

Stability of plasma creatinine concentrations in acute complex long-stay admissions to a general medical service

Donna Siriwardane, Richard Woodman, Paul Hakendorf, Jennifer H Martin, Graham H White, David I Ben-Tovim and Campbell H Thompson

ABSTRACT – Assessment of glomerular filtration rate (GFR) is essential for calculating safe dosages of renally cleared drugs. Formulae for estimating reliable GFRs assume that plasma creatinine concentrations are stable. This study evaluates the variability of plasma creatinine (PCr) concentrations in patients admitted acutely to hospital. From 2,293 newly admitted patients, those in whom a subsequent clinically significant change (>20%) in PCr had occurred were identified. Median age was 81.1 years. Median baseline PCr was 90 $\mu\text{mol/l}$ (eGFR 60 ml/min). In total, 46.3% of the patients had a PCr that varied >20% from baseline three to seven days following admission. A 10-year increase in age increased the odds of a rise in PCr over the next week by 11.1% (odds ratio=1.11, 95% confidence interval=1.03, 1.20; $p=0.007$). Overall, baseline creatinine was a poor predictor of subsequent variation in PCr. GFR formulae for calculating renally-cleared drug dosages should be used with caution in elderly patients admitted acutely to hospital.

KEY WORDS: creatinine, glomerular filtration rate, renal function

Introduction

Assessment of glomerular filtration rate (GFR) is integral to clinical decision making within an emergency department. In addition to its diagnostic utility, the assessment of GFR is important for estimating drug dose adjustment of renally-cleared drugs in the presence of renal impairment. Formulae have been developed to estimate GFR and these are based upon a patient's gender, age and serum creatinine concentration and weight.^{1,2}

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Several points are worthy of mention:

- the formulae were developed in volunteers and patients with renal disease in the absence of acute illness
- acute illness is a common reason for patients to be newly admitted to hospital
- these formulae assume that a patient's GFR is relatively stable, although the variability of serum creatinine concentrations over time is poorly defined in acutely ill patients presenting to emergency departments.

This study examined the within-patient variability in plasma creatinine (PCr) concentrations in a large cohort of patients with acute illness admitted to a hospital-based general medicine service. The aim was to determine if a patient's PCr concentration on admission remained clinically stable during the first three to seven days after admission.

Subjects and methods

This study was approved by the Department of Clinical Governance at Flinders Medical Centre. We identified 2,293 patients retrospectively, who were admitted to long stay wards (anticipated length of stay of greater than 48 hours). For the period January 2007 to May 2009 inclusive, PCr concentrations from patients in the emergency department and in the long stay general medical wards were merged with the hospital morbidity database to create a dataset for analysis.

Baseline creatinine for each patient admission was defined as the creatinine concentration recorded on day one of the hospital admission. Baseline PCr concentrations were compared with that concentration recorded for the same patient three to seven days later when illness acuity was likely to be reduced. PCr was classified as being clinically significantly different when either 20% higher or 20% lower than the baseline creatinine value. The cut-off of 20% was selected on the basis that it represented the minimum change in creatinine concentration for which there was a 99% probability that the combined effects of analytical imprecision and the intra-individual biological variation of creatinine were exceeded.

Statistics

The proportion of inpatients in whom there was a significant change (>20%) in PCr concentration from that registered at admission were identified. The independent ability of baseline

PCr and age to predict a subsequent greater than 20% variability in PCr was assessed using binary logistic regression. The diagnostic accuracy and predictive value of baseline creatinine values in relation to a subsequent variation in creatinine of 20% or more were assessed by calculating the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The PPV is the proportion of patients who tested 'positive' and who were correctly diagnosed. Baseline creatinine values were assessed at or above various pre-chosen cut-off values (from 30 to 300 $\mu\text{mol/l}$ in steps of 10 $\mu\text{mol/l}$). Subjects at or above the cut-off value were classified as being positive (predicted to have high subsequent variation), while those below the cut-off value were measured as negative (predicted to have subsequent stable creatinine). All analyses were performed using Stata version 11.0 (StataCorp, Texas, USA).

Results

Of the 2,293 patients with both a baseline and subsequent three to seven day PCr measurement, 42.2% was male. Other baseline characteristics of the population are presented in Table 1.

Since the median length of stay of patients was nine days, PCr concentrations recorded between three and seven days following admission are likely, in most patients, to reflect a lower acuity of illness than that observed upon admission. Nearly half of admitted patients had a PCr value that varied by over 20% in the three to seven days following admission (Table 2). There were 20 patients (0.9%) in whom the PCr both increased and decreased more than 20% from the baseline creatinine concentrations.

