Clinical Kidney Journal, 2019, vol. 12, no. 2, 248–252

doi: 10.1093/ckj/sfy069
Advance Access Publication Date: 31 July 2018
Original Article

ORIGINAL ARTICLE

A bedside clinical tool using creatinine kinetics to predict worsening renal injury and early recovery

Maurice I. Khayat[1], Jonathan M. Deeth[2] and Jonathan A. Sosnov[3]

[1]Department of Nephrology, Walter Reed National Military Medical Center, Bethesda, MD, USA, [2]Department of Anesthesiology, Walter Reed National Military Medical Center, Bethesda, MD, USA and [3]Department of Nephrology, San Antonio Military Medical Center, JBSA Ft Sam Houston, TX, USA

Correspondence and offprint requests to: Maurice I. Khayat; E-mail: maurice.i.khayat.mil@mail.mil

ABSTRACT

Background. Changing creatinine concentrations during acute renal failure are often confusing to clinicians to interpret and can cloud the patient's true current state of renal injury. By modifying the formula for kinetic estimate of glomerular filtration rate (KeGFR), a simple bedside clinical tool can be used to identify subtle changes in renal function.

Methods. The KeGFR was rewritten to instead calculate a predicted peak creatinine after renal injury. By comparing the changes in predicted peak creatinine at two or more subsequent time intervals, the patient's current state of renal injury can be determined: whether improving, worsening or unchanged from prior.

Results. Three case examples are provided using the equation for predicted peak creatinine. In each case, the creatinine concentration has continued to rise at three sequentially measured times. The change in predicted peak creatinine is analyzed for each case, demonstrating scenarios involving (i) improving renal injury, (ii) unchanged renal injury continued by unfavorable hemodynamics and (iii) worsening renal injury despite interventions.

Conclusions. The use of this model may provide clinicians with an easy bedside tool to assess a patient's state of acute kidney injury. Reassessment of how the creatinine is changing is already a nonquantitative part of a nephrologist's approach to acute kidney injury. Providing an assessment of the patient's changing renal function would be a useful addition to potentially detect early renal recovery or worsening renal injury and appropriately adjust treatment strategies.

Keywords: AKI, clearance, creatinine, creatinine clearance, GFR

INTRODUCTION

The traditional estimations of creatinine clearance and by extension glomerular filtration rate (GFR) were originally derived from the general concept of clearance [1]. Classically, the calculation has required both urine and serum measurements of creatinine [2, 3]. Due to difficulty obtaining serial urinary measurements in most patients, formulas requiring only a single serum measurement of creatinine have been derived [4–6]. A limitation of these improved equations is the underlying assumption that creatinine has reached equilibrium across the central and urinary compartments [5–7]. While relying on this steady state allows creatinine production and excretion to be systemically cancelled from the equation, this affords the clinician no gauge of how to interpret any estimated GFR (eGFR) when the serum creatinine is in flux [8, 9].

Received: 31.12.2017; Editorial decision: 25.6.2018

Such a problem typically manifests when attempting to interpret renal function during acute kidney injury (AKI) [1, 7–13]. The creatinine often continues to rise even as the patient is beginning to recover renal function [14]. Even experienced physicians may misinterpret this continued rise as worsening injury and may subsequently tailor their management incorrectly. Detecting true early recovery presents a diagnostic challenge: common methods have traditionally required either serial timed estimations of production and excretion [15] or serial urinary measurements to continually reassess clearance [6]. Similarly, worsening renal function can be difficult to ascertain as the continued rise of creatinine may be falsely written off as the natural course of the patient's existing injury.

Analysis of the 'rate-of-change' of serum creatinine over time provides a potential framework to better estimate a patient's GFR. Several mathematical formulations have been proposed in the literature [3, 7, 8, 10, 11]. Of particular interest is the 'KeGFR' equation for kinetic GFR estimation [7], which can compare change in eGFR by utilization of plasma creatinine concentrations measured at discrete time intervals. This has been explored as a predictive model in AKI and may have a favorable profile for adverse renal outcomes compared with the Modification of Diet in Renal Disease equation [16]. Similarly, investigation of its application in renal transplant recipients also illustrated the ability to potentially detect early delayed graft function [17, 18]. In a broader population, prediction of the need for renal replacement therapy (RRT) as well as early recovery by comparing change in eGFR at subsequent time intervals has also been described [19].

