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Investigating Access to, and Impact of, Hematopoietic Cell Transplant on Morbidity and Mortality of Children with Sickle Cell Disease

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Investigating Access to, and Impact of, Hematopoietic Cell Transplant on Morbidity and Mortality of Children with Sickle Cell Disease

By: Sadie F. Mason, M.D.

Background: Sickle cell disease (SCD) is associated with morbidity and midlife mortality. Hematopoietic cell transplant (HCT) is a curative therapy that can stabilize or prevent sickle-related organ dysfunction but can incur life-threatening complications. More information is needed about the long-term benefits of HCT over standard medical therapy for SCD.

Objective: To compare long-term outcomes between patients with SCD who underwent HCT and those who did not and to explore barriers to HCT for patients with SCD who did not proceed to HCT.

Methods: This IRB-approved, retrospective, single institution, cohort study of patients with SCD with or without HCT, matched 1:2. Cases included all patients who underwent HCT between 2010 and 2018. Controls were randomly matched on age, sex, disease genotype, and disease severity using transplant date as the match timepoint. Kidney function was compared between the two groups at pre-HCT and at 1-, 2-, 3-, and 5-years post-HCT. The number of hospitalizations in the 5 years pre-HCT (averaged) and in the 1-, 2-, 3-, and 5-years post-HCT were compared between the groups using Wilcoxon signed-rank tests. Overall survival at 5-years post-HCT was compared between the groups using the Kaplan-Meier analysis.

Results: Fifty-eight patients who underwent HCT were matched with 116 controls who continued with standard medical therapy. The median age of the cohort was 8 years (IQR=5-11), and 53% of the cohort were female. While there were differences in available data in renal function between the groups at some timepoints, these data were not evaluable due to the proportion of missing data. Greater than 1-year post-HCT, unscheduled hospitalizations were significantly decreased in the HCT group compared to the non-HCT group ($p<0.001$). Two patients in the HCT group died during the study period compared to 1 patient in the non-HCT group ($p=0.215$).

Conclusion: After 1-year post-HCT, the frequency of unscheduled hospitalizations was significantly lower for children who underwent HCT. There was no difference in survival between the two groups. Our data support the need for further study of the impact of HCT on other organ outcomes and longer-term follow-up to better assess survival and organ function in children with SCD.

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A. BACKGROUND

Sickle cell disease is an inherited red blood cell disorder

Sickle cell disease (SCD) is an inherited red blood cell disorder that is associated with significant health consequences and shortened lifespan.[1] It is an autosomal recessive disorder of hemoglobin, specifically a single nucleotide substitution in the β-globin subunit which allows hemoglobin to polymerize in the deoxygenated state, causing red blood cell (RBC) deformation (to the classic sickle shape), hemolysis, and anemia. The specific β-globin gene mutation associated with sickle hemoglobin (HbS) is most commonly found in individuals of sub-Saharan African ancestry but may be found in multiple other racial and ethnic groups worldwide, including individuals of Middle Eastern, Mediterranean, and Indian background. In the United States, there are an estimated 100,000 individuals living with SCD, while worldwide there is significantly higher disease burden with millions of individuals living with SCD.[2] For individuals with SCD, RBC pathology results in both acute episodes of vaso-occlusion and pain as well as chronic multi-organ damage, particularly to the brain, lungs, spleen, kidneys, liver, bones, and eyes.[3]

Genetic inheritance of SCD may be either homozygous inheritance of HbS (known as HbSS disease, the most common genotype) or compound heterozygous inheritance of HbS with a different Hb variant that may still result in RBC sickling and hemolysis. The second most common SCD genotypes is HbSC, which is associated with less hemolysis and anemia than HbSS, and may have less frequent acute complications; however, episodes of pain, and lung, eye, and bone complications remain prevalent. Disease phenotypes, however, regardless of genotype, vary widely with some patients

having few symptoms of their disease while others require frequent hospitalizations and suffer long-term consequences of the disease.

Hospitalizations and Emergency Department visits are common in children and adults with SCD

The Centers for Disease Control and Prevention estimate that almost all people living with SCD will require hospitalization more than once per year and will visit the emergency department (ED) at least 2-3 times per year on average.[4] For patients with Medicaid insurance, state-level data demonstrates that children with SCD have increased health care utilization compared to children who are of similar sociodemographic groups.[5,6] In fact, children with SCD were over 7 times more likely to be hospitalized than children without SCD.[5] Correlations have been observed between socioeconomic status and hospitalization needs, with higher rates of hospitalizations for patients with SCD covered by Medicaid as opposed to private health insurance.[7-9] Outside the United States and its health insurance structure, high hospitalization rates are demonstrated for patients with SCD.[8,10]

In addition to the economic burden of increased healthcare utilization there is also a quality of life burden associated with SCD. Adults with SCD note an impact on their work and non-work productivity, and caregivers of people with SCD also report a decreased Health Related Quality of Life (HRQOL).[11,12] In studies specifically looking at both self-reported and caregiver-reported HRQOL, both overall HRQOL and subdomains of HRQOL are decreased for children with SCD compared to healthy children.[13-15] It is clear that SCD significantly impacts affected patient's lives.

SCD leads to increased morbidity and mid-life mortality

The hallmarks of SCD are hemolytic anemia and vaso-occlusive events (VOEs). The pathophysiology of hemolytic anemia in SCD is complex and involves multiple pathways, including nitric oxide scavenging by cell-free hemoglobin (a byproduct of hemolysis), resulting in impaired vasodilation and vascular complications.[16] The chronic hemolysis associated with SCD not only causes anemia but also releases molecules that further exacerbate vascular injury and promote a pro-inflammatory state. Vaso-occlusion, caused by adhesion and obstruction of the blood vessels by sickled RBCs, leads to tissue ischemia and reperfusion injury. Acutely, these episodes of ischemia lead to painful episodes (VOEs), while over time they lead to progressive organ damage that can impact any organ system.[17-20]

Renal complications are particularly common in SCD because of the environment of the kidney: the hypoxia, hyperosmolarity, and acidosis of the renal medullary system promote HbS polymerization and therefore RBC sickling.[21,22] Sickle cell nephropathy, or chronic kidney disease (CKD) due to SCD, is identified in its earliest stages by albuminuria, or the abnormal excretion of albumin into the urine. Sickle nephropathy, is associated with early mortality in patients with SCD.[21,23] Albuminuria, defined as excretion of >30mg albumin per gram of creatinine,[24] can be transient in nature as values fluctuate over time, however persistent albuminuria at multiple time points is indicative of kidney disease.[25-27] The relationship between actual kidney function, glomerular filtration rate (GFR), and albuminuria changes over the first 2-3 decades of life. Early in life, chronic anemia is associated with hyperfiltration, and thus higher estimated GFR (eGFR) values than normal. This elevated filtration function, while not diagnostic of impaired kidney function currently, is associated with glomerular damage

as evidenced by increasing urine albuminuria in this population over time, and ultimately a diagnostic decline in kidney function. eGFR values may thus decline into an apparent "normal" range in the 2nd or 3rd decade of life, and later progress to renal failure in young adults with SCD, a major contributor to morbidity in this population.[28,29]

The cardiopulmonary system is also heavily impacted by SCD. Pulmonary hypertension (PH) impacts approximately 6-11% of adults with SCD and is strongly associated with increased mortality.[30] Tricuspid regurgitant jet velocity (TRV), measured by echocardiogram, acts as a non-invasive screening tool for PH, and serves as a surrogate for invasive diagnosis by right heart catheterization, making echocardiograms an important tool for diagnosing and monitoring this complication.[31,32]

Acute chest syndrome (ACS), an acute and potentially life-threatening complication of SCD, is a lung injury syndrome characterized by a new pulmonary infiltrate accompanied by chest pain, fever, tachypnea, wheezing, or cough. In children, asthma is a known risk factor for ACS, but the underlying etiology of the syndrome is multifactorial and includes infection, atelectasis, bone marrow fat embolization, and sequestration of RBCs in the lungs.[33-35] ACS is one of the leading causes of hospitalizations and mortality for patients with SCD, and, when recurrent, can also lead to chronic lung disease.[36]

