How Robust are our Methods of Detecting Impaired Glomerular Filtration Rate in the Intensive Care Unit?

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Abstract

Background: Serum creatinine is not a sensitive marker to assess early loss of renal function in acute kidney injury. Timed creatinine clearance and several formula used to predict glomerular filtration rate have not been validated.

Methods: In a prospective observational study in 50 adult patients admitted to the intensive care unit with apparent normal renal function, we assessed the glomerular filtration rate by the formula methods and timed creatinine clearance.

Result: The mean serum creatinine was 0.77mg/dl, SD $\pm$ 0.15 (range 0.5-1.14 mg/dl). The mean measured creatinine clearance was 87.15 ml/min/1.73m², SD $\pm$ 20.5 (range 56.9-137 ml/min/1.73m²). In 25 (50%) patients, one hour urinary creatinine clearance was <80 ml/min/1.73m² and in two (4%) patients, the creatinine clearance was <60 ml/min/1.73m². Spearman correlation coefficient and regression analysis revealed a statistically significant correlation for the Cockcroft-Gault and predictive equations when compared with measured creatinine clearance. The differences between the predictive equations and creatinine clearance, as illustrated by the $\pm$ 95% confidence interval in the Bland-Altman graphs was very significant [Cockcroft-Gault = -40.3 to 17.7 ml/min/1.73m², Modification of Diet in Renal Disease equation = -46.2 to 30.6 ml/min/1.73m² and the simplified Modification of Diet in Renal Disease equation = -72.8 to 24.8 ml/min/1.73m²].

Conclusion: Formula methods and creatinine clearance are more sensitive than serum creatinine in detecting early phase of acute kidney injury. However, there is no agreement between these methods of glomerular filtration rate estimation.

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Key Words : Acute kidney failure; Glomerular filtration rate

Introduction

Acute kidney injury (AKI) is a common clinical problem in critically ill patients and is associated with high hospital mortality, progression of preexisting chronic kidney disease (CKD) and development of end stage renal disease [1]. A major limitation in improving outcome from AKI has been the absence of a reliable marker for early diagnosis. The most common marker for evaluation of renal function in critically ill patients is serum creatinine [2]. However creatinine is not an ideal marker, as the serum levels depend not only on glomerular filtration rate (GFR) but also on creatinine generation, muscle mass, volume of distribution, age, gender and race [3,4]. Measuring 24 hours creatinine clearance (CCr) gives an estimate of GFR, but it tends to overestimate, as a result of increased tubular secretion in renal failure. The other major problems with creatinine clearance are the requirement for urine collection over 24 hours, which is invariably inaccurate and the variation in creatinine excretion rate with fluctuations in physiological conditions of critically ill patients [5]. Several formulae to predict GFR have been published,

but have not been validated in the setting of rapidly changing creatinine kinetics of AKI [2]. Hoste et al [6], evaluated three prediction equations for assessment of glomerular function (Cockcroft-Gault, Modification of Diet in Renal Disease [MDRD] and the simplified MDRD formula), compared them with one hour creatinine clearance and found the equations were not specific enough for assessment of renal function.

Material and Methods

A total of 50 adult patients greater than 18 years of age, admitted to the intensive care unit of a tertiary care hospital were studied. All patients had serum creatinine values within the normal range for our laboratory (0.5 - 1.4 mg/dL). Patients with known CKD or AKI were excluded from the study. To enable accurate collection of timed urine samples only patients with indwelling catheters were included. In order to ensure steady state values we included hemodynamically stable patients with difference of less than 0.3 mg/dl between the serum creatinine on the day of study and 24 hours later and a 24 hour urinary volume comparable to one hour urine volume extrapolated to 24 hour. In all patients an exactly timed one hour urine sample was collected. A timed urinary

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creatinine clearance over one hour was calculated by using the formula below:

$$\frac{\text{Urinary volume} \times \text{urinary creatinine concentration}}{\text{X } 1.73 \text{ m}^2 \text{ body surface area}} \\ \text{Serum creatinine} \times 60 \text{ minutes} \times \text{body surface area}$$

Serum creatinine was measured at the end of one hour of urine collection period. Prediction formulae used to assess GFR are shown in Table 1.

Statistical analysis included univariate analysis using chi-square for categorical variables and unpaired t-test for continuous variables. The precision of the different predictive equations used to estimate GFR as compared to CCr was evaluated by using Spearman correlation coefficient and linear regression analysis. Since correlation coefficient measures the strength of relationship between the two variables and not agreement between them, Bland and Altman plots were used to evaluate the agreement between GFR estimated by predictive equations and CCr. Data has been expressed in terms of mean $\pm$ standard deviation (SD). Statistical analysis was done with SPSS (version 13.0).

