original article

Incidence and outcome of acute kidney injury by the pRIFLE criteria for children receiving extracorporeal membrane oxygenation after heart surgery

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Ann Saudi Med 2017; 37(3): 201-206

DOI: 10.5144/0256-4947.2017.201

BACKGROUND: Acute kidney injury (AKI) is common in patients treated with extracorporeal membrane oxygenation (ECMO). The RIFLE criteria demonstrate clinical relevance for diagnosing AKI and classifying its severity.

OBJECTIVES: To systematically define the incidence, clinical course and outcome of AKI using the pediatric pRIFLE criteria.

DESIGN: Retrospective, medical records review.

SETTINGS: Pediatric cardiac surgical intensive care units at a tertiary care hospital in Riyadh.

PATIENTS AND METHODS: We reviewed the records of all pediatric patients that underwent cardiac surgery and required ECMO postoperatively between 1 January 2011 and 1 January 2016. AKI was classified according to the pRIFLE criteria 48 hours after ECMO initiation. Demographics and concomitant therapies for all patients were collected.

MAIN OUTCOME MEASURE(S): Outcome was assessed by recovery from AKI at time of discharge, ICU stay and mortality.

RESULTS: Fifty-nine patients needed ECMO after cardiac surgery during the study period. Their mean (SD) age and weight was 11.0 (16.5) month and 5.5 (3.6) kg, respectively. All patients had a central venoarterial ECMO inserted. Fifty-three patients (90%) developed AKI after ECMO initiation. The majority of patients (57%) were categorized as pRIFLE-Failure, having a higher mortality rate (28/34 patients, 82%) in comparison to the pRIFLE-Injury and pRIFLE-Risk groups. Twenty-nine patients (49%) required either peritoneal dialysis (PD), or renal replacement therapy (RRT) or both. For AKI vs non-AKI patients, there was a statistically significant difference between mean (SD) ECMO duration (9.0 [8.00] vs 6.0 [2.0] days; *P*=.02) and ICU stay (37.0 [41.0] vs 21.0 [5.0] days; *P*=.03), respectively. The overall mortality rate was 58%, with a significant difference (*P*=.03) between AKI and non-AKI groups. All the patients who survived had normal creatinine clearance at hospital discharge.

CONCLUSION: There is a high incidence of AKI in pediatric patients requiring ECMO after cardiac surgery, and it is associated with higher mortality, increased ECMO duration, and increased ventilator days.

LIMITATIONS: Single-center retrospective analysis and the small sample size limited the precision of our estimates in sub-populations.

Acute kidney injury (AKI) can be exacerbated by critical illnesses, preexisting medical conditions, and treatments received by patients, both before and during admission to the intensive care unit (ICU).

The incidence of AKI varies according to the definition used and the criteria used to define AKI. There is wide variation in the reported incidence of AKI in critically ill children that were admitted to a pediatric intensive care unit (PICU), ranging from 4.5% to 82.0%.[1,2] This wide range is partly due to the lack of a standardized definition of AKI. It was not until 2004 that Acute Dialysis Quality Initiative experts decided to formulate a standard definition of AKI in adults by developing the RIFLE classification. The RIFLE acronym stands for the increasing classes of severity from a low level (Risk) for renal dysfunction, (Injury) to the kidney, (Failure) of renal function, total (Loss) of renal function, and (End-stage) renal disease (ESRD).[3] The RIFLE criteria display clinical relevance in the diagnosis of AKI, aiding in the classification of severity, monitoring the progression of disease and predicting mortality rates in hospitalized patients, whether pediatric or adult.[4]

Following the development of the RIFLE classification, Akcan-Arikan and a group of researchers proposed the pediatric RIFLE (pRIFLE) criteria. Their classification was based upon the decrease in estimated creatinine clearance, and/or urine output measurement in relation to body weight.[5] Progression of AKI per RIFLE criteria is independently associated with an increase in mortality rates in the PICU while improvement is correlated with an incremental decrease in mortality.[6]

AKI is common in patients treated with venoarterial or venovenous extracorporeal membrane oxygenation (ECMO).[7] In this particular setting, using continuous renal replacement therapy (CRRT) may aid in optimizing fluid status, but can also impact patient outcome negatively.[8] Moreover, the need for renal replacement therapy (RRT) during ECMO is considered an independent an independent predictor of mortality.[9] The relationship between AKI, RRT, and survival in critically ill pediatric cardiac patients receiving ECMO is not well defined. In this study we aimed to define systematically the incidence and clinical course of AKI in children supported by ECMO after cardiac surgery, using the pRIFLE criteria, and to assess the outcome of these patients with AKI in comparison to those who did not develop AKI.

