Clinical Features and Risk Factors Associated with Mortality in Critically ill Children Requiring Continuous Renal Replacement Therapy

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Abstract

Background: The aims of this study were to describe the epidemiology and demographic characteristics of critically ill children requiring continuous renal replacement therapy (CRRT) at our pediatric intensive care unit (PICU) and to explore risk factors associated with mortality.

Methods: A retrospective cohort of 121 critically ill children who received CRRT from May 2015 to May 2020 in the PICU of a tertiary healthcare institution was evalauted. The demographic information, admission diagnosis, indication for CRRT, clinical variables at the initiation of CRRT, time related variables and the laboratory results at initiation of CRRT were compared between survivors and non-survivors.

Results: The most common diagnoses were renal disease (30.6%), hemato-oncological disease (12.4%), and sepsis (11.6%). The overall mortality was 29.8%. When compared according to diagnosis at admission, we found that patients with hemato-oncologic disease (73.3%) and those with pneumonia/respiratory failure (72.7%) had the highest mortality, while patients with renal disease had the lowest mortality (5.4%). The most common CRRT indications were: electrolyte or acid base imbalance (38.8%), acute kidney injury (29.8%) and fluid overload (14.9%). There was no relationship between mortality and indication for CRRT. The time interval between PICU admission and CRRT initiation was also unassociated with mortality (p=0.146). In patients diagnosed with sepsis, time until the initiation of CRRT was significantly shorter in survivors compared to non-survivors (p=0.004). Based on multivariate logistic regression, presence of comorbidity (odds ratio: 5.71; %95 CI: 1.16-27.97), being diagnosed with pneumonia/respiratory failure at admission (odds ratio: 16.16; %95 CI: 1.56-167.01), and high lactate level at the initiation of CRRT (odds ratio: 1.43; %95 CI: 1.17-1.79) were independently associated with mortality.

Conclusions: In the context of the population studied mortality rate was lower than previously reported. In critically ill children requiring CRRT, mortality seems to be related to underlying disease, presence of comorbidity, and high lactate levels at CRRT initiation. We also found that early initiation of CRRT in sepsis can reduce mortality.

Background

Continuous renal replacement therapy (CRRT) is an increasingly used renal replacement therapy (RRT) method that provides continuous fluid and solute clearance in hemodynamically unstable patients [1, 2].

The indications for CRRT in pediatric intensive care units (PICUs) include not only the treatment of acute kidney injury but also various other conditions, such as fluid overload, sepsis with multiple organ dysfunction syndrome, intoxication, acute attacks of metabolic diseases, and electrolyte or acid-base imbalances [3–5]. Although the use of CRRT is becoming frequent in PICUs, there are no definite guidelines for standard treatment, and the timing and extent of therapy and patient selection remains unclear. Although technological advances during last few decades have increased the safety of CRRT, the

mortality of children requiring CRRT remains rather high, varying from 27–57.2% in several reports [3, 6–15].

Although studies concerning factors which increase mortality in children requiring CRRT are limited (especially when compared to the extensive studies in adults), research has shown that the severity of fluid overload at CRRT initiation, presence of multiple organ dysfunction syndrome, Pediatric Risk of Mortality (PRISM) score, and receiving inotrope treatment are reportedly associated with mortality [6–9, 16]. The aims of this study were to describe the epidemiology and demographic characteristics of a large and diverse population of critically ill children who received CRRT in our PICU, and also to explore their risk factors for mortality.

Methods

This retrospective, single-center comparative study was conducted at the PICU of Medeniyet University, Goztepe Training and Research Hospital (Istanbul, Turkey) between May 2015 and May 2020. The study was approved by the institutional review board of our center (study registration number: 2019 – 0428). Due to the observational nature of the study, informed consent was waived.

Patients were excluded if they had received CRRT prior to admission to the our PICU, if they had incomplete documentation, if they previously received dialysis or if they received another mode of RRT like peritoneal or intermittent dialysis. Demographic information, laboratory results and CRRT specific data were extracted from patient medical records in addition to any other pertinent clinical information. Patient demographic data (age, weight, gender, presence of comorbidity and admission diagnosis) and severity of illness score (PRISM III) were recorded at admission to the PICU. The admission diagnoses were classified into eleven groups as follows: renal disease, hemato-oncologic disease, sepsis, pneumonia/respiratory failure, liver failure, cardiac arrest, metabolic disease, intoxication, acute abdomen, cardiopathies, and others.

Clinical data collected at CRRT initiation were as follows: indication for CRRT initiation, percentage of fluid overload (%FO), urine output (UO), need for invasive mechanical ventilation, presence of multiple organ dysfunction syndrome (MODS), and vasoactive inotrope support/score. The indications for CRRT initiation were classified as electrolyte or acid-base imbalance, acute kidney injury (AKI), fluid overload (FO), hyperammonemia, acute attack of metabolic disease, intoxication, tumor lysis syndrome, and rhabdomyolysis. The indications for commencing CRRT were identified from the documentation of the attending intensivist.

