The clinical utility of kinetic glomerular filtration rate

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Abstract

Background: In acutely unwell patients with rapidly changing renal function, estimating glomerular filtration rate (GFR) and predicting adverse renal outcomes are challenging and often inaccurate. Kinetic GFR (kGFR) is an estimate of immediate biomarker clearance derived from two discreet measurements that may better represent acute function. Our objective is to assess the clinical utility of kGFR as a predictive tool and examine the association of kGFR to adverse renal outcomes compared with measurements to traditional estimates.

Methods: We compared the association of kGFR and Modification of Diet in Renal Disease (MDRD) with acute kidney injury (AKI), renal replacement therapy (RRT), cardiovascular morbidity, 30-day mortality and new chronic kidney disease development. A total of 107 acute admissions to a medical high dependency and intensive care unit were assessed retrospectively. Creatinine measurements and outcomes were recorded and kGFR was calculated at the earliest possible time point. This was then compared with simultaneous MDRD estimated GFR.

Results: Mean age was 60 years old, AKI occurred in 25% of patients, acute cardiovascular events occurred in 13%, RRT was initiated in 15% and 30-day mortality was 30%. kGFR predicted the AKI more accurately than MDRD (area under the receiver operating characteristic curve (AUC) = 0.86 versus AUC = 0.64). kGFR predicted the need for RRT more accurately than MDRD (AUC = 0.901 versus AUC = 0.79). Neither kGFR nor admission MDRD was associated with 30-day mortality or cardiovascular morbidity.

Conclusions: Measuring kGFR in the acute setting could help clinicians better predict adverse renal outcomes.

Key words: Measuring kGFR in the acute setting could help clinicians better predict adverse renal outcomes.

Introduction

Interpreting an acutely unwell patient’s renal function is a challenge for the practicing nephrologist. Commonly used formulae such as the Modification of Diet in Renal Disease (MDRD) or Chronic Kidney Disease epidemiology collaboration (CKD-EPI) formulae are derived by measuring a circulating biomarker in large cohorts of patients with varying degrees of chronic kidney disease (CKD) and using stepwise regression analysis to create formulae that are then validated against a gold standard clearance technique [1, 2]. Unfortunately, current formulae fall short in the acutely unwell patient with rapidly changing renal function [3–8]. Although clinical parameters such as urine output, rising creatinine concentration and fluid balance can inform us at the bedside, a dynamic formula to help estimate rapidly changing glomerular filtration rate (GFR) would be a useful addition to our diagnostic arsenal. Although MDRD and CKD-EPI formulae have a role in longer term risk prediction, these formulae neither estimate the acute

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function [9, 10] nor help the physician predict adverse acute outcomes [4]. One issue is the frequent lack of baseline renal function estimates to help provide context for acutely estimated GFR (eGFR). Although models exist to allow the physician to ‘back calculate’ the baseline function based on assumed population GFR distributions, these lack accuracy in many patients [11, 12].

One method of estimating renal function acutely is by calculating a ‘kinetic GFR’ (kGFR) [13]. The kGFR is a mathematically derived estimate of the creatinine clearance calculated from two serum creatinine measurements at different time points. This has the advantage that it requires no additional test beyond those routinely ordered in acutely ill patients, is relatively easy to calculate and theoretically reflects dynamic changes in renal function. To date there are few studies assessing the role of kGFR in the Intensive Therapy Unit (ITU) setting.

Working from the hypothesis that an accurate estimate of acute function would correlate more closely with poor outcomes than conventional measures, we thus examine the association of kGFR with adverse renal outcome, with a view towards potentially using such a measure as a predicative tool in future.

Hypothesis: kGFR is a more accurate predictor of adverse clinic outcomes than changes in MDRD-estimated GFR.

