

# Estimating Creatinine Clearance in the Nonsteady State: The Determination and Role of the True Average Creatinine Concentration



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Creatinine clearance is a tenet of nephrology practice. However, with just a single creatinine concentration included in the denominator of the creatinine clearance equation, the resulting value seems to apply only in the steady state. Does the basic clearance formula work in the nonsteady state, and can it recapitulate the kinetic glomerular filtration rate (GFR) equation? In the kinetic state, a nonlinear creatinine trajectory is reducible into a “true average” value that can be found using calculus, proceeding from a differential equation based on the mass balance principle. Using the fundamental theorem of calculus, we prove definitively that the true average is the correct creatinine to divide by, even as the mathematical model accommodates clinical complexities such as volume change and other factors that affect creatinine kinetics. The true average of a creatinine versus time function between 2 measured creatinine values is found by a definite integral. To use the true average to compute kinetic GFR, 2 techniques are demonstrated, a graphical one and a numerical one. We apply this concept to a clinical case of an individual with acute kidney injury requiring dialysis; despite the effects of hemodialysis on serum creatinine concentration, kinetic GFR was able to track the underlying kidney function and provided critical information regarding kidney function recovery. Finally, a prior concept of the maximum increase in creatinine per day is made more clinically objective. Thus, the clearance paradigm applies to the nonsteady state as well when the true average creatinine is used, providing a fundamentally valid strategy to deduce kinetic GFRs from serum creatinine trends occurring in real-life acute kidney injury and kidney recovery.

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## BACKGROUND

The kinetic glomerular filtration rate ( $GFR_K$ ) is an attempt to track kidney function even while the serum or plasma creatinine concentration ( $[Cr]$ ) is changing over time. Essentially,  $GFR_K$  is a creatinine clearance ( $CL_{Cr}$ ) rate, and all clearances are based on the fundamental clearance equation. In the case of creatinine, it can be written as  $CL_{Cr} = \frac{U_{Cr} \times V}{P_{Cr}}$ , where  $U_{Cr}$  is urinary  $[Cr]$ ,  $V$  is urine flow rate (thereby incorporating time), and  $P_{Cr}$  is plasma  $[Cr]$ .<sup>1</sup>  $U_{Cr} \times V$  is usually measured from a 24-hour urine collection, but the duration could be longer or shorter. This clearance equation is always valid, in theory. It is easy to apply when  $[Cr]$  is basically stable, as in chronic kidney disease, but how is it applied when the  $[Cr]$  is evolving over time, such as in acute kidney injury (AKI) or renal recovery? The equation calls for only one creatinine value, but what value is chosen in the nonsteady state when there is a whole range of  $[Cr]$  values? We hypothesize that there must exist a correct  $[Cr]$ , probably some “average” value, that will make the basic clearance formula behave identically to any kinetic GFR equation.

## MASS BALANCE PRINCIPLE AND THE AVERAGE

At the heart of kinetic analysis, a pair of  $[Cr]$ s separated by a known interval comprises the basic data that are reported by the clinical laboratory. Connecting the  $[Cr]$  end points is a trajectory that is likely to be smooth and continuous. What is the  $[Cr]$ s’ average during that time? If a  $[Cr]$

trajectory is thought to be linear, one could compute the simple mean value of the  $[Cr]$  end points to use for the denominator of  $\frac{U_{Cr} \times V}{P_{Cr}}$ . Effectively, that is what was done in 2013 for the “algebraic”  $GFR_K$ .<sup>2</sup> By 2018, the  $[Cr]$  trajectory was being modeled based on the principle of mass balance, which asserts that the creatinine generation rate minus the creatinine excretion rate must equal the creatinine change rate. In mathematical terms, this translates into:

$$Gen - GFR_K \cdot [Cr]_t = \frac{d}{dt} ([Cr]_t \cdot V_t) \quad (1)$$

where creatinine generation rate ( $Gen$ ) is assumed to be constant, excretion rate is given by a  $GFR_K$  times the ambient  $[Cr]$  as a function of time ( $[Cr]_t$ ), and the instantaneous rate of creatinine change is described by the derivative with respect to time ( $\frac{d}{dt}$ ) of the ambient creatinine mass ( $[Cr]_t \cdot V_t$ ). Further, the volume as a function of time ( $V_t$ ) starts at an initial volume ( $V_0$ ) and changes at a fixed rate ( $\frac{\Delta V}{\Delta t}$ ) throughout some time ( $t$ ) between  $[Cr]$  measurements, so that  $V_t = V_0 + \frac{\Delta V}{\Delta t} t$ . The  $GFR_K$  itself can change during the period, notably while kidney function is decreasing steeply as in severe AKI. All of the evolving  $GFR_K$ s can be replaced by a single (and effectively constant) average value for that period. This replacement yields an identical result, as if the average  $GFR_K$  were acting on the  $[Cr]$  trajectory to give a total creatinine excretion and overall rate of  $[Cr]$  change.

As previously shown,<sup>3,4</sup> the solution to differential equation (1) is:

$$[Cr]_t = [Cr]_0 + \left( \frac{Gen}{GFR_K + \frac{\Delta V}{\Delta t}} - [Cr]_0 \right) \cdot \left[ 1 - \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t} t} \right)^{\left( 1 + \frac{GFR_K}{\frac{\Delta V}{\Delta t}} \right)} \right] \quad (2)$$

If equation (2) models the [Cr] trajectory, which is clearly nonlinear, the mean value of the 2 [Cr] end points is not the correct average. Instead, we must calculate the average of all [Cr]s traversed during the trajectory over some interval, using calculus. We postulate that if this “true average” is used in the denominator of  $\frac{U_{Cr} \times V}{P_{Cr}}$ , the resulting CL<sub>cr</sub> will equal the GFR<sub>K</sub> as calculated directly from equation (2).

**RATIONALE FOR THE AVERAGE**

Any continuous [Cr] trajectory obeying the mass balance differential equation should have a single middle value that represents its exact average; call it  $\overline{P_{Cr}}$ . When the horizontal line  $y = \overline{P_{Cr}}$  is superimposed on a graph of [Cr]<sub>t</sub> over some interval [a, b], it will divide the [Cr]<sub>t</sub> curve such that the area of [Cr]<sub>t</sub> below the  $\overline{P_{Cr}}$  average line balances out the area of [Cr]<sub>t</sub> above the average line (Fig 1). To be practical, we let the interval run from 0 to T, where T is the total time between 2 measured [Cr]s. In a way, every pair of consecutive [Cr] data resets the clock, and the duration between [Cr] end points is then simply T. Because the signed areas (above) add up to zero, an integral can be written as:

$$\int_0^T ([Cr]_t - \overline{P_{Cr}}) dt = 0 \quad (3)$$

Integration is linear, and the integral  $\int_0^T \overline{P_{Cr}} dt$  can be factored out as  $\overline{P_{Cr}} \int_0^T dt$  because  $\overline{P_{Cr}}$  is a constant. Solving equation (3) gives  $\overline{P_{Cr}} = \frac{\int_0^T [Cr]_t dt}{\int_0^T dt}$ . Moreover, because  $\int_0^T dt = T$ , we have:

$$\overline{P_{Cr}} = \frac{\int_0^T [Cr]_t dt}{T} \quad (4)$$

**PROVING THAT THE TRUE AVERAGE [Cr] FULFILLS THE DIFFERENTIAL EQUATION**

Differential equation (1) was previously solved<sup>3</sup> for [Cr]<sub>t</sub> using the usual methods, leading to equation (2). Instead, we can first manipulate equation (1) by the fundamental theorem of calculus to spawn the true average integral and gain insight into the role it plays:  $\frac{d}{dt}([Cr]_t V_t) = Gen - GFR_K \cdot [Cr]_t \Rightarrow d([Cr]_t V_t) = (Gen - GFR_K \cdot [Cr]_t) dt$ . Integrate both sides from time 0 to T:  $\int_0^T d([Cr]_t V_t) = \int_0^T (Gen - GFR_K \cdot [Cr]_t) dt \Rightarrow [Cr]_T V_T - [Cr]_0 V_0 = \int_0^T Gen dt - \int_0^T GFR_K \cdot [Cr]_t dt$ . The left-hand [Cr]<sub>T</sub> is now the later [Cr] end point measured by the laboratory. It is not to be confused with the

right-hand [Cr]<sub>t</sub>, which is still the [Cr] as a function of time. Continuing, the right-hand side can be integrated to give  $Gen \cdot T - GFR_K \int_0^T [Cr]_t dt$ . Well,  $\int_0^T [Cr]_t dt$  is the numerator of the supposed true average. From equation (4) then,  $\int_0^T [Cr]_t dt = \overline{P_{Cr}} \cdot T$ . Substitute this in to get  $[Cr]_T V_T - [Cr]_0 V_0 = Gen \cdot T - GFR_K \cdot \overline{P_{Cr}} \cdot T$ . Finally, solve for the GFR<sub>K</sub>:

$$GFR_K = \frac{Gen \cdot T - ([Cr]_T V_T - [Cr]_0 V_0)}{\overline{P_{Cr}} \cdot T} \quad (5)$$

**FUNDAMENTAL PROOF: STRENGTHS AND FLEXIBILITIES**

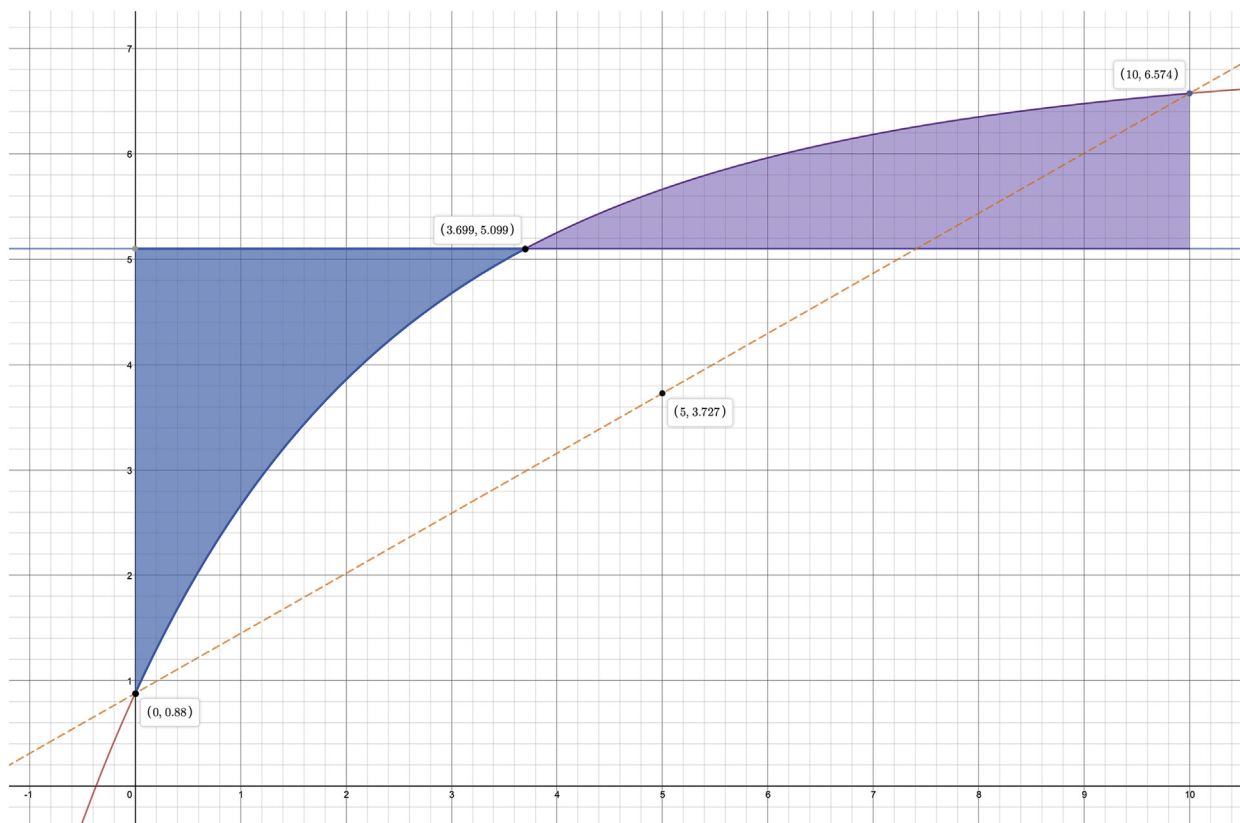
Assuming a constant average GFR<sub>K</sub> over a given period, any [Cr] function that follows the mass balance principle will necessarily produce a  $\overline{P_{Cr}}$ . In the differential equation, the  $\frac{d}{dt}([Cr]_t V_t)$  term has a volume as a function of time that does not have to be linear. It can be nonlinear in the model to better reflect reality. Similarly, the Gen does not have to be constant; it too can vary linearly or nonlinearly. In terms of creatinine gain, another source is absorption from food,<sup>5</sup> and that can be incorporated into the differential equation. In terms of creatinine loss, any (constant average) extrarenal clearances can be added in separately, as in  $(CL_{extra} + GFR_K) \cdot [Cr]_t$ . A fixed excretion rate independent of the ambient [Cr]<sub>t</sub> can also be included. These optional modules enable us to model clearance more realistically, and yet they all leave  $\int_0^T [Cr]_t dt$  intact, inserting a  $\overline{P_{Cr}}$  into the final equation. Thus,  $\overline{P_{Cr}}$  serves as the true divisor in  $\frac{U_{Cr} \times V}{P_{Cr}}$  whenever [Cr] is changing.