%FO was calculated using the following formula: (total fluid intake [L] – total fluid output [L] / (PICU admission weight [kg]) X 100 [9]. Analysis was performed separately for three FO categories (< 10%, 10–20%, and > 20%), which were defined based on previous studies [7, 13]. UO was calculated for the 24 hours before the initiation of CRRT. The vasoactive inotrope score was calculated using the following formula: (dose of dopamine + dobutamine + [100 X epinephrine] + [100 x norepinephrine] + [10 X milrinone] [in microgram/kg/min] + [10.000 X vasopressin] [U/kg/hr]) [17]. AKI was classified using the

Kidney Disease: Improving Global Outcomes (KDIGO) criteria based on changes in serum creatinine. If baseline serum creatinine was not available, we instead utilized the value of UO in the last 24 hours before CRRT initiation [12]. Finally, MODS was defined as the presence of at least three failed organs, according to the guidelines put forth by the Pediatric Sepsis Consensus Conference [18].

Biochemical variables collected at the initiation of CRRT were as follows: creatinine, hemoglobin, platelet count, pH, and lactate. Time-related variables were recorded as follows: time from PICU admission to CRRT initiation (hours), duration of CRRT (days), and length of PICU stay (days).

The indication for and timing of CRRT initiation were at the discretion of the attending pediatric intensivist. Initial CRRT was performed according to our institutional protocol. All CRRT treatments were performed using a Prismaflex control unit (Gambro, Sweden and Baxter, USA). Modality was continuous venovenous hemodiafiltration, and the dialysate rate, replacement fluid rate and ultrafiltration rate values were customized based on patients' diagnoses, hemodynamic parameters and fluid overload. During treatments, blood flow rate was set to 3 to 8 ml/kg/min, dialysate flow rate was set between 2 and 3 L/1.73 m^2/hr, replacement flow rate was 2 L/1.73 m^2/hr. Poly aryl ethylene sulphone (PAES) membranes (circuit volume 60 ml) or AN69 membranes (circuit volume 93 or 152 ml) were used. Heparinized saline (5 U/mL) was used for priming. In patients with high risk for hemorrhage, the circuit was primed with normal saline only. However, in children with a bodyweight of less than 10 kg, hemoglobin below 10 gr/dL, the circuit was blood-primed. Before March 2017 citrate anticoagulation was not performed at our center; thus, the anticoagulation protocol included heparin in all patients. After this date, anticoagulation was chosen based on patients' age, clinical characteristics and diagnosis. Regional citrate anticoagulation was preferred in patients older than 1 years, given that there were no contraindications; whereas systemic heparin was used in the presence of contraindications or intolerance (liver dysfunction, citrate toxicity). In patients younger than 1 year, systemic heparin anticoagulation was used when there was no risk for hemorrhage (decreased thrombocyte count, prolonged aPTT or INR). In the presence of risk for hemorrhage, systemic heparin infusion was begun after correction of coagulopathy-related problems.

Anticoagulation protocols were as follows: For heparin, infusion was started with 10 international units (IU)/kg/hr prefilter. The heparin dose was subsequently adjusted toward a target activated clotting time (ACT) of 180–220 seconds. For citrate administration, a Prismaflex system using an automated regional citrate anticoagulation method with commercially available citrate replacement solutions (Prismocitrate 18/0, Gambro, Lund, Sweden) and compatible bicarbonate dialysate solutions (Prism0cal B22 or Prism0cal, Gambro, Lund, Sweden) was used. Citrate flow was coupled to the blood flow and adjusted by the CRRT device to achieve the prescribed citrate dose (3 mmol/l of blood). Calcium compensation was determined according to systemic ionized calcium values. The filter target ionized calcium (iCa) level was between 0.25 and 0.35 mmol/L and the patient iCa target was between 1 and 1.2 mmol/L.

Statistical analysis

All data obtained from this research were transferred to the computer environment and evaluated in the IBM SPSS (Version 15.0) Statistical Package Program. The suitability of the data to normal distribution was evaluated with the Kolmogorov Smirnov test with Lilliefors correction. Number, percentage, median, interquartile range (25–75%) values were used to evaluate descriptive data. The Mann Whitney U and Chi-Square tests were used to compare quantitative and categorical variables (respectively) between survivors and non-survivors. Univariate and Multivariate Logistic Regression Analyses were used to identify factors that influenced mortality. Statistical significance threshold was accepted as $p \leq 0.05$.

Results

Patients' Clinical and Demographic Characteristics

The demographic, clinical and laboratory data of the all patients are compared as survivors and non-survivors, and presented in Table 1. The study group consisted of 121 children, 50.4% were male, and median age at CRRT initiation was 3.6 years (IQR, 1.30–10.80). The most common diagnoses at admission were: renal disease (30.6%), hemato-oncological disease (12.4%) and sepsis (11.6%). The median PRISM III score was 15 (IQR, 8.0-24.5). Among our patients 51.2% had comorbidities.