Patients with SCD are at high risk for cerebral infarcts or strokes. In SCD, stroke may be an overt (clinically obvious) event or it may be silent, with cumulative damage noted only on brain imaging. By the age of 14 years, 37% of patients with the HbSS genotype will have had a silent cerebral infarct, and without intervention, 11% of

patients with SCD will have had an overt stroke by the age of 20.[37-39] Silent cerebral infarct itself is a risk factor for further neurological injury and can lead to neurocognitive dysfunction.[19,38]

SCD-associated comorbidities, those mentioned above and others, lead to increased mortality for people living with SCD. The median survival in the United States for a patient with HbSS is 48 years, far lower than the 71.8 year average life expectancy of an unaffected Black American.[1,40] While disease modifying therapies such as hydroxyurea and chronic transfusion therapy can reduce disease complications and prolong life, standard medical therapies do not cure the disease.[41,42]

Hematopoietic Cell Transplant for SCD is curative and improves organ function but is high risk

Hematopoietic Cell Transplant (HCT), which involves chemotherapeutic depletion of host cells followed by hematopoietic reconstitution with donor cells, has been recognized as curative therapy for SCD for over 30 years. HCT has been shown to improve HRQOL for both pediatric and adult SCD patients,[43,44] and stabilization of some organ function and alleviation of major symptoms of SCD are also reported.[45,46] This treatment caries high risk of morbidity, as it requires intensive chemotherapy and significant immune suppression and there is a risk of alloimmunity from the donor cells. The treatment may also be fatal, with overall survival (OS) only 88% at 10 years post-HCT for those with SCD.[47] A significant risk factor for poor outcome is recipient age older than 13 years; for every 10-year increase in age, an older patient is 1.75 times more likely to die than a younger one.[47,48] These data support prioritizing transplant at a younger age to maximize survival, in addition to prevent cumulative organ dysfunction related to SCD.

The most challenging morbidity of HCT is graft-versus-host-disease (GVHD), which occurs when the engrafted cells attack the healthy organs of the recipient, leading to organ dysfunction and potential death. Severe GVHD is the most common cause of death after HCT for SCD.[47] Chronic GVHD (cGVHD), which occurs >1 year after HCT, affects between 5-62% of those with SCD who undergo HCT.[45,47,49] The risk of cGVHD is related to the degree of human leukocyte antigen (HLA) matching between donor and recipient, and the lowest risk can be achieved with a sibling or related donor who is fully HLA-matched to the recipient. While matched sibling donors (MSD) provide an ideal opportunity for curative HCT for children with SCD, only 20% of patients are estimated to have such a donor available.[50]

Balancing these risks of GVHD and death against the potential benefit of improved HRQOL and organ function for children with SCD is critical to optimize outcomes. Identifying those children who will derive the most benefit from HCT, optimizing survival and long term organ function, is therefore an urgent need.

B. METHODS

Study Aims

Primary aim: To compare long-term outcomes between patients with SCD who underwent HCT and those who did not undergo HCT.

Exploratory aim: To explore barriers to HCT for patients with SCD who did not proceed to HCT.

Study Design, Setting, and Sample

This single-center, retrospective matched cohort study was conducted at Children's Healthcare of Atlanta (CHOA), which cares for the country's largest population of pediatric patients with SCD at approximately 2,000 patients per year. Cases were all patients with SCD who underwent HCT at CHOA from 2010 to 2018 for the purpose of SCD curative therapy. Patients were excluded if they underwent HCT for other reasons (e.g. cancer therapy) or if they underwent transplant with genetically modified, autologous hematopoietic stem cells. Controls were patients with SCD treated at CHOA who continued with standard medical therapy. Transplant day acted as the match timepoint: each control's time zero was their matched case's transplant day. The study was approved by the Institutional Review Board (IRB) at CHOA (STUDY00001827).

Cohort Selection

Fifty-eight patients with SCD met our case criteria. For our controls, we screened all patients ages 1 year to 21 years with SCD who continued standard medical therapy and were treated at CHOA from 2010 to 2023 (N=4,276). Eligible patients were identified through the CHOA Sickle Cell Clinical Database, a comprehensive database of all patients seen and treated at CHOA from January 1, 2010 and onward, with clinical

information including SCD genotype, medical therapies, and healthcare utilization. Patients were excluded as controls if any of the following occurred: they underwent an HCT for SCD outside of the 2010-2018 window, underwent HCT for a reason aside from SCD (e.g. for cancer therapy), underwent HCT at another institution, or underwent gene therapy, leaving a total of N=4,134 patients. These patients were then matched with our Cases based on age (+/- 6 months from case date of birth), sex (male or female), disease genotype. Potential matches were removed from this initial matched pool if any of the following occurred: they had never had an outpatient clinic visit at CHOA, had not been seen at CHOA prior to the year HCT match timepoint, or had not been seen at CHOA at least twice in the 3 years post-HCT match timepoint. The remaining potential matches were then randomly matched in a 1 Case: 2 Controls fashion based on clinical disease severity.

Disease severity was uniquely defined for this study because the cohorts were likely to be disparate in terms of SCD complications at baseline. This measure was a composite score made up of three components, all occurring in the 5 years pre-HCT or pre-match timepoint: 1) the average number of hospitalizations per year, 2) need for intensive care unit (ICU) admission, and 3) need for chronic transfusion therapy (CTT). Total scores ranged from 0 to 5. Matching on disease severity was tiered, as it was unknown if there were sufficient patients at all disease severity levels in the control cohort. First, we matched controls based on a full score match for their case, meaning their total scores were the same. If there was not a full score match available, cases and controls were then matched based on grouped scores, meaning they were matched based on composite scores of 0-1, 2-3, and 4+. If no group match existed, cases and controls were matched based on CTT need, and if no CTT need match existed, they were

matched based on ICU need. Full details of cohort selection can be found in the Consort Diagram (Figure 1).

Study Measures

Primary Aim: To compare long-term outcomes between patients with SCD who underwent HCT and those who did not undergo HCT.

The primary outcome of this study was renal function, which was measured in two ways: the albumin/creatinine ratio (ACR) and the estimated glomerular filtration rate (eGFR). Both variables were assessed pre-HCT or pre-match timepoint and at 1-year, 2-years, 3-years, and 5-years post-HCT or post-match timepoint.

ACR is a urine test that is routinely measured in the outpatient setting (not during acute illness or hospitalization) in children with SCD. This variable was categorized in three ways, first as being normal (<30mg/g) or abnormal (≥30mg/g), second as being <100mg/g or ≥100mg/g, and third as a distribution of normal (0-29mg/g), microalbuminuria (30-299mg/g) and macroalbuminuria (≥300mg/g). The threshold of 100 mg/g was evaluated based on evidence that higher levels of albuminuria are more likely to represent persistent albuminuria.[21]

eGFR is an estimation of kidney glomerular filtration and for this study was calculated using Schwartz's formula:

$$eGFR = \frac{0.413\ x\ Height\ (cm)}{Serum\ Creatinine\ (\frac{mg}{dL})}$$

Patients who were missing either part of this equation (height or creatinine) were unable to have an eGFR calculated. We categorized this variable as low filtration (<90mL/min/1.73m^2), normal filtration (90-139 mL/min/1.73m^2), and hyperfiltration (≥140mL/min/1.73m^2).

The secondary outcomes of this study included scheduled hospitalizations, defined as planned admissions from clinic, unscheduled hospitalizations, defined as unplanned admissions from clinic, and emergency department (ED visits), defined as ED visits that did not result in hospital admission. Scheduled hospitalizations, unscheduled hospitalizations, and ED visits without hospitalization in both the HCT and non-HCT group were collected in aggregate for the 5-years pre-HCT and as individual years for 1-, 2-, 3-, and 5-years post-HCT. The pre-HCT data was then averaged over the 5-year pre-HCT time period to represent the average number of scheduled hospitalizations, unscheduled hospitalizations, and ED visits per year over the 5-year period. An additional outcome of acute care visits – a combination of unscheduled hospitalizations and ED visits – was assessed at yearly intervals for the 5 years pre-HCT and at 1-, 2-, 3-, and 5-years post-HCT or post-match timepoint.

