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Association of thrombocytopenia on secondary infection and mortality in pediatric intensive care unit patients receiving continuous renal replacement therapy

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ABSTRACT

Aims: Continuous renal replacement therapy (CRRT) is a widely used treatment modality in pediatric patients. We aimed to evaluate the susceptibility of thrombocytopenia to secondary infection and mortality during intensive care unit admission and the initiation of CRRT in patients admitted to the pediatric intensive care unit.

Methods: We conducted a retrospective study of patients in a tertiary pediatric intensive care unit who underwent CRRT between February 2021 and July 2024. The study included 34 patients who underwent CRRT.

Results: The study population consisted of patients with a median age of 26 months and 58.8% were male. At pediatric intensive care units (PICU) admission, 10 (29.4%) patients had thrombocytopenia, whereas 15 (44.1%) had thrombocytopenia at CRRT initiation. Patients with thrombocytopenia at the start of CRRT had a greater risk of mortality. Mortality approached significance in patients with thrombocytopenia at PICU admission. The risk of infection was significantly increased in patients with thrombocytopenia at the start of CRRT according to univariate and multivariate regression analyses (p=0.01).

Conclusion: The detection of thrombocytopenia at the beginning of CRRT is associated with a higher secondary infection rate and mortality during pediatric intensive care hospitalization. CRRT and thrombocytopenia negatively impact immune function, and further prospective studies are needed to assess their association with subsequent infection risk.

Keywords: Continuous renal replacement therapy, pediatric intensive care, secondary infection, thrombocytopenia, mortality

INTRODUCTION

Continuous renal replacement therapy (CRRT) is a widely used treatment modality in pediatric patients. However, the prognosis of pediatric patients is poor, with mortality rates ranging from 30% to 60% in pediatric intensive care units (PICU).[1-2] Although CRRT is increasingly used in clinical practice, the relationship between the survival rate does not increase in parallel. Its proven safety and efficacy make it the preferred treatment for critically ill pediatric patients. CRRT is an adjuvant treatment modality that removes fluid overload (FO), uremic toxins, endotoxins, proteins, and inflammatory mediators in critically ill patients.[3] The timing and indications for initiating CRRT are still under discussion. The most common indications for CRRT include acute kidney injury (AKI), FO, removal of toxic metabolites, inborn errors of metabolism, sepsis, and poisoning, as well as nonrenal indications such as removal of inflammatory mediators. AKI and FO are common in critically ill children and increase mortality.

The pathophysiology of sepsis-associated AKI is thought to involve microcirculatory dysfunction, inflammation, autophagy, the inflammatory pathway, vitamin D levels, and immunosuppression.[4] In patients undergoing CRRT for sepsis, immunosuppression also develops due to the elimination of cells responsible for body defense, such as platelets and leukocytes. CRRT also provides the removal of inflammatory mediators that cause sepsis. Sepsis is associated with the development of secondary infection by causing immunosuppression in both AKI and CRRT used in the treatment of sepsis.

Platelets are key components of both innate and adaptive immunity.[5] It is possible that platelet loss, which plays a role in innate and adaptive immunity, may lead to subsequent infection. Platelet depletion after the initiation of CRRT has been associated with increased mortality and a lack of renal recovery in survivors.[6] Thrombocytopenia is common in critically ill patients and is often associated with a negatively impacted prognosis. The incidence of thrombocytopenia varies among studies, ranging from 35% to 55% in studies of pediatric patients.[7] Decreased platelet production or increased destruction associated with therapeutic

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interventions and underlying diseases such as sepsis are causes of thrombocytopenia. Sepsis and multiorgan failure are the most important risk factors for the development of thrombocytopenia in intensive care patients, and markers related to disease severity, such as the need for mechanical ventilation and the duration of vasopressor use, have also been shown to be risk factors for thrombocytopenia. Thrombocytopenia is common in critically ill patients who require dialysis and negatively impacts prognosis. Thrombocytopenia developing before CRRT initiation and during follow-up is associated with increased intensive care unit mortality.[8]

AKI and thrombocytopenia, especially when secondary to sepsis, are common in critically ill children requiring dialysis. Thrombocytopenia is an independent risk factor for AKI and a marker of disease severity.[8] There is insufficient information in the literature about the incidence and outcome of thrombocytopenia in pediatric patients. In this study, we aimed to evaluate whether thrombocytopenia at admission to the intensive care unit and initiation of CRRT would be an independent risk factor for secondary infection and mortality in patients admitted to the PICU.