PATIENTS AND METHODS

We conducted a retrospective review of the medical records of all patients who underwent surgery and required ECMO postoperatively, in the period between 1 January 2011 and 1 January 2016 (5 years). An institutional review board approval and waiver of consent was obtained (RAC project no. 2161231). Data was reviewed for all patients on ECMO, and assigned to the appropriate pRIFLE strata (**Table 1**) based on 48-hour post-ECMO creatinine clearance levels and on reports that the severity of AKI is maximal within the first 2 days after the start of ECMO.[10] Estimated creatinine clearance was calculated by the Schwartz formula ([length (cm) × K (constant)/serum creatinine]).[11]

Information on patient demographics, diagnosis, cardiac surgical procedure(s), reason and duration for ECMO, baseline serum creatinine prior to surgery, duration of mechanical ventilation, duration of ICU and hospital stay, was gathered from medical records and the hospital electronic database. The cardiac surgical procedures were categorized according to the RACHS (Risk Adjusted Congenital Heart Surgery) Score (**Appendix 1**). Outcome data were predefined as the need for RRT, ICU and hospital stay, 28-day mortality and creatinine clearance for patients who survived at time of hospital discharge. All data was input into a predesigned data collection form specific for the study. All pediatric patients with congenital heart disease admitted to the Cardiac Surgical Intensive Care Unit after cardiac surgery who required ECMO postoperatively during the study period were included. Patients were excluded if they did not require ECMO support postoperatively during the study period or had a known renal abnormality preoperatively.

The statistical analysis was done using the software package SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics for continuous variables are reported as mean and standard deviation and categorical variables are summarized as frequencies and percentages. Continuous variables are compared by the independent t test, while categorical variables were compared and relative risks and confidence intervals calculated by the chi-square or Fisher exact test. The level of statistical significance was set at $P<.05$.

RESULTS

Fifty-nine patients, 30 males (52%) and 29 females (48%) needed ECMO after cardiac surgery during the study period. Their mean age was 11.0 (16.5) month and weight 5.6 (3.7) kg (**Table 2**). The mean preoperative serum creatinine level was 33.4 (13.7) μmol/L. The majority of the cardiac surgical procedures done were categorized as RACHS score 3 (57%) (**Figure 1**). All patients who required ECMO had central venoarterial cannulation. Eighteen patients (30%) had ECMO initiated in the operating room (OR), and 42 patients (70%) needed cannulation and ECMO initiation in the ICU. Sixty-one percent of the patients needed ECMO for postoperative low cardiac output syndrome (LCOS), and 39% required rescue ECMO after cardiac arrest. Fifty-three patients (90%) developed AKI after ECMO initiation as per pRIFLE criteria, with the majority of patients (57%) categorized as pRIFLE-Failure (pRIFLE-F), having a higher mortality rate (28/34 patients, 82%) in comparison to the pRIFLE-Injury (pRIFLE-I) and pRIFLE-Risk (pRIFLE-R) groups (**Figure 2**). Twenty-nine patients (49%) required either peritoneal dialysis (PD), or renal replacement therapy (RRT) or both. Six patients did not develop AKI.

There was a statistically significant difference between mean ECMO duration and ICU stay for patients with AKI [9.0 (8.0) and 37.0 (41.0) days, *P*=.02] and non-AKI patients [6.0 (2.0) and 21.0 (5.0) days, *P*=.03]. There was no significant difference (*P*=.5), between mortality for ECMO post-cardiac arrest and ECMO for LCOS. The overall mortality rate was 58%, with a significant difference between AKI and non-AKI patients (*P*=.03) (**Table 3**). The patients who developed AKI while on ECMO had a 4-fold higher risk of mortality in comparison to those who did not develop AKI (95% CI, 0.7-24) (*P*=.02).

