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Risk Factors for Severe Acute Kidney Injury after Pediatric Hematopoietic Stem Cell Transplantation

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Abstract

Risk Factors for Severe Acute Kidney Injury after Pediatric Hematopoietic Stem Cell Transplantation

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Background: Acute Kidney Injury (AKI) is common after Hematopoietic Stem Cell Transplantation (HSCT) and is associated with increased morbidity and mortality. Risk factors for AKI after HSCT are not fully understood, and there are limited pediatric studies that describe post HSCT AKI.

Objective: To assess unique risk factors for AKI in the HSCT population.

Design/Methods: We conducted a retrospective cohort study of patients < 20 years age who received an HSCT at Seattle Children's Hospital from 10/1/2008 to 7/31/2017 (n=484). We defined AKI using Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Severe AKI

was > KDIGO Stage 2. We collected information on demographics, baseline transplant characteristics (including conditioning regimen, donor type, cell source, indication for HSCT), post-HSCT complications (inotrope use, sepsis, ventilator use), and mortality at 1 year. Multinomial logistic regression was used to estimate the association between AKI and potential risk factors. We used adjusted cox proportional hazard ratios to evaluate differences in mortality between groups.

Results: 186 patients (38%) developed AKI. Of those with AKI, 79 (42%) had severe AKI and 27 (15%) required renal replacement therapy (RRT). There were no significant differences in demographics and indication for HSCT between the groups. Fluid overload was common in all groups with 53 (67%) of those with severe AKI with a fluid overload>10%. Nephrology consult was obtained in fewer than 50% of those with severe AKI. Children who received a cord blood transplant or mismatched transplant had a higher relative risk of severe AKI on univariable analysis only. In both univariable and multivariable analysis, the risk of severe AKI was lower in those who had myeloablative conditioning (RR 0.65 (95% CI 0.3-0.99)) and those who received Tacrolimus (RR 0.42 (95% CI 0.11-0.73)). . Risk of mortality was 4.61 (2.61-8.15) times higher in severe AKI compared to no AKI.

Conclusions: AKI and fluid overload are common in pediatric patients post HSCT. In our study, severe AKI was less frequent in those with received a myeloablative conditioning regimen or Tacrolimus and was associated with higher mortality. These risk factors could represent unique causes of AKI in this population that warrant further evaluation for use in predicting AKI after HSCT. Nephrology consultation was underutilized and often delayed.

Introduction:

Hematopoietic stem cell transplantation (HSCT) is a widely used and effective treatment for a variety of oncologic and non- oncologic diseases[1,2] and over 60,000 a year are performed worldwide[2]. Despite improvements in the transplantation process, post-transplant complications of HSCT continue to contribute significant morbidity and mortality [1,2].

Acute Kidney injury (AKI) is a common complication of HSCT and recent pediatric studies have found that 68- 84% of patients after HSCT experience AKI[3,4]. Mortality rates increase with severity of AKI and survival of those with severe AKI at one year after transplant can be as low as 20-40%[3–8]. Patients who develop AKI after HSCT also have higher rates of chronic kidney disease and long term mortality[8–10]. Given the increased mortality and morbidity associated with AKI in the HSCT population, better understanding of potential unique risk factors for AKI after HSCT could lead to strategies to improve outcomes for these patients.

Numerous studies have assessed risk factors for AKI among HSCT recipients[3,4,8–18,]. Some risk factors such as sinusoidal obstructive syndrome (SOS), sepsis, and amphotericin are reported consistently between studies [3,4,6,7,9,12–14]. Other potential risk factors specific to the transplantation that include donor source, conditioning regimen, cell source, and indication for HSCT are reported inconsistently[3,4,7,12,16]. The variation between studies is likely due to smaller sample sizes of many studies and variable definitions of AKI used previously[5,13,14,17]. Our study aimed to study the pattern of AKI after HSCT in the pediatric population and to evaluate transplant-specific risk factors for AKI.

Methods:

Patient Population and Study Design

This was a retrospective cohort study that included all patients less than 21 years of age who underwent HSCT at Seattle Children's Hospital (SCH) from September 2008 until July 2017. For patients who received more than one transplant, each transplant was considered separately in the data collection. Information was gathered for the duration of their first hospitalization for HSCT. Data were extracted from either the research database at the Fred Hutchison Cancer Research Center or directly from electronic medical records (EMR). Demographics and pre-transplant characteristics were obtained from the research database. Hospital characteristics including lab values, medications, anthropometrics, and post-transplant complications were retrieved from the EMR.