Further secondary outcomes included completion of echocardiograms at each time point and completion of pulmonary function tests (PFTs) at each time point. These were assessed for the 5 years pre-HCT or pre-match timepoint in aggregate (data was included if the patient had ever had an echo or PFT done in that time period) and individually at the 1-year, 2-years, 3-years, and 5-years post-HCT or post-match timepoint.

The tertiary outcome was overall survival. Patients were censored if they were dead or lost to follow-up at 1-year, 2-years, 3-years, and 5-years post-HCT or post-match timepoint.

Exploratory aim: To explore barriers to HCT for patients with SCD who did not proceed to HCT.

Our exploratory aim was only assessed in our control group, the 116 patients with SCD who continued standard medical therapy. The primary outcome of our exploratory aim was referral to the transplant team for consultation, and the secondary outcome was completion of consultation with the transplant team. Reason(s) for not proceeding to HCT that were available in the transplant consult notes were also collected.

Data Collection

Following IRB approval and matching, demographic and clinical data was collected from the CHOA electronic medical record (EMR), Epic (Verona, WI). While most laboratory and clinical data were collected based on CHOA lab and clinical visits, some data was collected from other institutions using the CareEverywhere feature of Epic.

Demographic variables included date of birth, sex assigned at birth, race, and insurance status. Clinical data included vital signs, laboratory results, medication information, imaging results, hospitalization dates and reasons for admission, and emergency department visit dates and reasons for visits.

Clinical data for the 5 years pre-HCT or pre-match timepoint was collected as total number of acute care visits for the 5 years or as the vital signs, laboratory and imaging results, and medication information closest to transplant day or match timepoint. Insurance status was similarly based on the insurance status of the patient on transplant day or the clinic visit closest to the match timepoint. Clinical data and insurance status for the 1-year, 2-years, 3-years, and 5-years post-HCT or post-match timepoint were collected based on the outpatient clinical visit or laboratory visits closest to that anniversary. Only outpatient visits were used for the collection of the post-HCT or post-match timepoint data collection, as patients were assumed to be in their normal

state of health at these visits thus lab values represent baseline function. Data was considered missing if there was no clinic visit in the specific year post-HCT or post-match timepoint.

When exploring reasons patients with SCD did not go forward with transplant, we exclusively assessed the 116 patients in our non-HCT cohort. Here, the entire chart – not just the 5 years pre-match timepoint and 5 years post-match timepoint – was queried and data on human leukocyte antigen (HLA) typing, transplant team referral, and transplant clinic visit was recorded. Based on what was available in review of notes from visits to the transplant team, we also collected information about reasons those who went for a transplant visit did not proceed with HCT.

Statistical Analysis

Descriptive statistics were performed to characterize the study population by calculating means with standard deviations (SD) for continuous variables and counts with proportions for categorial variables. We further used generalized linear mixed models, Chi-square tests, and Fisher's exact tests to assess difference between the HCT and non-HCT groups.

Our primary renal outcomes as well as our secondary outcomes of PFT and echocardiogram completion were assessed using Chi-square and Fisher's exact tests when appropriate. Our hospitalization-related secondary outcomes (scheduled hospitalizations, unscheduled hospitalizations, ED visits, and acute care visits) were continuous variables and were compared with Wilcoxon signed-rank tests. This non-parametric approach was utilized because it is robust when variables are non-normally distributed. Generalized Linear Mixed Models with a Poisson response were also used to predict the acute care visits outcome, with fixed effects specified for cohort, time, and

the cohort by time interaction and a random effect for matched clusters and time within participants. Kaplan-Meier curves were used to compare overall survival, our tertiary outcome, between the two groups.

For our exploratory aim, we further used descriptive statistics, specifically counts and proportions, to report whether controls had been referred to the transplant team and whether those referred came to the clinic appointment.

For all tests described, a p-value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS® software v9.4 (2012, SAS Institute, Cary, NC, USA).

C. RESULTS

Patient Characteristics

In this matched cohort study, 58 patients underwent HCT for SCD from 2010-2018 and met our criteria for inclusion as cases. They were compared to 116 patients who met inclusion criteria for controls. Sixty-three percent of cases and controls were matched fully on the severity score, 16% were matched based on grouped scores, 18% were matched on their need for CTT, and 3% were matched based on ICU admission alone. The mean age of the overall cohort (N=174) was 9.2 years (IQR 5-11), and 53% of patients were female (N=93). Most patients, 98% (N=170), identified as Non-Hispanic Black. There were 6 patients with HbSC genotype and 168 patients (96.6%) with either HbSS or HbSβ0 thalassemia genotypes. For the entire cohort, insurance status was missing for 18.4% of patients (N=32), and 51.2% (N=89) had public insurance compared to 30.4% (N=53) with private insurance. More patients in the HCT group (N=28, 48.3%) had private insurance compared to the non-HCT group (N=23, 21.6%; p=0.010).

Asthma was noted to be a pre-existing condition for 25% of all patients (N=43), and 16% (N=28) of patients had had a surgical splenectomy at the time of transplant day / match time point. The mean pre-HCT hemoglobin was 9.23 in both groups with a SD of 1.23. The absolute retic count between the two groups was significantly different (p=0.037) with a value of 256 for the non-HCT group compared to 308 for the HCT group. The mean number of total acute care visits for the HCT group was 13 (SD 9) within the 5 years pre-HCT compared to 11 (SD 8) for the non-HCT group (p=0.309). Patient characteristics for age, sex, race, disease genotype, insurance carrier, asthma as a prior medical condition, splenectomy status, pre-HCT laboratory results, and hospital admission data are available in Table 1.

In the HCT cohort, 93% (N=54) had an MSD transplant and 7% (N=4) had a matched unrelated donor transplant (Table 2). There were no patients who underwent haploidentical transplant in this cohort. Most patients received a bone marrow graft alone (90%, N=52), while 5% (N=3) received cord blood alone, and another 5% (N=3) received both cord blood and bone marrow from the same MSD. All patients received myeloablative intensity conditioning. Cyclosporine and methotrexate were the most used medications for GVHD-prophylaxis, with 62% (N=36) including Horse ATG as additional GVHD prophylaxis.

Renal Function: ACR and eGFR

There was missing data for ACR at all time points assessed with a total of 28% (N=48) missing pre-HCT and 45% (N=79), 44% (N=78), 42% (N=74), and 45% (N=79) missing in both groups at 1-, 2-, 3-, and 5-years post-HCT (Table 3). ACR was first assessed as normal versus abnormal using a cut point of ≥30mg/g. Pre-HCT, there was a higher proportion of patients in the normal range in the HCT group (86%, N=50) compared to the non-HCT group (50%; N=58). This trend of a higher percentage of patients in the HCT group falling into the normal range continued at the 1-, 2-, and 3-years post-HCT time points with 62% (N=36) of the HCT group vs 37% (N=43) of the non-HCT group; 65% (N=38) vs 36% (N=42); and 50% (N=29) vs 48% (N=56) falling in the normal range at 1-, 2-, and 3-years post-HCT, respectively. At 5-years post-HCT, 43% (N=25) of patients in the HCT group fell into the normal range compared to 45% (N=53) of the non-HCT patients. The degree of missing data precluded the planned statistical analyses.

ACR was next compared using a cut point of ≥100mg/g. Between 41-88% of patients in both the HCT and non-HCT cohorts had an ACR <100mg/g at all time points

(Table 4). When data was categorized as normal, microalbuminuria, or macroalbuminuria, differences were seen between the HCT and non-HCT groups. There were more patients with microalbuminuria and macroalbuminuria in the non-HCT group (N=11 and N=5, respectively) compared to the HCT group (N=1 and N=1, respectively) at the pre-HCT time point. This trend of a higher percentage of patients in the non-HCT group having micro- and macroalbuminuria compared to those in the HCT group continued across all time points post-HCT as well (Table 5). The degree of missing data precluded the planned statistical analyses.

