O R I G I N A L Acute kidney injury in the paediatric intensive care RTICLE unit: identification by modified RIFLE criteria

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Winnie KY Chan 陳桂如 TY Miu 繆定逸	Objective	To evaluate the prevalence and outcome of acute kidney injury in paediatric intensive care units using the modified RIFLE score (pRIFLE).
	Design	Historical cohort study.
	Setting	A paediatric intensive care unit in a regional Hong Kong hospital.
	Patients	All paediatric patients aged 1 month to 18 years admitted to a local paediatric intensive care unit in the years 2005 to 2007.
	Main outcome measures	For every paediatric intensive care unit admission, acute kidney injury was classified according to the pRIFLE criteria ("R" for risk, "I" for injury, "F" for failure, "L" for loss, and "E" for end-stage). Prevalence and outcome of acute kidney injury were therefore categorised according to the pRIFLE staging.
	Results	A total of 140 such patient admissions constituted the study population. The point prevalence of acute kidney injury in these patients on admission was 46% (n=59), whilst 56% (n=78) endured acute kidney injury at some time during their paediatric intensive care unit stay. Worsening of pRIFLE grading during their intensive care unit admission was observed in 20% of the patients who had no acute kidney injury on admission, in 30% of those who had an initial "R" grade, and in 40% of those who had an initial "I" grade of acute kidney injury. Overall mortality in this cohort was 12%, which was significantly higher among patients with acute kidney injury. Having acute kidney injury of grade "F" on admission to the paediatric intensive care unit was an independent predictor of mortality (hazard ratio=5.94; 95% confidence interval, 1.06-33.36; P=0.043).
	Conclusion	Among critically ill paediatric patients, the pRIFLE score serves as a suitable classification of acute kidney injury when stratified according to clinical severity. It also provides prognostic information on mortality and renal outcomes.

New knowledge added by this study

- The pRIFLE score provides a suitable means of classifying different stages of acute kidney injury among local paediatric patients with various critical illnesses.
- This is the first reported prevalence of acute kidney injury using the pRIFLE score in the local population.

Implications for clinical practice or policy

- Acute kidney injury can be identified early in the course of critical illness.
- The pRIFLE score can be applied as a suitable tool for identifying acute kidney injury and
- monitoring the progress of kidney function in critically ill paediatric patients.

Key words Acute kidney injury; Child; Intensive care units, pediatric; Outcome assessment (health care); Severity of illness index

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Introduction

Acute kidney injury (AKI), previously termed acute renal failure, is a serious condition that is commonly encountered among critically ill patients. It refers to the abrupt onset of renal dysfunction causing inability of the kidney to regulate acid-electrolyte balance, and failure to excrete fluid and waste products. In practical terms, it is most commonly characterised by an increase in serum creatinine and can manifest as mild impairment of renal function to frank acute renal failure requiring renal replacement therapy.^{1,2}

In 2004, the first consensus definition of AKI for the adult population, based on the RIFLE criteria, was proposed by the Acute Dialysis Quality Initiative Group.³ Since then, the classification has gained wide popularity in adult critical care and nephrology research.⁴

應用改良了的RIFLE分級評估兒童深切治療部 病人的急性腎損傷

- 目的 應用改良了的RIFLE分級(pRIFLE)評估兒童深切 治療部病人的急性腎損傷的患病率及結果。
- 設計 歷史隊列研究。
- 安排 香港一所分區醫院的兒童深切治療部。
- **患者** 2005年至2007年期間入住上述兒童深切治療部,年 齡介乎1個月至18歲的病人。
- **主要結果測量** 根據pRIFLE分級為每名病人的急性腎損傷作出以下 分類: R代表危險、I代表腎損傷、F代表腎功能衰 竭、L代表腎功能喪失及E代表終末期腎病。然後為病 人急性腎損傷的患病率及結果作評級。
 - 結果 共140名病人被納入研究範圍。病人入院時急性腎損傷的時點患病率為46%(59例),在入住兒童深切治療部期間他們的時點患病率則為56%(78例)。分別有20%病人入院時未有急性腎損傷、30%有R評級及40%有I評級的病人在入住深切治療部後,其pRIFLE評級變差。病人的總死亡率為12%,而患有急性腎損傷的患者死亡率較高。病人入住兒童深切治療部時評級為F是死亡率的一項獨立預測因子(危險比率=5.94;95%置信區間:1.06至33.36;P=0.043)。
 - 結論 pRIFLE評級能有效根據臨床嚴重程度評估兒科危重 病人的急性腎損傷。而且pRIFLE評級可為死亡率和 腎功能結果提供預後資料。

