Susceptibility to hyponatremia in the elderly: causes and consequences
Frenkel, Nanne

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Chapter 3

Predictive values of the Cockcroft-Gault formula and the modification of diet in renal disease (MDRD) formula for mortality in elderly people.

J.I. Rotmans, W.J. Frenkel, R.T. Krediet, S.E. de Rooij

Adapted from Journal of the American Geriatric Society; 2009:946-8.
ABSTRACT

Objectives: To study the predictive value of the Cockcroft-Gault formula and the MDRD-formula for mortality and functional condition in elderly patients with acute medical illness.

Design: Prospective cohort study.


Participants: Six hundred forty-seven patients (aged 65 years or older) no electively admitted to internal medicine wards (2002-2006).

Measurements: Blood samples and demographic characteristics were collected at admission. Renal function was estimated using the Cockcroft-Gault (CG)-formula and the Modification of Diet in Renal Disease (MDRD)-formula. Outcomes were death and functional condition (determined using the Katz independence of activities of daily life (ADL) index) at 3 months and 1 year after discharge.

Results: The mean estimated creatinine clearance (CG-formula) was 58±33 ml/min and the mean estimated glomerular filtration rate (MDRD-formula) was 65±37 ml/min/1.73 m2. In total 58 (9%) patients died in the hospital and another 187 (29%) patients died within 1 year after discharge. The CG-formula had a better prognostic value for death within 1 year after discharge (OR per 30 ml/min: 0.82; 95%-CI: 0.64-0.97, p=0.03) when compared to the MDRD-formula (OR per 30 ml/min/1.73m2: 0.91; 95%-CI: 0.76-1.03, p=0.15). With regard to their predictive value for functional condition (Katz-(I)ADL-index) at 3 months after discharge, the CG-formula (OR per 30 ml/min: -0.50; 95%-CI:-0.99;0.00, p=0.05) was superior to the MDRD-formula (OR per 30 ml/min/1.73m2: -0.31; 95%-CI:-0.78;0.18, p=0.21) as well.

Conclusion: In patient aged 65 years or older, the CG-formula has a better prognostic value for mortality risk and functional condition when compared to the MDRD-formula.
INTRODUCTION

Estimating the renal function of acutely admitted patients contributes to the assessment of their prognosis since an impaired renal function is associated with an increased risk of morbidity and mortality. Although the kidneys fulfill a variety of functions, the term ‘kidney function’ usually refers to the glomerular filtration rate (GFR). The golden standard for measuring the GFR is to determine the clearance of an exogenous agent such as inulin or iothalamate. However, these assays are laborious and expensive and therefore unsuitable for daily clinical practice. As an alternative, the clearance of (endogenous) creatinine is frequently used to estimate GFR. Currently, the Cockcroft-Gault (CG) and the Modification of Diet in Renal Disease (MDRD) are the most commonly used formulas to predict creatinine clearance. In recent years, the MDRD has been simplified to a formula which merely requires the plasma creatinine concentration and the age of the patient. In the CG-formula, the body weight is included as a variable as well.

A French study that included 2095 patients, showed that the estimated GFR (eGFR) using the CG-formula and the MDRD-formula almost equally deviate from the measured GFR (using 51Cr-EDTA). In the entire study population, the average difference in eGFR between both formulas was only 3 ml/min/1.73 m2. However, the eGFR using these formulas may diverge widely in patients ≥ 65 years. Although the CG- and the MDRD-formulas are solely validated in non-hospitalized patients with stable kidney function, they are frequently utilized during acute admission since there is no suitable alternative for rapid estimation of renal function available. During acute admission of elderly patients, clinicians not only would like to estimate renal function but also the risk of mortality. In the current study, we evaluated which method to estimate renal function has the highest predictive value for mortality and functional condition in patients of 65 years and older that were acutely admitted to the internal medicine ward of a tertiary hospital.

