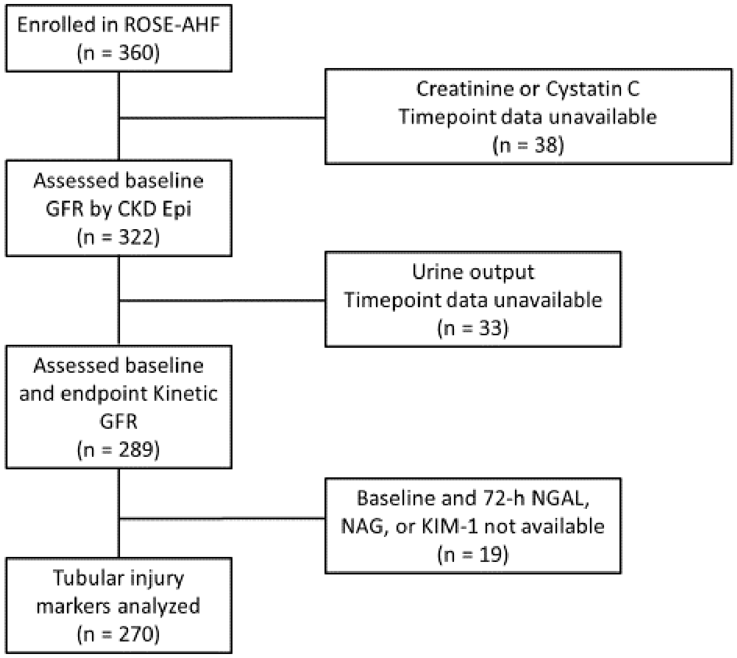
Supplemental Material Table of Contents

Supplementary Figure 1: Consort Diagram



Consort diagram of patient selection into the study cohort. GFR indicates glomerular filtration rate; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration; KIM-1, kidney injury molecule 1; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; and ROSE-AHF, Renal Optimization Strategies Evaluation.

Supplementary Table 1.

Sensitivity Analysis Total Body Water		
	$Cr_{Instant\ VD}$	$Cr_{72HR\ VD}$
	50% TBW	
Median Change	0.16 (0.10, 0.27)	0.04 (0.02, 0.07)
WRF	52	0
no WRF	218	270
	60% TBW	
Median Change	0.13 (0.08, 0.22)	0.04 (0.02,0.06)
WRF	35	0
no WRF	235	270
	70% TBW	
Median Change	0.11 (0.07, 0.18)	0.04 (0.02, 0.06)
WRF	16	0
no WRF	254	270
	80% TBW	
Median Change	0.10 (0.06, 0.16)	0.03 (0.02, 0.06)
WRF	7	0
no WRF	263	270

Sensitivity analysis with varying estimations of total body water based on body weight. WRF includes 72-hour changes in calculated creatinine ≥ 0.3 mg/dL. No WRF includes 72-hour changes in calculated creatinine < 0.3 mg/dL. TBW = total body water; WRF = worsening renal function

Appendix 1

Abbreviations
Cr = Creatinine
VD = Volume of distribution
CreGen = Creatinine generation
GFR = Glomerular filtration rate calculated with CKD-EPI
kGFR = Kinetic GFR

Calculating estimated volume of distribution & CreGen

$$V_{Baseline} = Weight\ Baseline \times 0.5$$

Calculating changes in estimated total body water, volume of distribution, based on measured intake and urine output

$$\Delta V_t = IV\ In_t + Oral\ In_t - UrineOutput_t$$

$$CreGen = Cr_{Baseline} \times GFR_{Baseline}$$

Derivation of the equations
To compare the cases below, we calculate the [Cr] that would result from each manipulation.

Instant hemoconcentration ($Cr_{Instant\ VD}$): If only the volume changes, then the creatinine mass stays the same. Therefore, the amount of creatinine before equals the amount of creatinine after, or

$$[Cr]_0 \cdot V_0 = [eCr_{Instant\ VD}]_t \cdot V_t$$

$$[eCr_{Instant\ VD}]_t = [Cr]_0 \cdot \frac{V_0}{V_t} \qquad (1)$$

Realistic hemoconcentration, stable GFR (Cr_{VD}): Volume change does not occur instantly, as above, but rather is spread over the time interval between [Cr] measurements. During that time, the kidneys continue to clear creatinine, which attenuates the rise in [Cr] due to hemoconcentration. To simplify the modeling, we assume that the volume changes at a constant rate, obtainable by dividing the net of the input/output volumes by the time interval (24 h), giving $\frac{\Delta V}{\Delta t}$. Then, for a constant $\frac{\Delta V}{\Delta t}$ rate and a renal clearance (GFR) that stays at baseline, the new [Cr] would be:

$$[eCr_{VD}]_t = [Cr]_0 + \underbrace{\left[1 - \left(\frac{V_0}{V_0 + \frac{\Delta V}{\Delta t} \cdot t}\right)^{\left(1 + \frac{GFR}{\frac{\Delta V}{\Delta t}}\right)}\right]}_{\text{Adjuster}} \cdot \underbrace{\left(\frac{CreGen}{GFR + \frac{\Delta V}{\Delta t}} - [Cr]_0\right)}_{\text{Gradient}} \tag{2}$$

In other words, the [Cr] in the future equals the [Cr] at the start plus an adjustment fraction times the gradient between the eventual [Cr] if allowed to reach steady state and the starting [Cr].