There was missing data for eGFR at all time points assessed with a combined 1% (N=2); 9% (N=17); 17% (N=30); 23% (N=40), and 29% (N=51) missing at pre-HCT, 1-, 2-, 3-, and 5-years post-HCT, respectively (Table 6). There was a similar distribution of patients in the low filtration, normal filtration, and hyperfiltration categories between the two groups pre-HCT, with >50% of patients in both groups having hyperfiltration. At all time points post-HCT, however, there were more patients in the non-HCT group with hyperfiltration when compared with the HCT group with 51% (N=59) vs 30% (N=17); 52% (N=60) vs 22% (N=13); 44% (N=51) vs 14% (N=8); and 35% (N=41) vs 7% (N=4) at 1-, 2-, 3-, and 5-years post-HCT. The degree of missing data precluded the planned statistical analyses.

Hospitalization and ED Visits

The median number of scheduled hospitalizations per year was 0 pre-HCT and at all time points post-HCT for both cohorts. The HCT cohort ranged from 0-0.8 pre-HCT, 0-1 at 1-year post-HCT, 0-2 at 2-years post-HCT, and 0-1 at 3-years post-HCT (Table 7). There were no scheduled hospitalizations in the HCT cohort at 5 years post-HCT. In comparison, the non-HCT group ranged from 0-2 pre-HCT, 0-9 at 1-year post-HCT, 0-

10 at 2-years post-HCT, 0-10 at 3-years post-HCT, and 0-2 at 5 years post-HCT. There was a significant difference in the number of scheduled hospitalizations per year between the groups only at 3 years post-HCT (p=0.037; Figure 2).

Pre-HCT, the median number of unscheduled hospitalizations for the HCT group was 0.9 (range 0-3.8) compared to 0.6 for the non-HCT group (range 0-5.4; p=0.659). At 1-year post-HCT, the median number of unscheduled hospitalizations was 1 (0-4) for the HCT group compared to 0 (0-7, p=0.685) for the non-HCT group. The median number of unscheduled hospitalizations for both groups was 0 at 2-, 3-, and 5-years post HCT. At 2-years post-HCT, the HCT group ranged from 0-3 compared to 0-8 (p<0.001) for the non-HCT group. At 3-years, the HCT group ranged from 0-1 compared to 0-8 (p<0.001) for the non-HCT group. At 5-years, the HCT group ranged from 0-1 compared to 0-13 (p<0.001) for the non-HCT group (Table 8 and Figure 3).

The median number of ED visits without hospitalization pre-HCT was 1 for both groups (range 0-4 for both groups, p=0.765). At 1-year post-HCT, the HCT group had a median of 0 with a range of 0-5 compared to a median of 1 with a range of 0-15 (p<0.001) for the non-HCT group. At 2-years post-HCT, the HCT group had a median of 0 with a range of 0-4 compared to a median of 1 with a range of 0-15 (p<0.001) for the non-HCT group. At 3-years post-HCT, the HCT group had a median of 0 with a range of 0-3 compared to a median of 1 with a range of 0-8 (p<0.001) for the non-HCT group. At 5-years post-HCT, the HCT group had a median of 0 with a range of 0-2 compared to a median of 1 with a range of 0-15 (p<0.001) for the non-HCT group (Table 9 and Figure 4).

The directly observed median number of acute care visits and interquartile ranges for the groups were similar at all time points pre-HCT. Post-HCT, the median

number of acute care visits per year in the HCT group decreases to 0 by 2-years post-HCT, while the median number in the non-HCT group remains 1-2 acute care visits per year. In the predictive model adjusted for baseline absolute reticulocyte count and insurance status, the predicted count of acute care visits does not vary by cohort at any time pre-HCT (all p-values >0.05). However, at 1-year post-HCT and beyond, the number of acute care visits was predicted to be lower in the HCT cohort by about 1 visit per year (LS mean difference -0.61, 95% CI: -1.03—1.19, p=0.004). This trend continues and by 5-years post-HCT, the predicted difference in acute care visits per year between the two groups is approximately 2 visits per year (LS mean difference -2.28, 95% CI: -2.96, -1.60, p<0.001; Table 10 and Figures 5 and 6).

There was no missing data for the pre-HCT time point for scheduled hospitalizations, unscheduled hospitalizations, or ED visits without hospitalizations, but there were some patients without visits at all time points or who lacked some of the post-HCT time points (N=2, N=7, N=14, and N=26 at 1-, 2-, 3-, and 5-years post-HCT, respectively).

PFT and Echocardiogram Completion

PFTs were not commonly obtained in the non-HCT group, constraining the ability to do this analysis. The HCT group had a PFT completion rate of 72% (N=42), 75% (N=43), 74% (N=39), 58% (N=29), and 85% (N=35) at the pre-HCT, 1-, 2-, 3-, and 5-years post-HCT time points, respectively. In comparison the non-HCT group had PFTs completed at a rate of 35% (N=41), 10% (N=12), 13% (N=15), 15% (N=17), and 25% (N=26) at the pre-HCT, 1-, 2-, 3-, and 5-years post-HCT time points, respectively (Table 11). The difference in completion rates was statistically significant at all time points (p<0.001).

Echocardiograms were also less commonly obtained in the non-HCT group, limiting the analysis. The HCT group had an echocardiogram completion rate of 100% (N=58), 56% (N=56), 87% (N=46), 80% (N=40), and 85% (N=35) at the pre-HCT, 1-, 2-, 3-, and 5-years post-HCT time points, respectively. In comparison, the non-HCT group had echocardiograms completed at a rate of 34% (N=40), 23% (N=26), 15% (N=17), 21% (N=23), and 29% (N=30) at the pre-HCT, 1-, 2-, 3-, and 5-years post-HCT time points, respectively (Table 12). The difference in completion rates was statistically significant at all time points ($p<0.001$).

Overall Survival

There were two deaths in the HCT group, both in the 1st year post-HCT. One death was secondary to GVHD and the second death was from sepsis without GVHD. In the non-HCT group, there was one death at 5-years post-match timepoint from cardiac arrest. There was no statistically significant difference in overall survival between the two groups ($p=0.215$; Figure 7).

HCT Referral and HCT Visit

In the non-HCT group (N=116), 25% (N=29) of the group was referred for a transplant consult. The referred group and the not-referred group were similar in demographics, aside from there being more (69%, N=20) females referred compared to males (31%, N=9). Most of the referred group (55%, N=16) had public insurance (Table 13). For those referred, 14% (N=4; Figure 8) did not attend a HCT consult visit. For the remaining 25 patients who did attend a consult visit, the reason for not proceeding to transplant was not apparent in the chart for 21% (N=6). Reasons that were apparent in the chart included no full siblings or no known matched sibling donor (55%, N=16),

available matched sibling donor but HCT deemed too high risk (7%, N=2), and available matched sibling donor but social barriers to HCT (3%, N=1).

D. DISCUSSION

The primary outcome of this retrospective matched cohort study of patients who underwent HCT for SCD and those who continued with standard medical therapy was kidney function as measured by ACR and eGFR. In the ~50% of patients who had ACR measured, the HCT group was significantly more likely than the non-HCT group to have an ACR in the normal range (<30mg/g) at the 2-, 3-, and 5-years post-HCT time points with 97%, 97%, and 100% of the HCT group falling in the normal range, respectively. At 1-year post-HCT, this difference between the groups was less noticeable, with both cohorts having >80% normal ACRs. When using a cut point of 100mg/g, likely to represent persistent albuminuria,[21] the HCT and non-HCT groups were similar in their distributions with most patients (>85% at all time points for both groups) having an ACR <100mg/g. Although limited by the high quantity of missing data which preclude conclusions, our data are consistent with normalization of renal function after transplant by this measure in those evaluable.