METHODS

This study forms a part of the DEFENCE study. This acronym stands for ‘Development of strategies enabling frail elderly new complications to evade’. This study was conducted during a 40-month period from 01 December 2002 until 31 March 2006 at the Academic Medical Centre (AMC) in Amsterdam. All consecutive patients aged 65 years or older acutely admitted to the Internal Medicine ward were enrolled. Patients were not eligible if (a) they were unable to speak or understand Dutch, (b) they or their relatives did not give informed consent for the study or (c) if they came from or were transferred to another ward than the internal medicine ward. The study was approved by the Medical Ethics Committee of the AMC. A detailed description of the study population has been published previously.
**Data Collection**

At admission, blood samples were collected from all patients and if possible, body weight was measured. Within 48 hours after admission, a multidisciplinary evaluation of the patient was performed by members of the geriatric research team. Both patients and relatives were interviewed with special attention to the functional condition of the patients. After three months and again 1 year after discharge patients and their relatives were contacted by telephone and interviewed again. The diagnoses at admission were scored according the ICD-9 classification. The Charlson comorbidity index was assessed at discharge.

**Estimating Renal Function**

Plasma creatinine concentrations were determined using an enzymatic method (CREA plus, Roche/Boehringer Mannheim). To estimate creatinine clearance (ml/min) the CG-formula was used:

\[
\text{CG} = \frac{(140 - \text{age}) \times \text{body weight}}{(72 \times \text{plasma creatinine}) \times 0.85 \text{ if females}}
\]

To estimate GFR (ml/min/1.73 m²) the MDRD4-formula was used:

\[
\text{MDRD4} = 186 \times \text{plasma creatinine} - 1.154 \times \text{age} - 0.203 \times 0.742 \times 1.21 \text{ if from African descent}
\]

Subsequently, the Kidney Disease Outcomes Quality Initiative (K-DOQI) classification was used to categorize the actual estimated renal function of admitted patients for both formulas separately. The plasma creatinine concentration was solely measured at acute admission. Therefore, the K-DOQI classification was only used to classify the renal function at time of admission and does not reflect the stage of chronic kidney disease of the study participants.

**Functional Condition**

The functional condition of the patients was assessed using the ‘Katz-activity of daily life (ADL) index’. The Katz (I)ADL index questionnaire is a validated 15-item scale that measures independence of the subject in basic and instrumental activities of daily living. Performance is graded according to the number of disabilities (a higher score indicates worse functional status). The internationally applied categories of the Katz (I)ADL index questionnaire score were used; 0 limitations was defined as no limitations, 1 to 3 limitations as mild, 4 to 6 as moderate, and 7 or more as severe functional impairment. The ‘Katz-(I) ADL-index’ consists of a version for the patient and one for his relatives. The final ‘Katz-(I) ADL-index’ was based on the score of the patient unless patients had severe cognitive impairments. Three months and one year after discharge, this index was assessed again.

**Statistical Analysis**

The predictive value of the different methods to estimate renal function was calculated using logistic regression analysis (mortality) and linear regression analysis (functional condition). The Cox regression model was used for multivariate analysis. P-values ≤ 0.05 were considered significant. SPSS 14.0 was used for all statistical calculations.
RESULTS

Among the 783 patients aged 65 and older who were eligible for the study, 136 patients (17%) did not provide informed consent. Therefore, 647 patients were enrolled in the study. Fifty-eight of patients (9%) died during admission and 187 patients (29%) died within a year after discharge: 113 patients (17%) within 3 months and 74 (11%) patients between 3 months and 1 year after discharge. The mean age at admission was 78 years, 54% of them were women. Plasma creatinine concentration was measured in 632 patients (98%); body weight was measured in 517 patients (82%). Patient characteristics are described in Table 1.

