Can creatinine clearance be accurately predicted by formulae in octogenarian in-patients?

E. RIMON¹, N. KAGANSKY¹, L. COJOCARU², J. GINDIN¹, A. SCHATTNER³ and S. LEVY¹

From the ¹Geriatric Department and ³Department of Internal Medicine A, Kaplan-Harzfeld Medical Center, and the Hebrew University and Hadassah Medical School, Jerusalem, and ²Statistical Department, Ashkelon Academic College, Israel

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Summary

Background: As serum creatinine is relatively inaccurate for estimating renal function, prediction formulae are commonly used for more precise renal function estimation. However, these equations have not been studied in acutely hospitalized octogenarian patients.

Aim: To compare three commonly used formulae for estimating GFR to measured creatinine clearance (CCR) in patients aged ≥80 years admitted to an acute geriatric department.

Design: Prospective, observational study.

Methods: Consecutive patients aged ≥80 years with urinary catheters, admitted over a 12-month period to the acute geriatric ward of a 600-bed university hospital, were enrolled in the study. All had an accurate 24-h urinary collection, as well as serum and urinary urea and creatinine determinations. CCR was calculated and compared with GFRs derived from the three formulae.

Results: Of the 154 patients enrolled in the study, 107 (69.5%) had normal serum creatinine (≤1.4 mg/dl), but 77/107 (50.0%) of these had measured CCR ≤60 ml/min/1.73 m². Mean CCR was 45.1 ml/min/1.73 m² declining at the rate of 1.1 ml/min/1.73 m² each year. Only 9% of patients according to the Cockcroft and Jelliffe formulae, and 17% by the MDRD formula, fell within ±10% and +10% of the measured CCR, which were the limits of agreement decided prior to the initiation of the study.

Discussion: Many elderly in-patients with moderate renal dysfunction will remain misidentified by relying on serum creatinine or commonly used prediction equations. The best practical approach in these patients is to avoid potentially nephrotoxic drugs and drugs excreted mainly through the kidneys.

Introduction

The elderly population has been growing quickly in the last decades, with a concomitant sharp rise in the rate of hospital admissions. Hospitalization due to acute illness is commonly associated with newly prescribed medications, many of which are excreted through the kidneys, or are nephrotoxic.

Patients over the age of 80 years have especially limited physiological reserves, making them vulnerable to acute diseases or to newly prescribed drugs. Structural and functional changes resulting from age, as well as systemic diseases affecting the kidney, often cause a significant decrease in renal function.¹,² Only about a third of the elderly
maintain normal renal function, while most have only 50% of glomerular filtration rate (GFR) or less left at the age of 80.\textsuperscript{3,4} This degree of impairment and its variability make the accurate measurement of renal function in elderly acutely-ill subjects very important, especially for drug dosing and for fluid and electrolyte balance.

Serum creatinine is relatively insensitive to significant decreases in GFR in the elderly, and is affected by the considerable decline in muscle mass with age, as well as by drugs and diet.\textsuperscript{5,6} The ‘gold standard’ determination of GFR is by measuring inulin clearance, but this is a cumbersome test, requiring intravenous infusion to reach a plasma steady state, accurate urine collection and a time-consuming chemical assay.\textsuperscript{7} The most common way for accurate measurement of renal function is by a 24-h urinary collection, i.e. the creatinine clearance (CCR) test, which can probably give a reasonable estimate of GFR.\textsuperscript{8} Since accurate urinary collection in elderly patients may be fraught with difficulties due to forgetfulness, confusion or urinary incontinence,\textsuperscript{9} a shortened collection period of 12 h has been proposed, but found inaccurate.\textsuperscript{10}

Several formulae have been developed instead, that estimate GFR from the patient’s age, sex, body size, and serum creatinine. These formulae are commonly used as surrogates of the patient’s GFR across all ages.\textsuperscript{11–16} Previous studies that examined reliability of these prediction formulae have included few participants over the age of 80 years. No study considered this age group as a separate one, and the results of those studies in the elderly were inconsistent: some studies found a good agreement between estimated GFR and calculated GFR in the elderly,\textsuperscript{13–16} while others did not.\textsuperscript{11,17–19}

Acutely hospitalized inpatients were included in only a few previous studies, with very few patients over the age of 80 years.\textsuperscript{20,21} We therefore examined the agreement between estimated CCR and the measured one, in acutely ill patients over the age of 80 years admitted to our hospital.