METHODS

The study was approved by the İzmir Bakırçay University Non-interventional Clinical Researches Ethics Committee (Date: 10.07.2024, Decision No: 1688). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This retrospective analysis included all hospitalized patients who underwent CRRT in the Pediatric Intensive Care Unit of Manisa City Hospital between February 2021 and July 2024. Many demographic and clinical variables, such as age, sex, laboratory results, PRISM III score, pediatric sequential organ failure assessment (pSOFA) score on the day that CRRT was initiated, number of days on mechanical ventilation, CRRT indication, dialysis catheter location, and culture results, were documented in the study. Also recorded were the platelet value at initiation of CRRT, number of days on CRRT, day on which CRRT was initiated in the ICU, time from initiation of CRRT to platelet nadir, and time from discontinuation of CRRT to discharge from the ICU. The study included individuals aged between 29 days and 18 years who underwent CRRT during their PICU stay and had complete and available data. AKI, fluid excess greater than 10% of the normal body volume, electrolyte imbalance, severe metabolic acidosis and acute metabolic disorder episodes are classified as criteria for CRRT. The total percent fluid overload (FO%) was calculated by employing the following formula: [(total fluid intake-total fluid output) (in liters)/admission body weight in kg]×100. The Vasopressor Index score (VIS) was calculated via the following equation: the sum of the dopamine dosage (g/kg/min), dobutamine dose (g/kg/min), 100 times the epinephrine dose (g/kg/min), 10 times the milrinone dose (g/kg/min), 10,000 times the vasopressin dose (U/kg/min), and 100 times the norepinephrine dose (g/kg/min).[9]

CRRT was initiated in critically ill children with FO>10% when diuretics failed to achieve or maintain negative fluid balance. Percutaneous insertion of double-lumen central venous catheters is often performed through the right internal jugular vein. While subclavian vein access was used in one patient due to thrombosis, femoral vein access was preferred in three patients. The PRISMAFLEX hemofiltration system apparatus was used for CRRT. Modifications were applied to the CRRT parameters, with blood flow rates ranging from 4 to 10 cc/kg/min. Adjustments were made to the dialysate and replacement settings following the clearance dose of 2000 cc/hour/1.73 m^2. Unfractionated heparin was used for anticoagulation.[10] However, patients with platelet counts less than $50\times10^3/mm^3$ were not anticoagulated, a larger catheter was placed, or the blood flow rate was kept high. The criteria for termination of CRRT are increased urine output, no fluid overload, decreased need for vasoactive drugs, and patient death. Patients with platelet counts $<100\times10^3/\mu l$ at PICU admission and CRRT initiation were evaluated as having thrombocytopenia. Patients who developed sepsis during CRRT or after CRRT was terminated and had positive blood cultures were considered to have secondary infection. Secondary infection was defined as a new antibiotic prescription for possible infection during CRRT and in the post-CRRT intensive care unit and subsequent detection of proven infection. Another endpoint evaluated as a secondary outcome was the development of septic shock during ICU follow-up, defined as suspected infection, hypotension refractory to fluid resuscitation, or at least 2 SIRS criteria positive and lactate elevation. Finally, mortality was defined as survival to discharge during the ICU stay.

The primary outcome included the development of a secondary infection in patients with platelet counts <100×103/μl at PICU admission and CRRT initiation. The secondary outcome was the association between secondary infection and mortality in patients with thrombocytopenia at PICU admission and the initiation of CRRT.

Statistical Analysis

The data analyses were performed via SPSS 22 software (SPSSX Inc., Chicago, IL, USA). The characteristics of the study population were described via frequency distributions for categorical variables and mean and standard deviation (SD) values, medians, and ranges for continuous variables, on the basis of the normal distribution of the data. The Kolmogorov-Smirnov test was used to evaluate the homogeneity of the data distribution. The statistical significance of continuous variable comparisons was determined via Student's t-test or the Mann-Whitney U test in pairs, depending on the distribution of the analyzed variable; if necessary, it was evaluated via one-way ANOVA or the Kruskal-Wallis test in multiple groups. The relationships among the parameters were investigated via Pearson correlation analysis. Comparisons of categorical variables were carried out via the chi-square test or Fisher's exact test. The power analysis of thrombocytopenia patients who underwent CRRT in adult intensive care was determined as 80%. In our study, 0.05 (1-alpha) and 0.8 effect sizes were calculated according to the sample number, and 80% power was calculated according to the independent samples t-test analysis.[11] All the statistical tests were two-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS

The study included a cohort of 34 patients who underwent CRRT from February 2021 to July 2024. Table 1 shows the patient characteristics. The study population consisted of patients with a median age of 26 months and an interquartile range (IQR) of 8-138 months. Additionally, 58.8% of the patients were male. The most common comorbidity in the entire sample was metabolic/genetic disease, which occurred in 15 individuals (44.1%). Sepsis was responsible for most PICU admissions, accounting for 47.1% of cases. At PICU admission, 10 (29.4%) patients had thrombocytopenia, whereas 15 (44.1%) had thrombocytopenia at CRRT initiation. The mortality rate in the PICU was determined to be 35.3%.