Table 1
Patients Variables and Diffrences Between Survivors Versus Nonsurvivors

Variable	All Patients (n = 121)	Survivors (n = 85)	Nonsurvivors (n = 36)	p
Age (yr), median (IQR)	3.6 (1.3–10.8)	3.6 (1.5–11.3)	4.2 (0.6–9.2)	0.400
Male gender, n (%)	61 (50.4)	43 (50.6)	18 (50.0)	0.953
Weight (kg), median (IQR)	18.0 (11.0-34.5)	17.0 (11.0–40.0)	19.0 (8.2–31.0)	0.407
PRISM III score, median (IQR)	15.0 (8.0-24.5)	12.0 (7.0-20.5)	23.0 (15.7–31.5)	**< 0.001**
Comorbidity, n (%)	62 (51.2)	35 (41.2)	27 (75.0)	**0.001**
Diagnosis at admission to PICU, n (%)				
Renal disease	37 (30.6)	35 (41.2)	2 (5.6)	**< 0.001**
Hemato-oncologic disease	15 (12.4)	4 (4.7)	11 (30.6)	**< 0.001**
Sepsis	14 (11.6)	10 (11.8)	4 (11.1)	1.000
Pneumonia / Respiratory failure	11 (9.1)	3 (3.5)	8 (22.2)	**0.003**
Liver failure	9 (7.4)	9 (10.6)	0 (0.0)	0.099
Cardiac arrest	9 (7.4)	5 (5.9)	4 (11.1)	0.533
Metabolic disease	8 (6.6)	5 (5.9)	3 (8.3)	0.924
Cardiopathies	5 (4.1)	4 (4.7)	1 (2.8)	1.000
Intoxication	5 (4.1)	4 (4.7)	1 (2.8)	1.000
Acute abdomen	3 (2.5)	1 (1.2)	2 (5.6)	0.437
Other	5 (4.1)	5 (5.9)	0 (0.0)	0.324
Clinical variables at initiation of CRRT				
% Fluid overload, median (IQR)	6.7 (0.0-19.7)	3.0 (0.0-13.5)	14.2 (0.0-24.4)	**0.008**
% Fluid overload, n (%)				

PRISM: pediatric risk of mortality score, PICU: pediatric intensive care unit, CRRT: continuos renal replacement therapy, IQR: interquartile range.

Boldface value represents statistical significance.

Variable	All Patients (n = 121)	Survivors (n = 85)	Nonsurvivors (n = 36)	p
<10%	63 (54.5)	50 (58.8)	16 (44.4)	0.138
10–20%	25 (20.7)	19 (22.4)	6 (16.7)	
>20%	30 (24.8)	16 (18.8)	14 (38.9)	
Urine output (mL/kg/hr), median (IQR)	0.2 (0.0-0.4)	0.3 (0.0-0.45)	0.10 (0.0-0.30)	**0.013**
Mechanical ventilation, n (%)	76 (62.8)	42 (49.4)	34 (94.4)	**< 0.001**
Multiple organ dysfunction syndrome, n (%)	61 (50.4)	29 (34.1)	32 (88.9)	**< 0.001**
Vasoactive support, n (%)	65 (53.7)	34 (40.0)	31 (86.1)	**< 0.001**
Vasoactive inotrope score, median (IQR)	10.0 (0.0-32.5)	0.0 (0.0–20.0)	35.0 (23.1–54.3)	**< 0.001**
Acute kidney injury stage 2 and 3, n (%)	61 (50.4)	39 (45.9)	22 (61.1)	0.126
Isolated acute kidney injury, n (%)	17 (14.0)	16 (18.8)	1 (2.8)	**0.020**
Time-related variables				
Time from PICU admission to CRRT initiation (hr), median (IQR)	7.0 (4.0–18.0)	7.0 (4.5–12.0)	10.0 (4.0-15.7)	0.146
Time to initiation < 24 hours, n (%)	94 (77.7)	71 (83.5)	23 (63.9)	**0.018**
Time to initiation ≥ 24 hours, n (%)	27 (22.3)	14 (16.5)	13 (36.1)	
Duration of CRRT (days), median (IQR)	3.0 (2.0–6.0)	1.2 (1.0-5.7)	4.0 (2.0–6.0)	**0.008**
Length of PICU stay (days), median (IQR)	7.0 (3.0–13.0)	4.5 (1.0-11.8)	7.0 (4.0-13.5)	**0.027**
Laboratory variables at initiation of CRRT				
Creatinine (mg/dL), median (IQR)	2.20 (0.85–4.36)	2.47 (0.92–5.06)	1.31 (0.72–2.56)	**0.004**
Hemoglobin (gr/dL), median (IQR)	8.8 (7.3–10.7)	8.7 (7.3–10.7	9.2 (7.2–10.6)	0.520

PRISM: pediatric risk of mortality score, PICU: pediatric intensive care unit, CRRT: continuos renal replacement therapy, IQR: interquartile range.