**Methods**

All patients ≥80 years of age, admitted over a one-year period to the acute geriatric ward at Kaplan Medical Center; a 600-bed university hospital, were enrolled in the study if they had urinary bladder catheters for at least 48 h before enrolment. Only patients with serum creatinine >2.5 mg/dl or patients who were considered terminally ill (estimation of <10 days survival) were excluded. A complete medical history was obtained from all participants, and their charts were reviewed. Five comorbidities were recorded: acute infectious illness, hypertension, heart failure, diabetes mellitus and rheumatic and autoimmune diseases. Patients’ medications were recorded as seven separate groups: diuretics, calcium channel blockers, beta blockers, ACE inhibitors, NSAIDS, H2 blockers, and antibiotics, and another two drugs were analysed separately (cimetidine and trimethoprim).

**Measurements**

**Measured CCR**

An accurate 24-h urinary collection was obtained and its volume recorded, together with serum blood urea nitrogen, serum creatinine, serum albumin, urinary creatinine, and patients’ weight and height. Urine flow rate was calculated from total urine volume (ml) divided by collection period (1440 min). Blood collection was performed in the morning, immediately following urine collection (which finished at 8 am). Levels of serum and urine creatinine were measured by using a kinetic alkaline picrate assay, using rate-blanking and compensation (normal range 0.7–1.5 mg/dl, 62–133 μmol/l).\textsuperscript{22} Serum urea nitrogen was measured by the urease method (normal range 12–50 mg/dl, 3.6–7.1 mmol/l) and albumin by the bromcresol green method (normal range 3.5–5.5 g/dl, 35–55 g/l). CCR was determined as usual:

\[
\text{CCR} = \frac{\text{urinary creatinine} \times \text{urinary volume}}{\text{serum creatinine}} / 1440 \text{ min}
\]

As CCR is based on an average body surface area (BSA) of 1.73 m\textsuperscript{2}, we corrected the CCR values for each patient according to BSA. This was calculated using the DuBois formula:\textsuperscript{23}

\[
\text{BSA} = \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \\
\times 0.007184
\]

Patients’ height was estimated from measurement of the distance between the knee and the ankle according to the formulae:\textsuperscript{24}

\[
\text{Height (men, cm)} = 64.19 - (0.04 \times \text{age (years)}) \\
+ (2.02 \times \text{knee height (cm)})
\]

\[
\text{Height (women, cm)} = 84.88 - (0.24 \times \text{age (years)}) \\
+ (1.83 \times \text{knee height (cm)})
\]
Calculated CCR

The following three formulae, which were validated by previous well-designed studies and included age as one of their variables, were used to estimate CCR.

Cockcroft and Gault: \[ \frac{[140 - \text{age}] \times \text{weight}}{(72 \times \text{Scr}) \times 1.73 \text{m}^2} \]

For female subjects, subtract 15%.

Jelliffe: \[ 98 - (16 \times [\text{age} - 20/20])/(\text{Scr} \times (\text{weight/70}) \times 0.9 \times 1.73 \text{m}^2) \]

MDRD: \[ 170 \times \text{Scr}^{0.999} \times \text{age}^{-0.176} \times \text{SUN}^{-0.170} \times \text{Alb}^{0.318} \]

(\times 0.762 if patient is female)

Where age is in years and weight in kg; Scr, serum creatinine; SUN, serum urea nitrogen; Alb, serum albumin.

Statistical analysis

The agreements between measured CCR and the different formulae were tested as described by Bland and Altman. A possible relation between the differences and the means was examined by calculating the rank correlation between the absolute differences and the means. The differences between measured CCR and formulae varied in a systematic way over the range of measurements, therefore a logarithmic (log) transformation of the data was used to remove the correlation between the differences and the means.

The limits of agreement were considered clinically appropriate if they were between −10% and +10% limits, as recommended by the National Kidney Foundation.

A possible relation between the differences and the means was examined by calculating the rank correlation between the absolute differences and the means. The Bland and Altman regression approach was used to calculate the limits of agreements (using log transformation of the data did not remove the correlation between the differences and the means, and therefore could not be used). Means were compared using Student's t-test. A p value <0.05 was considered significant. All statistical computations were two-tailed and were done using SPSS 11.0 software.

Results

During the year of the study, (1 August 2001 to 31 July 2002), 225 patients aged ≥80 years with urinary catheters were admitted to our acute geriatric ward, out of a total of 3461 admissions. Seventy-one patients were excluded from the study: 36 because of known significant renal failure (creatinine levels >2.5 mg/dl) and 35 who were considered terminally ill. Thus 154 patients (68.4%) were enrolled into the study (78 men, mean age 86.7 ± 5.3 years). Eighty patients were hypertensive, 35 had diabetes mellitus, 32 had heart failure and 54/154 (35%) had an acute infectious disease. Only 24 had no known comorbidity.

