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Modified RIFLE criteria in critically ill children with acute kidney injury

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A classification system has been proposed to standardize the definition of acute kidney injury in adults. These criteria of risk, injury, failure, loss, and end-stage renal disease were given the acronym of RIFLE. We have modified the criteria based on 150 critically ill pediatric RIFLE (pRIFLE) patients to assess acute kidney injury incidence and course along with renal and/or non-renal comorbidities. Of these children, 11 required dialysis and 24 died. Patients without acute kidney injury in the first week of intensive care admission were less likely to subsequently develop renal Injury or Failure; however, 82% of acute kidney injury occurred in this initial week. Within this group of 123 children, 60 reached pRIFLEmax for Risk, 32 reached Injury, and 31 reached Failure. Acute kidney injury during admission was an independent predictor of intensive care; hospital length of stay and an increased risk of death independent of the Pediatric Risk of Mortality (PRISM II) score (odds ratio 3.0). Our results show that a majority of critically ill children develop acute kidney injury by pRIFLE criteria and do so early in the course of intensive care. Acute kidney injury is associated with mortality and may lead to increased hospital costs. We suggest that the pRIFLE criteria serves to characterize the pattern of acute kidney injury in critically ill children.

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More than 30 acute kidney injury (AKI) definitions exist in the published literature.[1] Lack of a standardized definition that can be applied across patient populations (1) impedes rational comparison of studies that assess preventive and therapeutic AKI strategies, (2) limits generalization of data generated from single center studies, and (3) prevents patient stratification based on AKI severity. Recent pediatric AKI epidemiological data for critically ill children demonstrates a shift from primary renal disease to injury secondary to other systemic illnesses and/or their treatment.[2,3] Widespread availability of aggressive treatment options, such as bone marrow and solid organ transplantation for children, has led to increased exposure to nephrotoxic medications and more critically ill children receiving intensive care. The incidence of pediatric AKI in this at-risk population still remains unknown.

The reported mortality from AKI is still as high as 60% in critically ill children.[4] Most of the reported clinical studies of pediatric AKI focus on patients requiring renal replacement therapy (RRT), who have clearly experienced severe renal injury.[5–10] However, recent studies demonstrate that even a modest rise in serum creatinine (SCr) is a risk factor for mortality in adult and pediatric patients.[11,12] Thus, SCr may be an insensitive marker of early AKI and reliance on SCr hampers early AKI recognition. Extensive study has focused upon investigation of urinary biomarkers that detect AKI earlier than a rise in SCr.[13–15]

A new classification system, termed the 'RIFLE criteria,' has been proposed for use in critically ill adult patients by the Acute Dialysis Quality Initiative group.[1] RIFLE (acronym for Risk for renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease (ESRD)) aims to standardize the definition of AKI by stratifying patients based on changes in SCr levels from baseline and/or an abrupt decrease in urine output (UOP). We aimed to study a modified pediatric version of the RIFLE criteria (pRIFLE) to (1) describe the epidemiology and clinical course of AKI in critically ill children and (2) explore the potential relationships between AKI and renal and non-renal morbidities.

RESULTS

Group characteristics

We prospectively enrolled 150 critically ill patients (55.3% males) over a 12-month period. Mean age was 6.4 ± 6.4 years

(median = 4 years, range = 1 month–21 years). Mean Pediatric Risk of Mortality (PRISM II) score at pediatric intensive care unit (PICU) admission was 14.9 ± 8.4 (median = 15). Seventy-one percent of patients had preexisting chronic conditions. All patients received invasive mechanical ventilation (mean duration = 14.5 ± 17.6days; median = 9, range = 1–100 days). Fifty-three percent (80/150) of patients received vasoactive medications (17.5% received one, 18.1% two and 17.4% three or more). Mean PICU and hospital length of stay (LOS) were 16.6 ± 22.4 and 33.7 ± 38.1 days, respectively (median (range) = 10 (2–192), and 21 (2–24), respectively). Twenty-eight days and overall hospital mortality were 14% and 16%, respectively. Eleven patients (7.3%) received acute RRT.

Mean baseline estimated creatinine clearance (eCCl) for the entire cohort was 154 ± 93 ml/min/1.73 m^2 (median = 124 ml/min/1.73 m^2, range = 41–924 ml/min/1.73 m^2). Forty-one patients (27%) did not have baseline SCr values and were assigned baseline eCCl of 100 ml/min/1.73 m^2. Twenty-six patients had known pre-admission chronic neuromuscular disorders (NMd) associated with prolonged immobilization, resulting in severely decreased muscle mass (e.g., muscular dystrophy, cerebral palsy, quadriplegia, etc.). Mean eCCl for the NMd subset was 232 ± 173 ml/min/1.73 m^2 (median = 213 ml/min/1.73 m^2). Mean baseline eCCl for the non-NMd cohort ($n = 124$) was 138 ± 55 ml/min/1.73 m^2 (median = 118 ml/min/1.73 m^2).