Approvals from the institutional review boards of both Seattle Children's Hospital and the Fred Hutchison Cancer Research Center were obtained for this study.

Definitions

AKI was defined as a rise in serum creatinine (SCr) of ≥0.3 mg/dL or a >150% increase from a baseline creatinine using Kidney Disease: Improving Global Outcomes (KDIGO) criteria[18]. (>200% increase of SCr or initiation of dialysis). Urine output was not used to define AKI as this information is not consistently documented or readily available in the EMR. We considered creatinine obtained at admission prior to initiation of the conditioning regimen to be the baseline creatinine. Conditioning regimens were classified as myeloablative, reduced-intensity, and other. Myeloablative conditioning regimens were those that had high busulfan dosing (> 9 mg/kg) or total body irradiation with fractionated doses > 8 gy.

Percent fluid overload (FO%) was calculated with the formula described by Selewski, et al[19]:

FO% = (CRRT initiation weight (kg)– Hospital admission weight (kg))/Hospital admission weight (kg) × 100%. Our threshold for significant fluid overload was 10% based on the criteria used by Rondon, et al[20].

Statistical Analysis

Characteristics of the cohort were summarized using medians and interquartile ranges for continuous variables and frequencies and percentages for categorical variables. Multinomial univariate logistic regression was performed to assess risk factors for AKI. Age, gender and all statistically significant variables from univariable analysis were included in a final multinomial, multivariable logistic regression model. Kaplan-Meier survival curves and Cox proportional hazards regression models were used to assess the risk of mortality for those with no AKI, AKI stage 1, and severe AKI, controlling for matched transplant, gender, age at time of transplant, and stem cell source. The statistical analysis was performed using R via R Studio version 1.1442 (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Four hundred and eighty- four consecutive pediatric patients who underwent HSCT at Seattle Children's Hospital were included in this study. Demographic and clinical characteristics are described in Table 1. Median age for the cohort was 8.4 years and was similar between those with and without AKI. There was no difference in gender, race, and ethnicity across the groups. One hundred and seven (22%) patients had stage 1 AKI, and 79 (16%) had severe AKI. Twenty-

seven patients (6%) required renal replacement therapy. Patients with severe AKI were more likely to have received a cord blood transplant or a mismatched allogeneic unrelated transplant.

Anti-hypertensive medications and diuretics were commonly used in both patients with and without AKI. There was more antihypertensive use with AKI and less diuretic use. Patients with severe AKI were more likely to be admitted to the PICU and had higher rates of ventilator use. A greater proportion of patients with severe AKI were diagnosed with bacteremia and/or viremia. Significant fluid overload was common and worsened with severity of AKI. Frequency of nephrology consults increased with severity of AKI. Of those with severe AKI, 44% had a nephrology consults with 77% of those for the initiation of dialysis. Mortality was more common with severe AKI and was highest (63%) among those who required dialysis.

There was no association between race, ethnicity, gender, age, cyclosporine use, or hematologic diagnosis with AKI on univariable analysis. Patients with myeloablative conditioning regimens had a lower risk for severe AKI compared to reduced intensity conditioning regimens [RR 0.62 (95% CI 0.32-0.92)] (Table 2). In comparison to bone marrow transplants, cord blood transplants had an increased risk for AKI for AKI [Severe AKI RR 2.33 (95% CI 1.26-3.40)]. Allogenic unrelated and allogenic related transplants both had a larger risk of severe AKI compared to autologous, though this was not significant. There was a greater risk of stage 1 AKI and severe AKI for patients with mismatched transplants [Severe AKI RR 1.68 (95% CI 1.00-2.35)]. Tacrolimus was associated with a decreased risk for severe AKI [Severe AKI RR 0.53 (95% CI 0.22-0.84)].

