Original article

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Evaluation of the Cockroft–Gault, Jelliffe and Wright formulae in estimating renal function in elderly cancer patients

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Background: More elderly patients are being treated with chemotherapy. Reliable and accurate measures of renal function are needed to obtain predictable, safe and effective exposure to renally excreted drugs. The Jelliffe, Cockroft–Gault and Wright formulae have been used to evaluate renal function, although they have not been validated in elderly oncology patients. We performed a retrospective evaluation of these formulae using the [^{51}Cr]-ethylenediamine tetraacetic acid ([^{51}Cr]-EDTA) method of measuring glomerular filtration rate (GFR) as the 'gold standard'.

Patients and methods: Inclusion criteria were age ≥70 years and serum creatinine <250 μmol/l, performed within 4 weeks of glomerular filtration rate (GFR) measurement. Creatinine clearance was calculated using the Cockroft–Gault, Jelliffe and Wright formulae. The precision and accuracy of the three formulae were compared with the gold standard.

Results: Two hundred and twenty-five patients were evaluated: median age, 74 years (range 70–89); males, 108; females, 117; median creatinine, 84 μmol/l (range 44–186). Correlation coefficients of the Jelliffe, Cockroft–Gault and Wright formulae were similar. In the specific GFR ranges of 50–70, 70–90 and 90–120 ml/min, the bias [mean percentage error (MPE)] was +8%, –4% and –13%, respectively. The degree of bias was greater with the Cockroft–Gault and Jelliffe formulae across the same range of GFR with the MPE being –15%, –25%, –32% and –12%, –19% and –23%, respectively. All three formulae have reduced precision and greater bias at the extremes of GFR.

Conclusions: The Wright formula is the most accurate, precise and least biased formula for the calculation of GFR in elderly patients with a GFR >50 ml/min. These results allow the physician to make a decision regarding the use of the formula based on an expected degree of bias.

Key words: Cockroft and Gault, elderly, Jelliffe, renal function, Wright

Introduction

Treatment of elderly patients with cancer has been an increasing problem in cancer management, with 60% of all incident cancers and 70% of all cancer-related deaths occurring in patients >65 years of age [1]. This is likely to become an even greater problem in an ageing population. These patients have been underrepresented in clinical trials, which has made evidence-based treatment decisions difficult. There is now an increasing awareness of this problem and trials designed specifically for elderly patients are underway.

Age itself should not exclude patients from receiving appropriate chemotherapy. However, ageing is associated with changes in drug pharmacokinetics and pharmacodynamics; in addition, there is a decline in the glomerular filtration rate (GFR). Accurate evaluation of renal function is essential for the safe delivery of renally excreted chemotherapy agents while still maintaining efficacy.

A number of methods for evaluating renal function have been proposed although they have not been specifically evaluated in the elderly patient group. Serum creatinine is an unreliable measure, particularly in the elderly, due to the influence of a number of non-renal factors, such as reduction in body mass. Creatinine clearance measurements using 24-h urinary collections are cumbersome and unreliable. GFR is generally used as an index of renal function. The [^{51}Cr]-ethylenediamine tetraacetic acid ([^{51}Cr]-EDTA) method of measuring GFR [2] is widely accepted as the 'gold standard' in determining renal function; however, this method is relatively costly, invasive and is not available in many countries, including the USA.

Alternative, more convenient methods of GFR estimation have been proposed. Creatinine clearance (CrCl) is the most widely used estimation of GFR. Several formulae have been developed to estimate either CrCl or [^{51}Cr]-EDTA measurements of GFR including the Cockroft–Gault [3], Jelliffe [4] and Wright formulae [5].

These formulae have not previously been evaluated in an elderly cancer population. There are a number of issues specific to this

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group of patients, including a deterioration of renal function, concomitant medications and diseases, ascites and cachexia. These factors may independently influence the accuracy and bias of the formulae. Extrapolation of data accumulated on young, fit non-cancer patients may not be clinically relevant or applicable to the elderly cancer population. It is therefore important that the formulae are evaluated in the relevant patient group.

