Fluid Correction of Serum Creatinine Increases Diagnosis of Acute Kidney Injury and Changes Creatinine Trajectory

A Secondary Analysis of the PENUT Randomized Trial

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Question: Does correcting serum creatinine for fluid balance identify clinically important, previously missed episodes of AKI and strengthen association with outcomes?

Finding: In this secondary analysis of a randomized placebo-controlled trial in premature neonates, fluid correction increased the number of premature neonates diagnosed with acute kidney injury. Correction for fluid balance strengthened the association with clinical outcomes, including ventilation and severe lung disease.

Meaning: In premature neonates, failing to correct serum creatinine for fluid balance underestimates the prevalence and impact of acute kidney injury in premature neonates. Future studies should consider adjusting acute kidney injury for fluid status to improve identification of neonates at high risk for poor outcomes.

Methods and Materials

Design: Secondary analysis of Preterm Erythropoietin Neuroprotection Trial (PENUT), a Phase III randomized trial of erythropoietin in premature neonates (< 28 weeks).

Setting: 30 NICUs in the United States from 12/2013–9/2016

Participants: 923 extremely premature neonates born 24–27 weeks' gestation enrolled in the PENUT study

Exposure: Fluid corrected AKI (FC-AKI) during the first 14 postnatal days, calculated using Fluid Corrected-Serum Creatinine (FC-SCr, defined as SCr multiplied by FB divided by total body water [estimated 80% of birthweight]). FB calculated as percent change from birthweight.

Main Outcome and Measure: Invasive mechanical ventilation on postnatal day 14. Secondary outcomes included: death, hospital length of stay, and severe bronchopulmonary dysplasia

Results

A total of 8,757 serum creatinine values were obtained during first two postnatal weeks for the entire population, with a median of 11 per patient (IQR 7-13).

Uncorrected and fluid corrected serum creatinine (FC-SCr) is shown for the entire cohort (**Figure 1**). Correcting for fluid balance significantly altered the serum creatinine curve (p<0.0001).

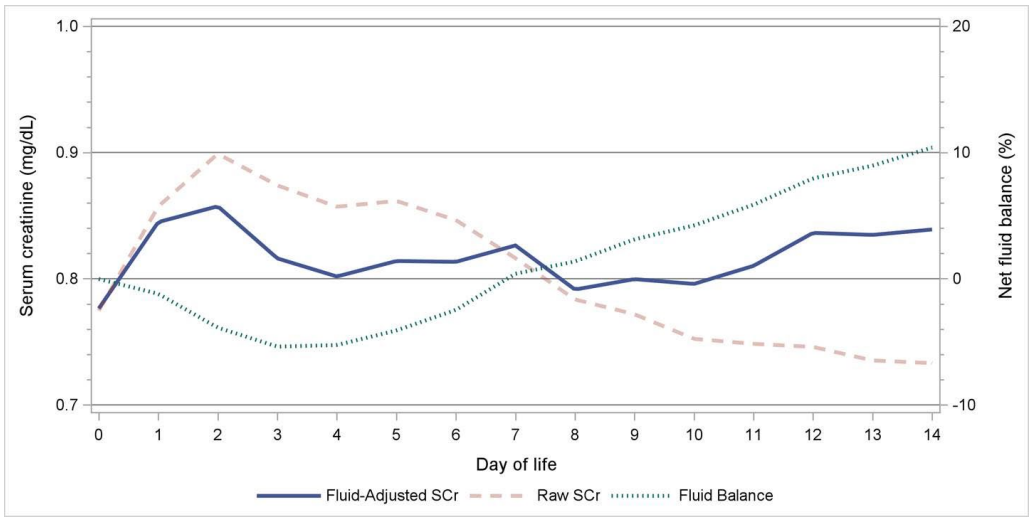

Figure 1. Serum creatinine curves prior to and after correction for fluid balance over the first 14 days of life

Correcting creatinine for fluid balance created a new serum creatinine curve for neonates over the first 2 weeks of life with a slow improvement in kidney function over time.

This challenges the often cited "peak and then fall" serum creatinine trajectory over the first several days postnatally.

