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ORIGINAL ARTICLE

Characteristics and outcomes of children ≤ 10 kg receiving continuous kidney replacement therapy: a WE-ROCK study

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Abstract

Background Continuous kidney replacement therapy (CKRT) is often used for acute kidney injury (AKI) or fluid overload (FO) in children ≤ 10 kg. Intensive care unit (ICU) mortality in children ≤ 10 kg reported by the prospective pediatric CRRT (ppCRRT, 2001–2003) registry was 57%. We aimed to evaluate characteristics associated with ICU mortality using a contemporary registry.

Methods The Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK) registry is a retrospective, multinational, observational study of children and young adults aged 0–25 years receiving CKRT (2015–2021) for AKI or FO. This analysis included patients ≤ 10 kg at hospital admission. Primary and secondary outcomes: ICU mortality and major adverse kidney events at 90 days (MAKE-90) defined as death, persistent kidney dysfunction, or dialysis within 90 days, respectively.

Results A total of 210 patients were included (median age 0.53 years (IQR, 0.1, 0.9)). ICU mortality was 46.5%. MAKE-90 occurred in 150/207 (72%). CKRT was initiated at a median 3 days (IQR 1, 9) after ICU admission and lasted a median 6 days (IQR 3, 16). On multivariable analysis, pediatric logistic organ dysfunction score (PELOD-2) at CKRT initiation was associated with increased odds of ICU mortality (aOR 2.64, 95% CI 1.68–4.16), and increased odds of MAKE-90 (aOR 2.2, 95% CI 1.31–3.69). Absence of comorbidity was associated with lower MAKE-90 (aOR 0.29, 95%CI 0.13–0.65).

Conclusions We report on a contemporary cohort of children ≤ 10 kg treated with CKRT for acute kidney injury and/or fluid overload. ICU mortality is decreased compared to ppCRRT. The extended risk of death and morbidity at 90 days highlights the importance of close follow-up.

Keywords Acute kidney injury · Critically ill infants · Continuous kidney replacement therapy · MAKE-90 · Fluid overload

Abbreviations

CKRT	Continuous kidney replacement therapy
ICU	Intensive care unit
ppCRRT registry	Prospective pediatric continuous renal replacement therapy registry
WE-ROCK	Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease
AKI	Acute kidney injury
FO	Fluid overload
MAKE-90	Major adverse kidney events at 90 days
PELOD-2	Pediatric logistic organ dysfunction score
KRT	Kidney replacement therapy
IRB	Institutional Review Board
CCHMC	Cincinnati Children's Hospital Medical Center
VIS	Vasoactive-inotrope score

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eGFR	Estimated glomerular filtration rate
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
IQR	Interquartile range
aOR	Adjusted odds ratio
CI	Confidence intervals
CVVHDF	Continuous veno-venous hemodiafiltration

Introduction

Acute kidney injury (AKI) and pathologic fluid overload (FO) are common in critically ill children ≤ 10 kg and are associated with adverse outcomes [1–3]. Some children with severe AKI may require kidney replacement therapy, delivered through peritoneal dialysis or extracorporeal therapy, most commonly continuous kidney replacement therapy (CKRT) [1]. Historically, CKRT utilization in infants and small children (weighing ≤ 10 kg) with AKI has been lower than that in older children, as the use of machines designed for older children and adults makes CKRT delivery technically challenging [4]. While newer devices have been developed (Carpediem™) or adapted (Aquadex™) for neonates and infants, the majority of children ≤ 10 kg continue to receive CKRT utilizing devices approved for larger children or adults [5, 6].

There are limited multicenter reports on the use of CKRT in infants and small children [4, 7]. The largest multicenter study, the Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry, performed almost 20 years ago, reported 57% intensive care unit (ICU) mortality among infants and small children ≤ 10 kg [4]. Since 2005, there have been changes in the care of these patients, including increased awareness and recognition of AKI and FO, and availability of newer CKRT filters and devices. However, the impact of those changes in a multicenter population have not been reported. In order to continue to improve outcomes in critically ill infants and young children treated with CKRT, a better understanding of the epidemiology and outcomes in a contemporary, multicenter cohort is greatly needed.

The Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK) is a multinational investigator group that was formed to study the epidemiology, practices, and clinical and patient-centered outcomes of children receiving CKRT for AKI and FO [8]. In this planned secondary analysis of the WE-ROCK registry, we specifically evaluated infants and small children weighing ≤ 10 kg who received CKRT. We aimed to describe (1) demographic and clinical characteristics; (2) practice variations (CKRT dosing, blood flow, anticoagulation); and (3) outcomes (ICU mortality, major adverse kidney events at 90 days (MAKE-90)) in this cohort. We hypothesized that there would be (1) lower ICU mortality in the contemporary cohort, (2) wide variation in CKRT practice, and (3) a significant burden of morbidity and mortality beyond ICU discharge.