The definition was later modified and evaluated in critically ill paediatric patients and was based on what were termed pRIFLE criteria.⁵ The classification consists of three levels of renal dysfunction with increasing severity, namely the "Risk (R)", "Injury (I)", and "Failure (F)", based on the degree of decrease in estimated creatinine clearance (eCCl) and urine output (Table 1). In addition to "R", "I" and "F", there are two levels of adverse clinical outcome: "Loss (L)" that refers to persistent renal failure for >4 weeks, and "End-stage (E)" that refers to persistent renal failure for >3 months. The pRIFLE criteria differs from the RIFLE criteria, in that only decrease in eCCl, and not the change in serum creatinine or glomerular filtration rate, is used to determine

TABLE I	. The	pRIFLE	classification
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grading. Furthermore, the eCCl is estimated using the Schwartz formula, which incorporates the height and serum creatinine level of the patient, and an age-adjusted constant,⁶ whilst also depending on a longer duration of urine output than in the adult RIFLE classification.

Before the introduction of the RIFIF criteria, numerous definitions for AKI existed in the literature.^{2,3} Hence, results of studies on the incidence, prognosis, and outcome of AKI were dependent on the definition and study population. With reference to the new definition, AKI incidence in the critically ill paediatric population was reported to range from 10% among patients admitted to the paediatric intensive care unit (PICU) to 82% among those receiving ventilatory support,^{5,7-9} and the reported figures in adults were similar (11% to 78%).9 As defined, the RIFLE criteria are demonstrably independent predictors of mortality in critically ill paediatric and adult patients.^{5,9,10}

The objective of this study was to determine the local prevalence and clinical course of AKI in critically ill paediatric patients admitted to the PICU using the pRIFLE score. It also aimed to determine the association between AKI and outcome.

Methods

The medical records of all patients admitted to the PICU of Queen Elizabeth Hospital of Hong Kong in the years 2005 to 2007 were retrospectively analysed. Records were excluded for: (1) patients younger than 30 days or older than 19 years; (2) those with pre-existing chronic renal failure; (3) those not having an indwelling urinary catheter for accurate urine output measurement whilst in the PICU, and (4) those admitted for postoperative care after elective surgery. Repeat admissions were counted separately, as different factors might contribute differently to the analysis.

Demographic data, underlying medical illnesses, diagnosis, and indication for admission were recorded. Potential prognostic factors included scores for PRISM III (the third-generation of Pediatric Risk of Mortality¹¹) that is a mortalitypredicting scoring system used in PICU, the number of organ failures¹² (as pre-defined), electrolytes and

Classification	Estimated creatinine clearance (eCCI)*	Urine output	
Risk	Decreases by 25%	<0.5 mL/kg/h x 8 hours	
Injury	Decreases by 50%	<0.5 mL/kg/h x 16 hours	
Failure	Decreases by 75% or eCCL <35 mL/min/1.73 m^2	<0.5 mL/kg/h x 24 hours or anuric x 12 hours	
Loss	Persistent failure >4/52 weeks		
End-stage	End-stage renal failure (persistent failure >3/12 months)		

* eCCl was calculated by using the Schwartz formula⁶

haemoglobin level, as well as resorting to ventilatory and/or inotropic support were collected. Urine output and fluid balance data were recorded. Fluid overload was defined by the following formula¹³:

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Total fluid intake (L) – Total fluid output (L)
Body weight on admission (kg) x 100%
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Baseline eCCl was determined using the lowest creatinine level up to 1 year before the current admission, which was available through the electronic laboratory database. As suggested in the original article on pRIFLE criteria,⁵ an assumed baseline eCCl of 100 mL/min/1.73 m² was assigned if no baseline data were available for calculation. The worst eCCl that could be obtained during a PICU stay was used for comparison with the baseline value.

