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Clinical features and risk factors associated with mortality in critically ill children requiring continuous renal replacement therapy

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Abstract

Introduction: The aims of this study were to describe the 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 evaluated.

Results: Overall mortality was 29.8%. In patients diagnosed with sepsis, time until CRRT initiation was significantly shorter in survivors compared to non-survivors ($p = 0.036$). Based on multivariate logistic regression, presence of comorbidity (OR: 5.71), diagnoses of pneumonia/respiratory failure at admission (OR:16.16), and high lactate level at CRRT initiation (OR:1.43) were independently associated with mortality.

Conclusion: In the context of the population studied, mortality rate was lower than previously reported. Despite having a large series, heterogenous characteristics and limitations in subgroups may have influenced results and survival.

KEYWORDS

comorbidity, continuous renal replacement therapy, critically ill children, lactate, mortality

1 | INTRODUCTION

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 acute kidney injury (AKI), fluid overload, sepsis with multiple organ dysfunction syndrome, intoxication, acute attacks of metabolic diseases, and

electrolyte or acid–base imbalances [3–6]. Although the use of CRRT is common in PICUs, there are no definite guidelines for standard treatment, and the timing and extent of therapy and patient selection remains unclear. Technological advances have increased the safety of CRRT, but the mortality rates of children requiring CRRT remains rather high, varying from 27% to 57.2% in several reports [3, 7–16].

Research focusing on factors associated with mortality in children requiring CRRT are limited (especially

when compared to the extensive studies in adults); however, 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 [7–10, 17]. The aims of this study were to describe the epidemiology and demographic characteristics of a large population of critically ill children who received CRRT in our general PICU, and also to explore risk factors associated with mortality.

2 | MATERIALS AND METHODS

This retrospective, single-center comparative study was conducted at the PICU of XXX between May 2015 and May 2020. At our center, all medical and surgical critically-ill patients, except for those with cardiac surgery, bone marrow transplantation and solid organ transplantation, are admitted into the general PICU. The total number of critically-ill children receiving treatment in the general PICU is around 400 per year.

The study protocol was in accordance with the Declaration of Helsinki. 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 our PICU, if they had incomplete documentation, if they previously received dialysis or if they received another mode of RRT (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. Patients with any chronic disease (e.g., congenital cardiomyopathy, malignancy, diabetes mellitus) affecting any organ or system before admittance to the PICU were accepted to have comorbidity. The admission diagnoses were classified into 11 groups as follows: renal disease, hematologic disease, sepsis, pneumonia/respiratory failure, liver failure, cardiac arrest, metabolic disease, intoxication, acute abdomen, cardiopathies, and others. Survival was defined as surviving until PICU discharge.

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), need for extracorporeal membrane oxygenation (ECMO), 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: $(\text{total fluid intake [L]} - \text{total fluid output [L]}) / (\text{PICU admission weight [kg]} \times 100)$ [10]. Analysis was performed separately for three FO categories (<10%, 10%–20%, and >20%), which were defined based on previous studies [8, 14]. UO was calculated for the 24 hours before the initiation of CRRT. The vasoactive inotrope score was calculated using the following formula: $(\text{dose of dopamine} + \text{dobutamine} + [100 \times \text{epinephrine}] + [100 \times \text{norepinephrine}] + [10 \times \text{milrinone}] \text{ [in } \mu\text{g/kg/min}] + [10\,000 \times \text{vasopressin}] \text{ [U/kg/h]})$ [18]. 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 [13]. 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 [19].

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).

Determining the indication for and the timing of CRRT initiation were at the discretion of the attending pediatric intensivist. Although patients requiring CRRT may have several different conditions—each of which may be separate indications for CRRT, only the most prominent condition was recorded as the CRRT indication as determined by the 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. During treatments, blood flow rate was set to 3–8 mL/kg/min and total clearance rate was set between 2 and 3 L/1.73 m²/h for the majority of patients, while higher total clearance rates (up to a maximum of 5 L/1.73 m²/h) were reached in cases with specific indications, such as intoxications or hyperammonemia. The dialysate flow rate, replacement fluid rate and ultrafiltration rate values were customized based on each patient's diagnosis, hemodynamic parameters and FO values. 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 g/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 of age, 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/h prefilter. The heparin dose was subsequently adjusted toward a target activated clotting time (ACT) of 180–220 s. 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 (Prismocal B22 or Prismocal, Gambro, Lund, Sweden) were 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.

2.1 | 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 $p \leq 0.05$.