Incidence and clinical course of AKI

Twenty-seven patients did not develop AKI and served as controls, 123 patients (82%) developed AKI by pRIFLE: 48.8% of these reached pRIFLEmax R ($n = 60$), 26.0% reached I ($n = 32$), and 25.2% reached F ($n = 31$). Table 1 displays the comparison of characteristics between patients with and without AKI. There were no statistically significant differences in any of the baseline demographic characteristics between patients with vs without AKI. PICU admission diagnoses, comorbidities, vasopressor requirements, peak mean airway pressures, and days of ventilation also did not differ between patients with vs without AKI.

Higher pRIFLEmax strata were associated with higher PRISM II scores. Mean PRISM II scores for controls, R, I, and F were 12.4 ± 7.2, 13.0 ± 7.7, 15.9 ± 8.0, and 19.6 ± 9.3, respectively ($P < 0.001$ by one-way analysis of variance).

Mean time to onset of the first pRIFLE stratum was 3.3 ± 3.1 days after PICU admission (median = 2, range = 1–14 days). Eighty-two percent (101/123) of patients developed AKI within the first 7 days of PICU admission (Figure 1). Patients who did not develop AKI within the first 7 days of PICU admission were very unlikely to subsequently develop severe AKI (negative predictive value (NPV) of reaching pRIFLEmax I or F = 95.1%, $P < 0.001$; NPV of reaching pRIFLEmax F = 97.7%, $P < 0.001$). Patients who remained free of AKI in the first 7 days did not receive RRT (NPV 100%, $P = 0.03$).

Table 1 | Comparison of characteristics of patients with versus without AKI

	Control n=27 (18%)	AKI by RIFLE n=123 (82%)
Continuous variables		
Mean ± s.d., median		
Age (years)	6.0 ± 6.6 (1.25)	6.5 ± 6.3 (4.0)
Weight (kg)	21.7 ± 18.1 (12.0)	26.1 ± 23.6 (16.0)
Height (cm)	103.9 ± 38.2 (87.0)	104.7 ± 38.4 (102.2)
PRISM II[a]	12.4 ± 7.2 (13.0)	15.4 ± 8.6 (16.0)
Baseline eCCl (ml/min/1.73 m^2)[b]	132 ± 46 (119)	159 ± 100 (129)
Peak mean airway pressure (mm Hg)	15.0 ± 8.2 (12.0)	17.2 ± 9.2 (14.0)
Days ventilated	10.7 ± 11.3 (8.0)	15.8 ± 18.7 (9.0)
PICU length of stay	10.1 ± 6.2 (9.0)	18.0 ± 24.3 (11.0)*
Hospital length of stay	20.5 ± 16.6 (14.0)	36.6 ± 40.1 (22.0)**
Categorical variables, N (%)		
Ethnicity		
Caucasian	11 (40.7)	41 (33.3)
African-American	5 (18.5)	25 (20.3)
Hispanic	8 (29.6)	55 (44.7)
Asian	3 (11.1)	2 (1.6)
Male	11 (40.7)	56 (45.5)
Comorbidities		
Present	17 (63)	89 (72.4)
Hematology/oncology	1 (3.7)	15 (12.2)
Cardiology	2 (7.4)	20 (16.3)
Other[b]	14 (52)	55 (44.7)
Admitting diagnosis		
Pneumonia	11 (41)	40 (33)
SIRS[c]/sepsis/septic shock	5 (18.5)	33 (26.8)
Cardiac arrest	6 (22)	12 (10)
Other	5 (18.5)	38 (30.9)
Clinical		
Need for pressors	13 (48.2)	66 (53.7)
Need for RRT[d]	0	11 (8.9)
28-Day mortality	3 (11.1)	18 (14.6)

AKI, acute kidney injury; eCCl, estimated creatinine clearance; PICU, pediatric intensive care unit; RIFLE, risk, injury, failure, loss and end-stage renal disease.
*$P < 0.07$; **$P < 0.05$.
[a]PRISM, Pediatric Risk of Mortality II score.
[b]Other includes the following diagnostic categories: endocrine, failure to thrive, gastrointestinal, rheumatologic, neurological (cerebral palsy, and epilepsy), orthopedic, pulmonary, psychiatric.
[c]SIRS, systemic inflammatory response syndrome.
[d]RRT, Renal replacement therapy.

Twenty-six percent of patients with initial pRIFLE R or I progressed to a higher pRIFLE stratum. Patients with initial pRIFLE I were more likely to progress to pRIFLEmax F than those with initial pRIFLE R (12/31 (39%) vs 3/76 (4%), $P < 0.0001$).

Figure 2 summarizes AKI distribution and outcomes comparing patients with and without chronic NMd. We chose to examine the NMd group separately because it is unknown whether change in SCr/eCCl is as reliable a marker of change in renal function in this unique group, owing to severely reduced muscle mass. The AKI prevalence and AKI

severity distribution did not differ between patients with vs without NMd.