Based on the percentage change in eCCl (comparing the worst and baseline value), and counting the consecutive hours with urine output of <0.5 mL/kg/h, the respective worst pRIFLE grade among either "R", "I", or "F" was assigned for each admission, on the first day and throughout the whole period of PICU stay. The eCCl-based RIFLE score (RIFLE_{Cr}) and urine output-based RIFLE score (RIFLE_{Cr}) and urine output-based RIFLE score (RIFLE_{Cr}) were recorded separately. Notably, AKI was defined as the patient having attained either "R", "I", or "F" grade by either RIFLE_{Cr} or RIFLE_{Ur} criteria. The primary outcome measure was mortality. Renal outcome was the secondary measure.

Data analysis

For data entry and statistical analysis, the Statistical Package for the Social Sciences (Windows version 16.0; SPSS Inc, Chicago [IL], US) was used. Scaled data were analysed as continuous variables, whereas ordinal or nominal data were analysed as categorical results. Distributions for continuous variables were tested for normality, and transformation attempted for non-normal distributions. Unpaired Student's t tests and Wilcoxon ranked-sum tests were used for comparisons between continuous variables, whereas categorical data were compared using Chi squared or Fisher's exact tests. Correlation between categorical data was determined using the gamma coefficient. Significant risk factors for mortality identified from the univariate analysis were selected for further evaluation to predict any independent effects on mortality. Hazard ratios (HRs) were estimated using the Cox proportional hazards model. Continuous variables were expressed as mean ± standard deviation (SD) and statistical significance was defined as any P<0.05.

Results

Demographic data

There were 640 admissions during the study period, admission stratified by RIFLE, grade

of which 140 were considered suitable for final analysis; exclusions being for the reasons listed above. Regarding these 140 PICU stays, 12 had missing baseline data but that obtained in the PICU thereafter was nevertheless available for analysis. In all, 13 patients accounted for 41 episodes of PICU stay, of which 22 were during the same hospitalisation. The mean patient age was 8.5 ± 6.4 years (range, 1 month - 18 years 10 months) and the male-to-female ratio was approximately 2:1 (66%:34%). The reasons for admission were categorised as: neurological (24%), respiratory (23%), cardiac (11%), trauma (9%), renal (6%), metabolic (5%), infection (4%), and other (19%). The mean PRISM III score for these admissions was 8.6 \pm 8.2 and the mean number of organ failure was 1.5 ± 1.4. Inotropic and ventilatory support (both invasive and non-invasive) were offered for 29% and 59% of these admissions, respectively; the mean duration of ventilatory support was 9 ± 14 days. Baseline creatinine was not available in 76 (54%) of the patients.

Prevalence and clinical course of acute kidney injury

Based on the RIFLE_{Cr}, the prevalence of AKI was 46% (59 of admissions to the PICU), and increased to 55% (77 admissions) during the PICU stay. Among those who developed AKI during their PICU stay, the mean time to do so was 4 ± 6 days; in 45 (58%) out of 77 instances, the maximal grade was attained 1 day after PICU admission. The progression of AKI after PICU admission based on the RIFLE_{Cr} is illustrated in Figure 1. Altogether 14 (20%) of the admissions with no AKI



FIG I. Progress of acute kidney injury (AKI) after paediatric intensive care unit (PICU) admission stratified by RIFLE_c grade

on admission showed worse RIFLE grading during their PICU stay; nine (13%) of them progressed to "R" grade, and five (7%) to "I" grade. Regarding instances of "R" grade on admission, nine (30%) progressed to "I" grade during PICU stay, while eight (40%)

TABLE 2. Distribution of acute kidney injury on admission and during paediatric intensive care unit (PICU) admission using different pRIFLE criteria

Grade	On admission (n=128)*	During PICU stay (n=140) [†]	
	RIFLE _{cr} ‡	RIFLE_{cr}	RIFLE _{ur} ‡
Nil	69 (54%)	63 (45%)	123 (88%)
R	30 (23%)	32 (23%)	4 (3%)
1	20 (16%)	28 (20%)	4 (3%)
F	9 (7%)	17 (12%)	9 (6%)

 Data were missing for calculation of RIFLE_{Cr} on admission for 12 patients, but their data during the PICU stays were available for analysis

⁺ The worst RIFLE grade (by either estimated creatinine clearance [eCCl] or urine output criteria) attained during PICU stay was used

 * RIFLE_{Cr} denotes RIFLE score by eCCl, and RIFLE_{Ur} RIFLE score by urine output



FIG 2. Survival during intensive care unit stays in patients with and without acute kidney injury (AKI) based on (a) RIFLE_c and (b) RIFLE_{Ur} P=0.011 for RIFLE_c and P=0.025 for RIFLE_{1r} by log-rank test

progressed from "I" grade on admission to "F" grade during their PICU stay. Among the 59 patients who had already developed AKI on PICU admission, only three (5%) improved: two from "R" grade to no AKI, and one from "F" to "I" grade.

