

**Utility of kinetic glomerular filtration rate for predicting severe persistent acute kidney injury  
in critically ill children and young adults**

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## Key Points

- KeGFR can be part of a multidimensional approach for AKI prediction combined with biomarkers, fluid corrected creatinine and renal angina
- KeGFR on Day 1 is not independently associated with severe day3 AKI in critically ill children and young adults

Acute kidney injury (AKI) is typically defined by changes in serum creatinine (SCr) and/or urine output. There are several limitations of SCr for the diagnosis of AKI (1,2). Kinetic estimated glomerular filtration rate (KeGFR), which relies on a combination of various factors including initial SCr, rate of creatinine production, volume of distribution (VD), and the change over time, allows one to estimate kidney function when the creatinine is changing acutely(3). KeGFR has been validated in various cohorts of adult patients but there is limited data in pediatrics(4-8). The purpose of this study was to assess the performance of KeGFR for predicting severe persistent AKI on day 3 of intensive care unit (ICU) admission in critically ill children. We hypothesized that, like in adults, KeGFR would predict AKI.

## Methods

We performed a secondary analysis of combined data from 2 cohorts (prospective data from the pediatric ICU (PICU) of Cincinnati Children's Hospital Medical Center from 09/2012-03/2014 and retrospective data from the PICU at Children's Hospital Colorado from 01/2014-12/2015). Patients aged 90 days-25 years were included. Exclusions included admission to a separate

cardiac ICU, a single measure of creatinine, presence of end stage kidney disease with dialysis dependence or a history of kidney transplant. The Institutional Review Board at each site approved the study with waiver of informed consent.

Demographics, clinical characteristics and outcomes were collected at the time of admission (Day0). Pediatric Risk of Mortality (PRISM-III) score was adjudicated during the first 4 hours of PICU admission (9). Baseline SCr was the lowest measured SCr up to 3 months prior to admission, or back calculated from a normative eGFR using modified Schwartz equation (10).

AKI was classified on Day0 and Day3 and defined using the Kidney Disease: Improving Global Outcomes (KDIGO) SCr criteria. Severe AKI was classified as KDIGO stage 2 or 3. Functional AKI (fAKI) was defined as Day0 AKI with return to baseline SCr by Day3 and persistent AKI (pAKI) was severe AKI with absence of recovery by Day3.

KeGFR was calculated on Days 1-3 and was calculated using the following formula:

$$\text{KeGFR} = \frac{\text{baseline SCr} \times \text{eGFR}}{\text{MeanSCr}} \times \left( 1 - \frac{24 \times \Delta \text{SCr}}{\Delta t \text{ (h)} \times \text{Max} \Delta \text{SCr/day}} \right)$$

$$\text{Max} \Delta \text{SCr/day} = \frac{\text{baseline SCr} \times \text{eGFR} \times 1.44}{\text{VD (L)}}$$

The volume of distribution (VD) of SCr is close to total body water (TBW), and TBW was estimated as previously described (2).

We also evaluated the change in keGFR (Day 2-Day1) in absolute values, and as a percentage of change from Day 1. Primary outcome was pAKI on day 3 based on the 16<sup>th</sup> acute dialysis quality

initiative guidelines and previous risk stratification tools (renal angina index), and secondary outcomes included mortality (11,12).

Data are presented as numbers, percentages for categorical variables and median, interquartile range(IQR) for continuous variables. Pearson's chi-squared test, or Kruskal-Wallis test, followed by pairwise Wilcoxon rank sum test were used to compare variables as appropriate. In order to assess the performance of KeGFR on day 0-1 for predicting day 3 severe pAKI, we performed a sensitivity analysis with generation of likelihood ratios. Multivariable regression models were used to determine the association of absolute and percentage change in SCr and KeGFR with pAKI and with mortality. Statistical significance level was set at  $p < 0.05$  level. Statistical analysis was performed using R version 3.5.0 (R Foundation, Vienna, Austria).