Eleven patients received RRT. Continuous venovenous hemodialysis was provided for 10 patients; one patient initiated hemodialysis but was converted to continuous venovenous hemodialysis after two treatments. Nine of these patients had pRIFLE F AKI and two had pRIFLE I at RRT initiation. The decision to initiate RRT was made on the basis of clinical and laboratory grounds by the attending nephrologist and not by using pRIFLE criteria. Two patients with pRIFLE I AKI were stem cell transplant recipients who required RRT for fluid overload prevention per our institution's protocol,[16] and the remaining nine patients were dialyzed primarily for uremia. These nine patients were older than the remaining 22 patients with pRIFLE F AKI who did not receive RRT (10.4 ± 5.5 vs 6.5 ± 6.6 years, $P < 0.05$), but did not differ significantly in gender distribution, PRISM II score, nor proportion diagnosed with sepsis (not shown). Although mortality was similar in the groups (29% for pRIFLE F and no RRT vs 22% in those who received RRT, $P > 0.05$), PICU LOS and hospital LOS were longer in those who received dialysis (PICU LOS: 12.6 ± 8.5 (median = 10) vs 25.3 ± 13.1 days (median = 22), respectively; hospital LOS: 40.7 ± 59.0 (median = 22) vs 60.6 ± 40.0 days (median = 46) respectively, both $P < 0.05$). This may have been explained by the fact that 71% (5/7) of non-surviving patients with pRIFLE F AKI who did not receive RRT died within 24 h of pRIFLEmax F attainment.

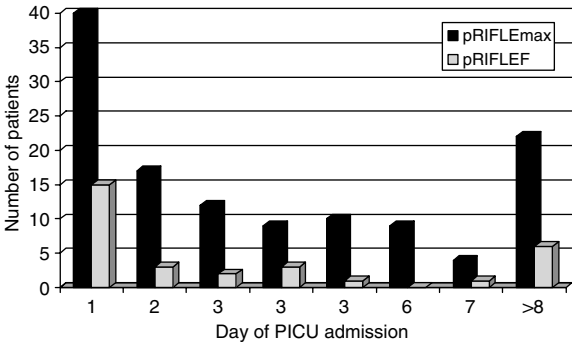

Figure 1 | Distribution of the day of admission that subjects reached pRIFLEmax ($n = 123$) and pRIFLE F stratum ($n = 31$). Black bars indicate numbers of subjects attaining their pRIFLEmax AKI on a given day, and gray bars indicate numbers of subjects attaining their first pRIFLE F on a given day. The majority of subjects (82%) reached their maximum pRIFLE stratum for AKI (black) within the first week of admission, and most patients who reached pRIFLE F AKI did so within the first week of admission (25/31 = 81%, gray bars).

Distribution of pRIFLE by SCr vs UOP criteria

Ninety-seven patients (81.5%) fulfilled $pRIFLE_{Cr}$ criteria and 65 (54.6%) fulfilled $pRIFLE_{UOP}$ criteria at some time during the study period. Of the 11 patients who received dialysis, four had not attained $pRIFLE_{UOP}$ status before initiating dialysis. These four patients were included in the group who only attained $pRIFLE_{Cr}$ for this analysis. All patients requiring dialysis attained their $pRIFLE_{Cr}$max before initiation of dialysis.

Table 2 lists outcome based on the type of RIFLE criteria achieved. Forty-three patients (35.0%) attained both $pRIFLE_{Cr}$ and $pRIFLE_{UOP}$ AKI ($pRIFLE_{Cr+UOP}$), 58 (47.2%) only $pRIFLE_{Cr}$ criteria and 22 (17.9%) attained only $pRIFLE_{UOP}$ (Table 2). Patients with $pRIFLE_{Cr}$ only tended to be younger (Table 2). Patients with $pRIFLE_{UOP}$ only had lower PRISM II scores ($P < 0.05$, analysis of variance), and none of them died or required dialysis. Mortality was higher for patients with $pRIFLE_{Cr}$ (SCr only or SCr + urine output) compared with the group that only attained $pRIFLE_{UOP}$ criteria (both $P < 0.05$). Mortality in the $pRIFLE_{Cr+UOP}$ group did not differ compared with the $pRIFLE_{Cr}$ only group.

Table 3 displays $pRIFLE_{Cr}$max and $pRIFLE_{UOP}$max for the 43 patients who attained pRIFLE AKI criteria by both SCr and UOP categories. Only six patients attained a $pRIFLE_{UOP}$max that was worse than their $pRIFLE_{Cr}$max; none of whom received dialysis or died. Only four patients attained any $pRIFLE_{UOP}$ before attaining any $pRIFLE_{Cr}$; none of these patients later received dialysis.

