Kidney360

Utility of Kinetic GFR for Predicting Severe Persistent AKI in Critically Ill Children and Young Adults

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KIDNEY360 2: 869–872, 2021. doi: https://doi.org/10.34067/KID.0006892020

Key Points

- Kinetic eGFR can be part of a multidimensional approach for AKI prediction combined with biomarkers, fluid corrected creatinine, and renal angina.
- Kinetic eGFR on day 1 is not independently associated with severe day-3 AKI in children and young adults who are critically ill.

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 eGFR (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 are limited data in pediatric populations (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 children who are critically ill. We hypothesized that, like in adults, KeGFR would predict AKI.

Materials and Methods

We performed a secondary analysis of combined data from two cohorts (prospective data from the pediatric ICU [PICU] of Cincinnati Children's Hospital Medical Center from September, 2012 to March, 2014, and retrospective data from the PICU at Children's Hospital Colorado from January, 2014 to December, 2015). Patients aged 90 days to 25 years were included. Exclusions included admission to a separate cardiac ICU, a single measure of creatinine, presence of ESKD 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 (day 0). The Pediatric Risk of Mortality III score was adjudicated during the first 4 hours of PICU admission (9). Baseline SCr was the lowest measured SCr up to 3 months before admission, or back calculated from a normative eGFR using a modified Schwartz Equation (10).

AKI was classified on day 0 and day 3 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 day-0 AKI with return to baseline SCr by day 3, and persistent AKI (pAKI) was severe AKI with absence of recovery by day 3.

KeGFR was calculated on days 1–3 and was calculated using the following formula:

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

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

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

We also evaluated the change in KeGFR (day 2−day 1) in absolute values, and as a percentage of change from day 1. The primary outcome was pAKI on day 3, on the basis of the 16th 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 with percentages for categoric variables, and medians with interquartile ranges for continuous variables. The Pearson chi-squared test, or Kruskal-Wallis test, followed by the pairwise Wilcoxon rank sum test, were used to compare variables as appropriate. 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

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with pAKI and with mortality. Statistical significance level was set at $P<0.05$. 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%) patients had AKI. By day 3, 107 recovered and were labeled as fAKI, and 83 were labeled as pAKI (severe AKI on day 3).

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 (22%) compared with those with no AKI (6%) and fAKI (5%). Severity of AKI was classified into discrete eGFR and KeGFR categories. The number of patients in each KeGFR category on day 0–1 and stage of day-3 AKI is summarized in Table 2. In the sensitivity analysis, there was a balance in sensitivity, specificity, and negative predictive value to rule out day-3 AKI if KeGFR <60 ml/min per 1.73 m^2. In addition, KeGFR of <60 ml/min per 1.73 m^2 on day 0–1 had a 16.1 greater likelihood of predicting day-3 pAKI (95% CI, 10.3 to 25.2), and outperformed other KeGFR categories and KDIGO assessment (Table 3).

In multivariable models (adjusting for age, diagnosis of sepsis, and Pediatric Risk of Mortality 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 ml/min per 1.73 m^2 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.* (5) reported in adult patients who were critically ill that there was poor agreement between AKI severity and the worst achieved KeGFR; specifically, patients met KDIGO criteria but maintained a KeGFR >70 ml/min per 1.73 m^2 or KeGFR declined to <45 ml/min per 1.73 m^2, but they had no AKI or only stage 1 AKI. 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 RRT, 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 (κ=0.71). A recent study evaluated the utility of KeGFR among pediatric heart transplant recipients for predicting subsequent creatinine-defined AKI in the first seven postoperative days (8). Even in this study, the area under the curve for each of the models, at two different time points for assessing KeGFR, were modest at best (area under the curve<0.75). Although

Table 1. Demographics, clinical characteristics, and outcomes associated with no, functional, and persistent AKI on the basis of creatinine corrected for fluid overload

Characteristic	No AKI (N=526)	Functional AKI (N=107)	Persistent AKI (N=83)
Sex (female)	282 (53)	67 (63)	45 (54)
Age (yr)	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[a]	60 (11)	14 (13)	20 (24)[b,c]
Sepsis	69 (13)	20 (19)	22 (27)[b,c]
PRISM-III	5 (2–10)	10 (3.5–17)[d]	12 (5–17)[b,c]
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 (55)	57 (54)	39 (47)
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)[d]	58.5 (28.6–80.3)[b,c]
eGFR on day 1	122.5 (104.9–144.6)	86.7 (72.9–103.7)[d]	51.6 (30.8–72.7)[b,c]
Day 3 creatinine	0.36 (0.26–0.52)	0.44 (0.27–0.61)	1.21 (0.89–2.52)[b,c]
KeGFR on day 3	128 (107.1–155.1)	105.4 (90.5–132)	45.8 (17.6–59.7)[b,c]
eGFR on day 3	129.1 (106.8–158.6)	108 (95.7–143.2)	44.3 (23.1–58.3)[b,c]
Need for MV	248 (46)	53 (50)	40 (48)
MV duration (d)	5 (2–8)	4 (2–7)	6 (4–9)
ICU LOS (d)	6 (4–11)	5 (4–10)	7 (4–11)
Mortality	35 (7)	5 (5)	15 (18)[b,c]