## Results

The datasets included 3760 patients (3576 at Colorado and 184 at Cincinnati). After excluding 3034 for missing data or ICU stay <48 hours, 726 patients with complete data were included. On Day 0, 190 (26%) had AKI. By Day 3, 107 recovered and were labelled as fAKI and 83 were labelled as pAKI (severe AKI on day3).

Patient characteristics are summarized in Table 1. Patients with pAKI were more likely to have a diagnosis of sepsis or a history of solid organ or stem cell transplant. They also had significantly higher mortality (21.6%) compared to those with no AKI (6%) and fAKI (5.2%). Severity of AKI was classified into discrete eGFR and KeGFR categories. The number of patients in each KeGFR category on day0-1 and stage of stage 3 AKI is summarized in Table 2. In the sensitivity analysis, there was a balance in sensitivity and specificity, and negative predictive value to rule out day 3 AKI if KeGFR < 60. In addition, KeGFR < 60 on day 0-1 had a 16.1 greater likelihood of predicting day 3 pAKI (95% CI: 10.3-25.2), and outperformed other KeGFR categories and KDIGO assessment (Table 3).

In multivariable models (adjusting for age, diagnosis of sepsis and PRISM-III score), there was no association between KeGFR or the change in absolute creatinine measurement and day 3 AKI.

## Discussion

In this study, KeGFR on day 0-1 differentiated between no AKI, fAKI and pAKI. KeGFR<60 on day 0-1 was associated with a higher likelihood of developing severe day 3 pAKI, and outperformed other KeGFR categories and standard KDIGO assessment.

It is possible, that both measures of renal function – KeGFR defined AKI and KDIGO defined AKI are complementary to each other where different prognoses may be evident from varying phenotypes of SCr trajectory over time (13). De Oliveira et al reported in critically ill adult patients that there was poor agreement between AKI severity and the worst achieved KeGFR – specifically, patients met KDIGO criteria but maintained a KeGFR >70mL/min/1.73m<sup>2</sup> or KeGFR declined to < 45mL/min/1.73m<sup>2</sup> but had no AKI or stage 1 only (5). It is important to note, that in this study, the worst KeGFR within the first 7 days of ICU stay was associated with worse short- and long-term outcomes including need for renal replacement therapy, hospital mortality and 1-year survival (5).

A prior study assessing KeGFR in children reported encouraging results in a small cohort (n=60) (4). AKI severity was graded using both KeGFR and KDIGO defined AKI (4). They found good agreement between KeGFR defined AKI and KDIGO defined AKI (Kappa=0.71). A recent study evaluated the utility of KeGFR among pediatric heart transplant recipients for predicting subsequent creatinine defined AKI in the first 7 postoperative days (8). Even in this study, the AUC for each of the models at 2 different time points for assessing KeGFR were modest at best (AUC<0.75). While we are able to demonstrate a high likelihood of day 3 severe pAKI in patients with a day0-1 eGFR<60, multivariable models using KeGFR demonstrated no association.

Furthermore, even percent changes in creatinine were not associated with pAKI. This could be secondary to the heterogeneity in volume of distribution in children, influence of muscle mass on SCr and creatinine generation, and inherent limitations of eGFR calculation in pediatrics (2,14). Given this, a modified version of the KeGFR should be constructed for use in children – and potentially another for neonates, and correction of creatinine for fluid balance should be considered (2). The potential limitations of the formula seem to derive from two places: the definition of baseline creatinine as well as the maximum increase in creatinine within 24 hours. The current formulas for each of these, makes the formula approximate the Schwartz formula, particularly in small children. Adjudication of evolving AKI and refinement of AKI phenotype using KeGFR in children would be immensely valuable as a potentially modified calculation could be done using existing measures of SCr, with less reliance on expensive biomarker tests. Given the advancements in electronic health records, KeGFR calculation could be automated, allowing for real time assessment with minimal added expense.