Based on the RIFLE_{Ur}, the prevalence of AKI was 12% (17 admissions) during their PICU stay. Similarly, among those who developed AKI during their PICU stays, the mean time to do so was 6 ± 9 days and in 7/17 (41%) of instances the maximal grade was attained 1 day after admission.

The overall prevalence of AKI during PICU stay (using either urine or eCCl criteria) was 56% (78 instances). Table 2 shows the distribution of different RIFLE categories.

The gamma coefficient between $RIFLE_{cr}$ and $RIFLE_{Ur}$ was 0.85 (P=0.001) on day 1 and 0.81 (P<0.001) during PICU stay, which indicates a good correlation between the two.

Mortality

The overall mortality at discharge from PICU of the whole cohort was 12% (17 patients). The mortality among patients with AKI was 21% (16 patients) using RIFLE_{Cr}, compared to 2% (1 patient) among those without AKI (P<0.001). Using RIFLE_{Ur}, the mortality was 41% (7 patients) in those with AKI, compared to 8% (10 patients) in those without AKI (P<0.001). Overall, a statistically significantly higher mortality was observed in patients with AKI.

Survival analysis also revealed that development of AKI by using RIFLE_{Cr} criteria was associated with a significantly higher mortality during PICU stay (HR=8.82; 95% confidence interval [CI], 1.15-67.87; P=0.037). This relationship was also observed using RIFLE_{Ur} (HR=3.08; 95% CI, 1.10-8.65; P=0.033). Figure 2 shows cumulative survival using different criteria (P=0.011 for RIFLE_{Cr} and P=0.025 for RIFLE_{Ur} by logrank test). Table 3 shows the HRs for mortality using the different RIFLE grading (on admission and during PICU stay).

Comparisons were carried out between survivors and non-survivors during PICU stay using univariate analyses. No statistically significant difference was noted between the two groups with respect to age and gender. Besides AKI, factors associated with mortality included higher serum creatinine (P=0.023), more severe acidosis (P<0.001), lower blood pressure (P=0.048), lower Glasgow Coma Scale scores (P=0.002) and higher PRISM III scores (P<0.001) on admission, and higher percentages having fluid overload (P=0.038) and inotropic or ventilatory support (P<0.001), as well as higher numbers of failed organs (P<0.001) during PICU stay. The multivariate Cox proportional hazard model did not show any statistically significant independent effect on mortality for patients with AKI developing during their PICU stay. However, having AKI of grade "F" as defined by RIFLE_{Cr} on admission was independently associated with mortality (HR=5.94; 95% CI, 1.06-33.36; P=0.043) [Table 4].

Renal outcome

Concerning renal outcomes, only eight (6%) out of the 140 admissions entailed continuous renal replacement therapy (CRRT) during the PICU stay. Among the 132 admissions that did not entail such support, 113 (86%) were discharged from the PICU with normal renal function, and 19 (14%) with renal impairment. For those who had received CRRT, only one (13%) of them was discharged with normal renal function; four (50%) were discharged with renal impairment and three others (38%) received longterm renal replacement therapy.

Discussion

Acute kidney injury in paediatric patients confers a relatively high mortality and remains a challenge to paediatric nephrologists and intensivists. It is now being recognised that AKI is not a single disease entity, but a complex disorder due to various aetiologies and has a wide range of manifestations. Although new biomarkers such as neutrophil gelatinase-associated lipocalin, cystatin C, and interleukin-18 are under investigations for the diagnosis of this entity,14 change in serum creatinine and urine output remain the most readily available and accepted methods. Before the introduction of the RIFLE criteria, the diverse definitions of this condition caused great confusion for both clinical management and comparison of research results. After its publication, the RIFLE score has become a widely accepted tool for defining AKI in adults.^{4,15} Although the number of relevant studies using the pRIFLE criteria is still limited, there is also support for their use in critically ill paediatric patients.