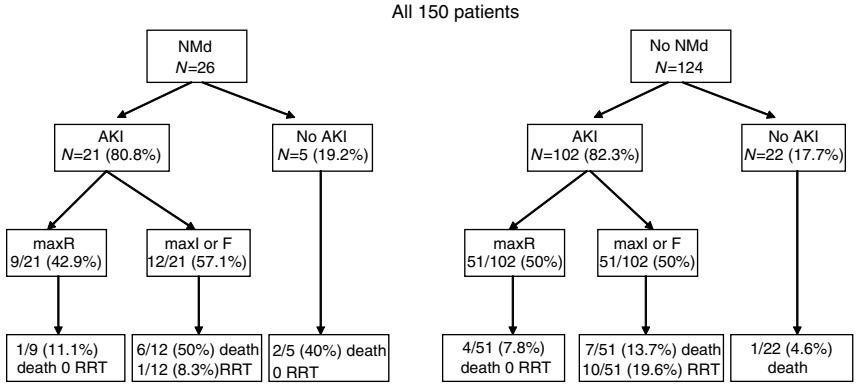

Figure 2 | Flow diagram indicating the distribution of AKI and outcome (survival and need for RRT), comparing patients with and without chronic a neuromuscular disease (NMd, neuromuscular disease; maxR/maxI/maxF, maxiumum pRIFLE stratum attained during admission; RRT, renal replacement therapy).

Table 2 | Comparison of characteristics and outcomes of patients with AKI, based on their attainment of pRIFLE criteria by urine output only ($pRIFLE_{UOP}$), by SCr only ($pRIFLE_{Cr}$), or by both ($pRIFLE_{Cr+UOP}$)

	$pRIFLE_{UOP}$ only N=22	$pRIFLE_{Cr}$ only[a] N=58	$pRIFLE_{SCr+UOP}$ N=43
Age			
Mean ± s.d. (median)	8.5 ± 5.9 (7.5)	4.3 ± 5.8 (1.0)[b]	8.6 ± 6.4 (8.0)
PRISM			
Mean ± s.d. (median)	10.6 ± 7.8 (8.0)[c]	15.8 ± 7.9 (15.5)	17.4 ± 9.1 (18.0)
Males			
N/total (%)	12/22 (54.6)	28/58 (48.3)	27/43 (62.8)
28-Day mortality			
N/total (%)	0	9/58 (15.5)[d]	9/43 (20.9)[d]
Need for dialysis			
N/total (%)	0	5/58 (8.6)	6/43 (14.0)[e]
pRIFLEmax			
pRIFLEmax R			
N/total (%)	18/22 (81.8)	29/58 (50.0)	13/43 (30.2)
pRIFLEmax I			
N/total (%)	3/22 (13.6)	16/58 (27.6)	13/43 (30.2)
pRIFLEmax F			
N/total (%)	1/22 (4.5)	13/58 (22.4)	17/43 (39.5)

ANOVA, analysis of variance; AKI, acute kidney injury; KI, kidney injury; pRIFLE, pediatric risk, injury, failure, loss and end-stage renal disease; PRISM, Pediatric Risk of Mortality score; SCr, serum creatinine.
[a]Patients who attained pRIFLE urine output criteria only after dialysis was initiated were included in the SCr pRIFLE only group.
[b]AKI patients who only attained pRIFLE criteria by SCr were statistically significantly younger than patients in the other groups ($P<0.05$, ANOVA).
[c]KI patients who only attained pRIFLE criteria by urine output had statistically significantly lower PRISM scores than the other two groups.
[d]28-day mortality was higher in both AKI groups with SCr pRIFLE criteria attainment ($P<0.05$) compared with the group with only urine output pRIFLE criteria.
[e]The need for dialysis tended to be higher in both groups that attained SCr pRIFLE criteria compared with the group that only attained urine output pRIFLE criteria, but the difference did not achieve statistical significance ($P<0.1$).

Table 3 | Two-by-two table depicting the maximum $pRIFLE_{Cr}$ and maximum $pRIFLE_{UOP}$ attained during the study period, in patients who attained pRIFLE AKI by SCr and urine output criteria

	Urine pRIFLEmax			
	R	I	F	Total
SCr pRIFLEmax				
R	13	5	1	19
I	5	3	0	8
F	3	3	10	16
Total	21	10	9	43

AKI, acute kidney injury; pRIFLE, pediatric risk, injury, failure, loss and end-stage renal disease; SCr, serum creatinine.
Dark gray: six patients had higher $pRIFLE_{UOP}$max than $pRIFLE_{Cr}$max.
Light gray: 26 patients had the same $pRIFLE_{UOP}$max as their $pRIFLE_{Cr}$max.