Fluid Corrected AKI Incidence

923 premature neonates were included. 215 neonates (23.3%) were diagnosed with AKI using uncorrected creatinine. After correction for FB, 13 neonates with AKI were reclassified as not having FC-AKI ("Over-Recognized AKI") and 111 previously without AKI reclassified as having FC-AKI ("Under-Recognized" AKI). Therefore, FC-AKI was diagnosed in 313 neonates (33.9%)

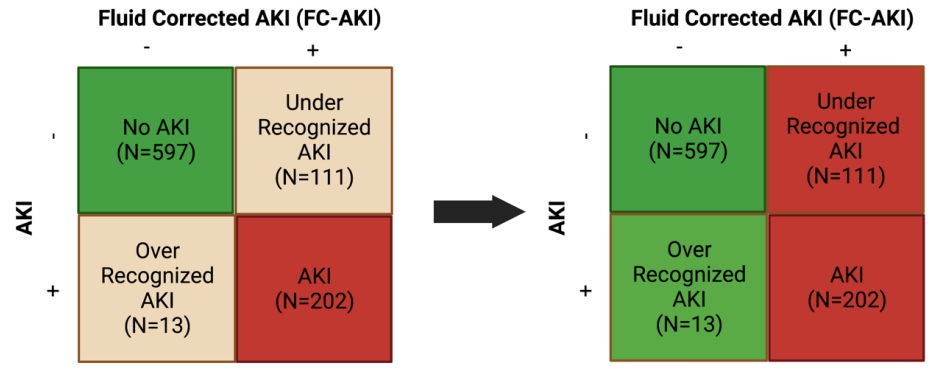

Figure 2. AKI distribution prior to and after correction for fluid balance

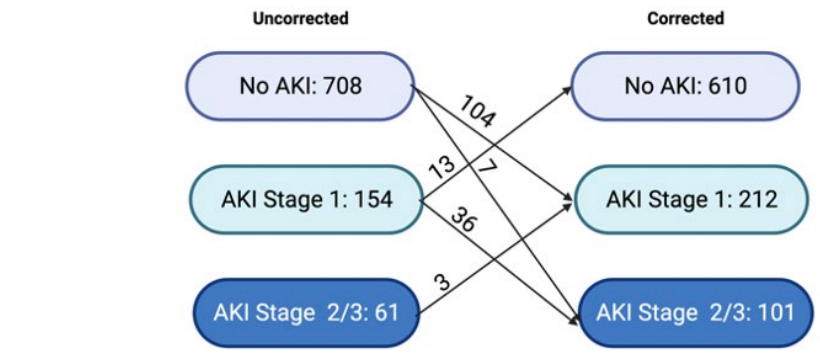

Figure 3. AKI class switching after correction for fluid balance

There was 87% concordance in AKI and a 95% concordance in Severe AKI in the two approaches.

Fluid Corrected AKI and Outcomes

Compared to those without AKI, neonates with Under-Recognized AKI were more likely to require ventilation on post-natal day 14 (p<0.001) and have longer hospital stays (p<0.001).

In multivariate analysis correction for FB strengthened the association with clinical outcomes, including ventilation (aOR 2.23, 95% CI 1.56-3.18) and severe bronchopulmonary dysplasia (aOR 2.05, 95% CI 1.15-3.64). These findings were similar in infants with Severe AKI (Stage 2/3).

	AKI		FC-AKI	
	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Mechanical Ventilation	2.90 (2.07-4.07)	1.75 (1.16-2.62)	3.25 (2.41-4.38)	2.23 (1.56-3.18)
Prolonged Hospital Stay	1.44 (1.05-1.96)	1.01 (0.72-1.42)	1.56 (1.19-2.06)	1.19 (0.89-1.61)
Mortality	1.69 (1.07-2.67)	1.01 (0.59-1.71)	1.32 (0.86-2.04)	0.81 (0.49-1.34)
BPD	1.27 (0.92-1.75)	0.90 (0.63-1.28)	1.22 (0.92-1.61)	0.92 (0.67-1.25)
Grade 3 BPD	2.38 (1.31-4.32)	2.03 (1.08-3.80)	2.24 (1.30-3.88)	2.05 (1.15-3.64)

Conclusions

Fluid correction increased the number of premature neonates diagnosed with AKI and strengthened the association with clinical outcomes including ventilation and severe lung disease. Failing to correct creatinine for FB underestimates the prevalence and impact of AKI in premature neonates. **Future studies should consider correcting AKI for FB to improve identification of neonates at high risk for poor outcomes.**