Patients with thrombocytopenia at the start of CRRT were younger than those without thrombocytopenia (p=0.01). Patients with thrombocytopenia at the start of CRRT had a greater rate of developing infection during PICU follow-up (p=0.01). Mortality was greater in patients with thrombocytopenia at PICU admission, but this difference was not statistically significant. Mortality was significantly greater in patients with thrombocytopenia at CRRT initiation (p=0.007) (Table 2).

The multivariate analysis included the following outcome measures; age, sex, PRISM III score, comorbidities, PICU admission diagnosis, VIS score, duration of mechanical ventilation, and duration of PICU stay. Regression analysis revealed that the risk increased with age in patients with thrombocytopenia at PICU admission and increased mortality. Patients with thrombocytopenia at the start of CRRT had a greater risk of mortality. Mortality approached significance in patients with thrombocytopenia at PICU admission. The risk of infection was significantly increased in patients with thrombocytopenia at the start of CRRT according to univariate and multivariate regression analyses (p=0.01) (Table 3).

Table 1. Patient use of CRRT

Characteristics	Total (n=34)
Age (month), median (IQR)	26 (8-138)
Sex, n (%)	
Female	14 (41.2)
Male	20 (58.8)
PRISM III score, median (IQR)	27.5 (20-32)
Comorbid condition, n (%)	
Genetic/metabolic	15 (44.1)
Other	19 (55.9)
PICU admission diagnosis, n (%)	
Sepsis	16 (47.1)
Respiratory system diseases	8 (23.5)
Acute attacks of metabolic diseases	2 (5.9)
Acute renal failure	4 (11.8)
Other	4 (11.8)
Need for inotrope, n (%)	28 (82.4)
Vasoactive inotropic score, median (IQR)	37.5 (20-90)
Thrombocytopenia at PICU admission, n (%)	10 (29.4)
Thrombocytopenia at the initiation of CRRT, n (%)	15 (44.1)
Infection after CRRT, n (%)	15 (44.1)
Invasive mechanical ventilation, n (%)	29 (85.3)
Duration of mechanical ventilation (days), median (IQR)	12 (7-15)
Duration of PICU stay (days), median (IQR)	14.5 (11.5-20)
PICU mortality, n (%)	12 (35.3)

CRRT: Continuous renal replacement therapy, IQR: Interquartile range, PRISM III score: Pediatric risk of mortality score, PICU: Pediatric intensive care units

Table 2. Comparison of primary and secondary outcomes in thrombocytopenia at PICU admission patients and in patients who had thrombocytopenia at CRRT initiation

	Thrombocytopenia at PICU admission			Thrombocytopenia at the initiation of CRRT		
Outcomes	**Yes (n=10)**	**No (n=24)**	**p-value**	**Yes (n=15)**	**No (n=19)**	**p-value**
Age (month), median (IQR)	17.5 (7-138)	29.5 (8-140)	0.55	9 (5-32)	86 (24-174)	0.01
PRISM III score, median (IQR)	24.5 (18.7-35.2)	29 (20-32)	0.93	25 (20-32)	28 (20-32)	0.97
Infection after CRRT, n (%)	6 (60)	4 (40)	0.22	10 (66.7)	5 (33.3)	0.01
Duration of mechanical ventilation (days), median (IQR)	12.5 (9.2-16.2)	12 (7-15)	0.85	10 (6-14)	14 (12-17)	0.05
Duration of PICU stay (days), median (IQR)	14.5 (5.7-21.2)	14.5(12-17.5)	0.87	14 (6-23)	15 (12-16)	0.93
Mortality	6 (60)	4 (40)	0.05	9 (60)	6 (40)	0.007

PICU: Pediatric intensive care units, CRRT: Continuous renal replacement therapy, IQR: Interquartile range

Table 3. Associations between variables and thrombocytopenia according to univariate and multivariate regression analyses

	Thrombocytopenia at PICU admission			Thrombocytopenia at the initiation of CRRT		
Variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age (month)						
Univariable	0.999	0.988-1.009	0.80	0.986	0.973-0.998	0.02
Multivariable	0.999	0.987-1.010	0.08	0.969	0.946-0.993	0.01
Infection after CRRT						
Univariable	0.400	0.088-1.813	0.235	0.179	0.041-0.786	0.02
Multivariable	0.404	0.080-2.031	0.271	0.018	0.001-0.413	0.01
Mortality						
Univariable	0.222	0.046-1.065	0.06	0.125	0.025-0.62	0.01
Multivariable	4.330	0.867-21.63	0.07	0.119	0.021-0.66	0.01

PICU: Pediatric intensive care units, CRRT: Continuous renal replacement therapy, OR: Odds ratio, CI: Confidence interval