Methods

Study population

Details of the WE-ROCK study methods and demographics of the overall cohort have been reported previously [8, 9]. Briefly the WE-ROCK study included children and young adults (0–25 years old) receiving CKRT for AKI or FO in an ICU from January 2015 to December 2021. This current analysis includes a subgroup of patients with an admission weight ≤ 10 kg. Exclusions include: CKRT for a non-AKI or non-FO indication, dialysis-dependent kidney failure, a severe congenital anomaly of the kidney and urinary tract likely to progress to kidney failure, concomitant use of extracorporeal membrane oxygenation (ECMO), and those treated with the Carpediem™ device, due to the presence of an existing registry focusing on the device [8]. Children receiving ECMO were excluded because of the significant morbidity and mortality seen in this cohort, and the desire to understand the effect of CKRT alone on outcomes. The study was performed in line with the principles of the Declaration of Helsinki. The Institutional Review Board at Cincinnati Children's Hospital Medical Center (CCHMC) and each participating site approved this study, with a waiver of informed consent in view of its retrospective nature. Data sharing agreements were instituted between each site and the data coordinating site (CCHMC).

Demographic and CKRT technique data

Demographic data including sex, age, and time from ICU admission to CKRT initiation were collected for all patients. Data at CKRT initiation included kidney function, presence of sepsis [10] within 24 h of ICU admission, Pediatric Logistic Organ Dysfunction 2 (PELOD-2) [11] score in the 24 h prior to CKRT initiation, fluid balance, and loop diuretic challenge. Details of CKRT prescription, including device, modality, filter, prescribed dose, and anticoagulation, were collected daily for the first 7 days the patient received CKRT, or until procedure termination if less than 7 days. CKRT dose was calculated as the prescribed effluent dose. While CKRT dose is the amount of blood cleared of solute over a unit of time, effluent flow is regarded as an acceptable surrogate of solute clearance for prescribing the dose [12]. CKRT dose was a key exposure variable. Fluid balance was defined using intake and output as has been previously described [13].

Outcomes of interest

The primary outcome was ICU mortality. Secondary outcomes included MAKE-90, CKRT duration, and ICU length of stay. MAKE-90, defined as a composite of death, dialysis-dependence, or persistent kidney dysfunction (> 25% decline in kidney function from baseline) [14], has been recommended by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) workgroup on clinical trials in AKI. We used this, as it allows for assessment of a greater percentage of patients with a clinically meaningful poor outcome and overcomes the limitation of competing risks (for example, mortality and persistent kidney dysfunction) [15]. We chose to assess MAKE at 90 days because this is the time when chronic kidney disease is diagnosed after AKI [16].

Statistical analysis

Continuous variables are reported as median with interquartile range (IQR) and were compared using Wilcoxon rank sum tests. Categorical variables are reported as proportion with percent and were compared using Chi-square tests. To examine the association between ICU mortality and CKRT dose, a univariate logistic regression model was used to model the probability of ICU mortality as a function of CKRT dose at initiation. CKRT dose at initiation was flexibly modeled using restricted cubic spline terms with four knots (5th, 35th, 65th, and 95th percentiles) to allow for potential non-linear associations [17]. A cubic spline plot (i.e., model-based predicted values) was generated to visualize the association between CKRT dose and ICU mortality. Predicted probabilities of ICU mortality as a function of CKRT dose were obtained via an inverse logit transformation of the log odds.

Multivariable logistic regression models were used to estimate adjusted odds ratio (aOR) and 95% confidence intervals (CI) to identify the risk factors associated with ICU mortality and MAKE-90. A priori relevant covariates were selected for each outcome based on the existing literature and clinical practice. For continuous covariates, linear associations with outcomes were assumed and odds ratios are presented as a comparison of the 75th versus 25th percentile (i.e., odds ratios per IQR increase). In all analyses, a p-value < 0.05 was considered statistically significant. All statistical analyses were performed using R (V4.3.1, https://www.r-project.org/). The rms package (version 6.7.1) was used to perform regression analyses.

Results

Patient characteristics

A total of 210 infants and small children from 32 centers in 7 countries were included in this analysis. Selected patient characteristics are displayed in Table 1. The weight range was 1.9–10 kg, median of 6.47 kg (IQR 3.73–8.69), and 75 (32%) weighed ≤ 5 kg. The age range was 1 day–4.4 years, median 0.53 years (IQR 0.1–0.9), with 47 (22%) younger than 1 month. The most common reason for admission was shock/infection/trauma (31%), followed by respiratory failure (22%); 80 (38%) had sepsis at ICU admission. Comorbidities were seen in 81%, with cardiac (27%), and gastrointestinal (26%) being most common, although only 18% had no comorbidity.