Table 1 shows renal function tests in the different subgroups of patients. Average urinary volume was 1284 ± 538 ml (range 600–3590 ml). Average serum creatinine was 1.3 ± 0.6 mg/dl, with a significant gender difference, but no difference in serum creatinine levels between diabetics, hypertensives, or patients with heart failure.

Average CCR was also almost the same in all these groups (overall 45.1 ml/min/1.73 m²) and decreased by about 1.1 ml/min/1.73 m² per year over the age of 80 years (Figure 1). Only 37/154 patients (24%) had a CCR >70 ml/min/1.73 m² and only four (2.6%) had a CCR >100 ml/min/1.73 m². Whereas 107/154 patients (69.5%) had normal serum creatinine (≤1.4 mg/ml), 77 of them (50%) had measured CCR of ≤60 ml/min/1.73 m².

The mean CCR of the patients with normal serum creatinine levels was 50.7 ± 24.0 ml/min/1.73 m².

Table 1 Association of renal function with demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>Serum creatinine (mg/dl)</th>
<th>Urinary volume (ml/24 h)</th>
<th>Creatinine clearance (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>154</td>
<td>1.3 ± 0.6</td>
<td>1284 ± 538</td>
<td>45.1 ± 25.6</td>
</tr>
<tr>
<td>Male</td>
<td>78</td>
<td>1.5 ± 0.7</td>
<td>1299 ± 577</td>
<td>47.3 ± 27.6</td>
</tr>
<tr>
<td>Female</td>
<td>76</td>
<td>1.1 ± 0.5†</td>
<td>1268 ± 497</td>
<td>42.5 ± 20.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35</td>
<td>1.3 ± 0.9</td>
<td>1392 ± 593</td>
<td>48.9 ± 25.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>80</td>
<td>1.3 ± 0.7</td>
<td>1275 ± 518</td>
<td>46.7 ± 24.9</td>
</tr>
<tr>
<td>Heart failure</td>
<td>32</td>
<td>1.4 ± 0.6</td>
<td>1201 ± 479</td>
<td>42.1 ± 22.6</td>
</tr>
<tr>
<td>Infectious illness</td>
<td>27</td>
<td>1.4 ± 0.7</td>
<td>1255 ± 546</td>
<td>44.9 ± 26.2</td>
</tr>
<tr>
<td>No known comorbidities</td>
<td>24</td>
<td>1.3 ± 0.7</td>
<td>1276 ± 549</td>
<td>45.4 ± 22.6</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, data are means ± SD. †p < 0.01 compared with male patients.
Calculated versus measured CCR

A positive significant correlation coefficient was found between the absolute values of the differences between the measured CCR and the formulae and their mean, i.e. there was an increase in variability of the differences as the magnitude of the measurement increased ($r = 0.409$ for Cockcroft and Gault formula, $r = 0.235$ for Jelliffe formula and $r = 0.513$ for MDRD formula, $p < 0.001$ for all three formulae). The Altman and Bland plots of the logarithmic transformation of the data are shown in Figure 2.

The mean of differences (bias) and 95% limits of agreement for all formulae are shown in Table 2. All three formulae overestimated CCR (negatively significant bias).

For the Cockcroft formula, in 95% of the cases the CCR would be between 0.23 and 1.53 times the estimated values (thus the measured CCR might differ from the Cockcroft formula by 77% below to

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**Figure 1.** Cross-sectional differences in creatinine clearance (CCR) with age. Values plotted indicate mean and 95% CI. The number of subjects in each group is indicated above the abscissa.

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**Figure 2.** Bland and Altman plots of the three different formulae in comparison with measured creatinine clearance (CCR). The differences between measured CCR and formulae are plotted against their average (after log transformation) with 95% limits of agreement. The middle line represents the regression line between the difference and the mean of measurements; the upper and the lower lines represent 95% regression based limits of agreement. Measures are expressed in units of ml/min/1.73 m$^2$. 
53% above). For the Jelliffe formula, in 95% of the cases the measured CCR would fall between 0.23 and 1.66 times of the calculated CCR (thus the measured CCR might differ from Jelliffe formula by 77% below to 66% above), and for the MDRD formula, in 95% of the cases the measured CCR would be between 0.35 and 2.45 times the calculated CCR (thus CCR might differ from the Jelliffe formula by 65% below to 145% above).

Only 9% of patients according to the Cockcroft and Jelliffe formulae, and 17% of the MDRD formula, fell within $\pm 10\%$ and $\pm 10\%$, which were the limits of agreement decided prior to the initiation of the study.

The results of method comparison analysis as described above, did not differ significantly when applied for each subgroup of patients separately (i.e. male, female, diabetics, etc.). The 24 patients who had no known comorbidities showed similar agreement between the measured and the calculated CCR to that of the other patients.