Pre-HCT, >50% of the patients with eGFR data available in both groups had hyperfiltration. Over time, this proportion of patients decreased for the HCT group such that by 5-years post-HCT, 64% fell into the normal range. The non-HCT cohort, in comparison, had only 52% in the normal range while 46% remained in the hyperfiltration range. Notably the HCT group also had more patients with low filtration at all time points post-HCT, ranging from 12-24% while the non-HCT group's proportion of patients with low filtration remained <5% at all time points. These differences between the groups are difficult to interpret because the interpretation of these data in the two populations is different. In the HCT cohort, this trend away from hyperfiltration toward normal eGFR is a positive expected outcome of HCT; other

studies have shown that rates of hyperfiltration decrease over time in patients who undergo HCT for SCD as their kidney function returns to normal post-HCT.[51,52] The 12-24% of patients with low filtration likely reflect renal injury incurred before and after transplant. However, it is unclear what values would suggest improvement in the non-HCT cohort. Hyperfiltration is expected in children with SCD but signifies ongoing renal injury from the underlying disease. In the natural progression of sickle nephropathy, patients often trend into the normal range of eGFR in their teen years, then progressing to low filtration indicative of chronic kidney disease in young adulthood, and consistent with our cohort with median age of 9 years and follow-up into early teens.[28,29] Thus, ongoing hyperfiltration, emerging normalization, and low values, all could signify renal injury and varying degrees of dysfunction in the non-HCT group, while the normalization in the HCT cohort rather indicates a positive trajectory of kidney function.[51,52] Based on this difference in meaning for the two groups, we recommend using the ACR for comparison of renal function between patients undergoing HCT to those who do not, though eGFR can be used to evaluate only the effect of transplant on renal function. Given the missing data in our study, more data is needed to conclusively assess kidney function in patients with SCD post-HCT and compare how it differs from patients with SCD on standard medical therapy.

Hospitalization needs significantly decreased post-HCT for the HCT group compared to the non-HCT group. There were statistically significant differences between the two groups in the number of scheduled hospitalizations per year at 3-years post-HCT, though the number of scheduled hospitalizations per year at all time points was low for the majority of patients in both cohorts (median number 0 at all time points for both groups). These admissions are often for fluids and blood transfusions before procedures

requiring sedation, so a decrease in the number of scheduled hospitalizations for the HCT group, who has been cured of their SCD and therefore no longer requires this pre-procedure precaution, is expected. Unscheduled hospitalizations, which are often for pain, infections, or SCD-associated organ dysfunction, also significantly decreased in the HCT group compared to the non-HCT group. This decrease was noted at all the time points >1-year post-HCT and likely reflects the improvement in symptoms of SCD post-HCT as well as the decreased number of potential complications of HCT as patients recover from the procedure. There were also decreased ED visits for the HCT group compared to the non-HCT group at all time points post-transplant. When unscheduled hospitalizations and ED visits are combined into the acute care visits variable, we again demonstrate, both in observed medians and in the modeled predictions, a decrease in the number of visits per year for the HCT cohort. At 5 years, this difference is nearly 2 visits per year. Our data support previous findings that HCT decreases hospital utilization for patients with SCD, which is beneficial in terms of the health of our patients and for resource utilization.[53,54]

We were unable to assess differences between the two groups' cardiac and pulmonary function because of the degree of missing data, particularly in the non-HCT group. This degree of missingness is in part related to differences in the recommended screening schedules for lung and cardiac complications between HCT and non-HCT SCD cohorts. As per American Society of Transplant and Cellular Therapy guidelines, our HCT team recommends performing yearly echocardiograms and yearly PFTs.[55] Our SCD team largely follows the American Society of Hematology guidelines and does not perform these tests on a yearly basis.[56] Instead, patients with SCD undergo an echocardiogram around age 8-10 years and, if normal, again around the time of

transition to adult care (18-21 years of age). PFTs are only performed in patients who have a history of ACS or asthma who are older than age 5 years. For pulmonary function, these recommendations would skew the captured non-HCT data towards worse pulmonary disease. To better assess the impact of HCT on cardiac and pulmonary function, a prospective study with more frequent echocardiogram and PFT testing for patients on standard medical therapy may be needed.

Overall survival was not different between the two groups. This finding was expected because survival after transplant should be high though could incur a slightly higher upfront mortality, while SCD patients without HCT typically do not experience increased mortality until adulthood.[1,47] It should be noted that the causes and timing of the few deaths did differ. Both deaths in the HCT group occurred within the 1st year post-HCT while the death in the non-HCT group occurred at 5 years post-match timepoint. One of the deaths in the HCT group was transplant related with multi-organ failure secondary to GVHD, while the other patient died of septic shock possibly related to her history of SCD and possibly related to impaired immune reconstitution after HCT. The death in the non-HCT group was SCD-related from cardiac arrest secondary to iron overload. While HCT is a high-risk therapy, studies have shown that the long term OS for patients who undergo HCT for SCD is >90%, and patients who are alive at 7-years post-HCT have a 97% probability of survival at 12-years post-HCT.[47,57] When compared to the known midlife mortality of SCD,[1,58] such a high OS makes HCT an appealing therapy, particularly when further out from HCT/match timepoint more deaths (5 in total) occurred in the non-HCT group. This finding, as well as the previously published data, further supports the idea that longer term follow-up is needed to detect differences in OS between HCT and standard medical therapy.

Our exploratory aim was intended to identify reasons patients in our non-HCT cohort did not undergo HCT. The majority of our non-HCT cohort was not referred for a transplant consultation, an early barrier. A nationwide study showed that 42% of responding pediatric hematologist/oncologists do not approach families of children with SCD about HCT, so it is likely that the high proportion of patients not referred to transplant in our study is not unique to our center.[59] Most of our referred patients did undergo a consultation with the HCT team, suggesting an interest in learning more about this curative therapy. Based on information available in the EMR, lack of a HLA-matched sibling donor was the most common barrier to proceeding with transplant. This large percentage of patients not undergoing HCT after consult who lack a MSD could suggest that a lack of suitable donor relative to disease severity is, in this cohort, a key reason to not proceed. Other complications of HCT such as GVHD and infertility may also impact patient/family decision-making.[60,61]

Notably over 70% of our non-HCT group relied on public health insurance. Studies have shown that fewer patients on Medicaid go to transplant, which our data also support.[62] While some of these differences between insurance types may be related to coverage options in a given state,[63] it is also possible that insurance status here acts as a surrogate for other socioeconomic and psychosocial factors that may impact a family's or medical team's decision to go forward with transplant. Further study of patient and family perceptions of the risks and benefits of HCT, as well as provider referral patterns, are needed to potentially improve access to this curative therapy.

This study has several limitations, the first of which is the retrospective design. We were limited by what information was available in the EMR and what studies had been completed at the given time points. There was therefore a high proportion of missing

data, making some variables, including our primary outcome, impossible to analyze in a meaningful way. We have only assessed a few outcomes important to patients with SCD. An important next step will be to investigate differences between our two cohorts in central nervous system function. Additionally, assessing the incidence and impact of aGVHD and cGVHD in our HCT cohort may provide more information about the morbidity of this therapy for families and providers. We also present single center data. While we do perform a large number of transplants for SCD each year, a single center experience introduces potential biases based on differences in practice that could affect these results.

Future directions for this work will focus on analyses that allow us to better understand the differences that we have seen between the two groups. Cumulative incidence models will also be helpful in further assessing the ACR data and will help to mitigate the impact of the degree of missingness. Despite the degree of missingness in the group data, we may be able to look within individual patients to see change in their kidney function data over time and compare that change to those of the individual's two matched controls. This more granular comparison between the two groups could give us a better understanding of how specific variables change over time. Longer term follow-up is needed to better assess not only OS but also the differences in end organ function between the two groups. Following this cohort 10 years post-HCT may provide us with an even better understanding of the impact of HCT on patients with SCD. Finally, a prospective study matching patients who undergo HCT and those who continue standard medical therapy would be the ideal way to study the impact of HCT on long term outcomes for SCD.

In conclusion, we have shown that both unscheduled hospitalizations and ED visits in SCD patients decrease post-HCT compared to the non-HCT group, indicating a potential benefit of HCT for patients with SCD. Our data suggest that HCT does not impair survival significantly within the first 5 years compared to those who didn't proceed to HCT. We ultimately hope that our data are informative as to the benefits and risks of HCT for SCD for providers as well as patients and their families, and that our data aid in the decision to refer to and potentially proceed with HCT, particularly in those suffering from severe SCD.

