Many of us were introduced to the following dilution equation in high school chemistry:
\[ M_1 V_1 = M_2 V_2 \]
where \( M \) = molarity (concentration) and \( V \) = volume. Reconfigured, it calculates a new concentration \( (M_2) \) in response to increases or decreases in volume. From the bounds of a chemistry textbook, a version of this principle is applied to clinical discussions and research of patients with AKI (1,2). Changes in GFR are often paralleled by changes in volume status. In this context, serum creatinine may reflect filtration and/or changes in total body volume (TBV) (concentration/dilution). Studies in critically ill adults found that correcting serum creatinine to account for potential dilution secondary to volume overload improved recognition of AKI and association with adverse outcomes (1–3). Similarly, studies of pediatric AKI have repeatedly found that volume-adjusting serum creatinine before applying creatinine-based AKI definitions resulted in a stronger association between AKI and mortality (4–6). However, the human body is not a simple static and closed system, suggesting the need for a methodologic examination of the relationship between creatinine concentration and volume-related effects.

In this issue of Kidney360, Maulion et al. elegantly took on the problem of creatinine dilution by performing secondary analysis of the ROSE-AHF trial (7). Participants in ROSE-AHF included 360 individuals with acute decompensated heart failure (ADHF) and at least one symptom and clinical sign of volume overload on history and physical (8). ROSE-AHF randomized participants to treatment with dopamine, nesiritide, or placebo. For 72 hours after admission, fluid balance, urine output, and body weight were closely monitored. Serum creatinine was measured every 24 hours. The primary end points were total diuresis and changes in cystatin C. No significant difference was noted in these end points between treatment arms.

The use of the ROSE-AHF study population is one of the key strengths of the analysis by Maulion et al. Loop-diuretic dosing was protocolized at 2.5× of home dosing, reducing the heterogeneity in dosing often encountered in clinical practice. Second, research has shown that assessments of body weight, fluid intake, and fluid output recorded as part of routine inpatient care are prone to error and poorly reflect true measurements (9). Intensive monitoring of input and output in ROSE-AHF participants greatly increased the validity of their data. Studying this problem in the context of ADHF was relevant because individuals hospitalized with ADHF have rapid changes in volume status and kidney function. Both have been associated with adverse outcomes (10).

Using serum creatinine and fluid balance data from the 72-hour study period, Maulion et al. calculated the expected change in serum creatinine in response to changes in TBV using three models. The models primarily differ in their assumption of serum creatinine as a reflection of generation and kidney clearance. The first model \( \text{eCR}_{\text{instant VD}} \) estimated how serum creatinine would change if the difference in TBV observed over 72 hours happened instantaneously. In this setting, the body is a container, and the creatinine mass is fixed. Not surprisingly, calculated changes in serum creatinine poorly estimated observed values. The second model \( \text{eCR}_{72\text{HR VD}} \) estimated GFR and creatinine generation using the baseline serum creatinine value. Next, they assumed that volume shift observed over 72 hours occurred at a linear rate. Finally, they incorporated these steady rates of creatinine generation, filtration, and observed 72-hour fluid balance to estimate changes in serum creatinine. The third model is most complex and uses creatinine at baseline and 72 hours to integrate kinetic eGFR into estimates of volume-dependent changes in creatinine. The 72-hour estimated creatinine is calculated assuming creatinine enters a steady state at that time and using the kinetic eGFR along with the MDRD formula to calculate estimated serum creatinine. Model 3 \( \text{eCR}_{72\text{HR Kinetic}} \) best approximates observed changes in creatinine—something expected because it incorporates the 72-hour creatinine in the equation. Yet, volume effects only accounted for a median of 3% of estimated changes in serum creatinine. The eCR\textsubscript{72HR Kinetic} model emphasizes that volume-related effects on serum creatinine concentrations are minimal.

The key takeaway from this study is that the volume effects on creatinine in clinical practice cannot be simplified to a basic dilution equation. In patients with ADHF, volume effects may in fact be nonconsequential.

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on changes in serum creatinine concentration. Notably, the authors estimate that a median TBV reduction of 7.5 L is required to generate a 0.3 mg/dl increase in serum creatinine if considering volume effects alone. Observed changes in creatinine were best approximated when changes in volume status were balanced by changes in eGFR, supporting the authors main conclusion that changes in creatinine most directly result from changes in filtration. However, discordance between observed and estimated creatinine in even the most complicated models again stresses the limitations of commonly used formulas to approximate the complex physiology of our patients.

This study generates important new perspectives to existing research and contributes to the argument against volume correction (11). The concept of volume-corrected serum creatinine was developed in a population primarily affected by volume overload. Maulion et al. suggest, at the very least, caution when applying volume correction in the opposite direction. The issue of how volume correction of serum creatinine might modify the strength of association with adverse outcomes was not included in this analysis. However, it raises the possibility that the benefit seen in previous AKI research might not be due to improved estimation of true GFR. Rather, volume correction of creatinine may just be an indirect way to include severity of volume overload into predictive models.

There are several important limitations to this study. Central are the fundamental assumptions required to generate the models. Creatinine generation and filtration were estimated using formulae not derived in heart failure population and are likely to be biased, given the reduced muscle mass in this population. Relatedly, a weakness of this and many previous studies of volume-corrected creatinine is the failure to incorporate urine creatinine (12). Urine creatinine would allow for more precise estimations of creatinine generation and filtration. It would also provide insight to how urinary filtration and volume relate, given that urine volume itself can be an unreliable indicator of creatinine clearance. Lastly, the authors might have considered comparing changes in serum creatinine to other markers of volume contraction such as hemoconcentration (13). Although the volume of distribution of creatinine is high, it would have been interesting to see the relationship with volume contraction reflected in the circulatory compartment.

In conclusion, Maulion et al. suggest caution when considering the relative contribution of volume effects to changes in serum creatinine in patients hospitalized with ADHF. This is especially important in the ADHF populations for whom volume contraction is common and identifying true changes in GFR can be important. Prospective clinical research projects dedicated to the questions of volume effects are needed. It will be important to include urine creatinine measurements and directly measured GFR in future research. Ultimately, we need to develop better diagnostic tools to measure real-time changes in kidney function in hospitalized patients with ADHF. Until then, correcting serum creatinine with back-of-the-envelope calculations should be avoided.

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Author Contributions
A.J. Kula wrote the original draft of the manuscript, and both authors reviewed and edited the manuscript.

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