AKI on admission: early reversal vs persistent AKI

We examined separately a subgroup of patients with AKI at the time of admission to the PICU (Figure 3). Fifty-two (42.3%) patients had AKI on the day of admission: 16 (30.8%) had pRIFLE R, 21 (40.4%) had pRIFLE I, and 15 (28.8%) had pRIFLE F. Patients with AKI on admission had higher PRISM II scores than patients who developed AKI after day 1 (18.9 ± 8.9 vs 12.8 ± 7.4, $P=0.0001$). A higher proportion of patients with AKI on admission received RRT than patients who developed AKI after day 1 (10/52 vs 1/71 ($P=0.001$)); the association between AKI on admission and the need for dialysis was independent of age and gender (logistic regression, $P=0.004$).

Renal function substantially improved (as defined by a decrease in pRIFLE stratum) within 48 h ('early reversal') in 46% of patients with AKI at PICU admission. Early reversal of AKI was more likely to occur in patients with pRIFLE R on admission (10/16, 62.5%), than in those with pRIFLE I (8/21, 38.1%) or F (4/15, 26.7%) on admission. Fewer patients in the early reversal group received RRT than in the group with persistent AKI (1/22 (4.5%) vs 10/30 (33.3%), respectively, $P<0.03$); this association was also independent of age and gender (logistic regression, $P=0.0001$).

Outcomes

AKI and LOS (PICU and hospital). In univariate analyses, patients with AKI tended to have a longer PICU LOS when compared with control patients (18.0 ± 24.3 vs 10.1 ± 6.2 days, $P=0.06$). Hospital LOS was significantly longer for patients with AKI compared with the control group (36.6 ± 40.1 vs 20.5 ± 16.6 days, $P=0.04$). Table 4 lists Cox regression analysis for PICU and hospital LOS adjusting for age and gender and accounting for death as a censoring event. The presence of any AKI, of pRIFLEmax I or F, and of pRIFLEmax F during the study period were each independently associated with longer hospital LOS. The presence of AKI during the study period was independently associated with longer PICU LOS. The presence of AKI pRIFLE I or F *on admission* was associated with longer hospital LOS. Patients with persistent admission AKI (no improvement within 48 h) did not demonstrate longer hospital or PICU LOS, compared with all other patients.

Mortality

Figures 2 and 3 display the distribution of survival outcome, examining the whole sample (Figure 2) and those with AKI on admission (Figure 3). Overall mortality rates did not differ between patients with AKI (14.6%) vs those without AKI (11.1%). However, patients with pRIFLEmax I or F during admission had over twice the mortality than patients with pRIFLEmax R or controls (21 vs 8%, respectively, $P<0.05$). Patients with pRIFLEmax F also had over twice the mortality rate of the rest of the cohort (25.8% for pRIFLEmax F vs 10.9% for all others, $P=0.03$).

Patients with chronic NMd had a higher mortality rate than the rest of the cohort (35 vs 10%, $P<0.05$; Figure 2). Because AKI rates were not different in the NMd group, NMd was not a confounder of the effect of AKI on mortality. Using logistic regression, controlling for age, gender, PRISM II

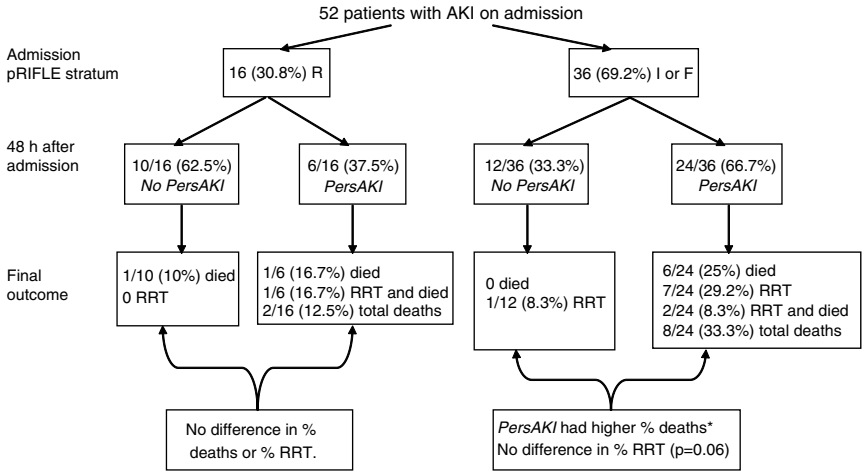

Figure 3 | Flow diagram of the course of AKI, for patients with AKI on the day of admission ($n = 52$). Most deaths occurred in patients with pRIFLE I or F on admission who had persistent AKI, defined as lack of improvement in AKI pRIFLE stratum within 48 h.