CKRT initiation

CKRT was initiated a median of 3 days (IQR 1, 9) after ICU admission and lasted a median of 6 days (IQR 3, 16). In the 24 h prior to CKRT initiation, the median PELOD-2 score was 7 (IQR 5,10) and VIS was 7 (IQR 0, 20). The median FO at CKRT initiation was 16.4% (IQR 6.3, 32.8) with 91 (43%) children having > 20% FO (Table 1).

CKRT technique

The most common CKRT modality was continuous venovenous hemodiafiltration (CVVHDF) in 146 (69%) patients, and polysulfone filters were most commonly used (80%) (Table 1). Anticoagulation strategies included citrate in 110 (52%), heparin in 64 (31%), no anticoagulation in 21 (10%) and other in 15 (7%, epoprostenol and bivalirudin). The most common catheter placement location was internal jugular vein ($n = 156$, 76%) with size ranging from 6 to 10 Fr. Median blood flow per body weight was 8 mL/kg/min (IQR 5.9, 11.3).

CKRT dosing

CKRT dose was calculated as the prescribed effluent dose. The median prescribed CKRT dose at initiation was 2104 mL/1.73 m^2/h (IQR 1564, 3027) or 63.8 mL/kg/h (IQR 49.2, 88.1), with 85% having a CKRT dose prescription of > 40 mL/kg/h. The median hourly dose increased over the first 7 days of treatment. There was wide variation between centers, with the median dose at initiation ranging from 27.8

Table 1 Patient characteristics and association with ICU outcome

Variable	Overall $N=210$	ICU outcome		p-value[2]
		Survival to ICU discharge $N=113$[1]	Death prior to ICU discharge $N=97$[1]	
Patient characteristics				
Female	90 (43%)	49 (43%)	41 (42%)	>0.9
Admission weight (kg)	6.47 (3.7, 8.7)	7.26 (4.5, 8.7)	5.90 (3.3, 8.7)	**0.022**
Weight categories (kg)				**0.009**
<5	75 (36%)	31 (27%)	44 (46%)	
5–10	135 (64%)	82 (73%)	53 (54%)	
Age, years	0.53 (0.1, 0.9)	0.57 (0.2, 0.9)	0.43 (0.08, 0.9)	0.15
Age				**0.3**
<1 month	47 (22%)	21 (19%)	26 (27%)	
1 month–1 year	120 (57%)	69 (61%)	51 (52%)	
>1 year	43 (21%)	23 (20%)	20 (21%)	
Admission category				**0.017**
Shock/infection/major trauma	65 (31%)	35 (31%)	30 (31%)	
Respiratory failure	47 (22%)	16 (14%)	31 (32%)	
Post-surgical/minor trauma	18 (8%)	13 (12%)	5 (5%)	
Post-cardiac surgery	15 (7%)	10 (9%)	5 (5%)	
Other cardiac disease	22 (11%)	9 (8%)	13 (13%)	
Other	43 (21%)	30 (26%)	13 (13%)	
Sepsis at ICU admission	80 (38%)	42 (37%)	38 (39%)	>0.9
Comorbidities*				
None	39 (18%)	25 (22%)	14 (14%)	0.2
Respiratory	34 (16%)	18 (16%)	16 (16%)	>0.9
Cardiac	57 (27%)	31 (27%)	26 (28%)	>0.9
Neurologic/neuromuscular	22 (10%)	13 (12%)	9 (9%)	0.7
Kidney/urologic	15 (7%)	9 (8%)	6 (6%)	0.8
Hematologic	21 (10%)	11 (9.7%)	10 (10%)	>0.9
Oncologic	24 (11%)	10 (9%)	14 (14%)	0.3
Immunologic	29 (14%)	9 (8%)	20 (20%)	**0.016**
Gastrointestinal	55 (26%)	31 (27%)	24 (24%)	0.7
Endocrinologic	4 (2%)	1 (1%)	3 (3%)	0.5
PRISM-III score at ICU admission	14 (10, 19)	14 (10, 18)	15 (10, 20)	0.3
Characteristics at CKRT initiation				
Vasoactive-inotrope score	7 (0, 20)	3 (0, 12)	13.5 (3, 27)	**<0.001**
PELOD-2 score	7 (5, 10)	6 (4, 8)	8 (6, 11)	**<0.001**
Percent fluid balance (ICU admit to CKRT initiation)	16.4 (6.3, 32.9)	16.6 (4.9, 30)	16.2 (7.2, 34.8)	0.2
Serum creatinine (mg/dL)	0.9 (0.6, 1.69)	1 (0.6, 2.1)	0.9 (0.5, 1.2)	**0.018**
Urine output in the 24 h prior to initiation (mL/kg/hour)	0.6 (0.1, 1.6)	0.8 (0.2, 1.8)	0.5 (0.1, 1.4)	0.2
Time from ICU admission to CKRT initiation (days)	3 (1, 9)	3 (1, 7)	4 (1, 13.7)	0.3
CKRT prescription at initiation				
CKRT modality				0.8
SCUF	3 (1.4%)	1 (0.9%)	2 (2.0%)	
CVVH	30 (14%)	15 (13%)	15 (15%)	
CVVHDF	145 (69%)	79 (70%)	66 (67%)	
CVVHD	25 (12%)	15 (13%)	10 (10%)	
mCVVH	7 (3%)	3 (3%)	4 (4%)	
Use of polysulfone filter	168 (80%)	91 (81%)	77 (79%)	0.9
Anticoagulation				0.7

