently associated with mortality. We found the Mayo Clinic equation to be the most accurate. It identified the least number of subjects with kidney dysfunction, produced the same average eGFR for the kidney dysfunction group as the other two equations but had the strongest risk prediction for mortality, suggesting that it more accurately predicts mortality related to reduced eGFR.

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References