Since the first providers to identify a potential AKI are generally not nephrologists and are generally more comfortable comparing changes in creatinine rather than eGFR, our aim is to manipulate the KeGFR equation to allow the clinician to determine changes in a patient's renal function by comparing the predicted peak creatinine values in a bedside tool for use in AKI. Using the modified equation it would thus be possible to determine whether the patient's renal injury is unchanged from prior, continuing to actively worsen or improving as may be expected from early recovery.

MATERIALS AND METHODS

The simple equation to provide a KeGFR as previously described is demonstrated below (Equation 1) [7]

$$KeGFR = \frac{SSPcr \times CrCl}{MeanPcr} \times \left(1 - \frac{24 \times \Delta PCr}{\Delta \text{Time (h)} \times MaxΔPCr/\text{day}}\right) \quad (1)$$

In this equation, steady-state plasma creatinine (SSPcr) and its corresponding creatinine clearance (CrCl) are used to estimate the production rate of creatinine. The underlying assumption is that the production rate is constant over the course of the episode of AKI, which allows the rate to be calculated a single time [7]. In the original article describing KeGFR, the steady state chosen was the patient's baseline and its corresponding eGFR thus calculated from their baseline creatinine concentration. As any steady-state plasma creatinine measurement may theoretically be used in this equation, we can instead explore the case in which CrCl equals KeGFR. This would be the case in an unchanging step-decrement injury that has neither improved nor worsened [14]. Steady-state plasma creatinine would then represent predicted peak creatinine should the KeGFR remain depressed at the same value. As CrCl and KeGFR are equivalent in this case, they are canceled from the equation. Solving for the SSPCr yields the modified equation demonstrated below (Equation 2)

$$\text{Predicted peak creatinine} = \frac{MaxΔPCr/\text{day} \times \Delta\text{Time} \times MeanPCr}{MaxΔPCr/\text{day} \times \Delta\text{Time} - 24 \times \Delta PCr} \quad (2)$$

As in the original article, we will set MaxΔPCr/day to 132.6 μmol/L (1.5 mg/dL) per day to set a good balance point in the variability of the formula output and cover the case for most patients, since the maximum plasma creatinine for anuric patients is a rise of 88–133 μmol/L (1.0–1.5 mg/dL) per day [7]. The result is the simple equation below, which estimates peak creatinine using two measured plasma creatinine values for any interval (Equation 3).

$$\text{Predicted peak creatinine} = \frac{132.6\,\mu\text{mol/L} \times \Delta\text{Time} \times MeanPCr}{132.6\,\mu\text{mol/L} \times \Delta\text{Time} - 24 \times \Delta PCr} \quad (3)$$

Comparing the predicted peak creatinine calculated at two time intervals yields information on the state of the patient's renal function compared with a single step decrement with unchanging renal injury [7]. A change in the KeGFR from improving or worsening renal function will be reflected in the respective change in predicted peak creatinine (higher if worsening and lower if improving). Comparing peak creatinine measurements is equivalent to comparing kinetic changes in KeGFR and affords two major advantages. First, physicians at the forefront of diagnosis and treatment of AKI, who are often not nephrologists, are more comfortable with the concept of the comparison of creatinine concentrations as opposed to changes in GFR. This likely stems from the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, which require such comparisons for diagnosis and staging [20]. Second, bypassing the requirement for a baseline creatinine allows for useful expansion of our bedside tool to the common case when a patient's historical creatinine measurement is very old or missing entirely.

RESULTS

The following case examples illustrate how the comparison can be used in each of the following scenarios: (i) an unchanging renal injury, (ii) a prerenal process with early intervention and improvement and (iii) continued worsening of renal function. In each case, the patient is a 60-year-old male with active lung cancer admitted with concern for respiratory failure secondary to presumed pulmonary sepsis, who subsequently receives piperacillin/tazobactam in the emergency department as well as a contrasted computed tomography scan to evaluate for pulmonary embolism. Repeat labs on admission reveal a worsening creatinine, and upon realization of the kidney injury, the patient empirically receives a 1 L intravenous bolus of isotonic fluid. The creatinine concentrations for each case are shown in Table 1. For simplicity, the first two creatinine values are the same for each case while the third is allowed to be varied.