Table 1 (continued)

Variable	Overall $N=210$	ICU outcome		p-value[2]
		Survival to ICU discharge $N=113$[1]	Death prior to ICU discharge $N=97$[1]	
None	21 (10%)	11 (9.7%)	10 (10%)	
Citrate	110 (52%)	63 (56%)	47 (48%)	
Heparin	64 (31%)	32 (28%)	32 (34%)	
Other	15 (7%)	7 (6%)	8 (8%)	
Prescribed CKRT dose (mL/per 1.73 m^2/h)	2104 (1564, 3027)	2038 (1543, 2809)	2195 (1761, 3092)	0.2
Prescribed CKRT dose (mL/kg/h)	64 (49, 88)	59 (49, 85)	71 (49, 102)	0.13
Blood flow rate scaled to body weight (ml/min per kg)	8 (5.9, 11.3)	7.6 (5.4, 10.2)	8.9 (6.7, 12.5)	**0.011**

[1]Statistics presented: *n* (%); median (IQR)

[2]Statistical tests performed: chi-square test of independence; Wilcoxon rank-sum test

ICU, intensive care unit; *CKRT*, continuous kidney replacement therapy; *PRISM-III*, Pediatric Risk of Mortality-III; *PELOD-2*, Pediatric Organ Logistic Dysfunction-2 score; *GFR*, glomerular filtration rate; *SCUF*, slow continuous ultrafiltration; *CVVH*, continuous venovenous hemofiltration; *CVVHD*, continuous venovenous hemodialysis; *CVVHDF*, continuous venovenous hemodiafiltration; *mCVVH*, modified CVVH done using Aquadex device

Percentages may not add up to 100 due to rounding

*Many patients had more than 1 comorbidity

to 187.8 mL/kg/h (861–4244 mL/1.73 m^2/h) (Supplementary Fig. 1). There was also a wide range of initial prescribed dose within centers that enrolled at least 5 patients in the study (Supplementary Fig. 2).

Mortality prior to ICU discharge

Overall, 97 (46.1%) died prior to ICU discharge. Of those, 41 patients died during their CKRT course (Fig. 1). A description of patient characteristics by ICU mortality is presented in Table 1. Those who died in the ICU had lower weights (5.9 kg vs. 7.3 kg, $p=0.022$), with those weighing ≤ 5 kg having higher mortality (59% compared to 40% mortality in those > 5 kg, $p<0.009$). There was no significant difference in mortality by age categories, with those younger than 1 month age (55%), 1 month to 1 year (43%) and older than 1 year (47%) (Table 2). Patients who died had higher PELOD-2 scores (8 vs. 6, $p<0.001$) and VIS (13.5 vs. 3, $p<0.001$) in the 24 h prior to CKRT initiation. Those with respiratory failure as the primary reason for admission, and those with immunologic co-morbidities (including patients with hematopoietic stem cell transplants), were more likely to die in the ICU (Table 1).

