Pre-transplant glomerular hyperfiltration is not a risk factor for increased renal morbidity and mortality in pediatric stem cell transplant patients

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Abstract

Low glomerular filtration rate (GFR) prior to stem cell transplant (SCT) is associated with increased morbidity and mortality. The implications of abnormally high GFRs, or glomerular hyperfiltration, prior to SCT are unknown. Twenty two of 74 consecutive pediatric SCT patients over 2 years old at a single center were hyperfiltrating prior to SCT, median nuclear medicine GFR 154 mL/min/1.73 m ^{2} (IQR 146, 170). There was no association between any demographic and hyperfiltration, nor between hyperfiltration and acute kidney injury ($P = 0.8$), renal replacement therapy ($P = 0.63$), event-free survival ($P = 1$), or chronic kidney disease ($P = 0.73$).

Introduction

Measurement of glomerular filtration rates (GFRs) prior to hematopoietic stem cell transplantation (SCT) is of the utmost importance. Regimen choices and study eligibility are restricted by minimum baseline rates, and it has been well demonstrated that pediatric patients who have a low GFR prior to SCT have an increased risk of acute kidney injury (AKI), chronic kidney disease (CKD), and death[1,2]Hyperfiltration, in which the GFR is abnormally elevated, is known to occur in pediatric oncology and hematopoietic stem cell transplant (SCT) patients. However there are no studies looking at the implications of pre-SCT hyperfiltration on outcomes.[3–5] We hypothesized that pre-SCT hyperfiltration is a risk factor for AKI, CKD, and mortality in pediatric patients.

Methods

We performed a single center IRB approved retrospective chart review of 80 consecutive pediatric allogeneic SCT patients transplanted between 2013 and 2015. Clinical data was reviewed through 2019. Baseline hyperfiltration status was determined using pre-SCT nuclear medicine GFR. Hyperfiltration was defined as a GFR[?]135 mL/min/1.73 m^2, which is the median value used in the literature.[6] A normal GFR was defined as a GFR between 90 and 135 mL/min/1.73 m^2. Demographics recorded included age, gender, primary diagnosis, exposure to chemotherapy prior to SCT, stem cell source and match, conditioning regimen, and if ex-vivo T cell depletion was utilized for graft versus host prevention. Outcomes assessed included AKI, defined as a doubling of creatinine in the first 100 days of transplant, need for renal replacement therapy, and 1 year event-free survival. In patients who had at least 2 years of follow up, the outcome of CKD was defined as a creatinine-based estimated GFR<90 or GFR[?]135 mL/min/1.73 m^2 at last follow up. Continuous and categorical data were summarized as median (interquartile range) and frequency (percent), respectively. Continuous data were assessed between hyperfiltration (Y/N) patients using a Wilcoxon rank

sum test. Categorical data were compared between hyperfiltration patients using Fisher's exact test. A p-value of <0.05 was considered significant.

Results

Six patients were excluded due to being less than 2 years old at the time of transplant, as GFR gradually increases during the first 2 years of life. There were 22 hyperfiltraters, making up 30% of the cohort. Median hyperfiltration GFR was 154 mL/min/1.73 m^2 (IQR 146, 170). There were no associations between hyperfiltration and transplant demographics (**Table 1**). Eleven patients were excluded from outcomes evaluation due to low pre-SCT GFR ($<$90 mL/min/1.73 m^2), and the outcomes of those with normal vs hyperfiltrating GFRs were compared. All of the 63 patients had 1 year follow up data; 37 patients had follow-up data past 2 years, for which the median follow up was 4.7 years. We found no association between baseline hyperfiltration and any of the outcomes (**Table 1**).

Discussion

In this study, we add to the small but important body of literature by evaluating the relationship between pre-SCT hyperfiltration, renal morbidity, and mortality. We found that pre-SCT GFR[?]135 mL/min per 1.73 m^2 was not associated with AKI, 1 year event-free survival, or CKD at a median follow up time of 4.7 years.