**CREATININE EXCRETION RATE**

By the process of elimination, the rest of equation (5) must fit the template of the basic clearance’s numerator, that is,  $U_{Cr} \times V$ , also known as the creatinine excretion rate. The non- $\overline{P_{Cr}}$  portion of equation (5) is, by inspection,  $\frac{Gen \cdot T - ([Cr]_T V_T - [Cr]_0 V_0)}{T}$ . Logically, Gen • T tells us how much creatinine was generated over an interval T, while  $[Cr]_T V_T - [Cr]_0 V_0$  tells us the delta in creatinine mass. Creatinine generation minus the Δ creatinine equals creatinine excretion, which is  $Gen \cdot T - ([Cr]_T V_T - [Cr]_0 V_0)$ . Next, divide this by T to get the creatinine excretion rate, recreating the above. Technically, a  $U_{Cr} \times V$  calculated in this way is the total creatinine elimination rate, which comprises urinary excretion (glomerular filtration plus tubular secretion) but also includes nonrenal excretion and creatinine degradation/metabolic conversion.

**SOLVING EXPLICITLY FOR  $\overline{P_{Cr}}$**

We have all the information to derive a formula for the true average [Cr]. The following is just one of many potential formulas for  $\overline{P_{Cr}}$ . The variations arise depending on the root differential equation. Equation (1), used for the model, lets the volume change at a linear rate,<sup>3,4</sup> but others may let the Gen change too or accommodate an extrarenal



**Figure 1.** True average creatinine concentration ( $[Cr]$ ) line divides a  $[Cr]$  versus time graph into equal areas. The red curve depicts the evolution of  $[Cr]$  (mg/dL) over time (days) if the glomerular filtration rate decreased from 100 to 10.104 mL/min and the volume kept increasing by 3.6 L/d. In 10 days,  $[Cr]$  has a calculus-average value of 5.099 mg/dL, which does not have to occur at the halfway point in time. The blue horizontal line  $y = 5.099$  divides the graph such that the signed areas between the curve and the line cancel each other out; that is, the blue area equals the purple area. Because the  $[Cr]$  trajectory had time to significantly curve away from the imaginary (dashed) line connecting the 2  $[Cr]$  end points, the true average  $[Cr]$  (5.099 mg/dL) must be used instead of the linear average  $[Cr]$  (3.727 mg/dL).

$CL_{Cr}$ , etc. In any case, the  $\overline{P}_{Cr}$  term will materialize, meaning that the true average  $[Cr]$  plays an inevitable role. The detailed methods (Item S1) contain the derivation of our true average  $[Cr]$ . The result is:

$$\overline{P}_{Cr} = [Cr]_0 + \left( \frac{Gen}{GFR_K + \frac{\Delta V}{\Delta t}} - [Cr]_0 \right) \cdot \left( 1 - \frac{V_0}{T \cdot GFR_K} \left[ 1 - \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t} T} \right)^{\left( \frac{GFR_K}{\frac{\Delta V}{\Delta t}} \right)} \right] \right) \quad (6)$$

Equation (6) gives the true average  $[Cr]$  over a generic period from 0 to  $T$ . To examine a special case, if  $[Cr]_t$  is stable, then for all  $t$  we have  $\frac{Gen}{GFR_K + \frac{\Delta V}{\Delta t}} - [Cr]_0 = 0$ , and equation (6) sensibly says that the true average is just the prevailing  $[Cr]_0$ . That way, the kinetic GFR reduces down to the steady-state GFR when  $[Cr]$  is stable, as required.

The true average  $[Cr]$  expression in equation (6) can be substituted into equation (5) to complete the  $U \times V/P$  version of the  $GFR_K$ . Although they appear vastly different,

equation (5) must be identical to equation (2) because they are both derived from differential equation (1). One can algebraically manipulate equation (5) to become equation (2), but this approach uses brute force, is not elegant, and proves equivalence between equations (5) and (2) only. In contrast, a proof by the fundamental theorem of calculus is widely applicable because it acts at the level of any root differential equation, which can be made as complex as desired.

### CALCULATING THE $GFR_K$ : CLINICAL CASE

We will calculate the  $GFR_K$  in a sample clinical case, using the new equation (5) that is based on the true average  $[Cr]$ . Its answer should be identical to the  $GFR_K$  from the old equation (2), that is, the gold standard, as guaranteed by our proof.

A woman in her 50s develops acute tubular necrosis, during which her  $[Cr]$  increases from 2.22 mg/dL at 04:22 to 3.49 mg/dL at 01:49 the next day. She weighs 101.4 kg, and the net of her inputs and outputs is +3,600 mL in 24 hours. The variables have the following values:  $[Cr]_0 = 2.22$  mg/dL,  $[Cr]_T = 3.49$  mg/dL,  $T = 21.45$  hours,  $V_0 = 101.4 \cdot 0.5 = 50.7$  L (if the creatinine's

volume of distribution is total body water),<sup>6</sup>  $\frac{\Delta V}{\Delta t} = \frac{3.6 \text{ L}}{24 \text{ h}} = 0.15 \frac{\text{L}}{\text{h}}$ , and  $V_T = V_0 + \frac{\Delta V}{\Delta t} T = 50.7 \text{ L} + 0.15 \frac{\text{L}}{\text{h}} \cdot 21.45 \text{ h} = 53.9175 \text{ L}$ . To get the creatinine generation rate, multiply any  $[Cr]$  by its estimated GFR as if in steady state. For this patient,  $Gen = 0.88 \frac{\text{mg}}{\text{dL}} \cdot 100 \frac{\text{mL}}{\text{min}} = 88 \frac{\text{mg} \cdot \text{mL}}{\text{dL} \cdot \text{min}}$ . With all the variables assigned (except one), we can solve for  $GFR_K$ .

**USING THE GOLD STANDARD [Cr] EQUATION**

Equation (2) is the direct solution to the differential equation in the case of a constant  $Gen$  and linear volume change. Equation (2) can be rearranged to solve for the  $GFR_K$ <sup>3</sup>:

$$GFR_K = \frac{Gen}{[Cr]_t} \left( 1 - \frac{[Cr]_t - [Cr]_0}{[Cr]_t \cdot \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t} t} \right) - [Cr]_0} - \left( 1 + \frac{GFR_K}{\frac{\Delta V}{\Delta t}} \right) \right) - \frac{\Delta V}{\Delta t} \tag{7}$$

$GFR_K$  is on both sides of the equation and cannot be solved for explicitly. Nevertheless, we can ascertain  $GFR_K$  accurately. One technique is to graph the 2 sides of equation (7) and see where they intersect. Another technique is to use Newton’s method.