Boldface value represents statistical significance.

Variable	All Patients (n = 121)	Survivors (n = 85)	Nonsurvivors (n = 36)	p
Platelet count, (X 10^9/ L), median (IQR)	107 (44.3–231)	67 (24.2–125)	127 (56.5–242)	**0.018**
pH, median (IQR)	7.17 (7.08–7.28)	7.20 (7.10–7.30)	7.11 (7.00-7.24)	0.054
Lactate, (mmol/L), median (IQR)	3.5 (1.5-6.0)	2.0 (1.1–4.3)	6.0 (4.6–12.0)	**< 0.001**
PRISM: pediatric risk of mortality score, PICU: pediatric intensive care unit, CRRT: continuos renal replacement therapy, IQR: interquartile range.				
Boldface value represents statistical significance.				

Before the initiation of CRRT median %FO was 6.7% (IQR: 0.00-19.70). When categorized, %FO was lower than 10% in 54.5% of patients, and higher than 20% in 24.8% of patients at baseline. The majority of patients were ventilated (62.8%) and required inotropic-vasopressor support (53.7%), and %50.4 of these patient had MODS. At the time of CRRT initiation, 50.4% of patients fulfilled the criteria for stage 2–3 AKI, while 14% had isolated AKI without need for additional support.

The median duration of CRTT was 3 days (IQR: 2–6 days). Median PICU length of stay from admission to death/discharge was 7 days (IQR: 3.0–13.0 days), and the median time from PICU admission to CRRT initiation was 7 hours (IQR: 3–13 hr). Time of CRRT initiation according to PICU admission diagnosis are detailed in Table 2.

Table 2
Relationship Between Timing of CRRT Initiation with Diagnostic Subgroup with Survival

Variable	All Patients		Survivors		Nonsurvivors		
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	p
Time from PICU admission to CRRT initiation (hr)	121	7.0 (4.0–18.0)	85	7.0 (4.5–12.0)	36	10.0 (4.0-15.7)	0.146
Time to initiation according to diagnosis (hr)							
Renal disease	37	6.0 (4.0–8.0)	35	6.0 (4.0–8.0)	2	11.5 (5.0–18.0)	0.508
Hemato-oncologic disease	15	6.0 (3.0–96.0)	4	3.0 (3.0-49.5)	11	10.0 (2.0-1080.0)	0.571
Sepsis	14	6.5 (6.0–12.0)	20	4.0 (3.5-5.0)	4	9.0 (6.0–18.0)	**0.004**
Pneumonia /Respiratory failure	11	120.0 (7.0-170.0)	3	10.0 (3.0–48.0)	8	166.5 (63.5–182.0)	0.194
Liver failure[a]	9	8.0 (6.0–8.0)	9	8.0 (5.0–12.00)	0	-	NA
Cardiac arrest	9	12.0 (5.0–22.0)	5	5.0 (4.0–12.0)	4	17.0 (9.0–29.0)	0.286
Metabolic disease	8	7.0 (4.5-9.0)	5	6.0 (6.0–8.0)	3	10.0 (3.0-288.0)	0.393
Intoxication	5	4.0 (3.0–6.0)	4	4.50 (2.5–39.0)	1	4.0 (4.0–4.0)	1.000
Cardiopathies	5	12.0 (10.0–24.0)	4	17.0 (7.0–60.0)	1	12.0 (12.0–12.0)	1.000
Acute abdomen	3	9.0 (2.0–20.0)	1	20.0 (20.0–20.0)	2	5.5 (2.0–9.0)	0.667

PICU: pediatric intensive care unit, CRRT: continuous renal replacement therapy, IQR : Interquartile Range, NA: not available.

Boldface value represents statistical significance.

[a] Sample size of one subgroup too small for comparition.

Variable	All Patients		Survivors		Nonsurvivors		
Other[a]	5	24.0 (14.0–24.0)	5	24.0 (14.0–24.0)	0	-	NA
PICU: pediatric intensive care unit, CRRT: continuous renal replacement therapy, IQR : Interquartile Range, NA: not available.							
Boldface value represents statistical significance.							
[a] Sample size of one subgroup too small for comparition.							

The three most common primary indications for initiating CRRT were: electrolyte or acid-base imbalance (38.8%), AKI (29.8%) and FO (14.9%). The distribution of CRRT indications are depicted in Table 3.