Materials and methods

The formula

The formula used is identical to that initially proposed by Chen and later used in subsequent papers [13–15]. As noted by Chen, calculating a kGFR is essentially a dynamic creatinine clearance rate between two time points [13]. When presented with two separate measurements of a serum biomarker (in this study, creatinine):

\[
kGFR = \left( \frac{\text{mean creatinine}}{\text{daily circulating creatinine}} \right) \times \left( 1 - \frac{24 \times \text{change in creatinine}}{\Delta t \times \text{max potential change in creatinine per day}} \right).
\]

Daily circulating creatinine is proportional to the estimated GFR (derived from the MDRD equation) and initial creatinine concentration. A conversion factor is required to account for the difference in the units. Because creatinine is measured in \( \mu \text{mol/L} \) but GFR is expressed in \( \text{mL/min} \), we must divide our calculation by 1000 to express the product correctly. To convert from \( \text{mL/min} \) to daily production, this is then multiplied by 1440 min/day. Overall, this gives a conversion factor of 1.44.

Thus, daily circulating creatinine is creatinine concentration \( \times \) eGFR \( \times 1.44 \). The maximum change in 24 h will be proportional to both daily production and also the patient’s body weight, which determines the volume of distribution of creatinine (0.6 \( \times \) body weight in kg).

The final formula used in this study is as follows:

\[
kGFR = \left( \frac{\text{Cr1} \times \text{eGFR} \times 1.44}{(\text{Cr1} + \text{Cr2})/2} \right) \times \left( 1 - \frac{24 \times (\text{Cr2} - \text{Cr1})}{t \times (\text{Cr1} \times \text{eGFR} \times 1.44)(0.6 \times W)} \right)
\]

where \( \text{Cr1} \) is the circulating creatinine concentration at admission, eGFR the MDRD-derived GFR at admission, \( \text{Cr2} \) the second recorded creatinine, \( t \) the time in hours between both creatinine measurements and \( W \) the patients weight in kilograms.

As has been suggested in a recent paper examining kGFR within the transplant population, for consistency we have used the admission creatinine as the baseline Cr1 value for all our calculations [14].

The formula will produce an equally valid output regardless of the units of measurement of creatinine used. The final units of kGFR are \( \text{mL/min} \), as the creatinine measurement units will cancel out algebraically [13]. Thus, should a physician input the creatinine measurements in \( \text{mg/dL} \) (\( \mu \text{mol/L} \) divided by 88.4) so long as the units used are internally consistent, the result will be meaningful.

Our primary aim was to investigate the utility of kGFR when compared with MDRD in predicting the occurrence of acute kidney injury (AKI) and the requirement for renal replacement therapy (RRT). Secondary outcomes were the association between kGFR and cardiovascular morbidity, 30-day mortality and changes in baseline eGFR 3 months following an acute admission. Cardiovascular events were defined as an event during inpatient stay, or readmission within 30 days with an acute coronary syndrome, cerebrovascular event or heart failure.

We also calculated the number of patients who had clinically significant changes in GFR estimates when measured by kGFR when compared with MDRD eGFR.

Classification of AKI is an area of ongoing debate. All current methodologies are imperfect, relying on estimations of rising biomarkers that are delayed until after injury has occurred and unknown baseline creatinine levels, and are often hindered by discordance between creatinine and urine output [16]. As it stands currently, there is no clearly optimal method of classification [17]. Thus, we defined AKI using AKIN criteria as a rise in serum creatinine of \( \geq 26.4 \mu \text{mol/L} \) or a percentage increase in serum creatinine of \( \geq 50\% \) [18].

This is a retrospective cohort analysis of all acute admissions to a district general hospital medical high dependency unit and ITU using biochemical and outcome data that had already been recorded as part of routine clinical care. Diabetes mellitus was defined as either a pre-existing diagnostic label on the community health records, or a new diagnosis as identified by the new presentation of diabetic ketoacidosis, HBA1c \( \geq 6.5\% \) (48 mmol/mol) or unequivocal hyperglycaemia and diagnosis by local endocrinologists.

Following ethical review, the NHS Research Ethics Committee granted a status of exemption.

Our calculation of kGFR was made using the first two measurements available during each admission as described above. Patients under 18 years of age, pregnant patients, patients already on chronic RRT or requiring RRT immediately on admission were excluded from analysis. Importantly, we included patients at all levels of CKD.

Creatinine measurements were analysed on C16000 Abbott Architect analysers using the Jaffe method (kinetic alkaline picrate).