In general, utilization of biomarkers for AKI prediction have been limited, particularly in adults by the effect of comorbidities (15). In order to improve prediction of AKI, and its associated outcomes, it is possible that we need a multidimensional approach, using risk prediction tools and biomarkers (12). KeGFR has the potential to fit into the portfolio of biomarkers allowing us to further refine the AKI phenotype in this approach of which the calculation can easily be incorporated into the electronic health records. Complementary use of biomarkers with KeGFR was highlighted by Dewitte et al particularly as it relates to renal recovery(16). In this study, early assessment of biomarkers demonstrated fair assessment of renal recovery and major adverse kidney events, but KeGFR improved prediction of AKI

recovery. Combining TIMP2\*IGFBP7 and KeGFR demonstrated improved performance for predicting major adverse kidney events at 24 hours after initial resuscitation. During the adjudication of AKI risk starting at the time of admission and through the first 12-24 hours, there may be several opportunities to implement a multidimensional approach through the use of biomarkers, changes in SCr, volume status and assessment of KeGFR. These parallel assessments may help refine the AKI phenotype and improve implementation of strategies to reduce AKI severity and duration through simultaneous avoidance of nephrotoxic medications, dose adjustments based on decrements in GFR and fluid overload.

The strength of this study is that we included a large number of patients from 2 centers, potentially making the findings more generalizable. There are however several limitations. First, we can only establish associations not causation. Second, we only assessed for the ability of KeGFR to predict day 3 AKI. It is possible that this time period from admission to day 3 may be too short to identify any benefits of KeGFR in predicting AKI. Baseline creatinine was missing for almost 50% of the patients, and it is possible that the calculated creatinine could have impacted our results. However, the proportion of patients with calculated creatinine was similar across the groups. Finally, we did not assess the utility of KeGFR on renal recovery due to limited follow-up creatinine data in the included cohorts.

In conclusion, KeGFR was not independently associated with severe day3 AKI in multivariable analysis. Future studies with a pediatric modified KeGFR, combined with biomarkers in a multidimensional approach for AKI prediction in critically ill children are



needed. Furthermore, the assessment of fluid corrected KeGFR for prediction of pAKI and AKI recovery are needed.

**Disclosures:**

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K Gist: Conceptualization; Formal analysis; Methodology; Writing - original draft; Writing - review and editing

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**Table 1. Demographics, Clinical Characteristics and Outcomes Associated with no, functional and persistent acute kidney injury based on creatinine corrected for fluid overload**

Characteristic	No AKI N=526	Functional AKI N=107	Persistent AKI N=83
Sex (Female)	282 (52.6)	67 (62.6)	45 (54.2)
Age, (years)	8.4 (2.2, 13.9)	9.1 (3.7, 15.4)	11.5 (2.8, 16.7)
Weight (kg)	24.6 (12.3, 45.9)	27 (13.4, 59.3)	31.5 (13.5, 55)
History of transplant*	60 (11.1)	14 (13)	20 (24.1) <sup>\$^</sup>
Sepsis	69 (12.8)	20 (18.6)	22 (26.5) <sup>\$^</sup>
PRISM-III	5 (2, 10)	10 (3.5, 17) <sup>#</sup>	12 (5, 17) <sup>\$^</sup>
Baseline creatinine	0.37 (0.26, 0.5)	0.38 (0.26, 0.53)	0.39 (0.27, 0.52)
Baseline eGFR	126 (126, 140)	126 (126, 140)	133 (126, 140)
Calculated baseline creatinine	286 (54.5)	57 (53.5)	39 (47.2)
Day 0 creatinine	0.41 (0.28, 0.58)	0.87 (0.65, 1.23)	0.89 (0.51, 1.85)
Day 1 creatinine	0.39 (0.28, 0.57)	0.68 (0.47, 0.87)	1.09 (0.65, 1.74)
KeGFR on Day 1	122.7 (105, 145)	91.2 (81.4, 114.5) <sup>#</sup>	58.5 (28.6, 80.3) <sup>\$^</sup>
eGFR on Day 1	122.5 (104.9, 144.6)	86.7 (72.9, 103.7) <sup>#</sup>	51.6 (30.8, 72.7) <sup>\$^</sup>
Day 3 creatinine	0.36 (0.26, 0.52)	0.44 (0.27, 0.61)	1.21 (0.89, 2.52) <sup>\$^</sup>
KeGFR on Day 3	128 (107.1, 155.1)	105.4 (90.5, 132)	45.8 (17.6, 59.7) <sup>\$^</sup>
eGFR on Day 3	129.1 (106.8, 158.6)	108 (95.7, 143.2)	44.3 (23.1, 58.3) <sup>\$^</sup>
Need for MV	248 (46.2)	53 (49.5)	40 (48.2)
MV duration (days)	5 (2,8)	4 (2,7)	6 (4, 9)
ICU LOS (days)	6 (4,11)	5 (4, 10)	7 (4,11)
Mortality	35 (6.5)	5 (4.6)	15 (18.1) <sup>\$^</sup>