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F. TABLES/FIGURES

Table 1. Baseline Demographic and Clinical Characteristics of Pediatric Patients with SCD, Overall and by Cohort

Variable	N	Overall N = 174[1]	Non-HCT N = 116[1]	HCT N = 58[1]	p-value[2]
Age at transplant (years)	174	9.2 (4.7)	9.2 (4.7)	9.2 (4.7)	0.957
Sex	174				
Male		81 (47%)	54 (47%)	27 (47%)	1.00
Female		93 (53%)	62 (53%)	31 (53%)	
Race	174				-
Non-Hispanic White		1 (0.6%)	1 (0.9%)	0 (0%)	
Non-Hispanic Black		170 (98%)	113 (97%)	57 (98%)	
Hispanic		1 (0.6%)	1 (0.9%)	0 (0%)	
Other		2 (1.1%)	1 (0.9%)	1 (1.7%)	
Genotype	174				-
HbSS/HbSβo		168 (96.6%)	112 (96.6%)	56 (96.5%)	
HbSC		6 (3.4%)	4 (3.4%)	2 (3.4%)	
Insurance	142				
Public		89 (51.2%)	62 (53.4%)	27 (46.5%)	**0.010**
Private		53 (30.4%)	25 (21.6%)	28 (48.3%)	
(Missing)		32 (18.4%)	29 (25%)	3 (5.2%)	
History of Asthma; % Yes	174	43 (25%)	29 (25%)	14 (24%)	0.901
S/p splenectomy? (% Yes)	174	28 (16%)	21 (18%)	7 (12%)	0.312
Pre-HCT Hgb	174	9.23 (1.23)	9.15 (1.29)	9.39 (1.11)	0.226
Pre-HCT Retic %	174	10.6 (5.4)	10.8 (5.5)	10.0 (5.1)	0.370
Pre-HCT absolute retic	172	273 (151)	256 (155)	308 (138)	**0.037**
(Missing)		2	0	2	
Pre-HCT serum creatinine	174	0.37 (0.14)	0.36 (0.14)	0.39 (0.14)	0.271
Scheduled Hospital Admission - (5yrs Pre HCT)	174	0.8 (1.3)	0.8 (1.4)	0.8 (1.1)	0.902
Unscheduled Hospital Admission - (5yrs Pre HCT)	174	5.0 (5.0)	4.4 (4.2)	6.2 (4.9)	**0.021**
Scheduled+Unscheduled Hospital Admission (5yrs Pre HCT)	174	5.8 (4.8)	5.2 (4.5)	6.9 (5.2)	**0.034**

[1] Mean (SD); n (%)
[2] Generalized Linear Mixed Models (GLMM)

Table 2: Transplant-Related Characteristics for HCT Group

Variable	N = 58[1]
Donor Type	
HLA-matched related	54 (93%)
HLA-matched unrelated	4 (6.9%)
HLA-mismatched related	0 (0%)
HLA-mismatched unrelated	0 (0%)
Type of Transplant	
Bone Marrow Alone	52 (90%)
Cord Blood Alone	3 (5%)
Cord Blood and Bone Marrow	3 (5%)
PBSC	0 (0%)
Conditioning Regimen	
Bu/Cy/Flu	36 (62%)
Bu/Flu ± TT	14 (24%)
Flu/Mel ± TT	8 (14%)
Bu/Cy	0 (0%)
Intent of conditioning regimen	
Myeloablative	58 (100%)
Reduced-intensity	0 (0%)
Non-Myeloablative	0 (0%)
Lymphocyte depleting antibody used in the conditioning regimen	
Horse ATG	36 (62%)
Rabbit ATG	14 (24%)
Alemtuzumab (Campath)	8 (14%)
GVHD prophylaxis	
Cyclosporine	58 (100%)
Methotrexate	56 (97%)
Mycophenolate mofetil	4 (6.9%)
Abatacept	4 (6.9%)
Tacrolimus	1 (1.7%)
Sirolimus	0 (0%)
Steroids	1 (1.7%)
Cyclophosphamide	0 (0%)
Other	2 (3.4%)

[1] n (%); Mean (SD)

Table 3: Renal Function in Pediatric Patients with SCD Assessed by ACR with Cut Point of ≥30mg/g, Overall and by Cohort

Time Point *Variable*	**Overall**, N = 174[1]	**Non-HCT**, N = 116[1]	**HCT**, N = 58[1]
Pre-HCT			
Normal	108 (62%)	58 (50%)	50 (86%)
Abnormal	18 (10%)	16 (14%)	2 (4%)
(Missing)	48 (28%)	42 (36%)	6 (10%)
1-Year Post-HCT			
Normal	79 (45%)	43 (37%)	36 (62%)
Abnormal	16 (10%)	11 (10%)	5 (9%)
(Missing)	79 (45%)	62 (53%)	17 (29%)
2-Years Post-HCT			
Normal	80 (46%)	42 (36%)	38 (65%)
Abnormal	16 (10%)	15 (13%)	1 (2%)
(Missing)	78 (44%)	59 (51%)	19 (33%)
3-Years Post-HCT			
Normal	85 (49%)	56 (48%)	29 (50%)
Abnormal	15 (9%)	14 (12%)	1 (2%)
(Missing)	74 (42%)	46 (40%)	28 (48%)
5-Years Post-HCT			
Normal	78 (44%)	53 (45%)	25 (43%)
Abnormal	17 (11%)	17 (15%)	0 (0%)
(Missing)	79 (45%)	46 (40%)	33 (57%)

[1] n (%)

p-values not calculated because of degree of missing data.

Table 4: Renal Function in Pediatric Patients with SCD Assessed by ACR with Cut Point of 100mg/g, Overall and by Cohort

Time Point *Variable*	**Overall**, N = 174[1]	**Non-HCT**, N = 116[1]	**HCT**, N = 58[1]
Pre-HCT			
<100	118 (68%)	67 (58%)	51 (88%)
≥*100*	8 (5%)	7 (6%)	1 (2%)
(Missing)	48 (27%)	42 (36%)	6 (10%)
1-Year Post-HCT			
<100	87 (50%)	47 (41%)	40 (69%)
≥100	8 (5%)	7 (6%)	1 (2%)
(Missing)	79 (45%)	62 (53%)	17 (29%)
2-Years Post-HCT			
<100	89 (51%)	51 (44%)	38 (66%)
≥100	7 (4%)	6 (5%)	1 (2%)
(Missing)	78 (45%)	59 (51%)	19 (32%)
3-Years Post-HCT			
<100	92 (53%)	62 (53%)	30 (52%)
≥100	8 (5%)	8 (7%)	0 (0%)
(Missing)	74 (42%)	46 (40%)	28 (48%)
5-Years Post-HCT			
<100	89 (52%)	64 (55%)	25 (43%)
≥100	6 (3%)	6 (5%)	0 (0%)
(Missing)	79 (45%)	46 (40%)	33 (57%)

[1] n (%)
p-values not calculated because of degree of missing data.

Table 5: Renal Function in Pediatric Patients with SCD Assessed by Level of ACR, Overall and by Cohort

Time Point *Variable*	**Overall** N = 174[1]	**Non-HCT** N = 116[1]	**HCT** N = 58[1]
Pre-HCT			
Normal[*]	108 (62%)	58 (50%)	50 (86%)
Micro albuminuria[**]	12 (7%)	11 (10%)	1 (2%)
Macro albuminuria[***]	6 (3%)	5 (4%)	1 (2%)
(Missing)	48 (28%)	42 (36%)	6 (10%)
1-Year Post-HCT			
Normal	79 (45%)	43 (37%)	36 (62%)
Micro albuminuria	10 (7%)	6 (5%)	4 (7%)
Macro albuminuria	6 (3%)	5 (4%)	1 (2%)
(Missing)	79 (45%)	62 (54%)	17 (29%)
2-Years Post-HCT			
Normal	80 (46%)	42 (36%)	38 (66%)
Micro albuminuria	13 (8%)	12 (10%)	1 (2%)
Macro albuminuria	3 (2%)	3 (3%)	0 (0%)
(Missing)	78 (44%)	59 (51%)	19 (32%)
3-Years Post-HCT			
Normal	85 (49%)	56 (48%)	29 (50%)
Micro albuminuria	9 (5%)	8 (7%)	1 (2%)
Macro albuminuria	6 (3%)	6 (5%)	0 (0%)
(Missing)	74 (43%)	46 (40%)	28 (48%)
5-Years Post-HCT			
Normal	78 (44%)	53 (45%)	25 (43%%)
Micro albuminuria	14 (9%)	14 (12%)	0 (0%)
Macro albuminuria	3 (2%)	3 (3%)	0 (0%)
(Missing)	79 (45%)	46 (40%)	33 (57%)

[1] n (%)
* Normal: 0-29mg/g
** Microalbuminuria: 30-299mg/g
***Macroalbuminuria: ≥300mg/g
p-values not calculated because of degree of missing data.