Table 3
Evaluation of CRRT indications according to mortality

Indication	All Patients (n = 121)	Survivors (n = 85)	Non-survivors (n = 36)	p
Electrolyte / acid base disturbance	47 (38.8)	31 (36.5)	16 (44.4)	0.411
Acute kidney injury	36 (29.8)	25 (29.4)	11 (30.6)	0.900
Fluid overload	18 (14.9)	12 (14.1)	6 (16.7)	0.719
Hyperammonemia	10 (8.3)	9 (10.6)	1 (2.8)	0.287
Acute attack of metabolic disease	6 (5.0)	4 (4.7)	2 (5.6)	1.000
Tumor lysis syndrome	2 (1.7)	2 (2.4)	0 (0.0)	0.882
Intoxication	1 (0.8)	1 (1.2)	0 (0.0)	1.000
Rhabdomyolysis	1 (0.8)	1 (1.2)	0 (0.0)	1.000
CRRT: continuous renal replacement therapy				

Comparison of Survivors and Non-survivors

The relationships between mortality and the demographic and laboratory findings of patients are detailed in Table 1. Overall, 29.8% (n = 36) of our patients had died. There were no differences between survivors and non-survivors in terms of age, gender or weight. The median PRISM III score ($p < 0.001$) and frequency of comorbidity ($p = 0.001$) were found to be significantly higher in the non-survivors group compared to survivors. With regard to admission diagnoses, those with hemato-oncological disease ($p < 0.001$) or pneumonia/respiratory failure ($p = 0.003$) had significantly higher mortality (73.3% and 72.7%, respectively); whereas lowest mortality was among patients with renal disease (5.4%) ($p < 0.001$).

Non-survivors had significantly higher %FO values compared to survivors (14.2% vs. 3.0%, p = 0.008). However, when %FO values were categorized (< 10%, 10–20% and > 20%), we found no differences between category distributions for survivors and non-survivors (p = 0.138). Median UO values over the 24 hours prior to CRRT were significantly lower in the non-survivor group compared to survivors (0.1 mL/kg/hr vs 0.3 mL/kg/hr; p = 0.013). At the initiation of CRRT, a higher proportion of non-survivors had required mechanical ventilation (94.4% vs 49.4%) and vasoactive support (86.1% vs 40.0%), while MODS was also more frequent in non-survivors (88.9% vs. 34.1%) compared to survivors (p < 0.001 for all). Also, median vasoactive inotrope score was significantly higher in non-survivors than survivors (0 vs. 35; p < 0.001). We also determined that the presence of isolated AKI was associated with higher in the survivor group (18.8% in survivors vs 2.8% in non-survivors, p < 0.001). There were no significant relationships between higher stage of AKI (stage 2 and stage 3) and mortality (p = 0.126). When the relationships between mortality and biochemical characteristics at CRRT initiation were evaluated, we found significantly lower serum creatinine (p = 0.004) and significantly higher platelet count (p = 0.018) and lactate levels (p < 0.001) in non-survivors when compared to survivors.

No significant difference in CRRT indications was found between non-survivors and survivors (Table 3).

The evaluation of time-related variables are detailed in Table 1 and Table 2. The duration of CRRT and length of PICU stay were significantly longer in non-survivors versus survivors (1.2 vs. 4 days; p = 0.008 and 4.5 vs. 7 days; p = 0.027, respectively). With regard to the timing of CRRT initiation, there was no significant difference between survivors and non-survivors. When survivors and non-survivors were divided according to early (< 24 hours) and late (≥ 24 hours) CRRT initiation, we found that a significantly higher percentage of survivors had early CRRT initiation (p = 0.018). Furthermore, among patients with sepsis as their admission diagnosis, median time from PICU admission to CRRT initiation was significantly shorter in surviving patients with sepsis compared to non-survivors with sepsis (4 hours vs. 9 hours; p = 0.004). The CRTT initiation times for other diagnoses at admission were similar between survivors and non-survivors.

In logistic regression analysis, we found that having renal disease as the admission diagnosis, higher UO and isolated AKI were associated with improved odds of survival. Whereas, high PRISM III score, presence of comorbidity, having pneumonia/respiratory failure or hemato-oncological disease at admission, high %FO, being classified in the > 20%FO group, requirement for mechanical ventilation at time of CRRT initiation and/or presence of MODS and/or vasoactive inotrope support, and high lactate levels were determined to be associated with increased risk or mortality (Table 4).

Table 4
Univariate and Multivariate Logistic Regression for Factors Associated With Mortality

	Unadjusted		Adjusted	
Variable	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Age	0.98 (0.90–1.04)	0.371		
Weight	0.99 (0.97–1.01)	0.315		
PRISM III score	1.09 (1.05–1.14)	**< 0.001**	0.94 (0.85–1.04)	0.230
Comorbidity	4.29 (1.80-10.22)	**0.001**	5.71 (1.16–27.97)	**0.032**
Diagnosis at admission to PICU				
Sepsis	0.94 (0.27–3.21)	0.918		
Renal disease	0.08 (0.02–0.37)	**0.001**	0.37 (0.02–7.66)	0.524
Liver failure	0.00 (0.00-..)	1.00		
Hemato-oncologic disease	8.91 (2.61–30.46)	**< 0.001**	3.91 (0.47–32.89)	0.209
Intoxication	0.58 (0.06–5.36)	0.630		
Cardiac arrest	2.00 (0.50–7.93)	0.324		
Metabolic disease	1.45 (0.33–6.44)	0.622		
Acute abdomen	4.94 (0.43–56.31)	0.198		
Cardiopathies	0.58 (0.06–5.36)	0.630		
Pneumonia / Respiratory failure	7.81 (1.94–31.50)	**0.004**	16.16 (1.56-167.01)	**0.020**
% Fluid overload	1.06 (1.02–1.11)	**0.004**	1.11 (0.96–1.29)	0.153
% Fluid overload more than 20%	2.74 (1.16–6.50)	**0.022**	0.50 (0.02–10.81)	0.662
Urine output	0.51 (0.27–0.99)	**0.048**	0.37 (0.13–1.09)	0.071
Mechanical ventilation	17.40 (3.93–77.08)	**< 0.001**	0.96 (0.01–127.00)	0.988
Multipl organ dysfunction syndrome	15.45 (4.98–47.92)	**< 0.001**	13.19 (0.14-1255.27)	0.267

