Original Article

Evaluation of Continuous Renal Replacement Therapy and Risk Factors in the Pediatric Intensive Care Unit

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ABSTRACT. Acute kidney injury (AKI) is one of the most common causes of increased mortality and morbidity in the pediatric intensive care unit (PICU). Continuous renal replacement therapy (CRRT) is the mainstay treatment for AKI in children as it allows continuous and programmed removal of fluids, which is tolerated better hemodynamically. Defining the risk factors of CRRT related to mortality and morbidity will help improve the outcomes of patients in the PICU. In this study, we aimed to determine the prognostic factors and outcomes of patients who received CRRT. This was a single-center, retrospective study on PICU patients requiring CRRT. Patients with a history of chronic renal failure and PICU stay duration of <24 h and those who died on the 1st day of admission were excluded from the study. A total of 447 patients admitted between October 2016 and March 2018 were included in the study. Children who received CRRT for the management of AKI and/or other nonrenal indications, such as metabolic acidosis, poisoning, electrolyte imbalance, and congenital metabolic diseases, were also included in the study. Fifty patients underwent CRRT. There was a statistically significant relationship between CRRT support and prognostic factors, including age (P = 0.012), inotropic drug usage (P = 0.000), concomitant infection (P = 0.010), blood component transfusion (P = 0.005), pediatric risk of mortality score (P = 0.027), and mortality (P = 0.003). The odds ratio for mortality was 5.396 (95% confidence interval: 1.732–16.809). In conclusion, CRRT is associated with increased morbidity and mortality in the PICU.

Introduction

Acute kidney injury (AKI) is one of the most common causes of increased mortality and morbidity in the pediatric intensive care unit (PICU). Peritoneal dialysis and continuous renal replacement therapy (CRRT) are the most frequently used treatment modalities for AKI in critically ill children. Despite the improvement in renal replacement therapies (RRTs) and treatment modalities in intensive care units (ICUs), the mortality of AKI is still high, ranging from 9% to 67%. CRRT is the
mainstay treatment for AKI in children as it allows continuous and programmed removal of fluids, which is tolerated better hemodynamically.\(^3\)

CRRT is currently being used for the treatment of several nonrenal indications, such as metabolic acidosis, poisoning, electrolyte imbalance, and congenital metabolic diseases, in the PICU.\(^1\) The success of CRRT depends on various factors, including body weight and age of the patient, underlying disease, duration of CRRT, fluid overload, inotropic drug usage, and mechanical ventilation (MV) support.\(^3\) While CRRT is an established treatment modality in developed countries, there is no adequate pediatric report from developing countries. Defining the risk factors of CRRT related to mortality and morbidity will help improve the outcomes of patients in the PICU. In this study, we aimed to determine the prognostic factors and outcomes of patients who received CRRT.

**Materials and Methods**

**Study design**

The data of all patients admitted for various critical illnesses in the PICU of Okmeydani Research and Training Hospital between October 2016 and March 2018 were reviewed in this study. We have a tertiary multidisciplinary PICU located in a training and research hospital in Istanbul, Turkey, to which approximately 20,000 patients are admitted monthly during the winter season and approximately 400 patients are admitted in the PICU each year. Our PICU provides health care for children aged from one month to 18 years; it has 12 beds, 11 incubators, two isolation rooms, and two Prismaflex™ hemofiltration machines (Baxter, USA).

**Patient population and data collection**

We performed a retrospective analysis of the records of all patients admitted in the PICU between October 2016 and March 2018. Patients with a history of chronic renal failure (CRF) and duration of stay in the PICU <24 h and those who died on the 1\(^{st}\) day of admission were excluded from the study. The study was approved by our local ethics committee (2018-907).