**Graphing**

Replacing  $GFR_K$  in equation (7) with the traditional  $x$ , we graph  $y = x$  and then at  $t = T$ :

$$y = \frac{Gen}{[Cr]_T} \left( 1 - \frac{[Cr]_T - [Cr]_0}{[Cr]_T \cdot \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t} T} \right) - [Cr]_0} - \left( 1 + \frac{3}{50} \cdot \frac{x}{\frac{\Delta V}{\Delta t}} \right) \right) - \frac{50}{3} \cdot \frac{\Delta V}{\Delta t}$$

With actual values entered, it equals:

$$\frac{88}{3.49} \left( 1 - \frac{3.49 - 2.22}{3.49 \cdot \left( \frac{50.7}{53.9175} \right) - \left( 1 + \frac{3}{50} \cdot \frac{x}{0.15} \right) - 2.22} \right) - \frac{50}{3} \cdot 0.15.$$

It is desirable to have  $GFR_K$  in mL/min, which is accomplished by a unit conversion of  $\frac{1,000 \text{ mL}}{\text{L}} \cdot \frac{\text{h}}{60 \text{ min}}$ .

giving rise to the  $\frac{50}{3}$  factor. The graph (Fig 2) shows 2 intersection points at -2.5 and 10.104. The -2.5 is an extraneous solution and can be ignored. Basically, it is the negative of  $\frac{\Delta V}{\Delta t}$ :  $-\frac{3.6 \text{ L}}{24 \text{ h}} \cdot \frac{1,000 \text{ mL}}{\text{L}} \cdot \frac{\text{h}}{60 \text{ min}} = -2.5 \frac{\text{mL}}{\text{min}}$ .<sup>3,4</sup> The real  $GFR_K$  is the 10.104 mL/min. This compares plausibly with the erroneous steady-state GFR for when the patient’s  $[Cr] = 3.49 \text{ mg/dL}$  that could be calculated as  $Gen/[Cr] = 88/3.49 \approx 25 \text{ mL/min}$ .

**Newton's Method**

From equation (7), we find a function that equals zero when the real  $GFR_K$  is plugged in:

$$f(GFR_K) = \frac{Gen}{[Cr]_T} \left( 1 - \frac{[Cr]_T - [Cr]_0}{[Cr]_T \cdot \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t} T} \right)^{\left( 1 + \frac{GFR_K}{\frac{\Delta V}{\Delta t}} \right)} - [Cr]_0} \right) - \frac{\Delta V}{\Delta t} - GFR_K.$$

Differentiate  $f(GFR_K)$  with respect to  $GFR_K$ —all other variables are effectively constants—and then iteratively apply  $GFR_2 = GFR_1 - \frac{f(GFR_1)}{f'(GFR_1)}$  until the calculations stabilize at the correct kinetic GFR. See [Item S1](#) for the Newton's method equation. With an initial guess of  $GFR_1 = 3$  mL/min, the  $GFR_2$  outputs stabilize after the seventh iteration ([Table 1](#)), so that the answer is 10.1043174912624..., shown to an unrealistic accuracy of decimal places to illustrate the convergence of the iterations. The value agrees well with the 10.104 found by graphing.

**USING THE TRUE AVERAGE [Cr] EQUATION**

**Graphing**

Replacing  $GFR_K$  with  $x$  in equation (5), we graph  $y = x$  for the left-hand side and then

$$y = \frac{Gen \cdot T - \frac{50}{3} ([Cr]_T V_T - [Cr]_0 V_0)}{[Cr]_0 T + \left( \frac{Gen}{x + \frac{50 \cdot \Delta V}{3 \cdot \Delta t}} - [Cr]_0 \right) \left( T - \frac{50 \cdot V_0}{3 \cdot x} \cdot \left[ 1 - \left( \frac{V_0}{V_0 + \frac{\Delta V}{\Delta t} T} \right)^{\left( \frac{3 \cdot x}{50 \cdot \frac{\Delta V}{\Delta t}} \right)} \right] \right)}$$

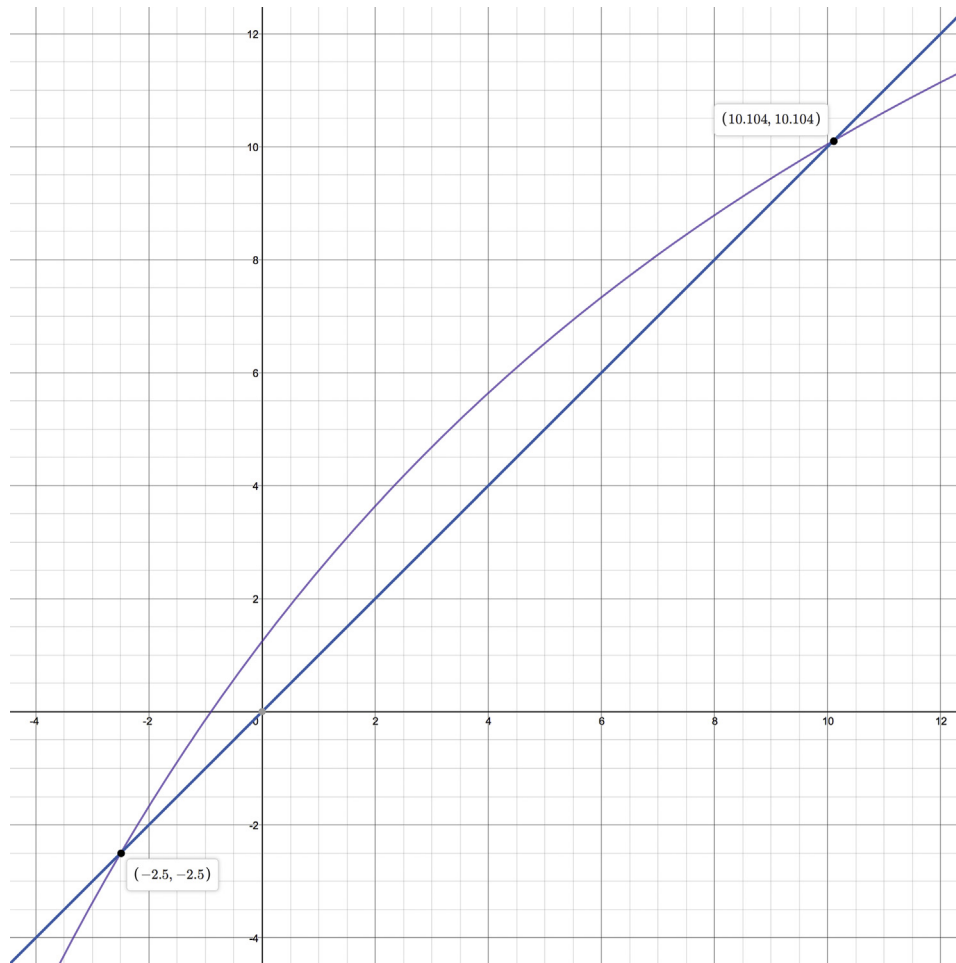
(which has unit conversions) for the right-hand side. With the clinical case values plugged in, it becomes

$$y = \frac{88 \cdot 21.45 - \frac{50}{3} (3.49 \cdot 53.9175 - 2.22 \cdot 50.7)}{2.22 \cdot 21.45 + \left( \frac{88}{x + \frac{50 \cdot 0.15}{3}} - 2.22 \right) \left( 21.45 - \frac{50 \cdot 50.7}{3 \cdot x} \cdot \left[ 1 - \left( \frac{50.7}{53.9175} \right)^{\left( \frac{3 \cdot x}{50 \cdot 0.15} \right)} \right] \right)}$$

The graph shows only 1 intersection with  $y = x$  ([Fig 3](#)), as opposed to 2 intersections for the gold standard. The kinetic GFR is 10.104 mL/min, matching the gold standard.