3 | RESULTS

3.1 | Patients' clinical and demographic characteristics

During the study period, a total of 148 patients received RRT, among which we included 121 patients who had undergone CRRT. The exclusion of 27 children was performed due to following reasons: having received CRRT prior to admission to our PICU ($n = 2$), incomplete medical data ($n = 6$), having previously received any type of dialysis treatment ($n = 14$), having received peritoneal dialysis during the same PICU admission ($n = 2$), having received intermittent dialysis during the same PICU admission ($n = 3$).

The demographic, clinical and laboratory data of all patients were 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.

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 patients 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 h (IQR: 3–13 h). Time of CRRT initiation according to PICU admission diagnosis are detailed in Table 2.

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 is depicted in Table 3.

3.2 | 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 and gender. Although there was

TABLE 1 Patients variables and differences between survivors vs 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
<10 kg	21 (17.3)	11 (12.9)	10 (27.7)	0.049
≥10 kg	100 (82.7)	74 (87.1)	26 (72.3)	
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 (%)				
<10%	66 (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/h), 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
ECMO, n (%)	7 (5.8)	3 (3.5)	4 (11.1)	0.102
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 stages 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

TABLE 1 (Continued)

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

Abbreviations: PRISM, pediatric risk of mortality score; PICU, pediatric intensive care unit; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.

TABLE 2 Relationship between timing of CRRT initiation with diagnostic subgroup with survival

Variable	All patients		Survivors		Nonsurvivors		p
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	
Time from PICU admission to CRRT initiation (h)	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 (h)							
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	5.5 (4.0–8.0)	10	4.5 (4.0–6.0)	4	10.0 (7.0–15.0)	0.036
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
Other ^a	5	24.0 (14.0–24.0)	5	24.0 (14.0–24.0)	0	–	NA

Abbreviations: PICU, pediatric intensive care unit; CRRT, continuous renal replacement therapy; IQR, interquartile range; VIS, vasoactive inotrope score; ARDS, acute respiratory distress syndrome; NA, not available.

^aSample size of one subgroup too small for comparison.

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

Abbreviation: CRRT, continuous renal replacement therapy.

no general relationship between patient weight and survival, we found that patients weighing <10 kg had significantly lower survival ($p = 0.049$). 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

TABLE 4 Univariate and multivariate logistic regression for factors associated with mortality

Variable	Unadjusted		Adjusted	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Age	0.98 (0.90–1.04)	0.371		
Weight	0.99 (0.97–1.01)	0.315		
Weight < 10 kg	0.39 (0.15–1.02)	0.054		
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
Extracorporeal membrane oxygenation	0.29 (0.06–1.38)	0.121		
Multiple organ dysfunction syndrome	15.45 (4.98–47.92)	<0.001	13.19 (0.14–1255.27)	0.267
Vasoactive support	9.30 (3.29–26.30)	<0.001	3.39 (0.31–37.13)	0.318
Acute kidney injury stages 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

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

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%) ($p < 0.001$). No significant difference in CRRT indications was found between non-survivors and survivors (Table 3).

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 h prior to CRRT were significantly lower in the non-survivor group

compared to survivors (0.1 ml/kg/h vs. 0.3 ml/kg/h; $p = 0.013$). 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 patients with isolated AKI had significantly greater survival ($p = 0.020$). There were no significant relationships between higher stage of AKI (stage 2 and stage 3) and mortality ($p = 0.126$). Requiring ECMO before CRRT initiation did not influence survival ($p = 0.102$). 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.

The evaluation of time-related variables is detailed in Tables 1 and 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 (4.5 hours vs. 10.0 hours; $p = 0.036$). The CRTT initiation times for other diagnoses at admission were similar between survivors and non-survivors.

In logistic regression analysis, we found that having primary renal disease as the admission diagnosis, higher UO and isolated AKI were associated with improved odds of survival. Whereas, higher 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, requiring 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 of mortality (Table 4).

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).

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, and provides a representative cross-section of a large general 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 [1–5]. Mortality rates for critically ill children receiving CRRT range from 27% to 57.2%, with some improvements over the last decade [3, 7–16]. The 29.8% mortality rate in our study stands as one of the lowest when compared to previous publications. It is well-established that mortality rate is higher among CRRT recipients with liver disease or transplantation, bone marrow transplantation, hemato-oncological malignancy, respiratory failure, and congenital heart disease [3, 4, 8–10, 14, 20, 21]. Also, survival likelihood is much greater in patients with primary renal disease, especially in isolated AKI [8, 9, 20, 21]. In the current study, a considerable proportion of patients had primary renal disease (30.6%). The highest mortality was observed in patients with hemato-oncological disease and pneumonia/respiratory failure, who collectively comprised 21.5% of our patients. The absence of patients with bone marrow or solid organ transplants and congenital heart disease could have been a particular factor that decreased mortality in our study.