All continuous variables are presented as median with interquartile range. Categorical variables are presented as number with percent. \*Includes solid organ or stem cell

*Acute kidney injury (AKI), fluid overload (FO), Number (N), percent (%), kilograms (kg), Pediatric Risk of Mortality-III (PRISM-III), Kinetic estimated glomerular filtration rate (KeGFR), Mechanical ventilation (MV), Intensive Care Unit (ICU), Length of Stay (LOS)*

#  $p < 0.05$  for Functional AKI compared to No AKI

\$  $p < 0.05$  for Functional AKI compared to Persistent AKI

^  $p < 0.05$  for Persistent AKI compared to No AKI

**Table 2. Number of patients with kinetic estimated glomerular filtration rate by category (columns) and day 3 acute kidney injury stage (rows). There is an increase in the number of patients with KDIGO stage and decrements in KeGFR.**

		KeGFR Day 0-1			
		>120	>90-120	60-90	<60
<b>KDIGO Day 3 AKI</b>	<b>Stage 0</b>	296	207	81	13
	<b>Stage 1</b>	15	13	24	10
	<b>Stage 2</b>	3	6	6	15
	<b>Stage 3</b>	1	5	4	27

*Kinetic estimated glomerular filtration rate (KeGFR), Kidney Disease: Improving Global Outcomes (KDIGO), Acute kidney injury (AKI)*

**Table 3. Sensitivity analysis and likelihood ratio for both KDIGO defined AKI on day 0-1 and categories of KeGFR for prediction of day 3 severe AKI**

Day 0-1	Sens	Spec	PPV	NPV	LR
No AKI/KDIGO 1	41 (29-53)	13 (11-16)	5 (4-6)	67 (60-72)	0.5 (0.4-0.6)
KDIGO 2 or 3	59 (47-71)	87 (84-89)	33 (27-40)	95 (94-96)	4.5 (3.4-5.9)
KeGFR > 120	5 (1-13)	52 (48-56)	1 (0-3)	83 (82-85)	0.1 (0.04-0.3)
KeGFR <120	85 (75-92)	47 (43-51)	15 (14-17)	97 (94-98)	1.6 (1.4-1.8)
KeGFR <90	70 (59-80)	80 (77-83)	28 (24-33)	96 (94-97)	3.6 (2.9-4.4)
KeGFR <60	57 (45-69)	96 (95-98)	64 (53-74)	95 (94-96)	16.1 (10.3-25.2)

*Kinetic estimated glomerular filtration rate (KeGFR), Kidney Disease: Improving Global Outcomes (KDIGO), Acute kidney injury (AKI), Sensitivity (Sens), Specificity (Spec), Positive Predictive Value (PPV), Negative Predictive Value (NPV), Likelihood Ratio (LR)*