Using Equation 3 above the predicted peak creatinine is calculated from the initial two creatinine values collected in a 12-h interval. The mean of the two creatinine concentrations is 93 μmol/L and the difference is 44 μmol/L. The calculation is shown below:

$$\text{Predicted peak creatinine} = \frac{132.6 \times (12.00 - 0.00) \times 93}{132.6 \times (12.00 - 0.00) - 24 \times 44} = 276\,\mu\text{mol/L}$$

Table 1. Sample serial creatinine values describing a single decrement of renal function with ongoing injury and no recovery (Case 1), an improving pre-renal renal injury (Case 2) and active worsening renal injury (Case 3)

		PCr (μmol/L)		
Event	*T* (h)	Case 1	Case 2	Case 3
Admission (t_1)	0.00	71	71	71
Morning labs (t_2)	12.00	115	115	115
Post-rounds recheck (t_3)	24.00	150	141	159

For our initial case (Case 1), an additional measurement at t3 is obtained (Table 1). A new predicted peak creatinine can be calculated in the same method by using the creatinine concentrations at times t2 and t3 as inputs. This yields a new predicted creatinine of 281 μmol/L (3.2 mg/dL). Note that the predicted creatinine has only varied by 2% from the original value, which suggests the renal injury is unchanged as compared with the original step decrement. It is theorized that the patient has acute tubular necrosis, but has neither worsened nor improved from his original state as his predicted peak creatinine (and thus his KeGFR) has not changed. Fluids goals are tempered from active resuscitation to maintaining a euvolemic state in an attempt to avoid overt hypervolemia.

Compare this with the second case (Case 2) where the patient's creatinine is continuing to worsen over the course of his presentation, but to a lesser degree than the initial scenario. Once more, using Equation 3 with the creatinine measurements at t2 and t3 in the table below, his predicted peak creatinine is instead discovered to be 211 μmol/L (2.4 mg/dL), a 24% improvement. Despite his rising creatinine, it appears that the correction of the patient's hypovolemia has likely begun to improve the patient's renal injury. If he maintains this trajectory, eventually his creatinine concentration will reflect his increase in renal function.

The final case (Case 3) explores the scenario in which the patient is actively worsening. Recalculation based on the third creatinine value at t3 demonstrates a worsening predicted peak of 407 μmol/L (4.6 mg/dL), which comprises a 47% worsening between the two predicted peaks. This affords the clinician evidence that the uptrend in creatinine does indeed represent an active worsening renal injury despite their initial interventions and should be monitored accordingly. Such changes in KeGFR from baseline injury are more visually recognizable when viewing the projected future creatinine curves graphically based on the value of the predicted peak creatinine for each case (Figure 1).

DISCUSSION

These cases highlight the common difficulty in interpreting a continuous uptrend in creatinine. Clinicians often incorrectly assume that there is worsening renal injury based upon the common, yet false assumption that creatinine must stabilize or improve before renal recovery occurs [14]. In Case 1, the suggestion of a non-changing renal injury allows for the temperance of intravenous fluids to lower the risk of hypervolemia. In Case 2, the improvement with correction of hypovolemia is suggestive of renal recovery even before the creatinine has begun to stabilize. Finally, in Case 3, the clinician is alerted to the patient's continued worsening renal decline despite their interventions and monitoring can be adjusted accordingly while a search for unaddressed nephrotoxic insults occurs.

Use of this model may provide the clinician with an easy bedside tool to assess a patient's AKI over time. Reassessment of how the creatinine is changing is already a nonquantitative part of a nephrologist's approach to AKI. Providing an analysis of the patient's changing renal function is a useful tool to both delineate the etiology of the AKI and, more importantly, to assess their response to therapeutic interventions and tailor management goals accordingly.

The application of this formula is subject to some limitations. First, one major assumption is that the production of creatinine remains constant over the course of the patient's episode of AKI, which may not be the case if critical illness is protracted or the patient receives surreptitious boluses of intravenous fluid, which may affect the volume of distribution of creatinine by altered production or accumulation of excess total body water, respectively [7]. One advantage of eliminating the need for a baseline creatinine is that two intervals relatively close in time can be compared as opposed to a continued comparison to a historical baseline. Presumably over a short time interval, production will be relatively constant even as it changes over a patient's hospital stay.

Second, many patterns of renal injury have been described and caution must be used when extrapolating three time points to an entire episode of AKI. Some patients have relapse after an initial recovery [21] and in this case extrapolation of the patient's course of injury will lead to erroneous results. However, this is also an advantage for our bedside tool—by tracking predicted peak creatinine at successive intervals the change will be detected and a 'double worsening' of renal function will be detected when it may otherwise be missed.