All continuous variables are presented as median with interquartile range. Categoric variables are presented as number with percentage. PRISM-III, Pediatric Risk of Mortality III; KeGFR, kinetic eGFR; MV, mechanical ventilation; ICU, intensive care unit; LOS, length of stay.
[a]Includes solid organ or stem cell.
[b]$P<0.05$ for functional AKI compared with persistent AKI.
[c]$P<0.05$ for persistent AKI compared with no AKI.
[d]$P<0.05$ for functional AKI compared with no AKI.

Table 2. Number of patients with kinetic eGFR by category and day-3 AKI stage

KDIGO Day 3 AKI	KeGFR Day 0–1			
	>120 ml/min per 1.73 m^2	90–120 ml/min per 1.73 m^2	60–90 ml/min per 1.73 m^2	<60 ml/min per 1.73 m^2
Stage 0	296	207	81	13
Stage 1	15	13	24	10
Stage 2	3	6	6	15
Stage 3	1	5	4	27

There is an increase in the number of patients with Kidney Disease Improving Global Outcomes stage and decrements in kinetic eGFR.

we are able to demonstrate a high likelihood of day-3 severe pAKI in patients with a day 0–1 eGFR of <60 ml/min per 1.73 m^2, 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 VD 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 and the maximum increase in creatinine within 24 hours. The current formulas for each of these measures make 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 because 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 has been limited, particularly in adults, by the effect of comorbidities (15). 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, where the calculation can easily be incorporated into the electronic health records. Complementary use of biomarkers with KeGFR was highlighted by Dewitte *et al.* (16), particularly as it relates to renal recovery. 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 (tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7) 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 two 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 affected our results. However, the proportion of patients with calculated creatinine was similar across the groups. Finally, we did not assess the

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	Sensitivity	Specificity	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 ml/min per 1.73 m^2	5 (1–13)	52 (48–56)	1 (0–3)	83 (82–85)	0.1 (0.04–0.3)
KeGFR <120 ml/min per 1.73 m^2	85 (75–92)	47 (43–51)	15 (14–17)	97 (94–98)	1.6 (1.4–1.8)
KeGFR <90 ml/min per 1.73 m^2	70 (59–80)	80 (77–83)	28 (24–33)	96 (94–97)	3.6 (2.9–4.4)
KeGFR <60 ml/min per 1.73 m^2	57 (45–69)	96 (95–98)	64 (53–74)	95 (94–96)	16.1 (10.3–25.2)

KDIGO, Kidney Disease Improving Global Outcomes; KeGFR, kinetic eGFR; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

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 day-3 AKI in multivariable analysis. Future studies with a pediatric-modified KeGFR, combined with biomarkers in a multidimensional approach for AKI prediction in children who are critically ill, are needed. Furthermore, the assessment of fluid-corrected KeGFR for prediction of pAKI and AKI recovery are needed.

Disclosures

R.K. Basu reports having consultancy agreements with Baxter Healthcare Solutions, BD, Biomerieux, BioPorto Diagnostics, and Potrero. S.L. Goldstein reports having consultancy agreements with Akebia, Bayer, Baxter Healthcare, BioPorto, CHF Solutions, Fresenius, Kaneka Corporation, La Jolla Pharmaceuticals, Otsuka, MediBeacon, Medtronic, Reata, and Renibus; serving as a scientific advisor for, or member of, MediBeacon; receiving research funding from Baxter Healthcare, BioPorto, and CHF Solutions; serving on a speakers bureau for Baxter Healthcare, BioPorto Diagnostics, and Fresenius; receiving honoraria from Baxter Healthcare and Fresenius; having ownership interest in MediBeacon; and having patents and inventions with Vigilanz. K.M. Gist reports having consultancy agreements with BioPorto. S. Menon reports having consultancy agreements with AKI Foundation and CHF Solutions. The remaining author has nothing to disclose.

Funding

None.

Author Contributions

M.F. Barhight, R.K. Basu, K.M. Gist, and S. Menon were responsible for methodology; M.F. Barhight and S. Menon were responsible for data curation; M.F. Barhight, K.M. Gist, and S. Menon wrote the original draft; R. K. Basu was responsible for validation; R.K. Basu, K.M. Gist, S.L. Goldstein, and S. Menon conceptualized the study; K.M. Gist and S. Menon were responsible for formal analysis; S. Menon was responsible for software; S.L. Goldstein provided supervision; and all authors reviewed and edited the manuscript.

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Received: November 17, 2020 **Accepted:** March 15, 2021