Table 1. Characteristics of 647 patients > 65 years of age, acutely admitted to the internal ward of the Academic Medical Centre in Amsterdam, during the period from 1st of December 2002 to 31st of March 2006

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>78.2 (5)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>295 (46%)</td>
</tr>
<tr>
<td>Body weight in kg, mean (SD)</td>
<td>71.5 (15)</td>
</tr>
<tr>
<td>BMI in kg/m², mean (SD)</td>
<td>24.9 (5)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>556 (86%)</td>
</tr>
<tr>
<td>Others</td>
<td>91 (14%)</td>
</tr>
</tbody>
</table>

Functional condition before admission

Katz-(I)ADL-index, mean (SD) | 5.5 (4.4)

Diagnosis at discharge

ICD-9-category, n (%) |       |
| Infectious disease    | 313 (53%) |
| Malignancy            | 142 (22%) |
| Gastro-intestinal disease | 216 (33%) |
| Cardiovascular disease| 63 (10%)  |
| Charlson comorbidity score at discharge, mean (SD) | 3.4 (2.3) |
Estimating Renal Function

The mean plasma creatinine concentration was 1.66 mg/dl (range 0.36-14.57 mg/dl). The mean estimated creatinine clearance (CG-formula) was 58 ± 33 (SD) ml/min and the mean eGFR (MDRD-formula) was 65 ± 37 (SD) ml/min/1.73 m2. The estimated creatinine clearance (CG-formula) was not adjusted for body surface area since body length was not assessed in a substantial amount of patients (n=209). In 129 of the 632 patients, the CG-formula could not be applied since the body weight of these patients was not measured. The mean difference between the 2 formulas was independent of age and estimated renal function (data not shown). The CG-formula resulted in a creatinine clearance < 60 ml/min in 56% of patients while in 48% of patients the MDRD-formula resulted in an eGFR < 60 ml/min/1.73 m2. In 40% of patients, de CG-formula and MDRD-formula resulted in a different K-DOQI stage of renal dysfunction.

Predictive Value of the CG-formula and the MDRD-formula for Mortality Risk

The CG-formula at acute admission had a higher predictive value for death within 1 year after discharge when compared to the MDRD-formula (table 2). A decrease in creatinine clearance (CG-formula) of 30 ml/min was associated with an 18% increase in mortality rate within one year after discharge from the hospital. The correlation between the eGFR (MDRD-formula) and mortality rate within 1 year after discharge was not statistically significant (p=0.15). The predictive value of both formulas for mortality increased when only patients with renal dysfunction stage ≥ 3 (according to the K-DOQI classification) were included in the analysis. The relation between estimated renal function and mortality for both formulas is depicted in figure 1. When patients were categorized according the K-DOQI classification, the CG-formula was also superior to the MDRD-formula in predicting mortality within 1 year after discharge (23% additional risk per increase in category and 15% additional risk per increase in category, respectively). Body weight at admission was strongly correlated with the risk of death within the first year after discharge (19% additional risk per 10 kg reduction in body weight). Multivariate analysis showed that the predictive value of body weight for mortality within the first year after discharge did not depend on age or sex. Furthermore, the predictive value of the CG-formula for mortality disappeared after correction for body weight (p=0.14). With regard to mortality risk within 3 months after discharge, the difference in predictive value of the CG-formula and the MDRD-formula was less distinct (table 2). Neither formula had a significant predictive value for in-hospital mortality. However, the blood urea nitrogen (BUN) concentration at admission did have a significant predictive value for in-hospital mortality (17 % additional risk per 15 mg/dL increase).
Predictive Value of the CG-formula and the MDRD-formula for Functional Condition

The mean Katz-(I)ADL-index at 3 months and 1 year after discharge were 5.5 (SD: 4.3) and 6.2 (SD: 4.8), respectively. The CG-formula at admission had a higher predictive value for functional condition at 3 months after discharge when compared to the MDRD-formula (table 3). Each increase in K-DOQI stage of renal dysfunction based on the CG-formula was associated with a significant, but small increase in Katz-(I) ADL-index (figure 2). The correlation between K-DOQI stage of renal dysfunction based on the MDRD-formula and functional condition at 3 months after discharge, did not reach statistical significance (p=0.16). No linear relation was observed between body weight at admission and functional condition at 3 months after discharge (p=0.8). Neither formula to estimate renal function had a significant predictive value for functional condition at 1 year after discharge (data not shown).
Table 3. Predictive value of different methods to estimate renal function for functional condition (Katz-I (ADL)-index) in patient ≥ 65 years old, acutely admitted to the department of Internal Medicine, 3 months after discharge.