Demographic data and reason for hospitalization were recorded. The patients were divided into two groups: with and without a history of CRRT. The patients’ sex and age; the need for invasive or noninvasive mechanical ventilation MV (NIMV); inotropic drug usage; concomitant infection; blood component transfusion; duration of hospitalization in the ICU; presence of multiple organ dysfunction syndrome (MODS); mortality; Pediatric Risk of Mortality (PRISM-III) score; laboratory parameters; and leukocyte, lymphocyte, and platelet counts in the first 24 h were considered as the possible risk factors for CRRT.

**Catheterization and continuous renal replacement therapy**

The indications for CRRT included fluid overload, electrolyte imbalance, metabolic acidosis, congenital metabolic disease, and intoxication. Some patients had more than one indication. Double-lumen central venous catheters were percutaneously placed along the femoral vein, jugular vein, or subclavian vein by a single specialist. The patients received sedation and analgesia prior to catheterization. Midazolam, ketamine, fentanyl, and propofol were used for sedation and analgesia. No neuromuscular blockers and local anesthetics were used. No surgical catheters were attached, and ultrasonography was not performed. Strict aseptic method was followed during catheterization. The catheters were attached using the Seldinger method and fixed to the skin using 2-0 sharp-pointed silk sutures. Anticoagulation was performed using unfractionated heparin and citrate. The dosage of heparin was adjusted on the basis of the activated partial thromboplastin time, which was checked every 4 h and maintained at 60–80 s. The dosage of citrate was adjusted on the basis of the blood gas findings in a 4-h period. Prismaflex™ hemofiltration systems and poly membrane (AN69) filters were used. The blood flow rate was 5–20 mL/kg/min. The dialysate flow rate, replacement fluid rate, and ultrafiltration rate...
were adjusted on the basis of the patients’ diagnoses. The dialysate flow rates were set between 2 and 10 L/1.73 m²/h.

**Statistical Analysis**

Statistical analysis was performed using the IBM SPSS statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as means ± standard deviations and categorical variables as frequencies (percentages). Student’s *t*-test was used for continuous variables with a normal distribution. Pearson’s Chi-square test and analysis of variance were used for the comparison of the categorical data between the groups. Univariate and multivariate binary logistic regression models were employed to calculate the odds ratios (ORs) with 95% confidence intervals (CIs) for prognosis. *P* <0.05 was considered statistically significant.

**Results**

**Demographics**

Between October 2016 and March 2018, 474 children were admitted to the PICU; of them, 447 were eligible for the present study. Twenty-seven patients were excluded because 17 had known CRF; five were diagnosed with end-stage oncology; two died in the first 24-h of hospitalization; and three had a PICU stay duration of <24 h. Of the 447 patients, 243 (54.4%) were boys and 204 (45.6%) were girls. The age distribution was between one month and 17 years, with a mean of 3.77 ± 4.71 years. The mean duration of hospitalization in the PICU was 7.09 ± 10.21 days.

Fifty patients underwent CRRT. Overall, septic shock, acute renal pathology, and respiratory failure were the main indications for CRRT. Inotropic drugs were used in 22 (44%) CRRT patients. MV was used in 16 (32%) CRRT patients, and NIV was efficient in 19 patients (38.0%). Plasma exchange was performed in 12 patients (24%). Five (10%) CRRT patients died during their stay in the PICU. The demographic data of the CRRT patients are shown in Table 1.

Further, 6.5-Fr (Able®, Orientama Jaya, Indonesia) hemodialysis (HD) catheters were used in six patients; 8-Fr HD catheters (Mahurkar™, Medtronic, USA) were used in 27 patients; 10-Fr HD catheters (Mahurkar™) in eight patients; and 11.5-Fr HD catheters (Mahurkar™) were used in nine patients. Prismaflex™ M60 was used as the HD filter in 37 patients; Prismaflex™ M100 in 10 patients; and Prismaflex™ HF20 in three patients.