**Newton's Method**

Equation (5) is amenable to Newton's method as well. Let  $f(GFR_K) = \frac{Gen \cdot T - ([Cr]_T V_T - [Cr]_0 V_0)}{P_{Cr} \cdot T} - GFR_K$ , find the derivative  $f'(GFR_K)$ , and apply  $GFR_2 = GFR_1 - \frac{f(GFR_1)}{f'(GFR_1)}$ . See [Item S1](#) for the Newton's method equation. For a fair comparison with the gold standard, also start with a guess of  $GFR_1 = 3$  mL/min. The  $GFR_2$  outputs stabilize after the third iteration ([Table 2](#)), as opposed to the seventh iteration for the gold standard. The  $GFR_K$ s are identical to the last decimal place shown ([Table 1 vs 2](#)).



**Figure 2.** Graph of the gold standard way to find the kinetic glomerular filtration rate ( $GFR_K$ ). Equation (7) cannot be rearranged to provide an explicit solution for  $GFR_K$ . However, the equality between the 2 sides of the equation means that they can be graphed separately and the intersection point(s) will provide the answer. The left-hand side is simply the line  $y = x$  and is shown as the diagonal blue line. The right-hand side is the more complicated portion (see text for details) and is shown as the purple curve. The line and curve intersect at 2 places. The 10.104 is the real  $GFR_K$ . The -2.5 is an extraneous value that can be disregarded.

### TRUE AVERAGE [Cr] IS NOT AT THE HALFWAY POINT OF EITHER [Cr] OR TIME

Having corroborated the  $GFR_K$  ( $\sim 10.104$  mL/min), we can plug it back into equation (6) to calculate the true average [Cr], which is seen to be 2.894... mg/dL. As expected, this is different from the mean, which is  $(2.22 + 3.49)/2 = 2.855$  mg/dL. During the [Cr] trajectory, when is the true average attained? It occurs at  $\sim 10.393$  hours. Again, this is distinct from the temporal midpoint, which occurs at  $21.45 \text{ h}/2 = 10.725 \text{ h}$ . Finally, the true average is not located where the tangent to the trajectory, or  $d[Cr]_t/dt$ , is parallel to the average slope between the [Cr] end points, or  $([Cr]_T - [Cr]_0)/T$ , recalling the mean value theorem. There are likely no shortcuts to the true average [Cr].

### MAXIMUM INCREASE IN [Cr] PER DAY

Equation (5) should be homologous to the original algebraic  $GFR_K$  equation,<sup>2</sup> but one variable, the maximum increase in [Cr] per day as if anephric, is notably absent.

The prior algebraic equation written in the current terminology (without unit conversions) is:

$$GFR_K = \frac{Gen}{[Cr]_{\text{Mean}}} \left( 1 - \frac{[Cr]_T - [Cr]_0}{\Delta[Cr]_{\text{Max/day}} \cdot T} \right) \quad (8)$$

Is equation (8) just a primitive version of equation (5)? In the evolution of  $GFR_K$  equations, 2 new features were added: the true average [Cr] replaces mean [Cr], and the volume of distribution is allowed to change instead of remaining fixed. If both features are removed, does the present equation (5) revert back to equation (8)? Yes, and the detailed methods (Item S1) show how. The maximum [Cr] increase is disguised within equation (5) and is unmasked in the special case of a stable volume. Though the maximum increase has a physiologic equivalent in  $\frac{Gen}{V_0}$ , we either calculate that fraction or subjectively choose its value based on our clinical judgment.<sup>2</sup> Nowadays, we can avoid a subjective maximum increase in favor of the total

**Table 1.** Outputs of Newton’s Method for the Gold Standard Equation (7)

| Iteration No. | Gold Standard             |
|---------------|---------------------------|
| Guess         | 3                         |
| 1             | 1190.538743092500000      |
| 2             | 22.714899713418800        |
| 3             | 12.296436181716700        |
| 4             | 10.270468202660900        |
| 5             | 10.105582472040500        |
| 6             | 10.104317566510400        |
| <b>7</b>      | <b>10.104317491262400</b> |
| 8             | 10.104317491262400        |
| 9             | 10.104317491262400        |

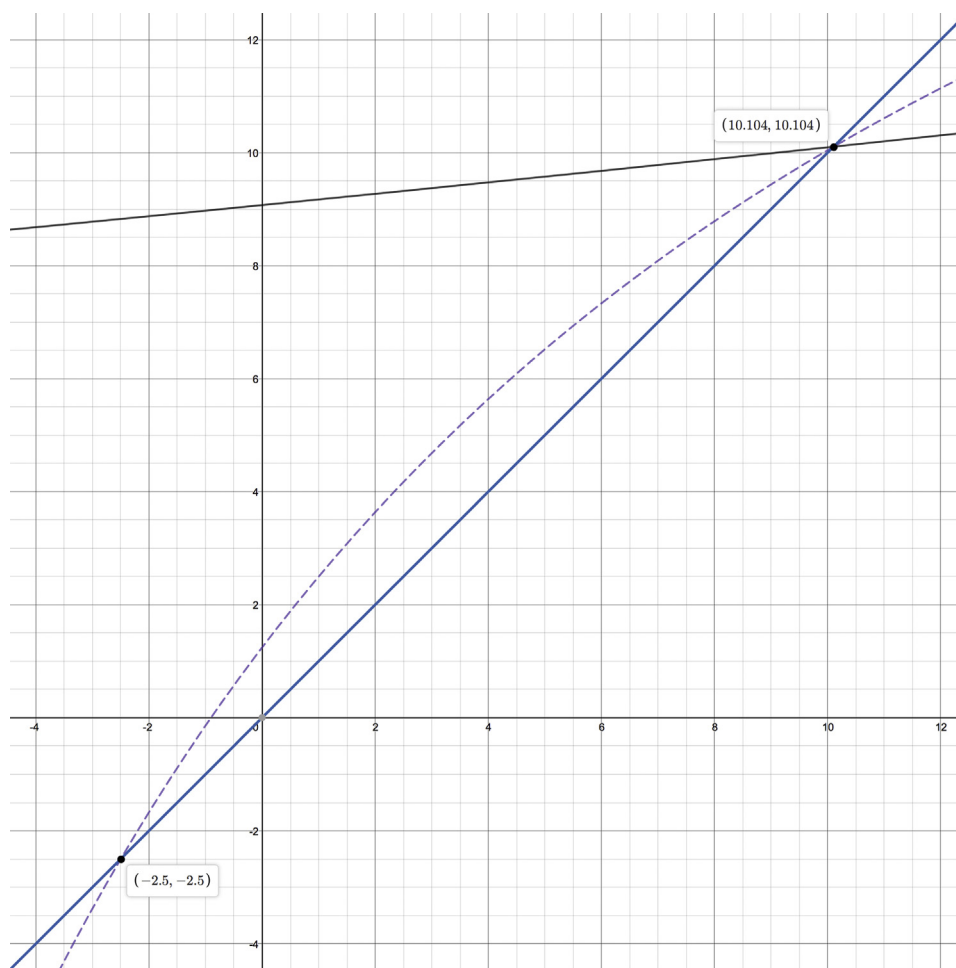
Note: The calculations stabilize by iteration 7.