Statistical analyses

All statistical analysis was performed in IBM SPSS Statistics Version 20.

Patient demographic characteristics were described. If a variable was considered binary/categorical then the number and percentage across the patient population is presented. If a variable is considered as continuous then the mean and standard deviation (SD) are presented (unless otherwise specified).

Univariate logistic regression was used to examine the effect of MDRD and eGFR on predicting the pre-specified outcomes.
Diabetes mellitus 3 (18.7) 11 (40.7) a 4 (5) 17 (15.8)
CKD at baseline 7 (43.7) 11 (40) a 9 (11.2) 27 (25.2)
Mean urine output on admission (mL/kg/h) 0.3 (3) 0.6 (2) 1 (0.49) 1.1 (2)
Mean arterial pressure on admission (mmHg) 70 (16.4) 83 (18.2) 82 (13.2) 97 (15.4)
Mean kGFR (mL/min/1.73 m²) 19.41 (20.8) a,b 29.7 (30)a 79 (36) 67 (35)
Mean MDRD eGFR (mL/min/1.73 m²) 37 (26.5) a,b 52.78 (36.6)a 68 (34) 64 (51)
Weight (kg) 80 (16) 83 (30.1) 74 (18) 76 (22.3)
Female 8 (50) 16 (59.3) 38 (47.5) 54 (50.5)

A total of 107 patients were assessed during a 2-month period (Table 1).

Receiver operating characteristic (ROC) analysis was used to find the optimal cut-point value for each assessment that best discriminates between selected pre-specified outcomes. Each ROC analysis shall include an ROC curve, a table with the sensitivities and specificities at certain assessment cut-points, the area under the ROC curve (AUC) and 95% confidence intervals (CIs). AUC curves were compared using the DeLong method [19]. The significance threshold was set at 0.05 for all calculations.

Results
A total of 107 patients were assessed during a 2-month period (Table 1).

The primary diagnoses at the time of admission to high dependency unit or ITU were sepsis (36.6%), respiratory failure (11.2%), alcoholic hepatitis (11.2%), diabetic ketoacidosis (7.5%), acute surgical emergency (6.5%), neurological emergency including stroke (6.5%) and other (12.1%).

The primary outcomes were recorded as follows: 30-day mortality in 27 patients (25%), RRT requirement in 16 patients (13%), acute kidney injury as defined by AKIN criteria [18] occurred in 27 patients (25%), RRT requirement in 16 patients (15%) and mean length of stay was 3.7 days (SD: 6).

Overall, there were 89 harmful events in this study population. Fifty (46.7%) patients had no adverse event, 29 (27.1%) patients had one event, 24 (22.4%) patients had two events and 4 (3%) patients had three events.

Of those patients who developed AKI, 19 patients (17.8%) developed AKIN grade 1 injury, 4 patients (3.7%) developed grade 2 and 1 patient (1%) developed grade 3 AKI.

For the purposes of calculating kGFR, the first available repeat creatinine measurement was used. The time interval prior to this repeat measurement varied between patients. The mean time between measurements was 27 h (SD: 17).

Primary outcomes
AKI. kGFR was significantly associated with AKI (P < 0.001). For each unit decrease in kGFR, there is an increased risk of developing AKI of 4%. Odds ratios and CIs are contained in Table 2. These odds are expressed per unit change in kGFR.

Although the mean kGFR and presenting MDRD eGFR were both significantly lower in those patients who developed AKI, kGFR explained 43% of the variance (Nagelkerke R² 0.437) in AKI compared with MDRD, which accounted for only 5% (Nagelkerke R² 0.057) (Table 1).

kGFR was a better predictor of AKI compared with the calculated MDRD at admission. ROC analysis: AUC = 0.86 (CI 0.77–0.94) versus AUC = 0.64 (CI 0.52–0.77). The difference between areas was 0.214 (P = 0.0001) (Figure 1).

We compared both models as predictors of risk and calculated a net reclassification index (NRI) for events and non-events. Using kGFR, of those patients who developed AKI, 23/27 patients had a decrease in risk. The average change in risk was 0.110 (P = 0.029) (Figure 1).

Sensitivity and specificity analysis for all outcomes can be found in Table 3.