Results

Of 50 critically ill patients, 36 (72%) were males and mean age was 51.5 years (range 20-75 year). The admission diagnosis is shown in Table 2. The mean serum creatinine was 0.77 ± 0.15 mg/dl, (range, 0.5- 1.1 mg/dl). The 24 hour urine volume during the day of the study was comparable with the urine volume obtained after extrapolation of the one hour urine volume of the study to a 24 hour urine volume; mean 1743 ± 308.4 ml/24 h, (range 1461-3113 ml/24 hours) vs 1582 ± 329.13 ml/24hours, (range 1164-3330 ml/24 h). The mean measured CCr was 87.15 ± 20.5 ml/min/ 1.73 m^2 , (range 56.9-137 ml/min/ 1.73 m^2). Urinary creatinine excretion for women was 874 mg/24h/ 1.73 m^2 (range 594-1442 mg/24h/ 1.73 m^2) and for men was 1014 mg/24 h/ 1.73 m^2 (range 575-1776 mg/24h/ 1.73 m^2). In 25(50%) patients the GFR (calculated from timed urinary creatinine clearance) was <80 ml/min/ 1.73 m^2 and in two (4%) patients, the CCr was <60 ml/min/ 1.73 m^2 (Group1). The remaining 25 patients had a CCr greater than 80 ml/min/ 1.73 m^2 (Group 2). Even though the mean serum creatinine values between the two groups did not differ significantly (0.72 ± 0.13 mg/dl vs 0.84 ± 0.16 mg/dl) and were in the normal range, there was a significant difference in the mean estimated creatinine clearance, 104.1 vs 70.2 ml/min/ 1.73 m^2 . There was a

Table 1

Prediction formulae for estimation of GFR [3,4,12]

Prediction formula	Equation
Cockcroft-Gault equation (calculated with actual body weight) [3]	$(140 - \text{age}) \times \text{body weight (Kg)} \times 1.73$ $(\times 0.85 \text{ if female})$
Original MDRD equation [4]	$\frac{\text{Serum creatinine} \times 72 \times \text{body surface area}}{170 \times \text{serum creatinine}^{-0.999} + \text{age}^{-0.176} \times \text{serum urea}^{-0.170} \times \text{albumin}^{0.318}}$ $\times (0.762 \text{ if female})$
Simplified MDRD equation [12]	$186 \times \text{creatinine}^{-1.154} \times \text{age}^{-0.203} \times$ $(0.742 \text{ if female})$

MDRD: Modification of Diet in Renal Disease

statistically significant correlation for the Cockcroft-Gault and MDRD equations compared with measured creatinine clearance (Table 4). There is a statistical limitation in using correlation coefficient and the corresponding p value, hence an alternative (Bland and Altman analysis) approach to assess the degree of agreement between two methods of measurement was used (Figs. 1-3). There was no significant bias between GFR estimated by the Cockcroft-Gault and MDRD equations [Cockcroft-Gault = -11.3 ml/min/ 1.73 m^2 , MDRD = -7.8 ml/min/ 1.73 m^2 and simplified MDRD equation = -24.0 ml/min/ 1.73 m^2]. The differences between the predictive equations and the CCr, as illustrated by the $\pm 95\%$ confidence interval (CI) in the Bland-Altman graphs (Cockcroft-Gault = -40.3 to 17.7 ml/min/ 1.73 m^2 , MDRD = -46.2 to 30.6 ml/min/ 1.73 m^2 and the simplified MDRD equation = -72.8 to 24.8 ml/min/ 1.73 m^2) was highly significant.

Discussion

Early detection of acute kidney injury is important in management of patients admitted to ICU and to prevent progression of renal failure. This also helps in modification of drug dosages based on renal function.

Table 2

Admission diagnosis of patients

Admission category	Number of patients
Septicaemia	09
Polytrauma	07
Cerebrovascular accident	06
UGI Bleed	04
Alcoholic liver disease	04
Unstable angina	03
Diabetic ketoacidosis	02
Accelerated hypertension	02
Status epilepticus	02
Pulmonary thromboembolism	02
Acute abdomen	02
Chronic obstructive airway disease	02
Miscellaneous	05
Total	50

Table 3

Comparison of various renal parameters in patients with measured creatinine clearance (CCr) greater or less than 80ml/min/ 1.73 m^2

Renal parameters	CCr > 80 ml/min/ 1.73 m^2	CCr < 80 ml/min/ 1.73 m^2	p
Serum creatinine (mg/dl) mean($\pm$ SD)	0.72 ± 0.13	0.84 ± 0.16	0.433
One hour urine volume (ml/hour) mean($\pm$ SD)	73.72 ± 13.7	58.12 ± 8.4	0.132
Measured mean CCr ml/minute/ 1.73 m^2	104.1	70.2	<0.001
Mean urinary creatinine excretion (mg/24h/ 1.73 m^2)	1137.3	813.2	<0.001
Vasoactive therapy	2 (8%)	10 (40%)	0.008
Mechanical ventilator	7 (28%)	16 (64%)	0.011