body water ( $V_0$ ) and the change rate in volume ( $\frac{\Delta V}{\Delta t}$ ). The latter is important because the resultant  $V_0 + \frac{\Delta V}{\Delta t} T$  serves as the updated  $V_0$  for the next contiguous pair of  $[Cr]$ s.

**APPLICATION TO PATIENT CARE**

The assessment of kidney function is arguably the primary job of a nephrologist. We first learned how to quantify clearance in the steady state, and that is succinctly and elegantly symbolized by the basic clearance equation. Then we learned how to track the clearance in the nonsteady state, even if  $[Cr]$  is changing rapidly, and that is codified by the  $GFR_k$  equation.<sup>2-4</sup> Superficially, the 2 equations may appear to be distinct, but deep down they are intimately related. The current work proves that  $GFR_k$  can be unified with steady-state GFR under the overarching and truly fundamental law of  $CL_{cr} = \frac{U_{Cr} \times V}{P_{Cr}}$ .

The veracity and applicability of the fundamental clearance in the kinetic situation expands our toolbox to evaluate kidney function. To shoehorn creatinine kinetics into a  $U_{Cr} \times V / P_{Cr}$  framework, one could have reasoned that the  $[Cr]$  would hold constant over some period that is infinitesimally small, satisfying the limitation of having a



**Figure 3.** Graph of the true average creatinine concentration ( $[Cr]$ ) way to find the kinetic glomerular filtration rate ( $GFR_k$ ). Equation (5) also does not have an explicit solution for  $GFR_k$ , but it too can be graphed to find the answer as represented by an intersection point. The left-hand side of the equation is the same  $y = x$  diagonal blue line as in Figure 2. However, the right-hand side (see text for details), using  $GFR_k$  as the independent variable, appears as the black curvilinear segment. The blue line and black segment also intersect at 10.104, the same average value obtained by the gold standard equation (7)—superimposed here for reference (purple dashed curve). Equations (5)—true average—and (7)—gold standard—will always yield the same answer for  $GFR_k$ , as proved by the mathematics, but equation (5) is not affected by an extraneous solution.

**Table 2.** Outputs of Newton's Method for the True Average  $[Cr]$  Equation (5)

| Iteration No. | True Average              |
|---------------|---------------------------|
| Guess         | 3                         |
| 1             | 10.086614275666200        |
| 2             | 10.104317382767700        |
| <b>3</b>      | <b>10.104317491262400</b> |
| 4             | 10.104317491262400        |
| 5             | 10.104317491262400        |
| 6             | 10.104317491262400        |
| 7             | 10.104317491262400        |
| 8             | 10.104317491262400        |
| 9             | 10.104317491262400        |

Note: Calculations stabilize by iteration 3, giving the same answer as in Table 1.

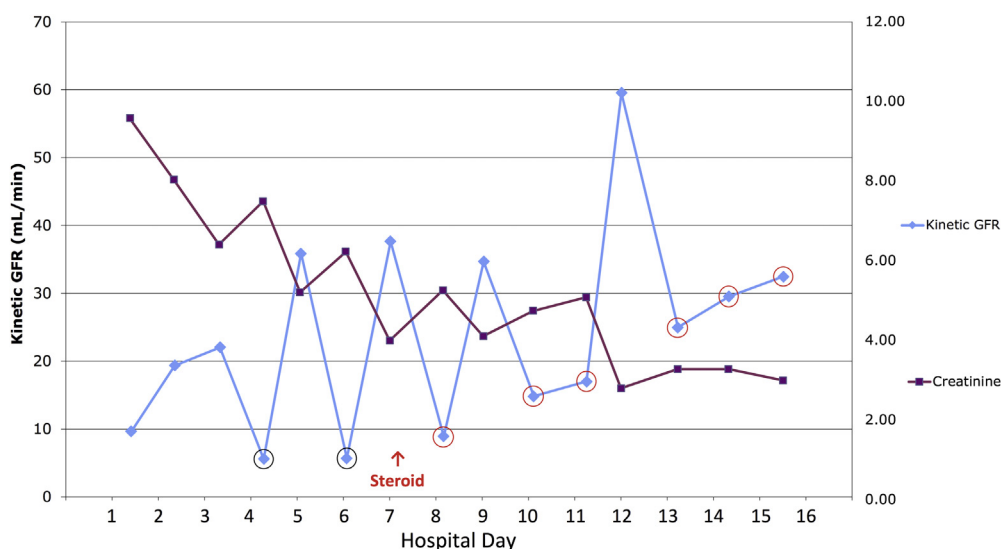
single  $P_{Cr}$  to work with. Unfortunately, trying to measure in that fleeting moment the  $U_{Cr} \times V$  and the  $P_{Cr}$  simultaneously is impractical and imprecise.<sup>7,8</sup> We demonstrated how  $U_{Cr} \times V / P_{Cr}$  can work on a macroscopic time scale that is convenient to the way we practice medicine. It frees one up to back calculate the  $U_{Cr} \times V$  through an algebraic argument, without needing to assay urine for the excretion rate. Further, this calculation is path-independent. It does not matter what tortuous route the  $[Cr]$  took between the end points; the end points contain the necessary information. Subsequently, the true average  $[Cr]$ , or  $\overline{P_{Cr}}$ , is

decoded by the calculus of equation (6), completing the clearance formula.

### AIDING CLINICAL DECISIONS: CLINICAL CASE

We used the  $GFR_K$  on the Nephrology consult service to guide patient management. A 74-year-old man with pancreatic adenocarcinoma was tolerating chemotherapy well. Two weeks before admission, his  $[Cr]$  was at its usual baseline of 1.10 mg/dL. He subsequently presented with oligoanuria and a  $[Cr]$  of 8.64 to 9.57 mg/dL. He was initiated emergently on hemodialysis. Several days later, kidney biopsy revealed acute interstitial nephritis, and 7 days after admission, high-dose corticosteroid treatment was initiated. In the setting of ongoing intermittent hemodialysis, the  $[Cr]$ s (Fig 4) became difficult to interpret.