RRT. Using kGFR predicted the need for RRT more accurately than MDRD. ROC analysis: AUC = 0.901 (CI 0.82–0.97) versus AUC = 0.79 (CI 0.66–0.92). The difference between areas was 0.110 (P = 0.029) (Figure 1).

The mean kGFR and presenting MDRD eGFR were both significantly lower in those patients who developed RRT (Table 1).

kGFR explained 49% of the variance (Nagelkerke R² 0.498) in RRT requirement compared with MDRD, which accounted for 22% (Nagelkerke R² 0.223).
Using kGFR, of those patients who required RRT, 14/16 had an increase in calculated probability of requiring RRT and 2/16 patients had a decrease in probability of requiring RRT. A net 75% had an increase in risk. The average change in risk was an increase of 0.19.

Of those who did not require RRT, 15/91 had an increase in calculated probability, 76/91 had a decrease and a net 57.0% had a decrease in risk. The average change in risk was 0.033.

**Secondary outcomes**

**30-day mortality and cardiovascular outcomes.** There was a poor correlation between both formulae and 30-day mortality and cardiovascular outcomes.

kGFR did not associate with 30-day mortality any better than MDRD eGFR. ROC analysis: AUC = 0.62 (CI 0.50–0.73) versus AUC 0.59 (CI 0.47–0.70). The difference between areas was 0.308 (P = 0.336).

kGFR did not associate with cardiovascular outcomes any better than MDRD eGFR. ROC analysis: AUC = 0.51 (CI 0.36–0.67) versus AUC 0.52 (CI 0.37–0.66). The difference between areas was 0.003 (P = 0.926).

NRI for both outcomes were less than 0.05 and were not clinically meaningful, and thus have been omitted for brevity.

**Significant changes in clinical filtration rate estimation.**

The kGFR differed from the MDRD eGFR by a mean of 16.6 mL/min/1.73 m² (0–67). This was most pronounced when the time intervals between measurements was shortest (range: 8–72 h).
Assuming that kGFR represents an estimation of creatinine clearance, and using an eGFR of 30 mL/min/1.73 m² to signify a clinically important threshold for drug dosing changes, 11% of patients would have had a potentially therapeutically significant change in GFR estimate, moving from above or below this cut-off if acute function was estimated by kGFR rather than MDRD.

### Discussion

This study serves as a proof of concept that kGFR is both clinically relevant and easily measurable in daily practice. We demonstrate that kGFR may have a role in predicting risk of adverse renal outcomes in acutely unwell patients. However, we failed to demonstrate any association between kGFR and the non-renal outcomes of 30-day mortality and cardiovascular death.

A recent study explored the addition of kGFR to currently available urinary biomarkers and found it may enhance their ability to predict renal recovery post-AKI [15]. This population was an exclusively intensive care population, in comparison with our mixed population of level 2 and level 3 care patients [20]. Without any additional biomarkers, we demonstrate comparable ROC AUC values, supporting the clinical utility of measuring kGFR.

The association of creatinine-based KDIGO criteria and kGFR with AKI and adverse events in a cohort of STEMI patients has been studied [21]. In contrast to our findings, the authors found superior sensitivity of KDIGO criteria in diagnosing AKI and predicting adverse outcomes compared with kGFR. Interestingly, they noted kGFR to have superior prediction in patients with pre-existing CKD. We found no difference between CKD and non-CKD groups in any outcome measure.

Future work should focus on validating kGFR as a risk prediction tool in larger and more diverse populations.

A second important area of future research is assessing the correlation of kGFR to measured renal function. As discussed, calculating a kGFR is providing the clinician with a creatinine clearance between two time points. This allows a subtler appreciation of changing kidney function and accounts for the diminishing returns on rising serum biomarker values on most estimates of GFR and influence on time intervals or body weight on overall assessment.

This could have implications for therapeutics as most published data on renal drug dosing usually refers to creatinine clearance rather than eGFR [22]. For pragmatic reasons, this is the current method of quantifying renal function used in the British National Formulary due to the widespread use of the eGFR estimating equations. However, there is a demonstrable difference between using these two methods of renal function estimation [23–25]. kGFR may provide a result more akin to true creatinine clearance and may have advantages in drug dosing over other GFR estimates in patients with rapidly changing renal function.