The value and usefulness of these formulae in clinical practice is dependent on the precision and bias of the calculated value. The degree of variation that is acceptable will depend on the particular clinical situation in which the formula is used. This is the first study to evaluate the precision and bias of these formulae in an elderly cancer population group across a range of renal function.

Patients and methods

This was a retrospective study of oncology patients >70 years of age who had undergone [^{51}Cr]-EDTA study in the Department of Nuclear Medicine at Guy's and St Thomas' Hospitals, London.

GFR was measured following the injection of 3 MBq [^{51}Cr]-EDTA diluted in 0.1% w/v excess EDTA solution [6]. Doses were drawn up by volume to give, as accurately as possible, a 10 ml tracer solution. Following injection, 5 ml whole blood was drawn from the opposite arm 2, 3 and 4 h later. The exact times of the injection and blood samples were noted to the nearest minute. Blood samples were centrifuged and 2 ml aliquots of plasma pipetted and counted, with appropriate standards and blanks, in an automatic γ counter. Patient height and weight were noted to allow a correction of GFR for body surface area using the DuBois formula. Values of the slope-intercept GFR (SI-GFR) were calculated by multiplying the volume of distribution by the slope of the single exponential fit to the three data points. After correction of the SI-GFR figures to a standard body surface area of 1.73 m^2, the Brochner–Mortensen equation [7] was used to correct for the missing area under the plasma clearance curve due to the early fast exponential. Finally, Brochner–Mortensen corrected GFR values were rescaled by body surface area in order to derive the true individual GFR figure for each patient.

CrCl was calculated using the Cockroft–Gault, Jelliffe and Wright formulae and compared with [^{51}Cr]-EDTA measurements of GFR. Age, height, actual body weight and gender were recorded at the initial visit. Serum creatinine (SCr) was measured using the Jaffe method. The SCr and ^{51}Cr-EDTA measurements were performed within 4 weeks of each other. Wright et al. [5] describe four formulae for the evaluation of GFR. The formula is modified according to the method of creatinine measurement (Jaffe or enzymatic) and the availability of serum creatinine kinase (CK) levels. The present data was calculated using the formula described for the Jaffe method of serum creatinine measurement without CK levels.

Cockcroft and Gault,

$$\mathrm{CrCl\ (ml/min)} = \{(140 - \mathrm{age}) \times \mathrm{wt} \times [1 - (0.15 \times \mathrm{sex})]\}/(0.814 \times \mathrm{SCr});$$

Jelliffe,

$$\mathrm{CrCl\ (ml/min)} = \{[98 - 0.8 \times (\mathrm{age} - 20)] \times [1 - (0.01 \times \mathrm{sex})] \times (\mathrm{BSA}/1.73)\}/(\mathrm{SCr} \times 0.0113);$$

Wright (without CK), using Jaffe serum creatinine,

$$\mathrm{GFR} = \{[6580 - (38.8 \times \mathrm{age})] \times \mathrm{BSA} \times [1 - (0.168 \times \mathrm{sex})]\}/\mathrm{SCr}.$$

CrCl, creatinine clearance; GFR, glomerular filtration rate (ml/min); sex: male, 0; female, 1; BSA, body surface area (DuBois); SCr, serum creatinine (μmol/l); wt, weight (kg).

Statistical analysis

Bland–Altman analysis [8] was used to evaluate the relationship between the [^{51}Cr]-EDTA measurements of GFR and the values calculated using the three formulae by determining the mean bias and the precision between the different figures. Bias was assessed as the mean percentage error (MPE) calculated as the mean percentage difference between the calculated clearances and the [^{51}Cr]-EDTA measurements of GFR over the range 50 to 120 ml/min. The precision was assessed by the mean absolute percentage error (MAPE) so that the results could be directly compared with those of other recent studies [5, 9]. MPE and MAPE were assessed for the GFR ranges 50–70, 70–90 and 90–120 ml/min.