Table 6: Renal Function in Pediatric Patients with SCD Assessed by eGFR Distribution, Overall and by Cohort

Time Point *Variable*	**Overall** N = 174[1]	**Non-HCT** N = 116[1]	**HCT** N = 58[1]
Pre-HCT			
Low filtration[*]	8 (5%)	5 (4%)	3 (5%)
Normal[**]	68 (39%)	44 (38%)	24 (41%)
Hyperfiltration[***]	96 (55%)	65 (56%)	31 (54%)
(Missing)	2 (1%)	2 (2%)	0 (0%)
1-Year Post-HCT			
Low filtration	10 (6%)	4 (3%)	6 (10%)
Normal	71 (41%)	42 (36%)	29 (50%)
Hyperfiltration	76 (44%)	59 (51%)	17 (30%)
(Missing)	17 (9%)	11 (10%)	6 (10%)
2-Years Post HCT			
Low filtration	10 (6%)	0 (0%)	10 (17%)
Normal	61 (35%)	35 (30%)	26 (45%)
Hyperfiltration	73 (42%)	60 (52%)	13 (22%)
(Missing)	30 (17%)	21 (18%)	9 (16%)
3-Years Post-HCT			
Low filtration	9 (5%)	2 (2%)	7 (12%)
Normal	66 (38%)	40 (34%)	26 (45%)
Hyperfiltration	59 (34%)	51 (44%)	8 (14%)
(Missing)	40 (23%)	23 (20%)	17 (29%)
5-Years Post-HCT			
Low filtration	10 (6%)	2 (2%)	8 (14%)
Normal	68 (39%)	47 (41%)	21 (36%)
Hyperfiltration	45 (26%)	41 (35%)	4 (7%)
(Missing)	51 (29%)	26 (22%)	25 (43%)

[1] n (%)
*Low filtration: <90mL/min/1.73m^2
** Normal: 90-139mL/min/1.73m^2
*** Hyperfiltration: ≥140mL/min/1.73m^2

Table 7: Scheduled Hospitalizations in Pediatric Patients with SCD, Overall and by Cohort

Time Period	N	**Overall**, N = 174[1]	**Non-HCT**, N = 116[1]	**HCT**, N = 58[1]	**p-value**[2]
Pre-HCT*	174	0 (0-2)	0 (0-2)	0 (0-0.8)	0.502
1-Year Post-HCT	172	0 (0-9)	0 (0-9)	0 (0-1)	0.129
(Missing)		2	1	1	
2-Yeasr Post-HCT	167	0 (0-10)	0 (0-10)	0 (0-2)	0.203
(Missing)		7	2	5	
3-Years Post-HCT	160	0 (0-10)	0 (0-10)	0 (0-1)	**0.037**
(Missing)		14	6	8	
5-Years Post-HCT	148	0 (0-2)	0 (0-2)	0 (0-0)	0.08
(Missing)		26	11	15	

*Note: Pre-HCT is an average of the 5 years pre-HCT
[1] Median (Range)
[2] Wilcoxon signed-rank test

Table 8: Unscheduled Hospitalizations in Pediatric Patients with SCD, Overall and by Cohort

Time Point	N	Overall, N = 174[1]	Non-HCT, N = 116[1]	HCT, N = 58[1]	p-value[2]
Pre-HCT*	174	0.8 (0-5.4)	0.6 (0-5.4)	0.9 (0-3.8)	0.659
1-Year Post-HCT	172	0.50 (0-7)	0 (0-7)	1 (0-4)	0.685
(Missing)		2	1	1	
2-Years Post-HCT	167	0 (0-8)	0 (0-8)	0 (0-3)	**<0.001**
(Missing)		7	2	5	
3-Years Post-HCT	160	0 (0-8)	0 (0-8)	0 (0-1)	**<0.001**
(Missing)		14	6	8	
5-Years Post-HCT	148	0 (0-13)	0 (0-13)	0 (0-1)	**<0.001**
(Missing)		26	11	15	

*Note: Pre-HCT is an average of the 5 years pre-HCT
[1] Median (Range)
[2] Wilcoxon signed-rank test

Table 9: Emergency Department Visits without Hospitalization in Pediatric Patients with SCD, Overall and by Cohort

Time Point	N	**Overall**, N = 174[1]	**Non-HCT**, N = 116[1]	**HCT**, N = 58[1]	**p-value**[2]
Pre-HCT*	174	1 (0-4)	1 (0-4)	1 (0-4)	0.765
1-Year Post-HCT	171	1 (0-15)	1 (0-15)	0 (0-5)	**<0.001**
(Missing)		3	1	2	
2-Years Post-HCT	167	0 (0-15)	1 (0-15)	0 (0-4)	**<0.001**
(Missing)		7	2	5	
3-Years Post-HCT	160	0 (0-8)	1 (0-8)	0 (0-3)	**<0.001**
(Missing)		14	6	8	
5-Years Post-HCT	148	0 (0-15)	1 (0-15)	0 (0-2)	**<0.001**
(Missing)		26	11	15	

*Note: Pre-HCT is an average of the 5 years pre-HCT
[1] Median (Range)
[2] Wilcoxon signed-rank test

Table 10: Comparison of Observed Versus Model-Estimated Acute Care Visits in Pediatric Patients with SCD by Cohort

Time and Cohort	Directly Observed Median (IQR)	Model-adjusted[1] Mean differences (95% CI)	p-Value
5 Years Pre-HCT			
HCT	1 (0, 2)	-0.1 (-0.55, 0.34)	0.643
Non-HCT	1 (0, 2)	Ref	
4 Years Pre-HCT			
HCT	1 (0, 4)	0.22 (-0.19, 0.63)	0.292
Non-HCT	1 (0, 3)	Ref	
3 Years Pre-HCT			
HCT	1 (0, 3)	-0.06 (-0.47, 0.35)	0.780
Non-HCT	1 (0, 3)	Ref	
2 Years Pre-HCT			
HCT	2 (1, 4)	0.05 (-0.34, 0.44)	0.800
Non-HCT	2 (1, 4)	Ref	
1 Year Pre-HCT			
HCT	1 (0, 4)	0.24 (-0.16, 0.63)	0.243
Non-HCT	2 (0, 3)	Ref	
1 Year Post-HCT			
HCT	1 (0, 2)	-0.61 (-1.03, -0.19)	**0.004**
Non-HCT	2 (0, 4)	Ref	
2 Years Post-HCT			
HCT	0 (0, 1)	-1.49 (-2.02, -0.97)	**<0.001**
Non-HCT	2 (0, 4)	Ref	
3 Years Post-HCT			
HCT	0 (0, 0)	-2.12 (-2.77, -1.46)	**<0.001**
Non-HCT	2 (0, 3)	Ref	
5 Years Post-HCT			
HCT	0 (0, 1)	-2.28 (-2.96, -1.6)	**<0.001**
Non-HCT	1 (0, 4)	Ref	

[1] Model has been adjusted for baseline (Pre) absolute retic and Insurance Type

Table 11: Assessment of Pulmonary Function via PFT Completion in Pediatric Patients with SCD, Overall and by Cohort

Time Point	N	Overall, N = 174[1]	Non-HCT, N = 116[1]	HCT, N = 58[1]	p-value[2]
Pre-HCT	174				**<0.001**
Yes		83 (48%)	41 (35%)	42 (72%)	
No		91 (52%)	75 (65%)	16 (28%)	
1-Year Post-HCT	172				**<0.001**
Yes		55 (32%)	12 (10%)	43 (75%)	
No		117 (68%)	103 (90%)	14 (25%)	
(Missing)		2	1	1	
2-Years Post-HCT	168				**<0.001**
Yes		54 (32%)	15 (13%)	39 (74%)	
No		114 (68%)	100 (87%)	14 (26%)	
(Missing)		6	1	5	
3-Years Post-HCT	161				**<0.001**
Yes		46 (29%)	17 (15%)	29 (58%)	
No		115 (71%)	94 (85%)	21 (42%)	
(Missing)		13	5	8	
5-Years Post-HCT	146				**<0.001**
Yes		61 (42%)	26 (25%)	35 (85%)	
No		85 (58%)	79 (75%)	6 (15%)	
(Missing)		28	11	17	