A 10-year increment in age increased the odds of a rise in creatinine of >20% over the next three to seven days by 11.1% (odds ratio (OR) = 1.11, 95% confidence interval (CI) = 1.03, 1.20; $p=0.007$). A 10 $\mu\text{mol/l}$ higher creatinine concentration on admission increased the odds of a >20% decrease in creatinine over the next three to seven days by 7.2% (OR=1.07, 95%

CI=1.06, 1.09; $p<0.001$). Similarly, a 10 $\mu\text{mol/l}$ higher serum creatinine concentration on admission decreased the odds of a >20% increase in creatinine over the next three to seven days by 7.7% (OR=0.92, 95% CI=0.90 to 0.95; $p<0.001$).

The overall performance of baseline creatinine as a predictor of subsequent variation in PCr was poor (Table 3). The overall diagnostic accuracy of baseline creatinine correctly identifying a 20% variation (either increase or decrease) in creatinine was also poor (area under receiver operating characteristic curve = 0.57) (Fig 1a). There were no baseline creatinine cut-off values that would allow a combination of both high sensitivity and high specificity (Fig 1b).

Discussion

Previously unreported in such a large and acutely unwell population, the admission PCr concentration predicted the concentration three to seven days later in nearly half of the acutely admitted elderly patients. Formulae for estimating renal function that rely upon the patient having a GFR at a steady state may therefore be usefully applied in only about half of the acute general medical

Table 3. Positive predictive value (PPV) and negative predictive value (NPV) of admission creatinine in relation to a variation in creatinine of >20% three to seven days after hospital admission.

Baseline creatinine cut-off level ($\mu\text{mol/l}$)	PPV (n=2,293)	NPV (n=2,293)
50	0.46	0.48
100	0.54	0.59
150	0.62	0.57
200	0.64	0.55
250	0.66	0.55
300	0.67	0.54

Table 1. Baseline characteristics.

	n	%
Gender (M/F)	967/1,326	42.2/57.8
	Median	Interquartile range
Length of stay (days)	9	6–14
Age (years)	81.1	71.6–86.7
Plasma creatinine ($\mu\text{mol/l}$)	90	68–127
estimated glomerular filtration rate (ml/min/1.73 m^2)	60	40–83

Table 2. Frequency of variability in serum creatinine over time.

	>20% increase	>20% decrease	stable creatinine (<20% change)
n (%)	416/2,293 (18.1)	664/2,293 (29.0)	1233/2,293 (53.7)

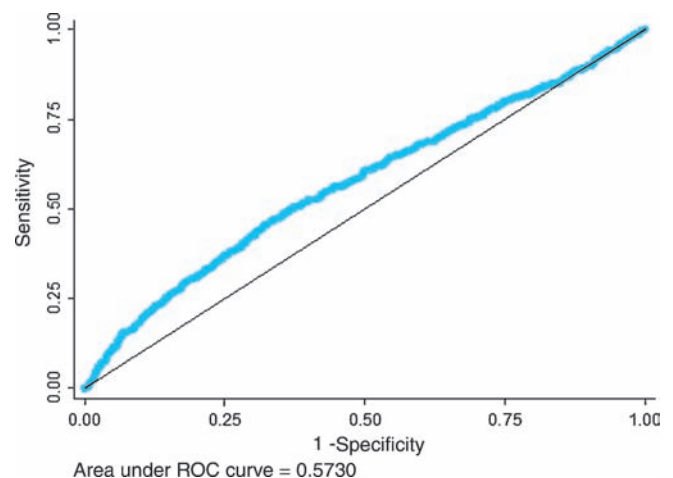


Fig 1a. Receiver operating characteristic curve assessing odds of having a greater than 20% decrease in subsequent creatinine measured three to seven days after admission.