For a baseline (i.e., preserved) GFR, the realistic hemoconcentration will not increase the [Cr] as much as the instant hemoconcentration, which admittedly is a worst-case scenario.

Equation (2) can replicate the *instant* hemoconcentration, by letting the time interval go to zero. Turning t into Δt and letting Δt approach zero, we can solve the limit as follows:

$$\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 + \left[1 - \left(\frac{V_0}{V_0 + \frac{\Delta V}{\Delta t} \cdot \Delta t}\right)^{\left(1 + \frac{kGFR}{\frac{\Delta V}{\Delta t}}\right)}\right] \cdot \left(\frac{CreGen}{GFR + \frac{\Delta V}{\Delta t}} - [Cr]_0\right) \right\}$$

$$\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 + \left[1 - \left(\frac{V_0}{V_0 + \frac{\Delta V}{\cancel{\Delta t}} \cdot \cancel{\Delta t}}\right)^{\left(1 + \frac{kGFR}{\cancelto{\pm\infty}{\frac{\Delta V}{\Delta t}}}\right)}\right] \cdot \left(\frac{CreGen}{GFR + \cancelto{\pm\infty}{\frac{\Delta V}{\Delta t}}} - [Cr]_0\right) \right\}$$

$$\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 + \left[1 - \left(\frac{V_0}{V_0 + \Delta V}\right)^{(1+0)}\right] \cdot (0 - [Cr]_0) \right\}$$

$$\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 + \left[1 - \left(\frac{V_0}{V_t}\right)\right] \cdot (-[Cr]_0) \right\}$$

$$\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 + \left[-[Cr]_0 + [Cr]_0 \cdot \left(\frac{V_0}{V_t}\right)\right] \right\}$$

$$\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 - [Cr]_0 + [Cr]_0 \cdot \frac{V_0}{V_t} \right\}$$

$$\lim_{\Delta t \to 0} \left\{ [Cr]_t = [Cr]_0 \cdot \frac{V_0}{V_t} \right\} \tag{3}$$

Thus, if the volume could change instantaneously, then Equation (3) replicates Equation (1).

Realistic hemoconcentration, kinetic GFR (CrKinetic): If realistic hemoconcentration accounts for only part of the [Cr] rise, then the rest must be explained by a change in clearance. But, $kGFR$ cannot be isolated and solved for in Equation (2). Rather, using a root-finding technique, like Newton's method is required to calculate an accurate value for kGFR.

$$kGFR_{n+1} = kGFR_n + \frac{[Cr]_0 + \left[1 - \left(\frac{V_0}{V_0 + \frac{\Delta V}{\Delta t}t}\right)^{\left(1+\frac{kGFR_n}{\frac{\Delta V}{\Delta t}}\right)}\right] \cdot \left(\frac{CreGen}{kGFR_n + \frac{\Delta V}{\Delta t}} - [Cr]_0\right) - [Cr]_t}{\left(\frac{V_0}{V_0 + \frac{\Delta V}{\Delta t}t}\right)^{\left(1+\frac{kGFR_n}{\frac{\Delta V}{\Delta t}}\right)} \cdot \frac{1}{\frac{\Delta V}{\Delta t}} \cdot \ln\left(\frac{V_0}{V_0 + \frac{\Delta V}{\Delta t}t}\right) \cdot \left(\frac{CreGen}{kGFR_n + \frac{\Delta V}{\Delta t}} - [Cr]_0\right) + \left[1 - \left(\frac{V_0}{V_0 + \frac{\Delta V}{\Delta t}t}\right)^{\left(1+\frac{kGFR_n}{\frac{\Delta V}{\Delta t}}\right)}\right] \cdot \frac{CreGen}{\left(kGFR_n + \frac{\Delta V}{\Delta t}\right)^2}} \quad (4)$$

If this Newton's $kGFR$ were allowed to drive the [Cr] trajectory all the way to a new steady state, and ignoring hemoconcentration effects, the [Cr] would eventually be

$$[eCr]_{Steady\ State} = \frac{CreGen}{kGFR_{Newton}} \quad (5)$$

For a slightly different answer, the 4-factor MDRD equation (2006) can be rearranged to yield a steady state [Cr] for the calculated $kGFR$.

$$[eCr]_{Steady\ State} = \left(\frac{kGFR_{Newton} \cdot Age^{0.203}}{175 \cdot race, gender\ factor(s)}\right)^{\frac{-1}{1.154}} \quad (6)$$

Example application

Two hypothetical subjects are provided with identical weight, baseline creatinine, and simplified changes in creatinine and urine output to illustrate the application of the various equations. Subject 1 has minimal net output over a 72-hour period of only 300 mL, but with an observed increase in creatinine from 1.0 to 1.3 mg/dL. Subject 2 has significantly more net output of 3L, however without changes in observed creatinine.