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 [14, 20, 22, 23]. We found no relationships between CRRT indications and mortality. Similarly, Şık et al. [22] also reported no relationship between mortality and CRRT indication. However, Cortina and colleagues [14] have reported that CRRT performed due to FO was associated with higher mortality rate compared to other indications.

The primary demographic characteristics that influence survival in CRRT recipients are age and weight. We found that age and weight, when assessed as continuous variables, had no influence on mortality in the current

study, similar to previous reports [3, 4, 24]. Of note, non-survivors were found to have lower weight at PICU admission in a study by Hames and colleagues [20]. When weight values were categorized, we found that weighing less than 10 kg significantly increased the likelihood of mortality. The prospective registry study by Askenazi et al. and the 10-year retrospective analysis of Rileys et al. both found higher mortality among CRRT recipients weighing less than 10 kg [21, 25]. In the light of these studies and our results with categorical analysis, we can feasibly suggest that age and weight are significant factors associated with survival in patients receiving CRRT.

As expected, PRISM III scores were higher among non-survivors. However, studies evaluating recipients of CRRT report varying results; while some studies have found relationships between PRISM III score and mortality, others have not [4, 9, 20, 22, 24]. Multiple studies have identified that the need for vasoactive support [11, 15, 16], need for mechanical ventilation [16, 20], presence of comorbidity [3, 23], and MODS [11, 14] were risk factors of mortality in recipients of CRRT. In the current study we did not find independent relationships between mortality and these factors, except for comorbidities.

In the literature, the median %FO values at the initiation of CRRT range from 6.3% to 21.0% [11, 14, 20, 22, 23]; 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 [7–10, 13]; however, conflicting results also exist [4, 20, 26]. 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 in multivariate analysis, we believe there should be continued emphasis on managing the fluid status of critically ill children since >20% FO has been reported as an independent risk factor for mortality in some studies, even though conflicting results exist [14, 20, 23].

The timing of CRRT initiation is still controversial in the literature [27]. 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, while the ELIAN study suggested lower mortality with early CRRT [28], the AKIKI trial showed no difference [29]. In our study, the median time of initiation was 7 h, which, compared with other pediatric studies, is very early [14, 20, 22, 23]. We focus on starting CRRT early in select patient groups, including those with sepsis and other acute clinical conditions (such as hemolytic uremic syndrome). Univariate analysis revealed that non-survivors were started on CRRT later than survivors; however, multivariate analysis revealed no significant relationship. Results in the literature are conflicting; some have reported increased survival with early CRRT [13, 14],

while others have found no relationship [4, 20, 22, 23]. Of note, patients with sepsis who had survived were found to have shorter time until CRRT initiation compared to non-survivors, even though the number of sepsis patients was limited. This particular relationship was also identified in the study by Cortina and colleagues; however, their results did not show statistical significance [14].

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 because the majority of patients with the lowest (5.4%) mortality rate (those with renal disease) had a diagnosis of hemolytic uremic syndrome—a disease characterized by low platelet count. Serum creatinine was also higher among those that survived; however, this might be associated with increased creatinine in patients admitted with renal disease who had very high survival. Other studies in the literature also report no relationship between creatinine and mortality in CRRT recipients [4, 20]. We only identified lactate as an independent risk factor in this study. In previous studies, Cortina et al. [14] and Fernandez et al. [15] have not found an association, and, while lactate levels were higher among non-survivors in a study by Choi et al. [16], it was not found to be an independent risk factor.

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 our population was quite large, patient heterogeneity was limited and the study involved smaller subgroups, which could be factors limiting the precision of our results. Another limitation is the method of calculating %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 CRRT. This can be a potential factor that affects survival, ventilation time and length of PICU stay.

Conduct of studies involving populations with greater heterogeneity and children with risk-factor diseases could facilitate better evaluation of the effects of early CRRT initiation on survival in critically-ill children.

5 | CONCLUSION

We identified that, presence of comorbidity, having pneumonia/respiratory failure at admission, and high lactate

at CRRT initiation as independent risk factors for mortality. In the context of the population studied, mortality rate was lower than previously reported. Despite having a large series, heterogenous characteristics and limitations in subgroups may have influenced results and survival. 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.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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