The sawtooth  $[Cr]$  pattern, typical of dialysis, is shown in purple, while its translation into  $GFR_K$  is presented in blue (Fig 4). On dialysis days, the  $GFR_K$  spiked up, but on nondialysis days, the  $GFR_K$  decreased to  $\sim 6$  mL/min consistently, indicative of a “native” kidney function that was not yet recovering. The first opportunity to measure the  $GFR_K$  off dialysis was on hospital day 8, when it had increased to  $\sim 9$  mL/min. We were cautiously optimistic about the effect of the steroids. The next native  $GFR_K$  came on hospital day 10, and it improved to  $\sim 15$  mL/min. Dialysis was skipped, and by the morning of hospital day



**Figure 4.** Early recognition of kidney recovery. A man had developed drug-induced severe acute interstitial nephritis that was treated with inpatient hemodialysis and steroids. His daily creatinine concentrations ( $[Cr]$ s) are graphed in purple. Dialysis made the  $[Cr]$  fluctuate, but was the kidney function getting better on the steroid therapy? The  $[Cr]$  pattern was analyzed using the kinetic glomerular filtration rate ( $GFR_K$ ) that accommodates body volume changes, for better accuracy. Looking at the graph of  $GFR_K$ s in blue, we see that the  $GFR_K$  spiked up if dialysis occurred in the past 24 hours and that the  $GFR_K$  dropped back down if dialysis did not occur. The latter  $GFR_K$  “valleys” (circled) represent the patient’s own native kidney function. Focusing on the valleys, we observed no evidence of kidney recovery until hospital day 6 when only dialysis was being done. When prednisone therapy was started on hospital day 7, the next  $GFR_K$  valley on day 8 already showed a hint of kidney function increase. This incipient kidney recovery became more established on subsequent days, allowing us to discontinue dialysis with confidence. The  $GFR_K$  reached  $\sim 32.5$  mL/min by discharge on day 15. As an outpatient, he was gradually weaned off prednisone, and 10 days after discharge a follow-up  $[Cr]$  had improved to 1.70 mg/dL.



11, the  $GFR_K$  increased further to  $\sim 17$  mL/min. Although the prednisone seemed to be working, one last dialysis was done on hospital day 11, causing the  $GFR_K$  to spike up on hospital day 12. The last few  $GFR_K$ s were off dialysis but kept increasing, so it was clear that the patient's kidneys were recovering. The clearance increased to  $\sim 32.5$  mL/min by discharge on hospital day 15. Thus,  $GFR_K$  analysis detected kidney recovery soon after treatment for nephritis was begun. A kinetic GFR calculator is available as online supplementary material ([Supplementary File 2](#)).

## VERSATILITY

The true average concept could also prove to be versatile. A [Cr] trajectory may defy mathematical modeling, but if we suspect that the evolution of [Cr] is still governed by the principle of mass balance, just in a complicated way, the inability to construct an accurate differential equation may not matter so much. We can infer the true average [Cr] by other means. One way might be to assay the plasma [Cr] frequently, or continuously if the technology allows, so as to finely trace the [Cr] trajectory. Then numerical techniques can be used to deduce where the horizontal line must be drawn such that the signed areas above/below the [Cr] curve sum to zero, as in [Figure 1](#). The proof by the fundamental theorem of calculus ensures that an average [Cr] obtained in this way would be valid. One uncertainty with this approach is whether the creatinine generation rate is constant. However, if we can describe how the  $Gen$  changes as a function of time, that is, a  $Gen_t$ , then the added creatinine is quantified by  $\int_0^T Gen_t dt$  and is used to solve for  $U_{Cr} \times V$ .

If the [Cr] is measured frequently, that would permit the  $GFR_K$  to be tracked more closely. For now, the mass balance differential equation treats  $GFR_K$  as having a single constant value on the interval between 2 [Cr]s. Therefore,  $GFR_K$  is the average clearance for that time. Because the [Cr] laboratory tests are typically drawn daily, the real-time change in  $GFR_K$  cannot be discerned. To approximate real time, the shortest time for the most severe AKI to exceed a [Cr] error threshold of 3% is about 10 to 20 minutes. Checking the [Cr] that frequently is likely impractical, notwithstanding the [Cr] assay lag time.

## LIMITATIONS

GFR is not synonymous with  $CL_{Cr}$ . The former refers to clearance done by the glomeruli, whereas the latter refers to clearance done by all routes. Although glomerular clearance is usually predominant, the additional nonglomerular routes include diffusion into the gut, degradation by bacterial creatinases, and, most importantly, renal tubular secretion of creatinine.<sup>9-12</sup> Technically, equation (5) calculates the kinetic  $CL_{Cr}$ , and this overestimates the  $GFR_K$ . One way to bring the kinetic  $CL_{Cr}$  closer to the true GFR is to administer cimetidine to inhibit tubular secretion of creatinine,<sup>13</sup> but this is not routinely done outside of clinical research. Another strategy is to change the assay from creatinine to inulin, which is freely filtered by glomeruli but not secreted or reabsorbed by

tubules. However, inulin is expensive to infuse, even as a bolus, and difficult to measure.<sup>14</sup> Behaving like inulin, an endogenous substance cystatin C might replace creatinine one day, but there is some extrarenal elimination and it is catabolized in the tubules with reabsorption of its metabolites.<sup>15</sup> Nevertheless, the  $GFR_K$  equation can be adapted to work with cystatin C.<sup>16</sup> Finally, the shortcomings that relate to the assumptions of the kinetic math model, such as a fixed creatinine generation rate or a linear rate of volume change, have been extensively detailed elsewhere.<sup>3,4</sup>

## MEAN [Cr] REDUX

In the algebraic  $GFR_K$ , the mean of the [Cr] end points was an approximation of the true average [Cr], which was not known in 2013, but the mean [Cr] seemed to work well enough. The original algebraic equation has been tested extensively in clinical research and has performed admirably.<sup>16-28</sup> In 2018, the  $GFR_K$  equation was upgraded with calculus to accommodate a volume that changes steadily.<sup>3</sup> To remodel the algebraic into a calculus version, we had to figure out the exact substitute for the mean. Is this true average worth using to gain extra precision in the  $GFR_K$ ? The mean is close enough to the true average when the time is kept to about 24 hours between [Cr]s, as is routinely done in the hospital. Plus, the mean is easier to use on rounds. The mean [Cr] would give a  $GFR_K$  of 10.243 mL/min for the first clinical case, which compares favorably with the 10.104 mL/min. However, the mean [Cr] should not be used in place of the true average when the [Cr] trajectory is significantly curved, such as in [Figure 1](#). The nonlinearity can become more pronounced over a longer period. Insisting on the true average [Cr] requires higher mathematics, and the added effort could decrease the method's adoption rate. Fortunately, the tedium of computation can be handled by computers. Clinical laboratories could even program in Newton's method to report the  $GFR_K$ s, as is already done with estimated GFRs like the MDRD (Modification of Diet in Renal Disease) Study equation or the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.<sup>29,30</sup>

## GENERALIZABLE?

The fundamental law of clearance really does apply beyond the steady state. We now have a general strategy to handle the more complex [Cr] trajectories that occur in real life. For example, AKI due to sepsis may entail a reduction in creatinine generation rate that will suppress an increase in [Cr] and mask the severity of AKI.<sup>31</sup> However, if the change in  $Gen$  is accounted for in the  $U_{Cr} \times V$  and in the true average [Cr], the resulting  $GFR_K$  will reflect the real extent of kidney function loss. Still, it remains to be seen whether the true average paradigm can be applied more universally to the continuous but non-smooth [Cr] functions that violate differential equation (1). In the meantime, the true average [Cr] concept may open up more avenues to explore in the field of  $GFR_K$ .