There were no differences between CKRT modality, filter type, or mode of anticoagulation by ICU mortality status. CKRT dose at initiation was similar between survivors and non-survivors. By day 3 of therapy, it was higher in those who did not survive with a median of 84.3 mL/kg/h (IQR 54, 114.8) compared to 63.6 mL/kg/h (IQR 43.3, 90.8) in those who survived, $p=0.017$. Considering the possibility that higher clearances in those who did not survive could reflect regional citrate use and accumulation, we evaluated

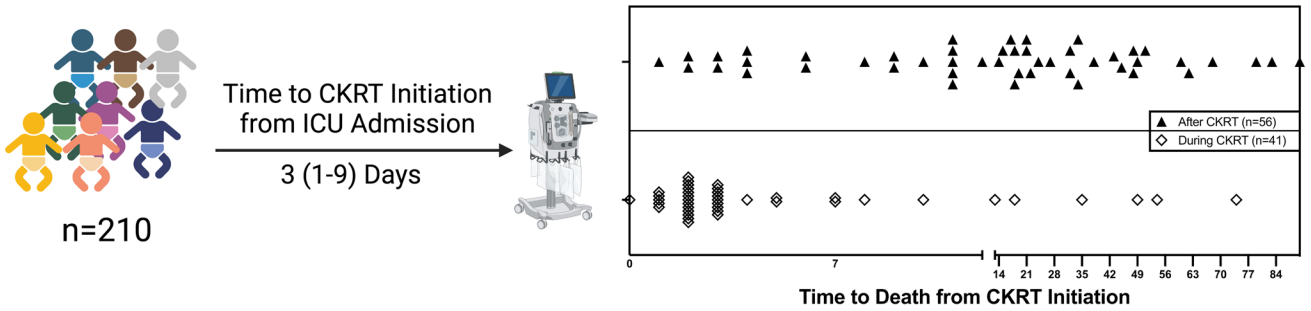

Fig. 1 Timeline up to 90 days from CKRT initiation. CKRT was initiated at a median (IQR) 3 (1–9) days after ICU admission. Open diamonds represent those who died during their CKRT course ($n=41$). Closed triangles represent those who died after coming off CKRT (8 patients died after their CKRT course beyond the 90 day mark). (Created with BioRender.com)