**Prognostic factors**

The patients were divided into two groups: with and without a history of CRRT. There was a statistically significant relationship between CRRT support and prognostic factors, including age (*P* = 0.012), inotropic drug usage (*P* = 0.000), concomitant infection (*P* = 0.010), blood component transfusion (*P* = 0.005), PRISM-III score (*P* = 0.027), and mortality (*P* = 0.003). There was also a statistically significant relationship between CRRT support and leukocyte count (*P* = 0.029), lymphocyte count (*P* = 0.011), platelet count (*P* = 0.000), levels of procalcitonin (*P* = 0.000), C-reactive protein (CRP) (*P* = 0.012), magnesium (*P* = 0.000), calcium (*P* = 0.012), lactate dehydrogenase (*P* = 0.012), uric acid (*P* = 0.000), and hypoalbuminemia (*P* = 0.000), during admission in the PICU (Table 2).

The ORs and relationship between the prognostic factors and CRRT were calculated using logistic regression models. The OR was 3.287 (95% CI, 1.402–7.707) for concomitant infection, 7.435 (95% CI, 1.430–36.669) for inotropic drug usage, 0.543 (95% CI, 0.052–5.691) for transfusion, 5.095 (95% CI, 1.664–15.600) for hypomagnesemia, 4.332 (95% CI, 2.112–8.887) for hypocalcemia, 3.778 for lymphopenia (95% CI, 1.314–10.867), and 5.336 (95% CI, 2.844–10.010) for hypoalbuminemia. The OR for mortality was 5.396 (95% CI, 1.732–16.809) (Table 3). The demographic findings of the patients who died during CRRT are reported in Table 4.

**Discussion**

AKI is associated with increased mortality in
critically ill children admitted to the PICU. The epidemiology of pediatric AKI has changed over the past decades. Congenital heart disease and solid organ and bone marrow transplantations are the current causes of pediatric AKI rather than primary renal diseases. RRT is the only supportive treatment of choice in patients with severe AKI. CRRT has become the most widely used RRT modality in PICU patients; it was applied in 69% of children with AKI in a recent report. In our study, 50 of 111 children (45%) received CRRT. Although CRRT is a life-saving treatment, it has some disadvantages, such as requirement of technical expertise, follow-up of hemodynamic and coagulation

Table 1. Demographic characteristics of the continuous renal replacement therapy patients in the pediatric intensive care unit (n=50).

| Characteristics                                      | n (%)/mean±standard deviation |
|------------------------------------------------------|--------------------------------|
| Sex                                                   |                                |
| Male                                                  | 30 (60.0)                      |
| Female                                                | 20 (40.0)                      |
| Intensive care hospitalization diagnosis              |                                |
| Septic shock                                          | 21 (42.0)                      |
| Respiratory disease                                   | 7 (14.0)                       |
| Neurological disease                                  | 4 (13.4)                       |
| Cardiovascular disease                                | 3 (6.0)                        |
| Intoxication                                          | 2 (4.0)                        |
| Trauma                                                | 2 (4.0)                        |
| Hematology-oncology-related diagnosis                 | 2 (4.0)                        |
| Acute renal pathology                                 | 9 (18.0)                       |
| Age (years)                                           | 5.31±5.04                      |
| Age distribution                                      |                                |
| 1 month to 2 years                                    | 24 (48.0)                      |
| 2–10 years                                            | 16 (32.0)                      |
| >10 years                                             | 10 (20.0)                      |
| Mechanical ventilation                                | 16 (32.0)                      |
| NIMV use                                              | 19 (38.0)                      |
| Inotropice drug usage                                 | 22 (44.0)                      |
| Duration of CRRT application (days)                   | 3.22±0.79                      |
| Plasma exchange                                       | 12 (24.0)                      |
| Duration of stay in the PICU (days)                   | 8.59±12.76                     |
| PRISM-III score                                       | 17.17±13.40                    |
| Blood transfusion                                     | 27 (54.0)                      |
| Citrate used patients                                 | 10 (20.0)                      |
| Catheter-related infection (days/1000)                | 4.64/1000                      |
| Mortality                                             | 5 (10.0)                       |
| Catheter diameter                                     |                                |
| 6.5 Fr                                                | 6 (12.0)                       |
| 8 Fr                                                  | 27 (54.0)                      |
| 10 Fr                                                 | 8 (16.0)                       |
| 11.5 Fr                                               | 9 (18.0)                       |
| Hemodialysis filter                                   |                                |
| 0.2 m²                                                | 3 (6.0)                        |
| 0.6 m²                                                | 37 (74)                        |
| 0.9 m²                                                | 10 (20)                        |