Glomerular hyperfiltration is a well described phenomenon in physiologic states, such as pregnancy and high protein intake, as well as many pathologic states, including diabetes mellitus, hypertension, hyperaldosteronism, and obesity.[7] Hyperfiltration has also been noted in 30 – 40 % of children with cancer at diagnosis and/or during initial stages of their chemotherapy, however the mechanisms driving the elevation in GFR in these patients poorly understood.[3,8]

One population in which hyperfiltration is a known phenomenon and may undergo SCT is patients with sickle cell disease. Hyperfiltration has been identified in half of young adults with sickle cell disease.[9] In a series of 18 pediatric patients with sickle cell disease undergoing nonmyeloablative SCT, 12/18 had a measured GFR and 8/18 had an creatinine based estimated GFR greater than 150 mL/min/1.73 m^2 prior to transplant. After SCT, overall GFR declined in the entire population with just 4/18 hyperfiltrating. One interpretation of this data is that the glomeruli can functionally normalize with resolution of the hematopoietic disease. An alternative hypothesis that the GFR declined due to AKI and it will continue to decline as seen in CKD. Similarly, a publication looking at kidney function in children after SCT showed a similar, and statistically significant decline from hyperfiltration to normal GFR in the first two years post-SCT.[11] Median pre-SCT measured by inulin clearance was 130 ml/min/1.73m^2(73-127 ml/min/1.73m^2), at 1 year was 123 ml/min/1.73m^2 (68–185 ml/min/1.73m^2), and at 2 years was 105 ml/min/1.73m^2 (81–177 ml/min/1.73m^2). Since the GFR decline is from elevated to normal, the changes are not captured in standard clinical and survivorship screening.

An additional limitation to understanding the epidemiology and implications of hyperfiltration in SCT patients is the lack of a uniform definition. A systematic review of over 400 studies showed numerous, variable thresholds applied, ranging from 90.7 to 175 ml/min/1.73m^2.[6] Method of GFR calculation is also of critical importance, as creatinine has been shown to be a less reliable biomarker in pediatric SCT patients.[12,13] For this study, we used measured nuclear medicine GFRs with an a priori cut off of 135 ml/min/1.73m^2 because it is the median value in the literature.[6] Using this threshold, there was no association between any demographic and hyperfiltration, nor between hyperfiltration and any outcomes. However, this threshold may be too low for the pediatric SCT population. Age- and sex-matched control groups may be necessary to define the hyperfiltration thresholds in this group. Multiple thresholds of increasing GFR, like the stages of increasing AKI severity, may be more informative than a single threshold.

Further research is needed to determine whether a different threshold for hyperfiltration would have prognostic value. Long-term follow up focused on hyperfiltrating patients to assess long term risk of CKD is also warranted.

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Tables/Figures

Table 1 . Pre-SCT Glomerular Hyperfiltration is Not Associated with Demographics or Outcomes

	n = 74^{+}	**Range, %**	**Range, %**	**Range, %**	**Hyperfiltration p-value**
Median age, years, interquartile range	10.5	(6, 14.3)	(6, 14.3)	(6, 14.3)	0.74
Male	50	68%	68%	68%	0.79
Primary disorder malignancy	24	32%	32%	32%	1.00
Chemotherapy prior to referral for HSCT	37	50%	50%	50%	0.44
Sibling Donor	29	39%	39%	39%	0.12
Match 10/10	57	77%	77%	77%	0.15
Transplant Source					0.14
Peripheral blood	9	12%	12%	12%	
Bone marrow	63	85%	85%	85%	
Cord blood	2	3%	3%	3%	
Myeloablative Allogeneic HSCT	45	61%	61%	61%	0.12
Total Body Irradiation	12	16%	16%	16%	0.41
Ex-vivo T cell depletion	7	9%	9%	9%	0.10
Outcomes^{+}					
Stage 2+ Creatinine AKI in 1st year	44	70%	70%	70%	0.80
Dialysis ever	5	8%	8%	8%	0.63
Event free survival	55	87%	87%	87%	1.00
Abnormal creatinine eGFR >2 years post-SCT	12 of 39	31%	31%	31%	0.73

$^{+}$Outcomes assessed in 63 patients.