We would like to provide two clinical scenarios which illustrate where using a kGFR could prove advantageous over traditional formulae in this regard.

### Example 1. Acute drug dosing

A 70-year-old, 70 kg white male is admitted from a rehabilitation hospital with a healthcare-associated pneumonia and admission creatinine of 350 μmol/L. This equates to an MDRD-derived eGFR of 15 mL/min/1.73 m².

The admitting house officer notes this reduced eGFR and commences the patient on a reduced dose of tazobactam (4.5 g IV bd) and diligently reduces his prophylactic tinzaparin dose to two-thirds of normal dose.

Twenty-four hours later, a repeat creatinine has risen to 300 μmol/L. This produces an MDRD eGFR of 18 mL/min/1.73 m². The astute nephrologist will recognize that this patient is improving and is excreting more creatinine than he is producing. Accordingly, his kGFR is calculated to be 34 mL/min. Without performing this calculation however, this improvement is not quantified or recognized and his drug doses remain sub-therapeutic.

### Example 2. How unwell is this patient?

A 65-year-old, 100 kg type 2 diabetic female presents with an infected diabetic foot ulcer. She is known to have CKD and her admission creatinine in 150 μmol/L (MDRD 30 mL/min/1.73 m²).

Twenty-four hours later, her creatinine has risen to 200 μmol/L (MDRD 22 mL/min/1.73 m²). Although it is noted that her creatinine has increased, her doctors felt that a rise of 50 μmol/L was rather small, and her eGFR had only dropped by 8 mL/min/1.73 m². They increased the rate of her IV fluids and her ace inhibitor was withheld.

This patient’s calculated kGFR is 10 mL/min however, representing a significantly impaired kidney, much worse than her clinicians likely realized. Later than night, she required emergency treatment for severe hyperkalaemia.

This dramatic decrease in renal function is not detected by the MDRD formula as it does not appreciate the importance of the patient’s weight, which influences the volume of distribution of the produced creatinine. The greater the weight, the larger the volume of distribution (weight in kg × 0.6 for creatinine). Were this patient’s creatinine to rise another 50 μmol/L to 250, this would signify an effective creatinine clearance of 5 mL/min/1.73 m², despite an MDRD of 17 mL/min/1.73 m².

### Limitations

A weakness of this study was that adequate urine output data were not available for statistical analysis. The authors appreciate that hourly urine output can be a predictor of AKI or of impending requirement for acute RRT [26, 27]. It has variable sensitivity however, and the most encouraging of previous studies has suggested decreasing urinary output has an ROC of
0.7 for detecting AKI [28]. Thus, while urine output compares favourably to kGFR it has the disadvantage of requiring more intensive nursing and urine monitoring and with an intrinsic degree of unreliability in measurement.

A further limitation is the high variance of kGFR and MDRD in this population. This variance was present in both MDRD and kGFR measurements, and reflects the real world variation in renal function that we saw in this patient group. It would be important to replicate these findings in larger cohorts with less variance to provide higher degrees of statistical power.

The follow up time was 1 month, which is potentially too short a time span to observe significant changes in mortality or cardiovascular outcomes. Although the association between AKI and subsequent adverse cardiovascular events is increasingly recognized [29], a longer duration of observation is required to detect any association between kGFR and adverse cardiovascular outcomes.

We note the dependence on serum creatinine as the circulating biomarker of choice. In an era where cystatin C is becoming more available, it is unclear whether this would have provided more clinically meaningful measurements of function. Previous work in the transplant population using a kGFR formulae suggests that creatinine and cystatin C are equivalent in this regard [14].

In conclusion, this study serves as a proof of concept that kGFR is both clinically relevant and easily measurable in clinical practice. kGFR is more predictive of impending AKI and requires for RRT than current estimates of renal function. In addition to this increased predictive accuracy, we demonstrate that measuring kGFR in the acute setting could help clinicians better understand rapidly changing renal function and more accurately dose drugs, and plan for replacement therapy.

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Conflict of interest statement

None declared.

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