Measurement of individual body surface area gave an average of 1.64 m$^2$ for all participants instead of the 1.73 m$^2$ that the formulae are based upon. Correcting the CCR of each participant to his own surface area did not significantly change the comparison of the results between the measured CCR and the formulae. Comparison analysis of the seven groups of drugs and of trimethoprim and cimetidin did not show any statistically significant differences.

### Discussion

To our best knowledge, this is the first study to evaluate estimated CCR against measured values based on a reliable 24-h urine collection in hospitalized acute geriatric patients over the age of 80. This age group is the most rapidly expanding segment in the population in Western countries. They usually have limited physiological reserves, which the acute illness reduces even further. These elderly people frequently have several chronic diseases and may receive multiple medications.

Decisions of dose adjustment in these patients are usually empirical, and patients may receive sub-optimal doses or on the contrary, toxic doses of needed drugs.

We found that renal function was moderately to severely impaired (CCR 60 ml/min/1.73 m$^2$ or less) in three-quarters of our patients. Very few of our patients (2.6%) had normal renal function (CCR of 100 ml/min/1.73 m$^2$ or more). Average CCR was 45.0 ml/min/1.73 m$^2$, which is about two-thirds of the expected CCR of non-hospitalized patients at the age of 80 years (Table 1). The decline in CCR with age, in this specific group of acutely ill patients, was at a rate of about 1.1 ml/min/1.73 m$^2$ per year over the age of 80 years (Figure 1). This adds information to the known literature, which usually ends at the age of 80 years.

As has been suggested recently, the Bland and Altman method should be used for measuring agreement in comparison studies, because it avoids the possible errors of the commonly used correlation analysis. According to this method, less than 20% of the results in this study fell within the limits of agreement that were decided prior to the initiation of the study, making these prediction equations problematic as a basis for decision-making or drug dosage in patients over 80 years old.

How can we explain the inaccuracy of the prediction equations in patients over the age of 80 years? All three formulae have been validated in young patients, based on the assumption that the amount of creatinine produced daily and excreted into the urine is dependent on renal function alone. Muscle mass was considered as a constant part of total body weight.

However, in the elderly, especially over the age of 80, lean body mass (i.e. muscle mass) decreases relative to total body weight. Consequently, the amount of creatinine produced per day, does not accurately reflect renal function. The diet of the elderly, especially acutely ill patients, may also influence serum creatinine. Moreover, the great variability in health status in this elderly popula-
tion makes it highly unlikely that a single equation will fit all patients.

The guidelines of the National Kidney Foundation, recommend the prediction equations as useful estimates of GFR, while measurement of creatinine clearance does not improve this estimate. These guidelines suggest some exceptions for that rule, including extreme age and muscle wasting (as well as vegetarian diet and severe malnutrition or obesity), where creatinine clearance can probably improve the estimate of GFR over that of the prediction equations.

As shown in previous longitudinal studies, about two-thirds of patients over the age of 80 years had 50% or more reduction in renal function in comparison with younger individuals at their thirties. On the other hand, the remaining third of those elderly had a relatively preserved renal function.

In order to overcome the problem of change in muscle mass with age, we calculated each participant’s body surface area and corrected the CCR, respectively. One possibility for the inaccuracy of the formulae in the elderly is the high incidence of comorbidity. Therefore, we examined separately all patients without any known comorbidity, but found no better results than in the rest of the patients.

One of the shortcomings of this study is the use of creatinine clearance rather than of inulin clearance. Inulin clearance is considered as the ‘gold standard’ for estimating GFR, but is impractical for routine use. Radioisotopic methods provide acceptable alternatives, but are time-consuming, expensive, and unavailable in many hospitals. The accuracy of measured CCR has been shown to correlate closely to GFR in younger patients, though one large study has shown that prediction equations are superior to the measured CCR. In a recent study in out-patient elderly, CCR was less accurate than some prediction equations, in comparison to radio-isotopic GFR measurement. In acutely ill patients with multiple comorbidities over the age of 80 years, no study has been published evaluating the reliability of measured CCR.

In conclusion, acutely ill hospitalized patients over the age of 80, with urinary catheters, have an extremely variable renal function, often moderately to severely impaired. Serum creatinine has a very weak association with CCR in this population. The formulae commonly used for predicting patients’ GFR are not accurate enough to be used in these patients. Measured CCR, based on a 24-h urinary collection, may also be imprecise for correctly determining renal function in the elderly. Until there is an accurate simple test for evaluating renal function in the elderly, nephrotoxic drugs or drugs excreted mainly through the kidneys, should be avoided as far as possible, and if mandatory, their blood levels should be carefully monitored.

References