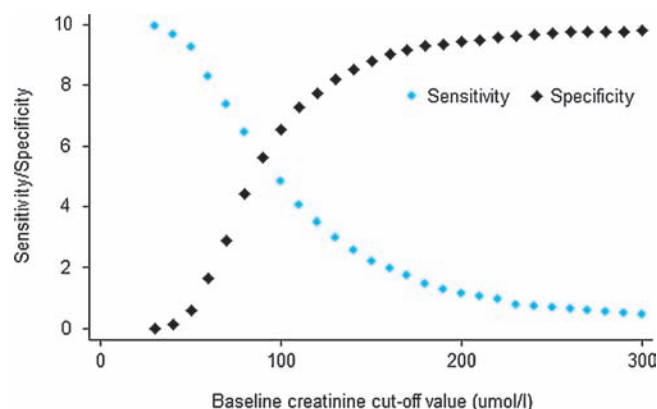


Fig 1b. Sensitivity and specificity of baseline creatinine to detect a greater than 20% variation in subsequent creatinine measured three to seven days after admission.

inpatient take. The risk of a patient's creatinine varying by more than 20% from baseline during the first week of their hospital admission was high across the range of baseline creatinines observed in this study. Within this elderly population, the likelihood of clinically significant variability of plasma creatinine concentrations during hospital stay increased with patient age.

For drugs that are largely excreted unchanged by the kidneys, significant acute changes in serum creatinine concentrations can be critical for both estimating appropriate dosages, and for appropriate interpretation of their plasma concentrations. For example, low molecular weight heparins or aminoglycosides are commonly used in general medicine in the hospital setting. Standard regulations for assessing bioavailability state that drug concentrations must lie within a narrow range (80–125%) of the reference mean.³ Based upon these findings, drug dosing of renally cleared drugs must be reviewed frequently.

Baseline creatinine was a significant predictor of subsequent variability in serum creatinine. However, as a prospective tool, baseline serum creatinine did not have a useful positive predictive value for subsequent significant variation across the range of cut-off levels for observed serum creatinine values at admission.

Both the Modified Diet in Renal Disease (MDRD) formula¹ and the Cockcroft Gault formula² are in common use although this is not yet validated in all patient groups. Serum or plasma creatinine is a variable in both equations. Hence serum creatinine differences unrelated to renal function will affect the estimation of renal function in very underweight or overweight populations, in populations with muscle wasting, in vegetarians or in those on a high protein diet. Neither of these equations has been validated for use in certain ethnic or specific populations including in Aboriginal or Torres Strait Islander groups, in the Asian population, in children or in pregnancy.⁴ At the lower range of renal function, the Cockcroft Gault formula tends to overestimate kidney function, especially in obese or fluid overloaded patients. Since the MDRD formula was derived from a population with advanced kidney failure, it may be less accurate in patients whose eGFR is greater than 60 ml/min/1.73 m².⁵ It is also important to note that neither formula is accurate in acute

renal failure or other situations in which there are sudden changes in renal function^{6,7} such as in ill hospitalised patients, particularly those who had an elevated blood urea nitrogen:serum creatinine ratio.⁸

Patients admitted to general medical services within major hospitals are acutely unwell and are often old with complex multisystem disease. Formulae to estimate GFR are intended to be applied to patients with stable renal function who are not currently unwell. During acute illness, patients are more likely to experience short-term fluctuations in renal function.⁹ In the original study by Cockcroft and Gault, the authors recruited participants ranging in age from 18 to 92 years. In total, 534 participants were recruited and two creatinine clearances were determined. Of these, 29 patients were rejected due to their values for creatinine clearance differing by greater than 20%, and the authors themselves warned that this equation may not be appropriate unless renal function was in a steady state.² Drug clearance is related to a metric of body size, which is not included in the MDRD formula but is in the Cockcroft Gault formula. Admittedly, in the Cockcroft Gault population, the relationship of total to lean body weight may be different from that in this study's cohort of general medical inpatients.

The MDRD study conducted by Kusek and colleagues recruited patients who had evidence of chronic renal disease, with serum creatinine of 124–619 umol/l in men and 106–619 umol/l in women. Other inclusion criteria were a decreased creatinine clearance of 16–70 ml/min/1.73 m² and those aged 18–70 years.¹⁰ An unstable GFR was not itself a criterion for exclusion from the original MDRD study. Due to its focus on patients with chronic renal failure, it has been suggested that the MDRD formula may underestimate GFR at higher values.¹¹ Although it is an important tool for estimating GFR, it still has some limitations and the context of an unstable GFR might be one of those.

Summary

Patients who are admitted to a hospital general medical service have significant acute medical illness and approximately 50% of them will have unstable renal function. It is difficult to predict those with a stable GFR allowing more reliable application of the Cockcroft Gault or MDRD formula for estimation of renal function. To facilitate, for example, appropriate drug dosing in newly admitted patients, other methods for estimating GFR are urgently required. About half the patients admitted to general medicine need their GFR re-estimated within a week of admission.

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