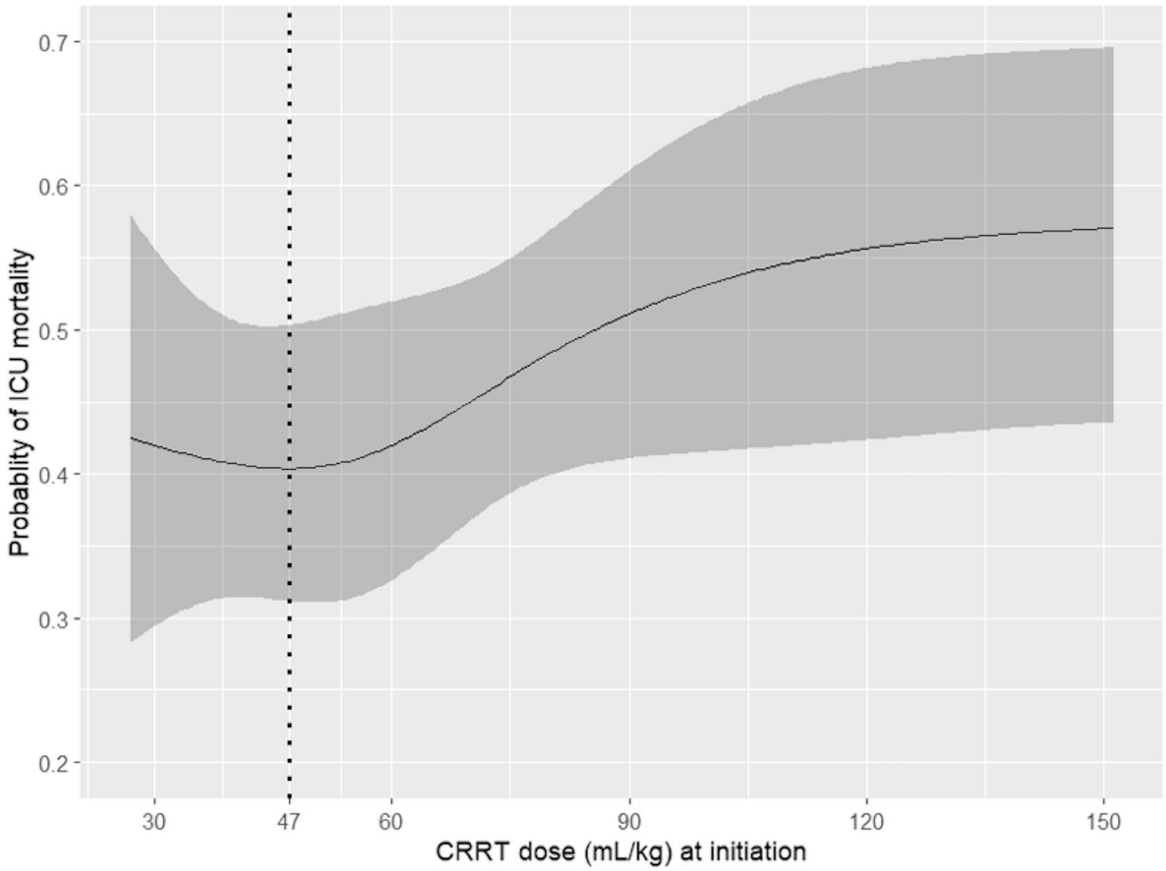

Fig. 2 Predicted probability of ICU mortality as a function of CKRT dose at initiation (ml/kg) from the logistic regression model. CKRT dose was modeled with restricted cubic splines (4 knots). The dotted line is CKRT dose of 47 ml/kg/h. Shaded areas are 95% CIs

Table 2 Key outcomes of infants receiving continuous kidney replacement therapy

Survival to ICU discharge ($n=210$)	113 (54%)
Survival to ICU discharge based on weight^	
< 5 kg	31 (41.3%)
5–10 kg	82 (60.7%)
Survival to ICU discharge based on age	
< 1 month	21 (44.6%)
1 month–1 year	69 (57.5%)
> 1 year	23 (53.4%)
CKRT duration (days) (survivors only)	6.00 (3.00, 16.00)
ICU length of stay (days) (survivors only)	32 (20, 56)
Presence of MAKE 90 ($n=207$)	150 (72%)
Components of MAKE 90 ($n=150$*)	
Death	100
Dialysis dependence	16
Persistent kidney dysfunction	50*

ICU, intensive care unit; *CKRT*, continuous kidney replacement therapy; *MAKE-90*, major adverse kidney events at 90 days. *Includes the sum of those alive with and without dialysis dependence. ^$p<0.05$

anticoagulation type and found no significant difference between proportion of patients receiving citrate compared to other anticoagulants.

The predicted probability of ICU mortality decreased slowly until a CKRT dose of 47 mL/kg/h and increased with further increases in dose ($p=0.349$) (Fig. 2). In the evaluation of CKRT dose at initiation by tertiles (< 53 mL/kg/h, 53–80 mL/kg/h, and > 80 mL/kg/h), the smallest and youngest infants received the highest dose. Median weight and age for those with a prescription > 80 mL/kg/h were 5.2 kg (IQR 3, 7.7) and 0.3 years (IQR 0.06, 0.6) compared to 8 kg (IQR 4.4, 9.6) and 0.6 years (0.1, 1), respectively, for those < 53 mL/kg/h. Those receiving a dose > 80 mL/kg had the highest rate of KRT dependence at hospital discharge and longest duration of mechanical ventilation (Supplementary Table 1), but there was no difference in ICU or hospital mortality.

In multivariable logistic regression analysis which included weight, percent fluid overload, PELOD-2 score, and CKRT dose at initiation, dose was not associated with

increased odds of death prior to ICU discharge (aOR 1.07, 95% CI 0.88–1.29). Only higher PELOD-2 score (aOR 2.64, 95% CI 1.68–4.16) at CKRT initiation remained statistically significantly associated with increased odds of death prior to ICU discharge (Table 3).

MAKE-90

MAKE-90 data were available in 207 patients of whom 150 (72.4%) fulfilled criteria, with death in 100 (67%), and persistent kidney dysfunction (> 25% decline from baseline kidney function or dialysis dependence) in 50 (33%) (Table 2). The cohort of 50 patients with persistent kidney dysfunction included 16 who were dialysis dependent at 90 days. In multivariable logistic regression analysis which included weight, percent fluid overload, CKRT dose at initiation, CKRT duration, and PELOD-2 Score at CKRT initiation, and the presence or absence of any comorbidity, PELOD-2 was associated with increased odds of MAKE-90 (aOR 2.20, 95% CI 1.31–3.69). Absence of any comorbid condition had a protective effect, with lower odds of MAKE-90 (aOR 0.29, 95%CI 0.13–0.65) (Table 4).

Discussion

In this secondary analysis of the multicenter international WE-ROCK registry, we describe the clinical characteristics, CKRT treatment, and outcomes in a large cohort of children weighing ≤ 10 kg requiring CKRT. This study shows that infants and small children with AKI and FO who weigh ≤ 10 kg at CKRT initiation have higher mortality prior to ICU discharge compared to children weighing > 10 kg (46% in children ≤ 10 kg vs. 36% for the entire WE-ROCK cohort). We also report that there remains a significant burden of morbidity and mortality at 90 days, with nearly half the survivors having persistent kidney dysfunction. Additionally we show that there are important and large variations in prescribed dialysis dosing, both within and between centers.