Table 1. Patient demographics

No. of patients	225
Median age, years (range)	74 (70–89)
Male, *n* (%)	108 (48)
Female, *n* (%)	117 (52)
Median SCr, μmol/l (range)	84 (44–186)
^{51}Cr-EDTA-GFR median, ml/min (range)	76 (23–172)

GFR, glomerular filtration rate; SCr, serum creatinine.

Results

The demographics of the patient population included are shown in Table 1. Two hundred and twenty-five patients were included in the analysis. All patients were >70 years of age; median age and medium SCr were 74 years (range 70–89) and 84 μmol/l (range 44–186), respectively, and the median [^{51}Cr]-EDTA GFR was 76 ml/min (range 23–172).

Scatter plots comparing the calculated and measured renal function are represented in Figure 1. The Pearson correlation coefficients were 0.663, 0.632 and 0.646 in the Cockroft–Gault, Jelliffe and Wright formulae, respectively.

The bias, measured by the mean percentage error (MPE) and the precision, measured by the mean absolute percentage error (MAPE) are demonstrated in Table 2. The Wright formula showed the least bias in the ranges of GFR presented. There was no bias detected in the whole group of patients with a GFR range of 50–120 ml/min using the Wright formula. When these were subdivided according to GFR range the bias was <13% at each level. The Wright formula overestimated GFR in the range of GFR <50 ml/min and underestimated in the higher range (GFR >120 ml/min). The bias was greater using the Cockroft–Gault and Jelliffe formulae, as shown in Table 2, which ranged from 12% to 23% and from 15% to 32%, respectively.

Discussion

The accurate evaluation of renal function is essential for the appropriate prescribing of renally excreted agents. Inadequate dosing may compromise efficacy while overestimation of renal function may impair safety. This is particularly important in elderly patients in whom age-related physiological changes result in reduced renal function. Calculated renal function estimation in cancer patients may be further compromised by factors such as cachexia, loss of muscle mass and ascites. To be clinically useful,