The remaining limitations are predominantly related to the value of *MaxΔPcr*/day and small increments of Δ*Time*. The KeGFR equation implies a constant production rate of creatinine, such that at any given time interval (Δ*Time*), the accumulation rate of creatinine when anuric (and thus KeGFR = 0) is expected to be increased to a maximum value of *MaxΔPCr*/day/(Δ*Time*/24 h). This is problematic in two major areas. First, if the rise in creatinine exceeds the upper limit of *MaxΔPCr*/day/(Δ*Time*/24 h) due to greater-than-estimated production, the denominator will be negative and both the KeGFR and predicted peak creatinine will be uninterpretable. Second, if the time interval of interest between measurements becomes too small, the allowable variation in creatinine is substantially reduced. Logically, this makes sense, as any significant variation in creatinine between two short measurements is likely due to simple assay variation and of questionable clinical significance. However, such variation will likely exceed the allowable limit of *MaxΔPcr*/day/(Δ*Time*/24 h) and again cause invalid results for both equations above. A reasonable expectation to minimize the first problem is to create a minimum acceptable time in which to interpret changes (i.e. 2–4 h as an enforceable minimum for Δ*Time*).

The limitation regarding the value of *MaxΔPcr*/day at 132.6 μmol/L (1.5 mg/dL) is also addressed in the original article [7]. Ideally, further studies aimed at determining a patient's production of creatinine, including their volume of distribution for creatinine, and how they change in critical illness is warranted in order to optimize GFR estimations [22]. However, from the standpoint of interpreting 'trends' an increase in the maximal allowable creatinine per day when needed may increase the usefulness of the equation. This change allows for the continued interpretation of changes in the scenarios above while ameliorating the numerical constraints of Equation 3, although the dampening effect may decrease its interpretability [7]. Further studies to determine the optimal maximum daily creatinine may also be warranted.

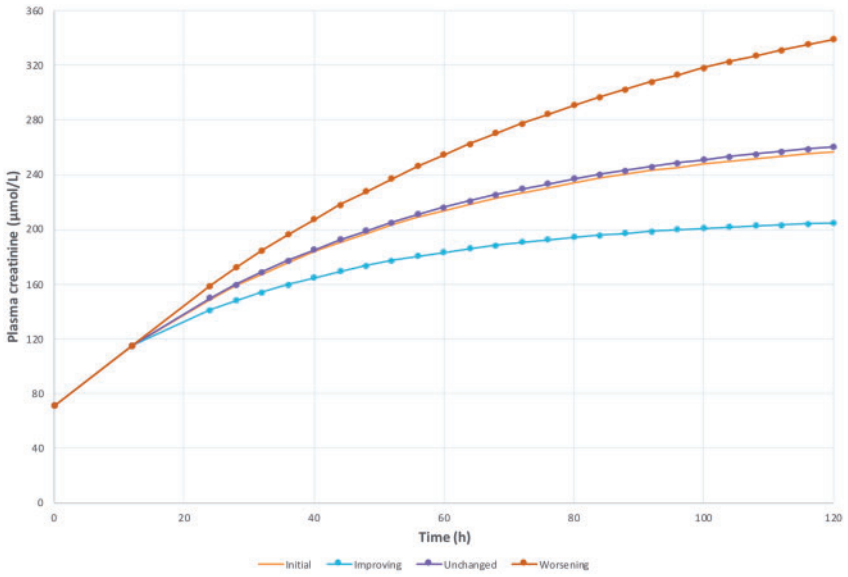

FIGURE 1: Plot of the projected plasma creatinine versus time illustrating three different clinical case scenarios. The initial projected creatinine based on the plasma creatinine concentrations at t_1 and t_2 (common to all case examples) is demarcated by the solid orange line. The projected creatinine curves based on the amended peak creatinine after recalculation at t_3 for each case (improving AKI, unchanged renal function and worsening renal injury) are superimposed as marked.

Additionally, cutoffs for allowable variation in predicted creatinine need to be established based on a validating data set. For purposes of the example problems, a cutoff of ±10% was used, which was chosen to be approximately three times the standard error of creatinine (8% variance) reported in some studies [23]. One area of future exploration may be the use of a Bayesian framework to calculate an individual's reference interval and to integrate this into a cutoff limit to define a clinically significant change in peak creatinine, similar to previous works attempting to establish an cutoff range for drug-induced AKI [24]. This would, however, detract slightly from the bedside aspect unless able to be calculated automatically by the electronic medical record.