The multivariable analysis included age, gender, stem cell source, matched status, conditioning regimen, and calcineurin inhibitor use for graft versus host disease (GVHD) prophylaxis (Table 3). A lower risk for severe AKI persisted in those who had myeloablative

conditioning [RR 0.65 (95% CI 0.30-0.99)] or tacrolimus use [RR 0.42 (95% CI 0.11- 0.73)]. Patients who received a cord blood transplant had a higher relative risk of AKI compared to those who received a bone marrow transplant, though this was no longer statistically significant (Table 3). Mismatched status was no longer associated with increased risk of AKI (Table 3).

The hazard of death at 1 year was four times higher for those with severe AKI compared to those with no AKI [RR 4.43 (95% CI 2.54-7.74)]. There were no differences in mortality between stage 1 AKI and no AKI (table 4).

Discussion

In our study, we found that AKI was common in the HSCT population. In the univariate model, there was an increased relative risk for AKI in patients who had mismatched or cord blood transplantations and a decreased relative risk for AKI in those who received myeloablative conditioning or Tacrolimus as GVHD prophylaxis. Myeloablative conditioning and tacrolimus use continued to be associated with a lower risk for severe AKI in multivariable analysis. Fluid overload was common in all groups with higher fluid overload in those with AKI. Mortality was significantly higher in patients who had severe AKI, though it was lower compared to prior studies[3–5,12–14].

We conducted one of the largest epidemiology studies of AKI after HSCT to date. In comparison to the two other large pediatric studies of AKI after HSCT, the incidence of AKI in our study was lower[3,4]. In the study by Koh et al, they excluded autologous patients, which historically have less AKI and could account for some of the variation between our studies as almost 20% of our population received autologous transplants. Our study evaluated incidence of AKI during the first hospitalization only, whereas the previous studies included the first 100 days

after transplantation. In addition, Kizilbash, et al used the pRIFLE criteria to define AKI, which has been noted to be more sensitive than the KDIGO criteria[21]used by us.

We observed an association between cord blood transplants and increased AKI risk. This was not significant in the multivariate analysis, though the relative risk was still elevated. This association has been demonstrated in both pediatric and adult studies including two recent larger studies by Kagoya and Kizilbash[3,16]. The higher risk of severe AKI after cord blood transplant could be explained in part by the higher rates of sepsis in cord blood transplantation compared to those who undergo transplantation with a different cell source [22–24], as sepsis is a known risk factor for AKI in HSCT patients[6,9,12,14,16]. In our study, 25% of patients who received a cord blood transplant had documented sepsis compared to roughly 10% of those who did not have a cord blood transplantation, which supports this hypothesis.

We found reduced risk of AKI with Tacrolimus when compared to other GVHD prophylactic regimens that did not include calcineurin inhibitors (CNI). This is a novel finding, as there are no prior studies that have assessed the risk of AKI with Tacrolimus compared to those who did not receive Tacrolimus. Typically, patients who received Tacrolimus were combined with those who received Cyclosporine in analysis as they are both calcineurin inhibitors (CNI). Studies assessing the association between AKI and CNIs in HSCT have yielded inconsistent results, with most showing no association between CNI use and AKI[4,6,7,12,13,16,25].

Fluid overload is an established independent risk factor for mortality in a variety of clinical settings[19,26] and has been shown to be associated with higher non relapse associated mortality after HSCT[17,20]. Fluid overload with severe AKI has also been found to be associated with worse renal recovery at one year after AKI[27]. As fluid overload was common in our study, interventions to prevent and reduce the severity of fluid overload represent methods of

improving outcomes in this population. Early nephrology involvement could be a way to improve fluid overload in this population. Additionally, early nephrology involvement with AKI has been shown in prior studies to reduce risk of morbidity and mortality, regardless of dialysis status[27–33]. This is thought to be mediated through changes in diuretic use, reduction in nephrotoxic medication administration, changes in initiation of dialysis, and changes in fluid management[27–33]. Post-discharge ongoing nephrology follow up for who experience AKI is also important as these patients have increased likelihood of developing CKD, hypertension, and early mortality[34–38].