	Subject 1	Subject 2
Age	50	50
Sex	Male	Male
Race	White	White
Baseline Weight (kg)	75	75
ΔV_{72Hr} (mL)	-300	-3000
$V_{Baseline}$ (L)	37.5	37.5
V_{72Hr} (L)	37.2	34.5
Baseline Creatinine (mg/dL)	1.0	1.0
GFR by CKD-EPI	87.37	87.37
Cr_{obs} 24 hours (mg/dl)	1.1	1.0
Cr_{obs} 48 hours (mg/dl)	1.2	1.0
Cr_{obs} 72 hours (mg/dl)	1.3	1.0
$eCr_{Instant\ VD}$	1.01	1.09
$eCr_{72HR\ VD}$	1	1.01
$eCr_{72HR\ Kinetic}$	1.22	0.96

Subject 1

$$V_0 = 75\ x\ 0.5 = 37.5$$

$$V_{72HR} = 37.5 - 0.3 = 37.2$$

eCrInstant VD

$$1.01 = 1.0 \cdot \frac{37.5}{37.2}$$

eCr_{72HR}VD

$$1.0 = [1.0]_0 + \underbrace{\left[1 - \left(\frac{37.5}{37.5 + \frac{-0.3}{72} \cdot 72}\right)^{\left(1+\frac{87.37}{\frac{-0.3}{72}}\right)}\right]}_{\text{Adjuster}} \cdot \underbrace{\left(\frac{87.37}{87.37 + \frac{-0.3}{72}} - 1.0\right)}_{\text{Gradient}}$$

$eCr_{72HR\ Kinetic}$

$$kGFR_{n+1} = kGFR_n + \frac{1.0 + \left[1 - \left(\frac{37.5}{37.5 + \frac{-0.3}{72}72}\right)^{\left(1 + \frac{kGFR_n}{\frac{0.3}{72}}\right)}\right] \cdot \left(\frac{87.37}{kGFR_n + \frac{0.3}{72}} - 1.0\right) - 1.3}{\left(\frac{37.5}{37.5 + \frac{-0.3}{72}72}\right)^{\left(1 + \frac{kGFR_n}{\frac{-0.3}{72}}\right)} \cdot \frac{1}{\frac{-0.3}{72}} \cdot \ln\left(\frac{37.5}{37.5 + \frac{-0.3}{72}72}\right) \cdot \left(\frac{87.37}{kGFR_n + \frac{-0.3}{72}} - 1.0\right) + \left[1 - \left(\frac{37.5}{37.5 + \frac{-0.3}{72}72}\right)^{\left(1 + \frac{kGFR_n}{\frac{-0.3}{72}}\right)}\right] \cdot \frac{87.37}{\left(kGFR_n + \frac{-0.3}{72}\right)^2}}$$

$$kGFR = 66.86$$

$$1.22 = \left(\frac{66.86 \cdot 50^{0.203}}{175 \cdot race, gender\ factor(s)}\right)^{\frac{-1}{1.154}}$$

Subject 2

$$V_0 = 75\ x\ 0.5 = 37.5$$

$$V_{72HR} = 37.5 - 3.0 = 34.5$$

eCrInstant VD

$$1.09 = 1.0 \cdot \frac{37.5}{34.5}$$

eCr_{72HR}VD

$$1.01 = 1.0 + \underbrace{\left[1 - \left(\frac{37.5}{37.5 + \frac{-3}{72} \cdot 72}\right)^{\left(1 + \frac{87.37}{\frac{-3}{72}}\right)}\right]}_{\text{Adjuster}} \cdot \underbrace{\left(\frac{87.37}{87.37 + \frac{-3}{72}} - 1.0\right)}_{\text{Gradient}}$$

$eCre_{72HR\ Kinetic}$

$$kGFR_{n+1} = kGFR_n + \frac{1.0 + \left[1 - \left(\frac{37.5}{37.5 + \frac{-3}{72}72}\right)^{\left(1 + \frac{kGFR_n}{\frac{-3}{72}}\right)}\right] \cdot \left(\frac{87.37}{kGFR_n + \frac{-3}{72}} - 1.0\right) - 1.0}{\left(\frac{37.5}{37.5 + \frac{-3}{72}72}\right)^{\left(1 + \frac{kGFR_n}{\frac{-3}{72}}\right)} \cdot \frac{1}{\frac{-3}{72}} \cdot \ln\left(\frac{37.5}{37.5 + \frac{-3}{72}72}\right) \cdot \left(\frac{87.37}{kGFR_n + \frac{-3}{72}} - 1.0\right) + \left[1 - \left(\frac{37.5}{37.5 + \frac{-3}{72}72}\right)^{\left(1 + \frac{kGFR_n}{\frac{-3}{72}}\right)}\right] \cdot \frac{87.37}{\left(kGFR_n + \frac{-3}{72}\right)^2}}$$

$$kGFR = 88.06$$

$$0.96 = \left(\frac{88.06 \cdot 50^{0.203}}{175 \cdot race, gender\ factor(s)} \right)^{\frac{-1}{1.154}}$$