Table 4 | The effect of different criteria for AKI on hospital and PICU length of stays, independent of age and gender[a]

	Hospital LOS-adjusted HR (95% CI)[b]	PICU LOS-adjusted HR (95% CI)[b]
AKI during the PICU stay		
Using SCr+urine output criteria		
Any AKI during admx[c]	0.6 (0.4–0.9)*	0.6 (0.4–0.9)*
pRIFLEmax I or F	0.6 (0.4–0.9)*	0.7 (0.5–0.9)*
pRIFLEmax F	0.6 (0.4–0.9)*	0.8 (0.5–1.2)
Using SCr criterion only		
Any AKI during admx[c]	0.5 (0.3–0.7)*	0.4 (0.3–0.6)*
pRIFLEmax I or F	0.5 (0.4–0.8)*	0.6 (0.4–0.8)*
pRIFLEmax F	0.6 (0.4–0.9)*	0.7 (0.5–1.1)
AKI on admission to PICU		
Using SCr+urine output criteria		
AKI on admx	0.7 (0.5–1.01)	0.9 (0.6–1.2)
AKI pRIFLE I or F on admx	0.6 (0.4–0.9)*	0.7 (0.5–1.03)
AKI on admx with persistent AKI[d]	0.8 (0.5–1.1)	0.8 (0.6–1.3)
AKI pRIFLE I or F on admx with persistent AKI	0.7 (0.4–1.1)	0.8 (0.5–1.2)
Using SCr criterion only		
AKI on admx	0.7 (0.5–0.96)	0.8 (0.6–1.2)
AKI pRIFLE I or F on admx	0.6 (0.4–0.9)*	0.7 (0.5–1.03)**
AKI on admx with persistent AKI[d]	0.8 (0.5–1.1)	0.8 (0.6–1.3)
AKI pRIFLE I or F on admx with persistent AKI	0.7 (0.4–1.1)	0.8 (0.5–1.2)

AKI, acute kidney injury; CI, confidence intervals; HR, hazard ratio; LOS, length of stays; PICU, pediatric intensive care unit; pRIFLE, pediatric risk, injury, failure, loss and end-stage renal disease; SCr, serum creatinine.
*Hazard ratio is significantly less than 1.0, indicating that the specified AKI criterion was associated with a longer length of stay (longer time to discharge).
**P=0.07.
[a]All analyses were also conducted including PRISM score, which is a risk of mortality score, but there was no effect of this factor on results shown.
[b]All Cox proportional hazards models fulfilled assumption of proportional hazard based on Schoenfeld residuals.
[c]Admx, admission.
[d]Persistent AKI was defined as a lack of improvement in pRIFLE AKI status by 48 h after admission.

score, the association between AKI during admission and mortality was no longer significant (Table 5). However, when AKI was defined only by SCr criterion, $pRIFLE_{Cr}$max I or F was independently associated with an increased risk of mortality (Table 5). When PRISM II score was removed from all regression models, the effects of the different expressions of AKI on mortality appeared more important, with most odds ratios increasing substantially (Table 5).

The presence of AKI on admission was not an independent risk factor for mortality. Patients with AKI on admission who did not improve in pRIFLE stratum within 48 h (persistent AKI, $n = 30$) did not have a higher risk of mortality compared with the rest of the cohort, when controlled for age, gender, and PRISM II score (Table 5).

DISCUSSION

The current prospective study shows pRIFLE to serve well to both classify pediatric AKI epidemiology and reflect the course of AKI in children admitted to the PICU. AKI classification using pRIFLE criteria revealed that AKI is very common in critically ill pediatric patients and is associated with significant morbidity.

AKI occurred very early in the PICU course, most often within the first week of admission, and patients who did not develop AKI within the first 7 days of PICU admission were very unlikely to develop AKI later. These data support previous pediatric studies demonstrating that children develop their maximum number of organ failures early in the intensive care unit (ICU) course, an epidemiologic pattern that differs from adult patients.[17,18] In addition, patients who did not demonstrate renal function improvement within 48 h of ICU admission were at greater risk of receiving RRT, which is similar to studies in adult patients.[19] These data suggest the need to study the effect of early initiation of aggressive measures to both prevent and treat AKI for critically ill children with AKI who do not improve

Table 5 | Association of different criteria for AKI and mortality and the effect of controlling for severity of illness (PRISM II score)

	28-Day mortality	
	Adjusted OR (95% CI)[a]	Adjusted OR (95% CI)[a] (no PRISM II score)
AKI during the PICU stay		
Using SCr + urine criteria		
Any AKI during admx[b]	1.1 (0.3–4.3)	1.4 (0.4–5.1)
pRIFLEmax I or worse	1.9 (.7–5.1)	1.7 (0.6–4.8)
Using only SCr criterion		
Any AKI during admx[b]	2.9 (0.8–10.9)	3.6 (1.0–13.1)
pRIFLEmax I or worse	3.0 (1.1–8.1)*	3.8 (1.4–10.0)*
AKI on admission to PICU		
Using SCr + urine criteria		
AKI on admx	1.2 (0.4–3.4)	1.8 (0.7–4.6)
AKI pRIFLE I or worse on admx	1.1 (0.4–3.4)	1.7 (0.6–4.8)
AKI on admx with persistent AKI[c]	2.6 (0.9–7.9)	3.9 (1.4–10.6)*,[d]
AKI pRIFLE I or worse on admx with persistent AKI	2.3 (0.8–7.2)	3.4 (1.2–9.8)*,[d]
Using only SCr criterion		
AKI on admx	1.7 (0.6–5.0)	2.5 (1.0–6.5)
AKI pRIFLE I or worse on admx	1.3 (0.5–4.0)	2.0 (0.7–5.4)
AKI on admx with persistent AKI[c]	2.6 (0.9–7.9)	3.9 (1.4–10.6)*,[d]
AKI pRIFLE I or worse on admx with persistent AKI	2.3 (0.8–7.2)	3.4 (1.2–9.8)*,[d]