There was a significant association between development of AKI and mortality (*P*=.02) (relative risk, 1.2, CI 0.9-1.5), and the odds of mortality were ten times higher in the AKI group as compared to the non-AKI group. Moreover, the odds of mortality were 23 times higher in the AKI pRIFLE-F group in comparison to pRIFLE-I and pRIFLE-R groups (*P*=.003) (relative risk 1.7, 95% CI 1.02-3.04)

All the patients who survived recovered renal function with lower trends in mean serum creatinine levels at hospital discharge (**Table 3**).

DISCUSSION

In this study, our aim was to systematically define the incidence and clinical course of AKI in children supported by ECMO after cardiac surgery, using the pRIFLE criteria for diagnosis of AKI. We decided to use the pRIFLE criteria for its diagnostic and prognostic sensitivity. It was recently reported by Daniel and colleagues to be the most sensitive test in detecting AKI.[12] Moreover, Zappitelli and coworkers found that small increases in the serum creatinine during the immediate postoperative period predict the development of AKI according to the pRIFLE criteria and that moderate-to-severe AKI is associated with increased morbidity and mortality irrespective of the need for ECMO support.[13] In their study group, AKI occurred in 36% of patients, mostly in the first 4 postoperative days. With further analysis for risk factors of post-cardiac surgery AKI using logistic regression, they reported that significant independent risk factors for AKI were bypass time, longer vasopressor use, and a tendency toward younger age.

According to the Extracorporeal Life Support Organization registry, renal dysfunction while receiving ECMO support is a well-described morbidity among cardiac patients.[14] Smith and colleagues demonstrated an incidence of acute renal failure of 71.7% in 45 pediatric cardiac patients requiring ECMO.[15] The definition for acute renal failure was a glomerular filtration rate of <35 mL/min/1.73 m^2 or electrolyte disturbance and/or fluid retention resulting in institution of continuous

Table 1. 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	< 0.5 mL/kg/h for 24 h or anuric for 12 h
Loss	Persistent failure > 4 weeks	
End-stage renal disease	Persistent failure > 4 weeks	

eCCl: estimated creatinine clearance.

Table 2. Characteristics of patients on ECMO with and without postoperative acute kidney injury.

Characteristic	Postoperative AKI (n=53)	No postoperative AKI (n=6)	*P* value
Age at surgery	10.3 (16.9)	17.8 (11.5)	.2
Weight at surgery	5.3 (3.7)	7.9 (2.9)	.1
Female (%)	47	67	.3
Preoperative serum creatinine (µmol/L)	34.4 (14.1)	24.7 (4.7)	.002
RACHS score (score, %)			
2	3 (6)	3 (50)	.0009
3	32 (60)	1 (16.6)	.046
4	15 (28)	1 (16.6)	.5
6	3 (6)	1 (16.6)	.3
Reason for ECMO			
Low cardiac output syndrome	34 (64%)	2 (33%)	.1
Cardiac arrest	19 (36%)	4 (67%)	.1

Data are mean and standard deviation or n (%). ECMO: extracorporeal membrane oxygenation, AKI: acute kidney injury, RACHS: Risk Adjusted Congenital Heart Surgery.