CRRT: Continuous renal replacement therapy, PICU: Pediatric intensive care unit, NIMV: Noninvasive mechanical ventilation, PRISM: Pediatric Risk of Mortality.
Table 2. Comparison of the intensive care unit risk factors of continuous renal replacement therapy usage.

| Risk factors                                      | Yes (n=50) | No (n=397) | P    |
|--------------------------------------------------|------------|------------|------|
| Sex, n (%)                                       |            |            |      |
| Male                                             | 30 (60.0)  | 213 (53.7) | 0.406|
| Female                                           | 20 (40.0)  | 184 (46.3) |      |
| Age (years)                                      | 5.31±5.04  | 3.55±4.63  | 0.012|
| Mechanical ventilation, n (%)                    | 16 (32.0)  | 106 (26.7) | 0.428|
| Inotropic drug usage, n (%)                      | 22 (44.0)  | 77 (19.4)  | 0.000|
| Concomitant infection at admission, n (%)        | 26 (52.0)  | 278 (70.0) | 0.010|
| NIMV, n (%)                                      | 19 (38.0)  | 185 (46.6) | 0.237|
| Blood component transfusion, n (%)               | 27 (54.0)  | 133 (33.5) | 0.005|
| PRISM-III score                                  | 17.17±13.40| 11.77±9.26 | 0.027|
| Leukocyte count (10^3/µL)                        | 10779±8297 | 13509±7670 | 0.029|
| Lymphocyte count (10^3/µL)                       | 2443±2251  | 3905±2934  | 0.011|
| Platelet count (10^3/µL)                         | 17779±121963| 36068±176890| 0.000|
| Procalcitonin level (ng/mL)                      | 27.75±21.95| 8.95±21.99 | 0.000|
| C-reactive protein level (mg/L)                  | 70.49±102.06| 44.02±67.75| 0.024|
| Sodium level (mmol/L)                            | 137.35±6.71| 138.11±5.25| 0.356|
| Chlorine level (mmol/L)                          | 100.64±9.49| 102.39±6.00| 0.108|
| Magnesium level (mg/dL)                          | 1.89±0.44  | 2.19±0.44  | 0.001|
| Calcium level (mg/dL)                            | 8.29±1.23  | 9.43±0.98  | 0.000|
| Gamma glutamyl transferase level (U/L)           | 52.22±88.46| 44.26±65.77| 0.526|
| Alanine aminotransferase level (U/L)             | 52.28±118.70| 52.47±257.69| 0.996|
| Aspartate aminotransferase level (U/L)           | 102.47±232.09| 92.59±475.79| 0.889|
| Lactate dehydrogenase level (U/L)                | 686.70±118.70| 441.50±348.84| 0.000|
| Uric acid level (mg/dL)                          | 6.18±3.30  | 4.17±2.45  | 0.000|
| Albumin level ≤2.5 g/dL, n (%)                   | 25 (50.0)  | 69 (17.4)  | 0.000|
| Duration of stay in the PICU (days)              | 8.59±12.76 | 7.15±9.96  | 0.357|
| Mortality, n (%)                                 | 5 (10.0)   | 9 (2.3)    | 0.003|
| MODS, n (%)                                      | 25 (50.0)  | 25 (6.3)   | 0.000|

CCRT: Continuous renal replacement therapy, PRISM: Pediatric Risk of Mortality, PICU: Pediatric intensive care unit, MODS: Multiple organ dysfunction syndrome; NIMV: Noninvasive mechanical ventilation.