PRISM: pediatric risk of mortality score, PICU: pediatric intensive care unit, CRRT: continuos renal replacement therapy, OR: odds ratio, CI: confidence interval.

Boldface value represents statistical significance.

	Unadjusted		Adjusted	
Vasoactive support	9.30 (3.29–26.30)	**< 0.001**	3.39 (0.31–37.13)	0.318
Acute kidney injury stage 2 and 3	1.85 (0.84–4.10)	0.128		
Isolated acute kidney injury	0.12 (0.02–0.97)	**0.046**	33.03 (0.62-1757.49)	0.085
Time from PICU admission to CRRT	1.01 (1.01–1.02)	**0.002**	1.01 (1.00-1.02)	0.402
Duration of CRRT	1.34 (0.42–5.07)	0.786		
Length of PICU stay	1.46 (0.36–6.38)	0.654		
Creatinine at CRRT initiation	0.98 (0.94–1.02)	0.404		
Hemoglobin at CRRT initiation	1.06 (0.91–1.22)	0.451		
Platelet count at CRRT initiation	1.00 (1.00–1.00)	0.146		
pH at CRRT initiation	0.11 (0.01–1.13)	0.063		
Lactate at CRRT initiation	1.28 (1.14–1.42)	**< 0.001**	1.43 (1.14–1.79)	**0.002**
PRISM: pediatric risk of mortality score, PICU: pediatric intensive care unit, CRRT: continuos renal replacement therapy, OR: odds ratio, CI: confidence interval.				
Boldface value represents statistical significance.				

Multivariate logistic regression analysis was conducted by creating a model with significant factors identified in univariate analysis. Presence of comorbidity (adjusted OR: 5.71; 95% CI: 1.16–27.97), being diagnosed with pneumonia/respiratory failure (OR: 16.16; 95% CI: 1.56-167.01) and high lactate level (OR: 1.43; 95% CI: 1.14–1.79) were found to be independently associated with mortality **(**Table 4**).**

Discussion

With this retrospective observational study, we aimed to describe epidemiological and clinical characteristics and to identify factors associated with mortality in our group of critically ill pediatric patients who had received CRRT. The current study is one of the largest single-center studies in the literature, including 121 pediatric patients from our PICU. Our study provides a representative cross-section of a large and heterogeneous PICU population receiving CRRT including all diagnostic subgroups.

The use of CRRT has become an integral part of modern critical care and is used for a variety of clinical situations in critical ill children with renal and non-renal indications [1–5]. However, despite its increased use, identifying the optimal indication and the optimal timing remains a problem in clinical practice. Mortality rates for critically ill children receiving CRRT range from 27–57.2%, with some improvements

over the last decade that may be associated with various factors, including increased use in non-critical children, better recognition of AKI in critically ill children, or increased safety due to technological refinements [3, 6–15]. The 29.8% mortality rate in our study stands as one of the lowest when compared to previous publications. However, it is apparent that children requiring CRRT represent a heterogeneous group, and previous studies have shown that outcome is closely related to underlying disease [3, 7–9, 13]. In our study, mortality in children with hemato-oncological disease or pneumonia/respiratory failure was very high (73.3% and 72.7%, respectively); whereas, children with primary renal disease had very low mortality rates (5.4%). These findings are comparable with data from the pediatric CRRT registry as published by Symons et al., Beschee et al., and Cortina et al. [3, 4, 13]. In our study, survival rate was higher among patients in whom CRRT was required for AKI without any other organ failure (94.1%). Hames et al. also found superior survival in patients treated for isolated AKI (85.7%) [19].

We found that age, sex and weight had no influence on mortality in the current study, similar to previous reports [3, 4, 20]. Non-survivors were found to have lower weight at PICU admission in a study by Hames and colleagues [19]. The PRISM III score, which is calculated in the first 24 hours of PICU admission, is a frequently utilized method of prognostic assessment in critically ill pediatric patients. As expected, PRISM III scores were higher among non-survivors. However, studies evaluating recipients of CRRT in the PICU report varying results; while some studies have found relationships between PRISM III score and mortality, others have not [4, 8, 13, 19–21]. In two studies by Golden et al. [16] and Şık et al. [21], it was found that mortality was associated with PRISM III score that was re-calculated immediately prior to beginning CRRT treatment. Multiple studies have identified that the need for vasoactive support [10, 14, 15], need for mechanical ventilation [15, 19], presence of comorbid factors [3, 22], and MODS [10, 13] were risk factors of mortality in recipients of CRRT. In the current study, although we found higher PRISM III and vasoactive support score, and higher frequency of mechanical ventilation, comorbidity and MODS in the non-survivor group, we did not find independent relationships between mortality and any of these factors.