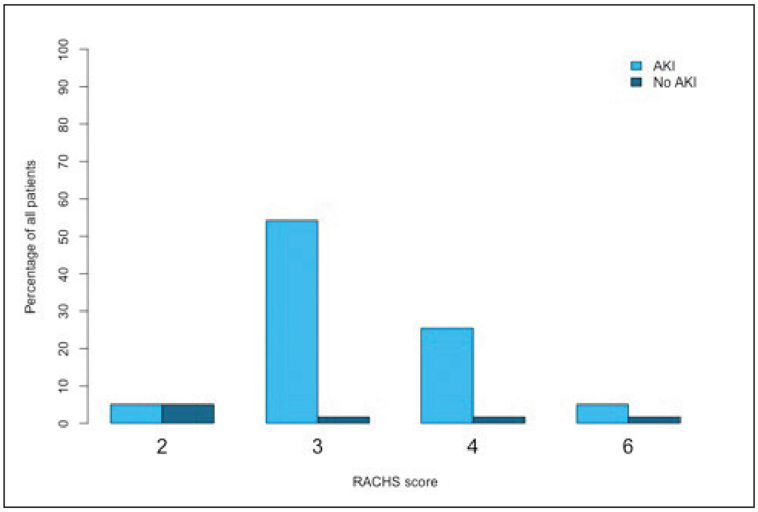

Figure 1. The percentage of patients for each RACHS score category for both acute kidney injury (AKI) and non-AKI patients. RACHS: Risk-Adjusted Congenital Heart Surgery.

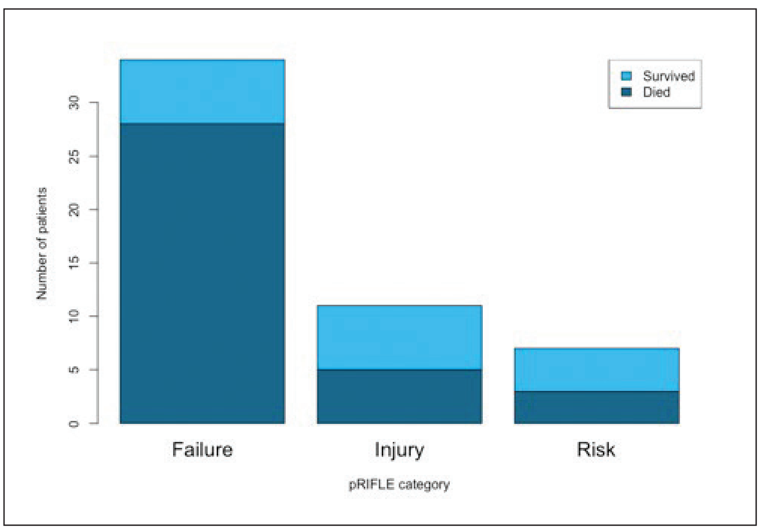

Figure 2. The percentage of patients in each pRIFLE category for all the 53 patients who develop acute kidney injury and corresponding mortality rates.

RRT. The incidence of AKI on ECMO in our pediatric population with a mixed sample of neonates, infants, and children after cardiac surgery was 90%, as defined by the pRIFLE criteria. The incidence in our study was higher than other reports, but we believe that a certain degree of renal insufficiency while on ECMO support is significantly more prevalent than what has been described. This reasoning may be partially a consequence of previous use of a somewhat less comprehensive definition of acute renal failure or the complexity of post cardiac surgery cases requiring ECMO support, especially in patients who develop AKI with a RACHS score 3 and above (as in our study), inferring that this population is at a higher risk of developing AKI.

Few studies have investigated the possible reasons for the clear association between ECMO and AKI. AKI could be associated with a number of conditions, which are primarily hormonal, hemodynamic and inflammatory in nature, derived from or related to extracorporeal therapy. The critical condition of patients treated with ECMO along with the countless variables related to technically elaborate extracorporeal treatment seldom allow for an accurate understanding of the pathophysiological mechanism responsible for AKI development during ECMO. Multidimensional evaluations in addition to multimodal therapies must be integrated in a versatile, patient-tailored multi-organ support therapy.[16]

We found no significant association between the indication of ECMO initiation either for LCOS or post-cardiac arrest and the development of AKI. Our findings are consistent with the report by Smith and coworkers who reported no association in a multiple regression analysis between reasons for ECMO and development of AKI post-cardiac surgery in pediatric patients requiring ECMO.[15] In our study, patients who developed AKI had a longer duration on ECMO. Another association noted in another series was duration of ECMO support and the development of acute renal failure.[15]