Table 3. Logistic regression analysis of the risk factors of continuous renal replacement therapy usage.

| Risk factors                                      | P         | Odds ratio | 95% confidence interval |
|--------------------------------------------------|-----------|------------|-------------------------|
| Sex                                              | 0.387     | 1.627      | 0.540–4.900             |
| Concomitant infection                            | 0.006*    | 3.287      | 1.402–7.707             |
| Mechanical ventilation                           | 0.434     | 0.498      | 0.086–2.873             |
| NIMV                                             | 0.940     | 1.033      | 0.439–2.433             |
| Inotropic drug usage                             | 0.017*    | 7.435      | 1.430–36.669            |
| Blood component transfusion                      | 0.610     | 0.543      | 0.052–5.691             |
| Hyponatremia                                     | 0.716     | 1.430      | 0.209–9.789             |
| Hypomagnesemia                                   | 0.004*    | 5.095      | 1.664–15.600            |
| Hypocalcemia                                     | 0.000*    | 4.332      | 2.112–8.887             |
| Lymphopenia (<3000 10^3/µL)                      | 0.014*    | 3.778      | 1.314–10.867            |
| Hypoalbuminemia                                  | 0.000*    | 5.336      | 2.844–10.010            |
| Length of PICU stay (<7 days)                    | 0.085     | 1.525      | 0.469–4.963             |
| Mortality                                        | 0.004*    | 5.396      | 1.732–16.809            |

*P<0.005, PICU: Pediatric intensive care unit; NIMV: Noninvasive mechanical ventilation.
Table 4. Characteristics of the patients who died during continuous renal replacement therapy follow-up.

| Characteristics               | Patient number |
|-------------------------------|----------------|
|                               | 1              | 2              | 3              | 4              | 5              |
| Gender                        | Male           | Male           | Male           | Male           | Male           |
| Age (years)                   | 5 years        | 13 months      | 16 years       | 12 months      | 9 months       |
| Hospitalization diagnosis     | Septic shock   | Septic shock, meningococcemia | Leukemia, septic shock | Multiple congenital anomaly, septic shock | Immunodeficiency, septic shock |
| Length of PICU stay           | 48 days        | 44 h           | 9 days         | 5 days         | 46 h           |
| Duration of CRRT application  | 42 days        | 40 h           | 196 h          | 25 h           | 36 h           |
| PRISM-III score               | 37             | 31             | 26             | 41             | 52             |
| Plasma exchange               | 5 times        | 2 times        | 6 times        | -              | -              |
| Duration of MV support        | 48 days        | 44 h           | 9 days         | 5 days         | 48 h           |
| ECMO                          | 8 days         | 12 h           | 8 days         | -              | -              |
| Catheter Infection            | Yes            | No             | No             | No             | No             |
| Organism                      | *Acinetobacter baumannii* | -              | -              | -              | -              |
| Complication                  | Catheter-related sepsis | -              | Local hematoma, hemorrhage | -              | -              |
| Catheter size                 | 10 Fr          | 8 Fr           | 8 Fr           | 8 Fr           | 6.5 Fr         |
| Location                      | Femoral        | Femoral        | Subclavian     | Jugular        | Jugular        |

PICU: Pediatric intensive care unit, CRRT: Continuous renal replacement therapy, PRISM: Pediatric Risk of Mortality, MV: Mechanical ventilation, ECMO: Extracorporeal membrane oxygenation.
parameters, and need for vascular access and anticoagulation. In our study, there were 24 patients (48%) under two years of age. For this reason, we closely controlled the clinical and laboratory parameters of the patients during CRRT in our unit. We did not observe serious mechanical complications (e.g., pneumothorax or severe hemorrhage) related to CRRT. However, catheter-related infection developed in two of our patients.

Effective anticoagulation of the extracorporeal circuit is mandatory to prevent clotting of the circuit or filter membrane. The most common mode of anticoagulation was systemic application of unfractionated heparin. Another anticoagulation agent is citrate. Citrate is reported to decrease the risk of bleeding owing to its anticoagulation effect. In the study by Wu et al, patients who received CRRT with a high risk of bleeding were recommended to use citrate as the anticoagulant agent. In our study, the citrate solution was only used in a small number of patients because its use in pediatric patients is not recommended in our country (20.0%). These patients were older than five years of age who had a high risk of bleeding.