While CKRT has become the modality of choice in critically ill older children with severe AKI and FO, there is a paucity of data on infants and small children treated with CKRT ≤ 10 kg. Most studies of CKRT in this population are single-center and small [18, 19]. In a retrospective cohort of 85 infants < 10 kg from 5 United States centers from 1993 to 2001, Symons et al. reported ICU mortality of 62% ICU

Table 3 Multivariable regression model for ICU mortality

Variable	Reference	Contrast	aOR (95% CI)
Weight (kg)	3.7	8.7	0.63 (0.35–1.11)
Percent fluid overload	6.3	32.9	1.07 (0.89–1.29)
PELOD-2 score at CKRT initiation*	5.0	10.0	**2.63 (1.68–4.14)**
CKRT dose at initiation (mL/kg/h)	49.2	88.1	1.06 (0.88–1.29)

ICU, intensive care unit; *CKRT*, continuous kidney replacement therapy; *PELOD-2*, Pediatric Organ Logistic Dysfunction-2 score

*Statistically significant

Adjusted odds ratio (aOR) and 95% confidence intervals (CI) obtained by logistic regression. aORs for continuous predictors scaled to reflect the interquartile range odds ratio (i.e., reference = 25th percentile, contrast = 75th percentile)

Table 4 Multivariable regression models for major adverse kidney events at 90 days (MAKE-90)

Variable	Reference	Contrast	aOR (95% CI)
Weight (kg)	3.7	8.7	0.60 (0.31–1.17)
No comorbidity*	No	Yes	**0.29 (0.13–0.65)**
PELOD-2 score at CKRT initiation*	5.0	10.0	**2.20 (1.31–3.69)**
Percent fluid overload	6.3	32.9	1.07 (0.84–1.37)
CKRT dose at initiation (mL/kg/h)	49.2	88.1	0.94 (0.78–1.12)
CKRT duration (days)	3.0	16.0	1.33 (0.998–1.78)

CKRT, continuous kidney replacement therapy; *PELOD-2*, Pediatric Organ Logistic Dysfunction-2 score

*Statistically significant

Adjusted odds ratio (aOR) and 95% confidence intervals (CI) obtained by logistic regression. aORs for continuous predictors scaled to reflect the interquartile range odds ratio (i.e., reference = 25th percentile, contrast = 75th percentile)

[7]. Among a similar but prospective cohort in the ppCRRT registry, which enrolled patients from 2001 to 2005, Askenazi et al. reported 56% mortality in 84 patients [4]. In a more contemporary retrospective cohort of 51 infants weighing ≤ 10 kg, 47% died in the hospital [6]. Many of these studies included infants with severe congenital kidney disease and those who received CKRT for a non-AKI/FO indication (i.e., ingestion or inborn errors of metabolism), groups which have usually had better outcomes compared to those with AKI and/or FO [4, 6, 7]. In the current study, we focused on a less heterogenous population, and limited enrollment to only those treated with CKRT for AKI and/or FO, and excluding concurrent ECMO use that has a substantial negative effect on survival. After excluding those with inborn errors of metabolism, the mortality in the ppCRRT cohort was 62% compared to 46% in our study [4]. While there are significant differences between these studies, we may be seeing some improvement in the outcomes of infants receiving CKRT over time, which are likely related to overall improvements in ICU care, along with better recognition of AKI and FO [9, 20, 21].

As recognition and ICU survival of critically ill children of all ages with AKI have improved, there has been a shift to include the outcomes of persistent kidney dysfunction captured in MAKE-90. However there are limited follow-up data on neonates and infants treated with CKRT, particularly focusing on MAKE-90 or other long-term outcomes. Most studies include all children < 18 years, and have been from either small single center studies or large claims-based data [22, 23]. Using province-wide health administrative databases of children aged 0–18 years hospitalized in Ontario, Canada, Robinson et al. reported that those who survived an episode of pediatric AKI requiring dialysis were at significantly increased risk of a composite outcome of kidney failure or death versus an age-matched control population that did not have AKI requiring dialysis [23]. At a median follow-up of 9.6 months, death occurred in 6.7% and kidney failure in 2.6%, along with hypertension, chronic kidney disease, and repeat episodes of AKI. More recently, Gulcek et al. reported on 109 patients weighing < 15 kg who received various modalities of acute KRT including CKRT, HD, and PD [24]. ICU mortality was seen in 64 (58.7%). At a mean follow-up of 2.9 ± 2.1 years, 34 patients (including 3 who received CKRT) were evaluated, and 22 patients (64.7%) were reported to have ≥ 1 kidney risk factor including elevated blood pressure/hypertension, abnormal eGFR, and/or proteinuria. We show high rates of MAKE-90 in children ≤ 10 kg, with 50% of survivors having abnormal kidney function at 90 days, including many still requiring dialysis. The high rates of persistent kidney dysfunction highlight the need for close follow-up in this at-risk population, as has been previously recommended [25–27].