In the present study, the most common primary indication for initiating CRRT was electrolyte or acid-base imbalance, followed by AKI and %FO. Although the distribution of primary CRRT indications vary from study to study, they are generally in agreement with the aforementioned findings [13, 19, 21, 22]. We found no relationships between CRRT indications and mortality. Similarly, Şık et al. [21] also reported no relationship between mortality and CRRT indication. However, Cortina and colleagues [13] have reported that CRRT performed due to FO was associated with higher mortality rate compared to other indications.

In the literature, the median %FO values at the initiation of CRRT range from 6.3–21.0% [10, 13, 19, 21, 22]; in the current study we report a value of 6.7%. Multiple studies have demonstrated that higher FO at the time of CRRT is an independent risk factor for increased mortality and morbidity [6–9, 12]; however, conflicting results also exist [4, 19, 23]. In the present study, non-survivors were found to have a significantly higher degree of FO compared to survivors (3.0% vs 14.2%). Although this was not associated with mortality on multivariate analysis, we believe there should be continued emphasis on managing the fluid status of critically ill children. This may be especially true in patients with respiratory disease. When these characteristics were evaluated with regard to diagnoses, we found that non-

survivors admitted with pneumonia/respiratory failure had a median fluid accumulation of 17.9%, which was a higher value compared the 7.0% in survivors. Thus, it is possible that this characteristic may have contributed to the high mortality rate for this subgroup of patients. In the current study, %FO was greater than 20% in 18.8% of survivors and 38.9% of non-survivors; however, statistical significance was not found in terms of mortality. It must be noted that several studies have reported > 20% FO as an independent risk factor for mortality; whereas others have not identified a relationship [13, 19, 22].

AKI is common in pediatric patients admitted to the PICU, and its frequency rises with increasing severity of illness [13, 24]. The recently published prospective multicenter study, Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology, found that AKI developed in 26.9% and severe AKI was present in 11.6% of critically ill children and young adults. The study concluded that severe AKI was associated with higher mortality rate [25]. In our study, even though we found higher KDIGO stages (stage 2 + 3 AKI) in non-survivors compared to survivors (61.1% vs. 45.9%), statistical results showed no significance. Our results were similar to those reported by Cortina and colleagues who did not find any relationship between severe AKI and mortality [13].

The time to initiate CRRT is still controversial in the literature [26]. The varying definitions of early versus late initiation further compounds this problem. Two randomized controlled trials in critically ill adults with AKI showed conflicting results. The “Effect of Early vs Delayed Initiation of Continuous Renal Replacement Therapy on Mortality in Critically Ill Patients with Acute Kidney Injury (ELAIN)” trial demonstrated lower mortality when patients received early CRRT (within 8 hours of diagnosis of KDIGO stage 2 AKI) compared to those who had been treated with a delayed strategy (within 12 hours of stage 3 AKI or no initiation) [27]. However; the “Artificial Kidney Initiation in Kidney Injury (AKIKI)” trial did not show a difference in mortality between patients assigned to receive early versus late CRRT [28]. For this trial, all patients had stage 3 AKI, and early initiators received RRT immediately after developing stage 3 AKI; whereas late initiation was performed only if they had an acute indication for CRRT. The detailed comparison of the two studies further supports our belief that the variation in definitions (or rather, a lack of definitive characterization) remains as an important problem. In our study, the median time of initiation was 7 hours, which, compared with other pediatric studies, is very early [13, 19, 21, 22]. This characteristic difference was due to the traditional approach taken our unit, which focuses on starting CRRT early in select patient groups, including those with sepsis and other acute clinical conditions (such as hemolytic uremic syndrome). In our study, univariate analysis revealed that non-survivors were started on CRRT later than survivors (with respect to time from PICU admission). However, multivariate analysis did not identify CRRT initiation time as a factor that contributed to mortality. The definition of early or late CRRT treatment varies in pediatric studies, and the majority of research on this topic has assessed the time from PICU admission to CRRT initiation in order to determine whether it is associated with mortality. However, results are conflicting. Some studies in pediatric patients have reported increased survival with early CRRT [12, 13], while others have found no relationship [4, 19, 21, 22].