DISCUSSION

Our results suggest that in children undergoing CRRT in the PICU, the thrombocytopenia at PICU admission and CRRT initiation are associated with an increased risk of infection and mortality during PICU follow-up. Mortality was increased in patients with thrombocytopenia at PICU admission, but this difference was not statistically significant. Mortality was significantly greater in patients with low platelet counts at CRRT initiation. Although thrombocytopenia is known to be associated with an increased rate of infection, one study showed that thrombocytopenia at CRRT initiation is independently associated with subsequent infection and mortality.[8]

Sepsis that develops during follow-up in patients with AKI is the most common cause of death, and AKI is also the most common organ dysfunction in sepsis patients. Impaired immune function due to malnutrition in patients undergoing CRRT can lead to infection.[12] Furthermore, uremia and acidosis frequently have negative effects on immunity because they interfere with white blood cell function, phagocytosis, and endothelial function in AKI patients.[13] Secondary infection is a significant source of morbidity and mortality in patients treated with CRRT, and CRRT is known to have a bidirectional relationship with sepsis.[14] In the PICARD study, 49% of patients who were followed for AKI and received RRT developed sepsis, and the mean time to onset of sepsis was 4 days (IQ range 2-7 days) after the start of RRT.[15] In a study conducted with 55 pediatric intensive care patients who underwent CRRT, 78.2% had one or more infections during or after CRRT. Catheter-related infections are common in 64.3% of cases.[16] Immunosuppression in patients with hemodialysis catheters placed for CRRT in intensive care patients or due to both sepsis and therapies used may be associated with an increased rate of secondary infection.

The risk of infection during follow-up was significantly increased according to multivariate regression analysis in patients with thrombocytopenia at the initiation of CRRT (p=0.01). Infection was detected in 6 (60%) patients with thrombocytopenia at PICU admission, and secondary infections were detected in 10 (66.7%) patients with thrombocytopenia at the start of CRRT. The agents isolated in culture were *Pseudomonas aeruginosa* in 6 (17.6%) patients, *Klebsiella pneumoniae* in 5 (14.7%) patients, *Acinetobacter baumannii* in 1 (2.9%) patient, and *Candida albicans* in 3 (8.8%) patients. Gram-negative bloodstream infection was detected in 48.8% of thrombocytopenic patients and was significantly more common than in patients without thrombocytopenia (p=0.007).[17] Similarly, in our study, the agents isolated from patients were gram-negative, and no gram-positive agents were detected.[18] Catheter retention has been associated with a higher risk of infection and mortality.[19] Our patients also had dialysis catheters and central venous catheters, which created a predisposition to infection.

In our study, thrombocytopenia during PICU admission was not significantly associated with mortality according to the univariate analysis (p=0.06). The univariate and multivariate statistical analyses revealed that mortality in patients with thrombocytopenia at the initiation of CRRT was substantial (p=0.01). A study in pediatric intensive care patients reported that a low platelet count may indicate a poor prognosis and may also be independently associated with mortality in critically ill children. They concluded that thrombocytopenia is generally associated with sepsis and a higher mortality (p=0.0053) rate than that in nonthrombocytopenic patients.[20] In a study of 541 adult patients, a platelet count <150×10^3/µl at the start of CRRT was associated with mortality. The observed in-hospital mortality also increased significantly with worsening thrombocytopenia (p=0.05).[8] In a study of 797 CRRT patients discharged from an adult intensive care unit, a platelet count reduction of >40% from pre-CRRT was associated with an increase in post-ICU infections, independent of the presence of baseline thrombocytopenia.[21] Therefore, risk factors associated with thrombocytopenia should be closely monitored by physicians to determine the outcome in critically ill children because of their association with poor prognosis and mortality.

Limitations

This study has several limitations. Tests were not available to diagnose potentially significant thrombocytopenia, such as heparin-induced thrombocytopenia, but heparin was used less frequently and was not used at all in patients with low platelet counts (50×10^3/µl). This study is a retrospective examination conducted at one PICU. There is a need for further prospective studies that include larger cohorts of patients. Furthermore, the sample size is limited, diminishing our estimations' accuracy and posing difficulties in extrapolating general conclusions from the identified associations.

CONCLUSION

Thrombocytopenia is a prevalent condition in patients requiring dialysis in pediatric intensive care and impacts negatively on their survival. The detection of thrombocytopenia at the beginning of CRRT is associated with a higher secondary infection rate during pediatric intensive care hospitalization. Thrombocytopenia present at the beginning of CRRT is associated with higher pediatric intensive care mortality. CRRT and thrombocytopenia negatively impact immune function, and further prospective studies are needed to assess their effects on subsequent infection risk.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the İzmir Bakırçay University Non-interventional Clinical Researches Ethics Committee approved the study (Date: 10.07.2024, Decision No: 1688).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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