In the current study, we also looked at sub-populations and patient characteristics associated with adverse outcomes. While the severity of illness at CKRT initiation was associated with worse MAKE-90, the absence of any comorbidity was associated with lower odds of developing MAKE-90. Over 80% of those in our cohort had at least 1 comorbidity. This reflects the increasing medical complexity of infants and small children admitted to ICUs, where the proportion of children with chronic comorbidities has increased significantly in the last decade [20]. These children experience higher mortality and longer ICU stays than children without chronic medical conditions [20].

To continue improving outcomes in infants and small children treated with CKRT, a critical step is understanding the characteristics and heterogeneity in CKRT prescription and delivery. One of the most interesting findings we report is the variation in CKRT dosing. Pediatric CKRT prescriptions have been extrapolated from adults [28, 29], with a dose of 2000 mL/1.73 m^2/h approximating adult weight-based doses (25–30 mL/kg/h for a 70 kg patient) [30]. However, there are wide variations reported in clinical practice, ranging from < 1000 to > 4000 mL/1.73 m^2/h, which equated to 20–150 mL/kg/h [31]. We report similar variation not only between centers, but also within the same center. The dose variance in this population takes on particular importance when one considers that weight-based dosing and BSA-based dosing diverge at lower weights. This nonlinear relationship between weight and BSA results in a disproportionately higher dose in neonates and infants. The current study shows that most patients are prescribed a dose > 40 mL/kg/h, which would be considered a high dose in adults. While high-dose CKRT has been studied extensively in adults without consistent evidence of benefit, little is known about its impact on outcomes in small children. The potential consequences of such high doses are loss of proteins, amino acids, phosphorus, and other micronutrients [32]. However, we acknowledge that details of individual CKRT treatments, notably delivered dose, reasons for dose increase, and the change in clinical status and severity of illness scores over the duration of therapy was not collected. This limits our ability to assess differences in prescribed and delivered dose, or the reasons in changes in CKRT dose over time. While we did not see a significant relationship between dose and outcomes, this highlights the opportunity for the development of standardized protocols for dosing in this population and the systematic study of dosing in this population.

The primary strength of this study is it represents a large contemporary report of infants weighing ≤ 10 kg receiving CKRT, including data from 32 centers across 7 countries. Nonetheless, we acknowledge several important limitations.

Registry data are subject to center and patient selection bias. Given the study design and its retrospective nature, we only collected information on those who started CKRT for AKI and FO. The study also lacks information on those with severe AKI/FO who may not have received CKRT due to their size, or severity of illness, or lack of appropriate resources, or may have received peritoneal dialysis or kidney support with Carpediem™. While CKRT use is becoming increasingly common in pediatric patients with critical illness, peritoneal dialysis remains the most common modality of KRT in infants and small children worldwide [33]. All sites included in WE-ROCK are tertiary or quaternary care centers in North America, Western Europe, the United Kingdom, and Australia; therefore, the findings may only be applicable to centers with similar practice models and resources. Sites were permitted to participate in WE-ROCK by including 10 or more consecutive patients. While this was done to promote inclusion and participation from sites that do not have significant research resources due to lack of funding for WE-ROCK, we recognize this may have resulted in site selection bias as only sites with some research resources were able to participate.

We highlight that survival in infants and small children who weigh ≤ 10 kg at CKRT initiation is improving. Furthermore, we describe that many survivors have kidney sequelae at 90 days. There is significant practice variation in CKRT dosing with marked differences between and within centers. When dosing was adjusted for weight, 85% of neonates received a dose higher than the "high dose" CKRT described in adult studies. This study highlights the need for evidence-based guidelines for CKRT prescription in infants and small children, as well as a standardized approach to follow-up for those that survive to discharge to ensure monitoring for medium- and long-term kidney-related complications.

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Data availability De-identified summary data are available upon request through the WE-ROCK collaborative. Under the current approval by the Institutional Review Board at Cincinnati Children's Hospital Medical Center (CCHMC), and the data use agreements signed by the individual participating sites and CCHMC, analyses are done by the data coordinating center at CCHMC. The data from the WE-ROCK collaborative will be made available to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal following an application process and execution of a data use agreement as required by the IRB at the CCHMC.

Declarations

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