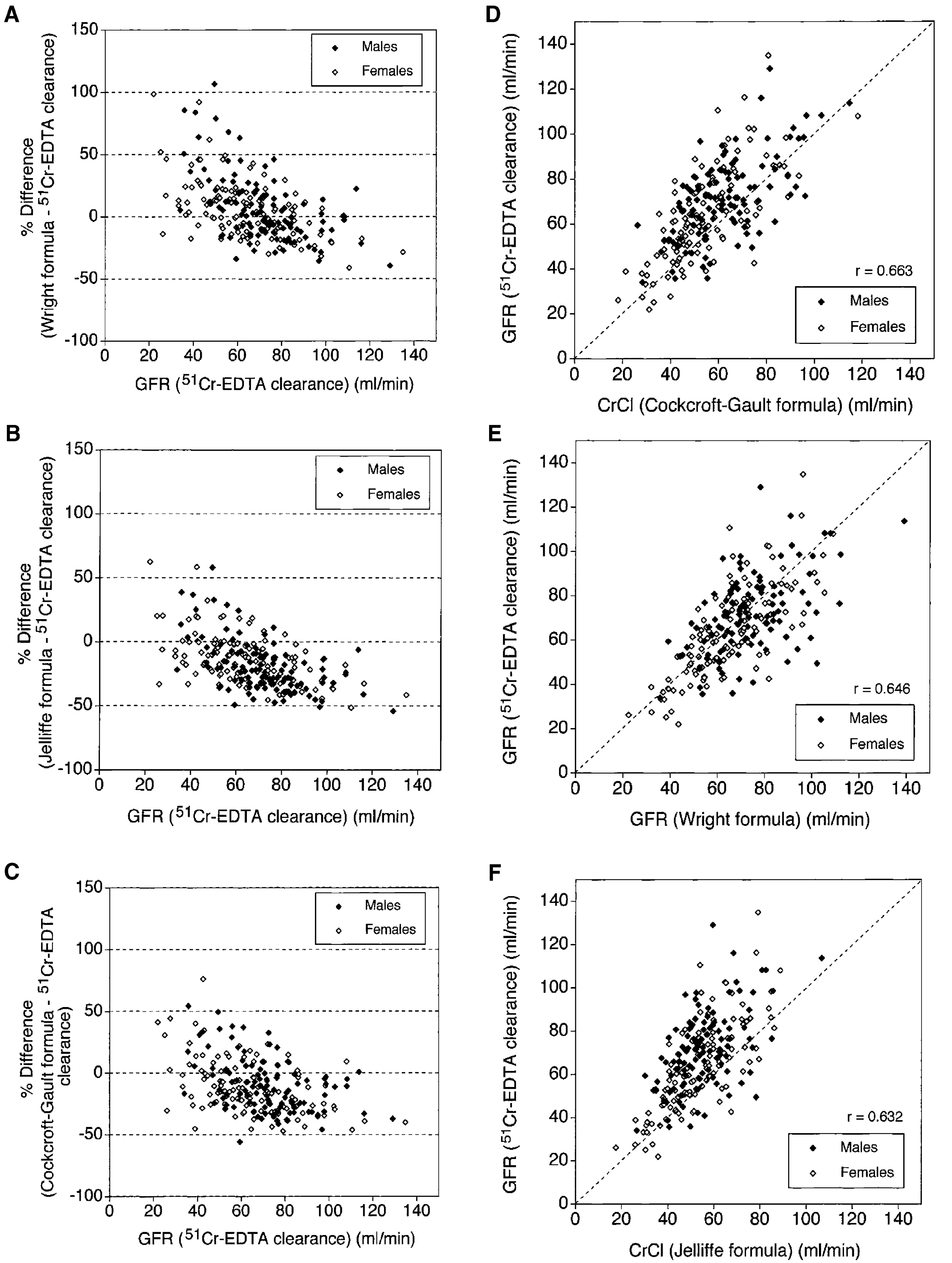

Figure 1. Scatter plots comparing calculated and measured renal function using the Cockroft–Gault, Jelliffe and Wright formulae.

Table 2. Bias and precision

GFR (ml/min)	MPE, % (MAPE)		
	Jelliffe	Cockroft–Gault	Wright
50–70 (n = 86)	–15 (17)	–12 (18)	8 (17)
70–90 (n = 72)	–25 (15)	–19 (18)	–4 (14)
90–120 (n = 25)	–32 (17)	–23 (17)	–13 (17)
50–120 (n = 183)	–22 (18)	–16 (18)	0 (17)

Negative values represent the percentage underestimation, while positive values represent the percentage overestimation.
GFR, glomerular filtration rate; MPE, mean percentage error; MAPE, mean absolute percentage error.

the method of assessment of renal function needs to be accurate, reproducible, easily calculated, convenient and cost effective.

In this retrospective analysis of a large cohort of elderly cancer-specific patients, we have demonstrated that the Wright formula is the most precise and least biased formula over a range of GFR levels. We have previously evaluated these formulae as a measure of renal function in elderly patients with various diagnoses, including cancer and renal disease, and demonstrated similar results [9]. Other groups have also shown the Wright formula to be superior over that of Cockroft–Gault and Jelliffe [5, 10].

Wright et al. developed four formulae for estimating renal function [5], which vary according to the method of creatinine measurement—either Jaffe or enzymatic—and the addition or exclusion of creatinine kinase measurements. In this study, the Wright formula was used with the Jaffe method of creatinine measurement and with the exclusion of creatinine kinase. The validity of the other Wright formulae in this specific patient group was not studied in this retrospective evaluation.