## SUPPLEMENTARY MATERIAL

## Supplementary File 1 (PDF)

Item S1: Detailed methods.

## Supplementary File 2 (XLSX)

Kinetic GFR Calculator

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## REFERENCES

- Rose BD, Post TW. *Clinical Physiology of Acid-Base and Electrolyte Disorders*. New York, NY: McGraw-Hill; 2001.
- Chen S. Retooling the creatinine clearance equation to estimate kinetic GFR when the plasma creatinine is changing acutely. *J Am Soc Nephrol*. 2013;24(6):877-888.
- Chen S. Kinetic glomerular filtration rate equation can accommodate a changing body volume: derivation and usage of the formula. *Math Biosci*. 2018;306:97-106.
- Chen S. Kinetic glomerular filtration rate in routine clinical practice-applications and possibilities. *Adv Chronic Kidney Dis*. 2018;25(1):105-114.
- Dominguez R, Pomerene E. Calculation of the rate of absorption of exogenous creatinine. *Proc Soc Exp Biol Med*. 1945;60:173-181.
- Bjornsson TD. Use of serum creatinine concentrations to determine renal function. *Clin Pharmacokinet*. 1979;4(3):200-222.
- Doolan PD, Alpen EL, Theil GB. A clinical appraisal of the plasma concentration and endogenous clearance of creatinine. *Am J Med*. 1962;32:65-79.
- Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. *Clin Chem*. 1992;38(10):1933-1953.
- Jones JD, Burnett PC. Creatinine metabolism in humans with decreased renal function: creatinine deficit. *Clin Chem*. 1974;20(9):1204-1212.
- Mitch WE, Collier VU, Walser M. Creatinine metabolism in chronic renal failure. *Clin Sci (Lond)*. 1980;58(4):327-335.
- Seifter JL. Urinary creatinine-splitting bacteria after ileal-loop diversion causing underestimate of glomerular filtration rate. *Am J Med*. 2014;127(12):e11-e12.
- Jones JD, Burnett PC. Implication of creatinine and gut flora in the uremic syndrome: induction of "creatininase" in colon contents of the rat by dietary creatinine. *Clin Chem*. 1972;18(3):280-284.
- Zaltzman JS, Whiteside C, Cattran DC, Lopez FM, Logan AG. Accurate measurement of impaired glomerular filtration using single-dose oral cimetidine. *Am J Kidney Dis*. 1996;27(4):504-511.
- Traynor J, Mactier R, Geddes CC, Fox JG. How to measure renal function in clinical practice. *BMJ*. 2006;333(7571):733-737.
- Inker LA, Levey AS, Coresh J. Estimated glomerular filtration rate from a panel of filtration markers-hope for increased accuracy beyond measured glomerular filtration rate? *Adv Chronic Kidney Dis*. 2018;25(1):67-75.
- Pianta TJ, Endre ZH, Pickering JW, Buckley NA, Peake PW. Kinetic estimation of GFR improves prediction of dialysis and recovery after kidney transplantation. *PLoS One*. 2015;10(5):e0125669.
- Dewitte A, Joannes-Boyau O, Sidobre C, et al. Kinetic eGFR and novel AKI biomarkers to predict renal recovery. *Clin J Am Soc Nephrol*. 2015;10(11):1900-1910.
- 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(4):312-316.
- Koratala A, Singhanian G, Alquadan KF, Shimada M, Johnson RJ, Ejaz AA. Serum uric acid exhibits inverse relationship with estimated glomerular filtration rate. *Nephron*. 2016;134(4):231-237.
- Seelhammer TG, Maile MD, Heung M, Haft JW, Jewell ES, Engoren M. Kinetic estimated glomerular filtration rate and acute kidney injury in cardiac surgery patients. *J Crit Care*. 2016;31(1):249-254.
- O'Sullivan ED, Doyle A. The clinical utility of kinetic glomerular filtration rate. *Clin Kidney J*. 2017;10(2):202-208.
- de Oliveira Marques F, Oliveira SA, de Lima ESPF, et al. Kinetic estimated glomerular filtration rate in critically ill patients: beyond the acute kidney injury severity classification system. *Crit Care*. 2017;21(1):280.
- Weinberg L, Harris L, Bellomo R, et al. Effects of intraoperative and early postoperative normal saline or Plasma-Lyte 148(R) on hyperkalaemia in deceased donor renal transplantation: a double-blind randomized trial. *Br J Anaesth*. 2017;119(4):606-615.
- Hekmat R, Eshraghi H, Esmailpour M, Hassankhani GG. Kinetic glomerular filtration rate estimation compared with other formulas for evaluating acute kidney injury stage early after kidney donation. *Exp Clin Transplant*. 2017;15(suppl 1):104-109.
- Bairy M, See FHW, Lim RS. Using the kinetic estimating glomerular filtration rate equation for estimating glomerular filtration rate and detecting acute kidney injury: a pilot study. *Nephron*. 2018;140(4):231-239.
- Khayat MI, Deeth JM, Sosnov JA. A bedside clinical tool using creatinine kinetics to predict worsening renal injury and early recovery. *Clin Kidney J*. 2019;12(2):248-252.
- Yoshida T, Matsuura R, Komaru Y, et al. Kinetic estimated glomerular filtration rate as a predictor of successful continuous renal replacement therapy discontinuation. *Nephrology (Carlton)*. 2019;24(3):287-293.
- Basu RK. Targeting acute kidney injury: can an innovative approach to existing and novel biomarkers shift the paradigm? *Nephron*. 2019; <https://doi.org/10.1159/000500421>.
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. 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(6):461-470.
- Ix JH, Wassel CL, Stevens LA, et al. Equations to estimate creatinine excretion rate: the CKD Epidemiology Collaboration. *Clin J Am Soc Nephrol*. 2011;6(1):184-191.
- Doi K, Yuen PS, Eisner C, et al. Reduced production of creatinine limits its use as marker of kidney injury in sepsis. *J Am Soc Nephrol*. 2009;20(6):1217-1221.