AKI, acute kidney injury; CI, confidence intervals; LOS, length of stays; OR, odds ratio; PICU, pediatric intensive care unit; PRISM, Pediatric Risk of Mortality score; pRIFLE, pediatric risk, injury, failure, loss and end-stage renal disease; SCr, serum creatinine.
*$P < 0.05$.
[a]In the first column, all odds ratios are adjusted for age, gender, and Pediatric Risk of Mortality score; in the second column, odds ratios are only adjusted for age and gender.
[b]Admx, admission.
[c]Persistent AKI was defined as no improvement in pRIFLE AKI status by 48 h after admission.
[d]When PRISM II score was removed from the logistic regression model, AKI on admission with persistent AKI was a significant predictor of mortality (only adjusted for age and gender).

within 24–48 h. Numerous single center and one multicenter study of children requiring continuous renal replacement therapy have shown a strong association between the degree of fluid overload at continuous renal replacement therapy initiation and mortality.[7–10,16] We suggest that the pRIFLE criteria may be used to provide guidance as to the potential for renal function improvement and may assist in clinical decisions regarding RRT initiation. The high prevalence of AKI on admission to PICU in our sample suggests that study of risk factors (clinical and biochemical) for developing AKI, may need to include data from patients before ICU admission.

Other secondary outcomes were notable as well. The presence of RIFLE I or F AKI (defined by SCr criterion only) during admission was associated with an increased risk of mortality, even when adjusted for PRISM II score. This finding is important since PRISM II does not contain a direct measure of renal function in its calculation. Surprisingly, the prevalence of comorbidities, sepsis or other admission diagnoses were no different for patients with vs without AKI, even though AKI was associated with mortality, suggesting that AKI is an independent risk factor for death. Although this observation is consistent with similar results from recent study of RIFLE criteria in critically ill adult patients,[20,21] it should be interpreted with caution because our sample size may not have been large enough to detect differences between subgroups. Future study should evaluate the interaction of diagnosis and AKI on mortality risk. When PRISM II scores were excluded from analysis, the effect of AKI on mortality appeared substantially stronger, stressing the importance of controlling for severity of illness when assessing for associations between AKI and mortality.

Approximately 71% of patients who attained pRIFLE F AKI did not receive RRT, which might suggest that the pRIFLE criteria is overly sensitive for identifying severe AKI. However, over two-thirds of these patients died within 24 h of pRIFLEmax F attainment. Had these patients survived, it is possible that they would have required RRT. Although these findings are purely descriptive, they do further indicate that patients with severe AKI tend to be more severely ill, and that future studies evaluating risk factors for initiation of RRT may need to account for censoring owing to death.

Our evaluation for potential differences in outcome as a function of attaining AKI by serum SCr vs UOP vs both revealed that SCr demonstrated stronger associations with outcomes. Future studies may be needed to determine if UOP is in fact necessary for early AKI diagnosis; however, we still suggest assessment of both the SCr and UOP measures for AKI.

Potential limitations of our study include the relatively small sample size of 150; however, this cohort comprises the largest prospective evaluation of pediatric AKI and the only study describing AKI in a general PICU population (as opposed to specific subgroups). Another potential concern is the use of an assumed baseline eCCl of 100 ml/min/1.73 m^2 for patients without a known baseline creatinine, in about one-fourth of the patients. The potential danger of this assumption would be to misdiagnose a patient with AKI based on a relative decrease in eCCl if in fact the patient had chronic kidney disease. Whether or not such misdiagnosis would lead to unnecessary evaluation or treatment is currently not known, but clinicians should exercise caution when classifying patients with AKI using pRIFLE, or any system using eCCl change, when a baseline creatinine level is unknown. Finally, the decision to initiate RRT was not directed by a clinical algorithm as part of this study, but rather was left to the discretion of the attending nephrologist. Thus, RRT provision was not a hard end point for this study.