Across the range of GFR levels studied, the MPE, a measure of bias, was zero when using the Wright formula. When this was evaluated at different levels of GFR, we showed that there was an overestimation and underestimation in the lower and higher GFR ranges, respectively (Table 2). Similar variations in bias have been shown by others in younger population groups [10]. In the specific GFR ranges of 50–70, 70–90 and 90–120 ml/min, the bias was +8%, –4% and –13%, respectively. The degree of bias was greater with the Cockroft–Gault and Jelliffe formulae across the same range of GFR with the MPE being –15%, –25%, –32% and –12%, –19% and –23%, respectively. All three formulae have reduced precision and greater bias at the extremes of GFR.

Due to the particular issues regarding renal function in elderly patients, it is essential that these patients are studied as a separate group. This provides data that is reliable and clinically relevant to this patient population. Extrapolation of results from a mixed group of patients, in which the elderly have only minimal representation, is sub-optimal.

The Jelliffe and Cockroft–Gault formulae demonstrate significant bias in this elderly population. This may be due to the differences between the study population and the data set from which the original formulae were derived. Neither the Jelliffe nor Cockroft–Gault formulae were developed from a population of patients with cancer. The Jelliffe formula was derived from 128 serial observations in 15 patients (nine male and 16 female) who had undergone renal transplantation. This formula includes a 10% reduction in CrCl for females; this figure stems from the assumption that females have 90% of the creatinine production of males due to their smaller muscle mass. The Cockroft–Gault equation was derived from a data set of 249 men, all of whom were inpatients in a veterans' hospital. The patients were aged from 18 to 92 (mean age, 57 years) and 59 (24%) were >70 years of age. The formula was derived using 24-h creatinine clearance values as the standard. Although no females were used in the data set, the Cockroft–Gault method assumes a reduction in GFR of 15% for this population. The Wright formula, however, was developed using data from patients with cancer via a population kinetic method. The [^{51}Cr]-EDTA was used as the gold standard of GFR measurement.

The MPE values seen using the Wright, Cockroft–Gault and Jelliffe formulae in the elderly group were 0, –16, and –22, respectively. This compares with the data from an Australian study [10], which was also a cancer-specific population. These formulae were evaluated in 122 patients retrospectively using [^{99m}Tc]-DTPA as the 'gold standard'. The median age in that study was 61 years (range 21–83). In the range of GFR values from 50 to 100 ml/min, the MPE for the Wright, Cockroft–Gault and Jelliffe formulae were +5, –7 and –15, respectively. Although it is difficult to compare these data directly, it does show that the Cockroft–Gault and Jelliffe formulae underestimate GFR to a greater extent in elderly patients. It has been shown that decreasing renal function results in increased underestimation of CrCl when the Cockroft–Gault formula is used. The larger underestimation in the elderly may be explained by the reduced renal function that is seen with advancing age. Despite this, the Wright formula produced results in GFR estimation that were no more biased than the results seen in the younger cohort.

Evaluation of the precision and bias of these formulae in a cancer-specific elderly patient population has not been previously reported. This study has shown the degree of bias and imprecision that can be expected at various levels of GFR. It has been performed in a large and specific patient group. The fundamental question regarding the use of these formulae in estimating renal function is "What degree of bias is acceptable in clinical practice?" It is difficult to answer this question and provide guidelines as it is dependent on the particular clinical situation and treatment objectives. The degree of bias with the Wright formula is dependent on the GFR; in the range of GFR values from 50 to 120 ml/min, the bias is <13%.

The results of this study allow the physician to make a decision regarding the use of the formula, based on an expected degree of bias. It is likely in most clinical situations, where the GFR is in the normal range, that the Wright formula would provide an adequate estimation of renal function. This avoids the need for 24-h urine collection or [^{51}Cr]-EDTA-GFR evaluation, with the associated difficulties, inconvenience and cost.

Despite this being a study in an elderly population of patients with a diagnosis of cancer, these results need to be confirmed prospectively. The impact of factors that may influence the accuracy of the formulae, such as the presence of ascites, cachexia, concomitant medications and prior chemotherapy, needs to be evaluated.

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