<table>
<thead>
<tr>
<th></th>
<th>Increase in Katz-I(ADL)-index OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine</td>
<td>0.01 (-0.96;0.97)</td>
<td>0.99</td>
</tr>
<tr>
<td>(per 0.3 mg/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CG-formula</td>
<td>-0.50 (-0.99;0.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>(per 30 ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDRD-formula</td>
<td>-0.31 (-0.78;0.18)</td>
<td>0.21</td>
</tr>
<tr>
<td>(per 30 ml/min/1.73 m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K-DOQI classification</td>
<td>0.57 (0.06;1.07)</td>
<td>0.03</td>
</tr>
<tr>
<td>based on CG-formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(per stage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K-DOQI classification</td>
<td>0.16 (-0.31;0.63)</td>
<td>0.50</td>
</tr>
<tr>
<td>based on MDRD-formula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(per stage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (per 10 kg)</td>
<td>0.04 (-0.14;0.24)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

**CI:** confidence interval.

**DISCUSSION**

The present study revealed that in elderly patients the CG-formula at admission has a higher predictive value for mortality within the first year after discharge than the MDRD-formula. In addition, both formulas had a weak prognostic value for the functional condition of patients at 3 months after discharge. This study was not designed to evaluate which formula is the most reliable for estimating renal function in patients aged 65 years and older. Indeed, we did not compare both formulas with a validated standard for measuring GFR such as the inulin clearance. Previous studies have suggested that in this group of patients the MDRD-formula provides a better estimate of renal function than the CG-formula\(^5\).\(^{11}\). Therefore, the observed difference in prognostic value for mortality between both formulas does not have to reflect a more accurate estimation of renal function. More likely, the better prognostic value of the CG-formula relates to the body weight at admission since this variable appeared to be an independent predictor of mortality within the first year after discharge; moreover body weight is not included as a variable within the MDRD-formula. The observed relation between body weight and mortality is in concordance with previous studies\(^12\).
\(^{13}\) which suggested that moderate overweight (body mass index 25-30 kg/m²) protects against mortality in the elderly, especially in patients with poor health status\(^14\). A possible explanation for this phenomenon is that geriatric patients with a large nutritional reserve do have a better resistance against (chronic) disease while a low body
mass index reflects progression of disease, ultimately leading to cachexia. The observed relation between blood urea nitrogen concentration (as a measure for protein catabolism) and mortality provides additional support for this hypothesis. In comparison with mortality risk, the CG-formula showed a weak prognostic value for functional condition of patients. Most likely, the latter relates to the fact that renal dysfunction is only symptomatic in advanced stages.

Figure 1. Relationship between estimated renal function using the CG-formula (A) and the MDRD-formula (B) and mortality risk within the first year after discharge. (C) Relationship between body weight and mortality risk within the first year after discharge. The curved lines represent the 95%-confidence intervals.

Figure 2. Relationship between K-DOQI classification based on the CG-formula (A) and the MDRD-formula (B) and the Katz-(I) ADL-index at 3 months after discharge. A higher Katz-index indicates a reduced degree of independence with regard to ADL-tasks. The curved lines represent the 95%-confidence intervals.
CONCLUSION

The CG-formula at acute admission of patients aged 65 and older has a better prognostic value for mortality within the first year after discharge from an internal medicine ward when compared to the MDRD-formula. Body weight at admission is a good predictor of mortality within the first year after discharge and the blood urea nitrogen concentration at admission is the only variable with prognostic value for in-hospital mortality. Measuring these parameters could therefore improve the assessment of the prognosis of elderly patients, acutely admitted to the hospital.
REFERENCES