Several studies have shown that AKI after cardiac surgery confers a significant increased risk of mortality and morbidity for both adults and pediatrics with a reported 4-fold increase in the mortality rate.[1,17-19] The mortality rate in our study for patients who developed AKI was 3-fold higher than those without AKI. In an adult study, it was found that AKI in conjunction with ECMO is associated with increased mortality rates of up to 80%.[20] Additionally, we observed an association between advanced AKI (pRIFLE-F) and a significant stepwise increase in mortality risk in this exclusive post-cardiac surgery ECMO population. Zappitelli and coworkers associated moderate-to-severe AKI (pRIFLE injury and failure) with increased hospital mortality in children who underwent cardiac surgery.[13] Another study showed that following adjustment for known predictors of mortality, AKI and RRT independently predict the rate of mortality in neonates and children that receive ECMO.[6] Keeping in mind that failure of an additional organ has undesirable effects on patient outcome, the remarkable increase in mortality because of the association between ECMO and RRT is far from surprising.

In a study that focused specifically on infants who underwent cardiac surgery and developed AKI, the authors concluded that the underlying reasons for the increase in AKI-related mortality risk are not well understood, but may include worsening fluid overload and pulmonary mechanics; these conditions necessitate prolonged mechanical ventilation and potentially increased exposure to invasive infection.[17] Additionally, recent evidence suggests that kidney injury or failure can lead to cardiac dysfunction as a result of inter-organ "crosstalk" that is independent of the adverse renal consequences of serum electrolyte and fluid dysregulation.[21] Simultaneous cardiac and renal dysfunction is referred to as cardiorenal syndrome.[21]

In one study, all classification systems were associated with significantly higher serum creatinine and lower estimated creatinine clearance at any measurement points, including preoperative levels.[12] We also observed a higher mean serum creatinine for patients who develop AKI in comparison to those who did not have AKI, both at baseline and at the time of hospital discharge for those who survived. Furthermore, glomerular filtration rates have been reported to be significantly lower just before the institution of ECMO support among patients who ultimately developed kidney injury, indicating that despite instituting mechanical support, those having preexisting renal injury could exhibit a predisposition for the development of AKI.[15]

There is consensus among experts that implementing novel renal monitoring modalities based on relevant pathophysiology will provide novel strategies for preventing and treating AKI. Ultimately, earlier detection with biomarkers may enable early evidence-based risk stratification for diagnostic evaluation, monitoring AKI, and initiating renal protective interventions for patients on ECMO.[22]

Ascertainment of AKI risk factors, testing novel therapies, and optimizing the timing and delivery of RRT may positively impact survival in infants who undergo surgery for congenital heart disease, especially those who may require postoperative ECMO support.

Systems for classifying AKI can and should be used at the bedside to risk stratify these infants. Our results also raise the issue that follow-up of longer-term outcomes in these groups may demonstrate persistent morbidity that is not yet identified.

Although we were able to find statistically significant associations, the small sample size in this single-center retrospective analysis limited the precision of our estimates in subpopulations. In addition, we were not able to completely stratify for severity of illness or multiple organ dysfunction since there is no defined severity of illness score for pediatric cardiac patients on ECMO.

In conclusion, we found a high incidence of AKI in pediatric patients requiring ECMO after cardiac surgery that was associated with higher mortality, increased ECMO duration, and increased ventilator days. This highlights the importance of recognizing AKI in these patients and the potential benefits of preventing progression of AKI or implementing early intervention. The pediatric-validated pRIFLE classification system is substantially useful in this particular patient population.

Table 3. Outcome of patients with postoperative acute kidney injury.

Outcome parameter	Postoperative AKI (n=53)	No postoperative AKI (n=6)	*P* value
ECMO duration (days)	9.0 (8.0)	6.0 (2.0)	.02
Ventilation duration (days)	26.0 (28.0)	16.0 (6.0)	.03
ICU stay (days)	37.0 (41.0)	21.0 (5.0)	.009
Hospital stay (days)	46.0 (43.0)	37.0 (22.0)	.6
Serum creatinine at discharge (μmol/L)	59.0 (35.0)	26.0 (7.0)	.02
In-hospital mortality (%)	62	17	.03

Data are mean and standard deviation. AKI: acute kidney injury, ECMO: extracorporeal membrane oxygenation.

Conflict of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial in the subject matter or materials discussed in this manuscript.

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