There are several limitations to this study. Given the retrospective design, some factors associated with AKI such as sinusoidal obstructive syndrome, were not included. AKI was diagnosed using only serum creatinine values, which means patients with AKI that would have been diagnosed by oliguria alone are not classified as having AKI. Prior studies have shown that urine output identifies AKI earlier than creatinine and identifies up to twice as many patients as creatinine alone[39,40]. Another obstacle for assessing the risk of AKI due to specific transplant characteristics is the complex interplay between these characteristics. For example, all patients who have cord blood transplantations are allogenic unrelated transplants. Thus, in multivariable analysis, some of the risk from AKI due to a single factor may be reduced or eliminated by controlling for an associated factor. To avoid this, we did not include donor source in our multivariable analysis, though this does not fully address this concern. Controlling for associated factors could explain some of the changes in strength and even direction of association with AKI that we observed in our multivariable analysis.

Our study identified unique risk factors associated with severe AKI after HSCT. Further studies are needed to assess their use, in combination with other known risk factors for AKI, for

the prediction of AKI in this population via a risk score specific to HSCT. Risk factors for AKI could also be combined with more sensitive biomarkers for AKI, such as NGAL and Cystatin C, which have recently been shown to successfully identify AKI early in this population[41]. We also observed that many patients with severe AKI did not have nephrology involvement, and that there was prevalent fluid overload. Late or absent nephrology involvement and fluid overload have both been shown to lead to poor outcomes in numerous studies and were present in our patient population. Decreasing fluid overload and increasing early nephrology involvement represent potential areas of improvement in management of these patients that have the potential to lead to improvements in morbidity and mortality after HSCT.

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Table 1. Selected Pediatric HSCT Patient Characteristics, by AKI level, Seattle Children's Hospital,
(9/2008-7/2017)

	No AKI (N=298)	**AKI Stage 1 (N=107)**	**AKI Stage 2/3 (N=79)**
Female Gender	131 (44.0)	46 (43.0)	31 (15.0)
Age at Transplant (years), Median (IQR)	8.7 (9.5)	7.0 (11.2)	6.6 (12.6)
Race			
Caucasian	213 (71.5)	72 (67.3)	51 (64.6)
African American	14 (4.7)	4 (3.7)	6 (7.6)
Asian	26 (8.7)	12 (11.2)	9 (11.4)
Native Hawaiian/Pacific	3 (1.0)	2 (1.9)	1 (1.3)
Islander	5 (1.7)	2 (1.9)	2 (2.5)
American Indian/ Native	15 (5.0)	4 (3.7)	4 (5.1)
Alaskan	22 (7.4)	11 (10.3)	6 (7.6)
Multiple			
Unknown			
Hispanic	46 (15.4)	22 (20.6)	15 (19.0)
Matched Transplant	229 (76.9)	64 (59.8)	46 (58.2)
Conditioning Regimen			
Reduced intensity	50 (16.8)	24 (22.4)	24 (30.4)
Myeloablative	121 (40.6)	35 (32.7)	28 (35.4)
Other	127 (42.6)	48 (44.9)	27 (34.2)
Diagnosis			
Oncologic	202 (67.8)	65 (60.8)	48 (60.8)
Non-Oncologic	96 (32.2)	42 (39.3)	31 (39.2)
Stem Cell Source			
Bone Marrow	140 (47.0)	36 (33.6)	26 (32.9)
Peripheral Blood	115 (38.6)	37 (34.6)	20 (25.3)
Cord Blood	43 (14.4)	34 (31.8)	33 (41.8)
Donor Type			
Allogenic related	88 (29.5)	21 (19.6)	15 (19.0)
Autologous	58 (19.5)	22 (20.6)	8 (10.1)

Allogenic unrelated	152 (51.0)	64 (59.8)	56 (70.9)
Diuretic Use	166 (55.7)	49 (45.8)	29 (36.7)
Inotrope Use	7 (2.4)	2 (1.9)	12 (15.2)
Anti-Hypertensive Use	79 (26.5)	44 (41.1)	37 (46.8)
GVHD Prophylaxis			
Other/None	63 (21.1)	22 (20.6)	19 (24.1)
Tacrolimus Including	145 (48.7)	40 (37.4)	20 (25.3)
Cyclosporine Including	90 (30.2)	45 (42.1)	40 (50.6)
Bacteremia	30 (10.1)	11 (10.3)	22 (27.9)
Viremia	8 (2.7)	3 (2.8)	6 (7.6)
Fungemia	3 (1.0)	5 (4.7)	2 (2.5)
Nephrology Consult	27 (9.1)	16 (15.0)	35 (44.3)
Ventilator Use	13 (4.4)	3 (2.8)	31 (39.2)
GVHD	206 (69.1)	78 (72.9)	58 (73.4)
Peak Fluid Overload >10%	109 (36.6)	59 (55.1)	53 (67.1)
Mortality	53 (17.8)	20 (18.7)	27 (34.2)