Timing the initiation of CRRT from PICU admission can be somewhat arbitrary, as it does not appropriately categorize patients who arrive to the PICU with normal renal function and subsequently

develop AKI later during the course of their PICU stay. Kaddourah et al. [25] performed a prospective, multicenter observational study evaluating RRT recipients among critically ill patients with AKI older than 12 years old. Late RRT, defined from PICU admission, was associated with increased mortality; but when it was defined based on a blood urea nitrogen threshold, there was no difference in mortality. Conversely, mortality was lower for late RRT initiation when timing was based on a serum creatinine threshold. Although very interesting and informative, this study did not evaluate stage of AKI as a factor. In a study by Hames and colleagues, the time until CRRT initiation from the development of stage 3 AKI was reported to be significantly longer in non-survivors. However, the time between peak creatinine level measurement and CRRT was reported to be unassociated with survival [19].

We also evaluated whether CRRT initiation time was influential on survival with regard to admission diagnoses. Patients with sepsis who had survived were found to have shorter time until CRRT initiation compared to non-survivors. This particular relationship was also identified in the study by Cortina and colleagues; however, their results did not show statistical significance [13]. It has been previously reported that early CRRT may be utilized in patients with sepsis –even in the absence of AKI– in order clear inflammatory mediators, correct acid-base imbalance and prevent FO [13, 29].

In the present study, overall median CRRT duration was 3 days. Although median CRRT duration was longer in non-survivors, multivariate regression did not yield a significant difference between groups. This was consistent with the report of the “Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry” and another smaller study of 190 patients, both of which found no significant difference in terms of survival rate based on duration of CRRT [3, 12]. Furthermore, we also report a significantly longer PICU stay in non-survivors (7.0 vs 4.5 days), but multivariate regression again showed no significant effect on survival, similar to other pediatric series [20–22].

The relationships between survival and some pre-CRRT biochemical/hematological characteristics were also assessed. Platelet count was significantly lower in survivors compared to non-survivors. This was possibly due to the fact that the majority of patients with the lowest (5.4%) mortality rate (those with renal disease) had a diagnosis of hemolytic uremic syndrome –a disease that is characterized by low platelet count. Serum creatinine was also higher among those that survived; however, this can also be associated with the increase in creatinine levels in patients that were admitted with renal disease (who had very high survival). Other studies in the literature also report no relationship with creatinine and mortality in CRRT recipients [4, 19]. We only identified lactate as an independent risk factor in this study. Even though the literature reports different results, Cortina et al. [13] and Fernandez et al. [14] have not found an association between mortality and lactate levels. Furthermore, although lactate levels were higher among non-survivors in a study by Choi and colleagues [15], it was not found to be an independent risk factor on mortality. However, in an adult study comprised of CRRT recipients due to AKI development after cardiac surgery, it was reported that > 5 mmol/L lactate level at CRRT initiation was associated with mortality (94.1%) [30].

There are several limitations to this study. This is a retrospective analysis and is therefore reliant on accurate documentation in medical records. The fact that this was a single center study also limits generalizability, especially due to likely variations in practice and patient diagnoses, as standardized management guidelines do not exist for CRRT. Although the study population was relatively large, it is also heterogeneous and involves smaller subgroups, which limits the precision of our estimates and makes it difficult to draw general conclusions from the associations observed. Another limitation is the method of calculating of %FO, which was performed by evaluation of fluid from PICU admission to CRRT initiation, and it is apparent that some patients might have received larger fluid volume before admission to our unit. Insensible losses were also not accounted for in the fluid balance calculation. Another potential limitation is lack of data regarding the rate of fluid removal after initiating CRRT. This can be a potential factor that affects survival, ventilation time and length of PICU stay.

Conclusion

In the population studied, the mortality was lower when compared to previous publications reporting data from children receiving CRRT. We identified that, presence of comorbidity, having pneumonia/respiratory failure at admission, and high lactate at CRRT initiation as independent risk factors for mortality. There was no relationship between mortality and FO or CRRT initiation time. This may have been, at least in part, due to our decisive approach to initiate CRRT as soon as possible in critically ill children. Consequently, our study reports a median of 6.7% FO at CRRT initiation and a median of 7 hours from PICU admission to the initiation of CRRT, which are among the lowest values in the literature for the initiation of CRRT. Multicenter prospective studies focusing on pediatric CRRT recipients could identify parameters to create scoring systems for the need of CRRT, and could affect the outcome of these patients.

List Of Abbreviations

CRRT: continuous renal replacement therapy, PICU: pediatric intensive care unit, PRISM: Pediatric Risk of Mortality, UO: urine output, %FO: percentage of fluid overload, MODS: multiple organ dysfunction syndrome, AKI: acute kidney injury, KDIGO: Kidney Disease: Improving Global Outcomes, PAES: Poly aryl ethylene sulphone, ACT: activated clotting time

Declarations

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Author’s Contributions

All authors have agreed on the final version of this manuscript. DM: study design, statistical analysis, drafted the manuscript, and is responsible for the overall content. TC: Data extraction and quality

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Availability of data and materials

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Ethics approval and consent to participate

The study was approved by the institutional review board of our center (study registration number: 2019-0428). Due to the observational nature of the study, informed consent was waived.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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