Heparin-related thrombocytopenia also increases the risk of bleeding. As an adverse effect of systemic heparin therapy, the complex of heparin and platelet factor 4 can trigger the production of antibodies. This antibody production may result in decreased platelet count and increased need for transfusion. However, this effect was not evaluated in our study. We found a significant correlation between blood transfusion and CRRT. As acute renal failure and CRRT support are the components of multiple organ failure, the bleeding disorders can explain the need for blood transfusions in these patients. However, we did not observe significant bleeding during CRRT needing blood component transfusion.

Infection is an important problem among patients in the PICU, and sepsis is a well-established risk factor for the development and poor prognosis of AKI. Severe AKI is reported nearly in 20% of patients presenting with sepsis. There is a high incidence of sepsis-associated AKI in critically ill patients. In our study, sepsis and septic shock were the most common underlying disorders in the patients needing CRRT, with a rate of 42%. In these patients, CRRT was used for the treatment of multiple organ failure. AKI is often seen as a component of MODS in critically ill children.

We noted a significant relationship between CRRT and concomitant infection, increased procalcitonin and CRP levels, and leukocytosis. The common point of the patients who died was that they were admitted to the PICU with septic shock.

Another important cause of mortality and morbidity in CRRT patients is catheter-related bloodstream infections. For this reason, all the patients with HD catheters were treated with five rules called the “central line bundle.” Catheter-associated sepsis was detected in two of the CRRT patients, and one of them died. The frequency of catheter-related bloodstream infection was 4.64/1000 catheter days, which was consistent with the literature. A large cohort study on adult patients showed an overall incidence of CRRT catheter colonization and bloodstream infection of 1.9 and 38.9/1000 catheter days, respectively. In another study, the incidence of catheter-related infections in HD patients was 23/1000 catheter days.

Children who receive CRRT have an increased mortality, which is higher than the predicted severity of their underlying disease. Most studies have used the PRISM-III score, which is calculated at the time of PICU admission and is associated with PICU mortality risk. We also used the PRISM-III score and found that the patients who received CRRT had higher scores. In our logistic regression analysis, we found that the need for CRRT increased the mortality by 5.4 times. In addition, the survival rate of our patients who received CRRT was 90%, which is similar to that of the study by Foland et al. The mortality in the infant age group who received CRRT is reported to be 40%. In our study, 24 patients (48.0%) were under two years of age, and three of them died (12.5%).
Various risk factors for mortality were evaluated in PICU patients, except for the PRISM-III score. Alves et al reported that hypomagnesemia is an independent risk factor for worse prognosis in critically ill patients with AKI. We also found a significant relationship between hypomagnesemia and CRRT (OR, 5.095). The same relationship was found with hypocalcemia, hypoalbuminemia, and hypocalcemia. However, there was no correlation between other electrolyte deficiencies (i.e., sodium and chlorine) and CRRT, similar to the finding of the study by Choi et al. The most important risk factor for CRRT in our study was inotropic drug usage (OR, 7.435). This may be because 42% of the patients who received CRRT had septic shock.

Hypoalbuminemia was associated with a higher mortality in children (OR, 5.336). The need for MV support is another risk factor associated with poor prognosis in PICU patients. However, we did not find any significant correlation between CRRT and MV usage (invasive or noninvasive).

**Conclusion**

CRRT is closely related to increased mortality and morbidity. There are some limitations in our study. First, our study was a retrospective and single-center study. Second, we do not have cardiovascular surgery and bone marrow and solid organ transplantation units in our hospital. Third, the risk factors that increase mortality could not be evaluated statistically because the number of CRRT patients who died was small. There is a need for large-scale prospective studies in the pediatric age group to support this finding.

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