N(%) unless otherwise stated
Graft Versus Host Disease (GVHD)

Table 2. Unadjusted Associations Between Pediatric HSCT Patient Characteristics and AKI Diagnosis, Seattle Children's Hospital, 9/2008-7/2017

	AKI Stage 1 vs No AKI RR (95% CI)	**AKI Stage 2/3 vs No AKI RR (95% CI)**
Female	1.00 (0.66-1.34)	0.86 (0.50-1.21)
Stem Cell Source		
Bone Marrow (ref)	Reference	Reference
Cord Blood	1.73 (1.03-2.44)	2.33 (1.26-3.40)
Peripheral Blood	1.21 (0.71-1.70)	0.90 (0.41-1.40)
Donor Type		
Autologous (ref)	Reference	Reference
Allogenic Unrelated	0.94 (0.55-1.34)	2.26 (0.68-3.85)
Allogenic Related	0.68 (0.32-1.04)	1.33 (0.25-2.41)
Mismatched	1.57 (1.05-2.10)	1.68 (1.00-2.35)
GVHD Prophylaxis		
Other/None (ref)	Reference	Reference
Cyclosporine	1.22 (0.67-1.76)	1.25 (0.64-1.86)
Tacrolimus	0.92 (0.49-1.35)	0.53 (0.22-0.84)
Conditioning Regimen		
Reduced Intensity (ref)	Reference	Reference
Myeloablative	0.78 (0.42-1.13)	0.62 (0.32-0.92)
Other	0.97 (0.56-1.38)	0.55 (0.28-0.82)
Hematologic Diagnosis		
Non-Oncologic (ref)	Reference	Reference
Oncologic	0.83 (0.55-1.11)	0.83 (0.49-1.17)

Table 3. Adjusted Associations Between Pediatric HSCT Patient Characteristics and AKI Diagnosis, Seattle Children's Hospital, 9/2008-7/2017

	AKI Stage 1 vs No AKI RR (95% CI)*	**AKI Stage 2/3 vs No AKI RR (95% CI)***
Stem Cell Source		
Bone Marrow (ref)	Reference	Reference
Cord Blood	1.64 (0.58-2.70)	2.26 (0.74-3.77)
Peripheral Blood	1.22 (0.60-1.84)	0.57 (0.13-1.01)
Mismatched	1.58 (0.79-2.37)	0.77 (0.28-1.25)
GVHD Prophylaxis		
Other/None (ref)	Reference	Reference
Cyclosporine	1.25 (0.41-2.09)	0.50 (0.13-0.88)
Tacrolimus	1.44 (0.62-2.27)	0.42 (0.11-0.73)
Conditioning Regimen		
Reduced Intensity (ref)	Reference	Reference
Myeloablative	0.82 (0.41-1.23)	0.65 (0.30-0.99)
Other	1.41 (0.66-2.17)	0.60 (0.19-1.00)

**Adjusted for age at transplant, sex, and the other characteristics listed*

Table 4. Adjusted Cox Proportional Hazard Ratios in Pediatric HSCT Patients, Seattle Children's Hospital, 9/2008-7/2017

	HR (95% CI)
Acute Kidney Injury	
None	Reference
AKI 1	0.70 (0.32-1.57)
AKI 2/3	4.61 (2.61-8.15)
Age at Transplant	1.00 (0.96-1.05)
Patient Sex	
Male (ref)	Reference
Female	1.07 (0.65-1.77)
Mismatched	3.53 (1.82-6.84)
Stem Cell Source	
Bone Marrow (ref)	Reference
Cord Blood	0.94 (0.42-2.08)
Peripheral Blood	2.90 (1.51-5.57)

**Adjusted for characteristics included in the table*

Figure 1. 1-Year Survival Probability by Level of AKI in Pediatric HSCT Patients, Seattle Children's Hospital, 9/2008-7/2017