Finally, future research will be needed to validate the KeGFR equation itself by comparison to patients' directly measured GFR by measurement of inulin clearance or via nuclear quantification. In the interim, this may be a useful bedside tool for rapid assessment of patient kidney function. Additional areas of investigation for renal recovery would be to use the equation during RRT in anuric patients to determine creatinine kinetics during a 'fixed' GFR. Validation with hard outcomes such as has been done with KeGFR would also be of benefit [19], especially if this equation can be used to be predict need for RRT. In the interim, this equation may be a useful bedside tool for rapid assessment of a patient's trajectory during their course of AKI.

ACKNOWLEDGEMENTS

The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense or US Government.

AUTHORS' CONTRIBUTIONS

Research idea and study design was conceived by M.I.K., J.M.D. and J.A.S.; data analysis/interpretation was done by M.I.K. and J.M.D.; statistical analysis was performed by M.I.K. and J.M.D.; and supervision or mentorship was carried out by J.A.S. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. *Clin Chem* 1992; 38: 1933–1953
2. Jelliffe RW. Estimation of creatinine clearance when urine cannot be collected. *Lancet* 1971; 1: 975–976
3. Chiou WL, Hsu FH. A new simple and rapid method to monitor the renal function based on pharmacokinetic consideration of endogeneous creatinine. *Res Commun Chem Pathol Pharmacol* 1975; 10: 315–330
4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41
5. Levey AS. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461–470
6. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
7. Chen S. Retooling the creatinine clearance equation to estimate kinetic GFR when the plasma creatinine is changing acutely. *J Am Soc Nephrol* 2013; 24: 877–888
8. Yashiro M, Ochiai M, Fujisawa N *et al.* Evaluation of estimated creatinine clearance before steady state in acute kidney injury by creatinine kinetics. *Clin Exp Nephrol* 2012; 16: 570–579

9. Lippi G, Guidi GC. Acute kidney injury: time to shift from creatinine to the estimated glomerular filtration rate? *Crit Care* 2008; 12: 423; author reply 423
10. Jelliffe R. Estimation of creatinine clearance in patients with unstable renal function, without a urine specimen. *Am J Nephrol* 2002; 22: 320–324
11. Pickering JW, Frampton CM, Walker RJ *et al*. Four hour creatinine clearance is better than plasma creatinine for monitoring renal function in critically ill patients. *Crit Care* 2012; 16: R107
12. Poggio ED, Nef PC, Wang X *et al*. Performance of the Cockcroft-Gault and modification of diet in renal disease equations in estimating GFR in ill hospitalized patients. *Am J Kidney Dis* 2005; 46: 242–252
13. Barraclough K, Harris M, Montessori V *et al*. An unusual case of acute kidney injury due to vancomycin lessons learnt from reliance on eGFR. *Nephrol Dial Transplant* 2007; 22: 2391–2394
14. Moran SM, Myers BD. Course of acute renal failure studied by a model of creatinine kinetics. *Kidney Int* 1985; 27: 928–937
15. Pickering JW, Mellas J. A simple method to detect recovery of glomerular filtration rate following acute kidney injury. *Biomed Res Int* 2014; 2014: 542069
16. O'Sullivan ED, Doyle A. The clinical utility of kinetic glomerular filtration rate. *Clin Kidney J* 2017; 10: 202–208
17. Endre ZH, Pianta TJ, Pickering JW. Timely diagnosis of acute kidney injury using kinetic eGFR and the creatinine excretion to production ratio, E/eG—creatinine can be useful! *Nephron* 2016; 132: 312–316
18. Pianta TJ, Endre ZH, Pickering JW *et al*. Kinetic estimation of GFR improves prediction of dialysis and recovery after kidney transplantation. *PLoS One* 2015; 10: e0125669
19. Dewitte A, Joannès-Boyau O, Sidobre C. Kinetic eGFR and novel AKI biomarkers to predict renal recovery. *Clin J Am Soc Nephrol* 2015; 10: 1900–1910
20. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; 2: 1–138
21. Kellum JA, Sileanu FE, Bihorac A. Recovery after acute kidney injury. *Am J Respir Crit Care Med* 2017; 195: 784–791
22. Clark WR, Mueller BA, Kraus MA *et al*. Quantification of creatinine kinetic parameters in patients with acute renal failure. *Kidney Int* 1998; 54: 554–560
23. Coresh J, Astor BC, McQuillan G. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* 2002; 39: 920–929
24. Sottas PE, Kapke GF Leroux JM. Adaptive Bayesian analysis of serum creatinine as a marker for drug-induced renal impairment in an early-phase clinical trial. *Clin Chem* 2012; 58: 1592–1596

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