In our cohort, the period prevalence of AKI during PICU stays was 56% using either RIFLE_{Cr} or RIFLE₁₁. It was lower than the reported figure of 82% in the original article on pRIFLE.5 However, in that cohort all the patients had respiratory failure and were in receipt of mechanical ventilation, whereas our study subjects comprised individuals with and without respiratory failure. Similar to the population characteristics of our cohort, Schneider et al⁹ evaluated 3396 PICU admissions with mixed disease diversity and reported a lower AKI prevalence of 10%. In contrast to our data, their study used only the change in serum creatinine to define AKI and not the change in eCCl. Patients without an indwelling urinary catheter were excluded from our analysis; the original article on pRIFLE⁵ evaluated the urine criteria only in patients with indwelling urinary catheters.

TABLE 3. Hazard ratios of mortality at discharge from paediatric intensive care unit (PICU) based on RIFLE criteria on admission and during PICU stay

Grade	Hazard ratio (95% confidence interval)*		
_	On admission	During PICU stay	
_	RIFLE _{cr}	RIFLE _{cr}	RIFLE _{ur}
R	1.60 (0.27-9.59)	4.66 (0.48-45.11)	2.36 (0.30-18.68)
I	4.43 (1.07-18.42)	12.28 (1.51-99.84)	3.32 (0.42-26.14)
F	6.64 (1.09-40.36)	10.59 (1.16-97.03)	3.29 (0.97-11.11)
Either R, I, or F	3.41 (0.93-12.43)	8.82 (1.15-67.87)	3.08 (1.10-8.65)

As compared to no acute kidney injury

TABLE 4. Adjusted hazard ratios of mortality at discharge from the paediatric intensive care unit (PICU) based on RIFLE criteria on admission and during PICU stay

Model	Variable [‡]	Adjusted hazard ratio (95% confidence interval)
1*	Grade "F" by RIFLE _{cr} on admission	5.94 (1.06-33.36)
2*	Grade "I" or "F" by $RIFLE_{Cr}$ on admission	0.61 (0.16-2.28)
3*	Any AKI by RIFLE _{cr} on admission	0.83 (0.21-3.33)
4*	Grade "F" by RIFLE _{cr} during PICU stay	0.54 (0.13-2.28)
5*	Grade "I" or "F" by RIFLE _{Cr} during PICU stay	1.07 (0.30-3.76)
6*	Any AKI by RIFLE _{cr} during PICU stay	2.29 (0.29-18.34)
7†	Grade "F" by RIFLE _{Ur} during PICU stay	0.40 (0.09-1.69)
8†	Grade "I" or "F" by RIFLE_{Ur} during PICU stay	0.46 (0.12-1.75)
9†	Any AKI by $RIFLE_{Ur}$ during PICU stay	0.60 (0.17-2.06)

Variables include PRISM III score, fluid overload %, and RIFLE grading as charted

Variables include PRISM III score and RIFLE grading as charted

RIFLE_{cr} denotes RIFLE score by estimated creatinine clearance, $RIFLE_{Ur}$ RIFLE score by urine output, and AKI acute kidney injury

Regrettably, a large number of our admissions were excluded as they lacked such urinary catheters to accurately document the hourly urine output. The excluded subjects may theoretically represent a less critically ill population. Whether this could bias the estimation of the true AKI prevalence requires further evaluation.

Another limitation was that the baseline creatinine level was not available in 54% of our cohort, and an assigned eCCl of 100 mL/min/1.73 m² was used to represent the baseline value. For those with available baseline serum creatinine levels, the mean eCCl was 197 mL/min/1.73 m², far exceeding the assigned value of 100 mL/min/1.73 m². The original article on pRIFLE reported that 27% of patients did not have baseline creatinine levels.⁵ Another study concerning AKI among burn patients reported 97% as not having baseline creatinine levels and they were assigned an eCCl of 120 mL/min/1.73 m²; their reported AKI prevalence was 46%.8 Undoubtedly, the proportion of patients without baseline creatinine levels and the value of assigned eCCl could affect the RIFLE grading and hence the AKI prevalence.