Because of the dependency of SCr levels on muscle mass, it is extremely difficult to interpret in patients with severely reduced muscle mass (such as those with quadriplegia, cerebral palsy or other neuromuscular disorders), as is

Table 6 | Pediatric-modified RIFLE (pRIFLE) criteria

	Estimated CCl	Urine output
Risk	eCCl decrease by 25%	<0.5 ml/kg/h for 8 h
Injury	eCCl decrease by 50%	<0.5 ml/kg/h for 16 h
Failure	eCCl decrease by 75% or eCCl <35 ml/min/1.73 m^2	<0.3 ml/kg/h for 24 h or anuric for 12 h
Loss	Persistent failure >4 weeks	
End stage	End-stage renal disease (persistent failure >3 months)	

eCCl, estimated creatinine clearance; pRIFLE, pediatric risk, injury, failure, loss and end-stage renal disease.

evidenced by our data where patients in the NMd category had mean eCCl of 232 ml/min/1.73 m^2. We thus questioned whether the pRIFLE criteria would be less useful in this group. The finding that the distribution of AKI severity was almost identical in the NMd group (Figure 2) is highly suggestive that *change* in eCCl, as assessed by pRIFLE, is a valid way of evaluating AKI in patients with severely reduced muscle mass. What is not known is whether progressive muscle – wasting associated with prolonged ICU admission,[22,23] which may be associated with declining levels of SCr independent of renal function, leads to a decrease in the utility of pRIFLE for describing AKI.

We conclude that multidimensional AKI classification and stratification systems, such as pRIFLE, can serve well to improve understanding of AKI epidemiology and potentially optimize evaluation and treatment for AKI in children. Furthermore, as SCr and UOP seem to be late markers of renal injury, use of classification systems will be essential to assess the potential utility of urine and other serum biomarkers to detect AKI earlier and direct therapies to prevent or mitigate AKI in children prior to a rise in SCr concentration.

MATERIALS AND METHODS

We prospectively studied patients admitted to the Texas Children's Hospital PICU using pediatric-modified RIFLE (pRIFLE) criteria (Table 6) to define the clinical course of AKI in the critically ill pediatric patients. All children aged between 30 days to 21 years with respiratory failure (defined as requiring invasive mechanical ventilation) and/or cardiovascular failure (defined as requiring infusion of vasoactive medication(s)) who had indwelling Foley catheters were eligible for enrollment. Patients with known end-stage renal disease at PICU admission or who were immediately status-post renal transplant were excluded. The Institutional Review Board of Baylor College of Medicine approved the study protocol and parents/legal guardians provided written informed consent before patient enrollment.

UOP and SCr concentrations were recorded daily for up to 14 days and eCCl was calculated using the Schwartz formula.[24] For determination of baseline eCCl, the lowest value of SCr in the 3 months preceding study enrollment was obtained from the hospital database. If no previous SCr was available, the patient was assumed to have normal renal function and assigned a baseline eCCl of 100 ml/min/1.73 m^2, as suggested. Data were reviewed daily and patients were assigned to the appropriate pRIFLE strata (R, I or, F) if they fulfilled either UOP (pRIFLE$_{UOP}$) or SCr (pRIFLE$_{Cr}$) criterion or both (Table 1). At the end of follow-up, patients were classified according to the maximum pRIFLE stratum achieved within the 14 days of observation (pRIFLEmax). Additional data collected included demographics, PICU admission and discharge diagnoses, the presence of chronic illnesses, duration of invasive mechanical ventilation, peak mean airway pressure reached, maximal number of vasoactive medication infusions, and the need for dialysis. PRISM II scores[25] were recorded for each patient on PICU admission, as a surrogate marker for severity of illness. Hospital and PICU LOS, and 28 day and hospital mortality were recorded.

Comparison of pre-renal azotemia vs acute tubular necrosis

Intravascular fluid depletion is a common cause of increased SCr/decreased glomerular filtration rate in the pediatric setting (commonly referred to as 'pre-renal azotemia'), particularly early in the PICU admission. Such patients will often respond solely to fluid repletion, with a return of SCr to baseline values within 24–48 h of fluid resuscitation. On the basis of this rationale, we chose to compare the renal outcome and mortality of patients with early AKI reversal (improving pRIFLE stratum within 48 h of ICU admission) vs patients with persistent AKI (no improvement in pRIFLE stratum by 48 h), to serve as a surrogate for pre-renal azotemia vs acute tubular necrosis.

Statistical analysis

All statistical analyses were performed using STATA® (StataCorp, College Station, TX, USA) software. Continuous variables were expressed as mean $\pm$ s.d. and median, and categorical variables as proportions (%). Continuous variables were compared using analysis of variance and Student's *t*-test. χ^2 and Fisher's exact tests were used for comparison of categorical variables. The outcomes examined were mortality, and PICU and hospital LOS. Multiple logistic regression was used to evaluate the presence of AKI and other relevant variables as risk factors for mortality. Cox-multiple regression was performed to evaluate the effect of AKI on time to PICU and hospital discharge, accounting for death as a censoring event. Continuous variables with a non-normal distribution were log-transformed to a normal distribution for use in parametric analyses. In all analyses, a *P*-value of <0.05 was considered statistically significant.

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