Table 4**Comparison between measured creatinine clearance and prediction equations for assessment of glomerular filtration rate**

	Median (range)	R (vs. urinary creatinine clearance)	p	Regression analysis
One hour urinary creatinine clearance (ml/min)	80.15 (56.9-137.0)			
Cockcroft-Gault (actual body weight) (ml/min/1.73 m ²)	95.25 (60.6-155.6)	0.473	0.001	Y = 58.63+0.602 X
MDRD (ml/ min/1.73 m ²)	91.05 (68-142)	0.715	0.001	Y = 47.04+0.590 X
MDRD Simplified (ml/min/1.73 m ²)	106.50 (71-180)	0.474	0.001	Y = 62.232+0.376 X

Y= equation for assessment of GFR, X= urinary creatinine clearance, R= correlation coefficient

Fig. 1 : Bland and Altman analysis of measured creatinine clearance (CCr) compared with GFR calculated by Cockcroft-Gault (CG) formula using actual body weight (abw). **Fig. 2 :** Bland and Altman analysis of measured creatinine clearance (CCr) compared with GFR calculated by Modification of Diet in Renal Disease (MDRD)

Serum creatinine can be easily measured and is most often used to assess the glomerular filtration rate in intensive care units [7]. Because of the nature of creatinine kinetics a large change in GFR would be required to raise serum creatinine values from normal to the elevated range [8]. GFR measured by more accurate techniques may be reduced by up to 50% before serum creatinine becomes elevated. However, once serum creatinine is elevated even small changes in GFR would raise the serum creatinine exponentially. Though

Fig. 3 : Bland and Altman analysis of measured creatinine clearance (CCr) compared with GFR calculated by Simplified Modification of Diet in Renal Disease (MDRDs)

serum creatinine concentration is inversely proportional to GFR, the relationship is not absolute, as serum creatinine levels are also affected by generation, extra renal elimination and tubular secretion of creatinine [9]. As a normal serum creatinine does not exclude the possibility of a reduced GFR, nor does a stable but elevated serum creatinine exclude a further decline in GFR if there are concomitant changes in creatinine generation as seen in patients with reduced muscle mass and poor protein intake. This was evident in our study, where patients with normal serum creatinine values, had a significant fall in GFR as estimated by creatinine clearance and predictive formulas.

The urinary or plasma clearance of several exogenous markers like inulin, 99mTc diethylene triamine penta acetic acid (DTPA) provides accurate measurement of GFR [10]. However, these tests are expensive and not easily available. Serum concentration of cystatin C has been shown to be a more accurate guide of falling GFR in critically ill patients [11].

Predictive formulas overcome some of these limitations by incorporating known demographic and clinical variables. We used the Cockcroft-Gault formula and MDRD equations to measure renal function. Both these formulas have their limitations. The Cockcroft

Gault formula was developed in whites and a non vegetarian population, while MDRD equation was validated in patients with chronic kidney disease [12]. The accuracy of creatinine clearance measurement is limited because as GFR falls, tubular creatinine secretion is increased and the rise in serum creatinine is less. Thus creatinine excretion is much greater than the filtered load resulting in over estimation of the GFR [13,14]. However in patients on vegetarian diets and with rapidly changing kidney function, the use of clearance measurement is recommended as a measure of GFR [15]. Hence, we took the timed creatinine clearance in our patients as a more accurate estimate of GFR. The main drawback with 24 hour clearance is the accurate collection of urine and the assumption that patients are in a steady state of creatinine balance. This assumption is invalid for patients with rising or falling serum creatinine as occurs in acute kidney injury. To overcome these problems we took patients with indwelling urinary catheter, where urine volumes could be accurately measured and excluded patients with rapidly changing renal function. For ease of collection we calculated creatinine clearance in one hour timed urine collection samples. We ensured our patients were in a steady state, by excluding those who had greater than 0.3 mg/dl variation of serum creatinine over a 24 hour period and where the 24 hour urinary volume was not comparable with the one hour urine volume extrapolated to 24 hours.

In our study there was a statistically significant correlation between the predictive formulas and the timed CCr values in patients with normal creatinine values. We applied the Bland and Altman analysis to assess the degree of agreement between the formula method and CCr. The strength of agreement was minimal, thereby suggesting that the assessment of renal function would vary depending on the method used. These findings are in agreement with other studies [6].

Serum creatinine is an insensitive marker to predict GFR in critically ill patients admitted to the ICU. The predictive equations and clearance measurements have not been validated for this study population, but they reflect the impaired renal function with normal serum creatinine more accurately. We recommend that creatinine clearance and not serum creatinine, should be used to estimate GFR and early loss of kidney function.

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Conflicts of Interest

None identified

Intellectual Contribution of Authors

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