The majority of patients attained their maximal RIFLE grade on the first day after PICU admission, and the distribution was similar to that of multiple organ dysfunction among critically ill children.¹⁶ Furthermore, 31 (24%) out of 128 admissions had progression of AKI during PICU stay; the percentage increased to 29% (17/59 admissions) if only grade "R" and "I" grades were included, which was akin to the figure reported by others.^{5,9} Similar to the persistence of multiple organ dysfunction, persistence or worsening of AKI has also been demonstrated to confer a poor prognosis.^{5,9,17} This also supports early initiation of appropriate measures to prevent or reverse AKI to alter the prognosis. General measures such as adequate fluid resuscitation for pre-renal AKI, and cautious use of nephrotoxic medications with dosage adjustment as needed are essential. The use of furosemide for inducing diuresis is a common practice for critically ill adult and paediatric patients,^{2,18} however, controversy exists concerning this practice. Lack of clinical effectiveness or even a detrimental effect on survival and renal recovery was suggested in a recent review, which has led to uncertainty about its widespread use.¹⁸ Together with its associated ototoxicity when administered in high dose, further evaluation of its clinical benefits in children with AKI is therefore warranted.

The mortality in our patients with AKI was comparable to that in other recent studies of paediatric subjects, which ranged from 8.9 to 33.6%.^{5,7-9,19-21} Clearly, mortality was higher in patients with AKI either on admission or during their PICU stay. Our data also showed a remarkably high mortality of 41% among patients with AKI based on the RIFLE_{Ur} criteria. Any factors that potentially affect mortality during PICU stay could confound the association between AKI and mortality. Indeed, previous studies in paediatric AKI had reported that oliguria and anuria were associated with mortality.^{20,21} After adjusting for such potential confounders, having AKI with grade "F" based on RIFLE_{cr} on admission was also found to be an independent predictor of mortality. We failed to demonstrate that AKI conferred an independent risk on mortality as the RIFLE score became worse, which could be due to the relatively small number of subjects within each stratum. However, the trend of increasing mortality as RIFLE scores worsened was clearly evident. It must be stressed that the initial design of RIFLE was not to predict mortality, but provide a classification scheme to identify AKI with various degrees of clinical severity.

The pRIFLE classification serves as an appropriate means of stratifying patients with different severities of injury; renal replacement therapy was deemed needed only in patients with RIFLE_{Cr} grade "I" or above. And even among those without CRRT, in terms of renal outcome our data showed that patients having AKI had a worse prognosis than those without. Long-term studies have shown that survivors of AKI may have persistently abnormal renal parameters and even develop chronic renal failure warranting long-term renal replacement therapy.^{22,23} A longitudinal study in adults has also shown worse long-term survival among survivors of AKI compared to the general population.²⁴ Hence, regular monitoring of renal parameters should be considered in all PICU survivors with AKI, especially among those discharged with abnormal renal function.

Although this was a single-centre study, our hospital drains a regional population of around 500 000 inhabitants and the PICU receives critically ill patients from 1 month of age up to 18 years of age who have various surgical, medical, and traumatic conditions. Hence, its results can probably give an insight into these problems for the entire territory.

One limitation of our study was the exclusion of patients lacking an indwelling urinary catheter. Others were that a relatively high proportion of patients lacked baseline creatinine levels, and the sample size was small conferring low statistical power. The number of subjects within each RIFLE stratum may not have been large enough to demonstrate associations between outcome and RIFLE staging, particularly the RIFLE criteria obtained on admission to the PICU. Potentially, this was more reflective of pre-PICU admission status and may be more relevant as a parameter to predict PICU outcome. Furthermore, volumes of fluid intake and output could be affected by many other external factors, hence influencing the accuracy of fluid overload status calculations. However, the formula used is widely accepted for such calculations.²⁵ Lastly, owing to manpower limitations, the first author was the person who extracted the data from medical records, and this may have potentially caused bias, but was minimised by using a standard data collection sheet pre-designed before the data extraction process. Moreover, exclusion criteria had been set before the data collection and were strictly adhered to throughout the study.

Conclusion

This study supports use of the pRIFLE score as a useful tool for AKI classification and as a means of offering a prognostic value with respect to mortality and renal outcome. Development of AKI in critically ill paediatric patients is associated with worse outcomes. A standardised universal classification scheme such as pRIFLE score could benefit not only future paediatric AKI research but also aid its early identification in critically ill patients.

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