[1] n (%)
[2] Pearson's Chi-squared test

Table 12: Assessment of Cardiac Function via Echocardiogram Completion in Pediatric Patients with SCD, Overall and by Cohort

Time Point	N	Overall, N = 174[1]	Non-HCT, N = 116[1]	HCT, N = 58[1]	p-value[2]
Pre-HCT	174				**<0.001**
Yes		98 (56%)	40 (34%)	58 (100%)	
No		76 (44%)	76 (66%)	0 (0%)	
1-year Post-HCT	172				**<0.001**
Yes		82 (48%)	26 (23%)	56 (98%)	
No		90 (52%)	89 (77%)	1 (1.8%)	
(Missing)		2	1	1	
2-Years Post-HCT	168				**<0.001**
Yes		63 (38%)	17 (15%)	46 (87%)	
No		105 (63%)	98 (85%)	7 (13%)	
(Missing)		6	1	5	
3-Years Post-HCT	161				**<0.001**
Yes		63 (39%)	23 (21%)	40 (80%)	
No		98 (61%)	88 (79%)	10 (20%)	
(Missing)		13	5	8	
5-Years Post-HCT	146				**<0.001**
Yes		65 (45%)	30 (29%)	35 (85%)	
No		81 (55%)	75 (71%)	6 (15%)	
(Missing)		28	11	17	

[1] n (%)
[2] Pearson's Chi-squared test

Table 13: Demographics and Clinical Characteristics of the Non-HCT SCD Cohort, Overall and by HCT Referral Status

Variable	N	Overall N = 116[1]	Not Referred N = 87[1]	Referred N = 29[1]	p-value[2]
Age at transplant (years)	116	9.2 (4.7)	9.5 (4.8)	8.2 (4.3)	0.187
Sex	116				0.053
Male		54 (47%)	45 (52%)	9 (31%)	
Female		62 (53%)	42 (48%)	20 (69%)	
Race	116				-
Non-Hispanic White		1 (0.9%)	1 (1.1%)	0 (0%)	
Non-Hispanic Black		113 (97%)	84 (97%)	29 (100%)	
Hispanic		1 (0.9%)	1 (1.1%)	0 (0%)	
Asian		0 (0%)	0 (0%)	0 (0%)	
Other		1 (0.9%)	1 (1.1%)	0 (0%)	
Genotype	116				0.678
HbSS/HbSβo		112 (97%)	83 (95%)	29 (100%)	
HbSC		4 (3.4%)	4 (4.6%)	0 (0%)	
Insurance	88				0.335
Public		62 (70%)	46 (72%)	16 (67%)	
Private		25 (28%)	18 (28%)	7 (29%)	
Combined		1 (1.1%)	0 (0%)	1 (4.2%)	
Uninsured		0 (0%)	0 (0%)	0 (0%)	
(Missing)		28	23	5	
Splenectomy	116	21 (18%)	17 (20%)	4 (14%)	0.587
Pre-HCT Hgb	116	9.15 (1.29)	9.14 (1.34)	9.17 (1.14)	0.930
Pre-HCT Retic %	116	10.8 (5.5)	11.0 (5.7)	10.4 (5.1)	0.656
Pre-HCT absolute retic	116	256 (155)	258 (160)	250 (142)	0.813
Pre-HCT serum creatinine	114	0.37 (0.14)	0.37 (0.14)	0.36 (0.13)	0.595
(Missing)		2	2	0	
Hospital Admission (Unscheduled + ED Visits) 5-years Prior	116	11 (8)	11 (9)	12 (8)	0.686

[1] Mean (SD); n (%)
[2] random intercept logistic regression

Figure 1: CONSORT Diagram of Pediatric Patients with SCD at CHOA Included in HCT Cohort (Cases) and Matched Medically Treated Cohort (Controls)

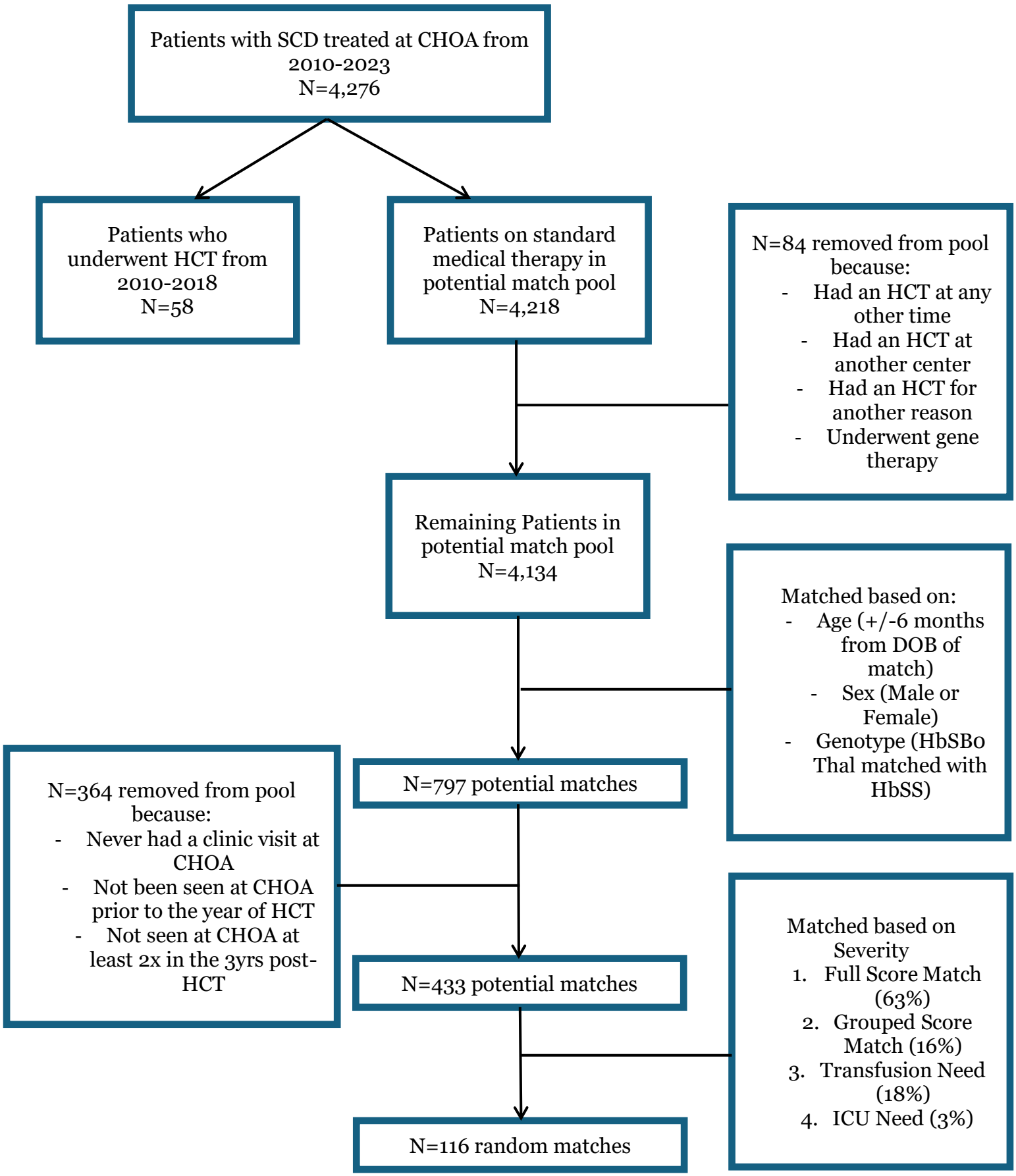
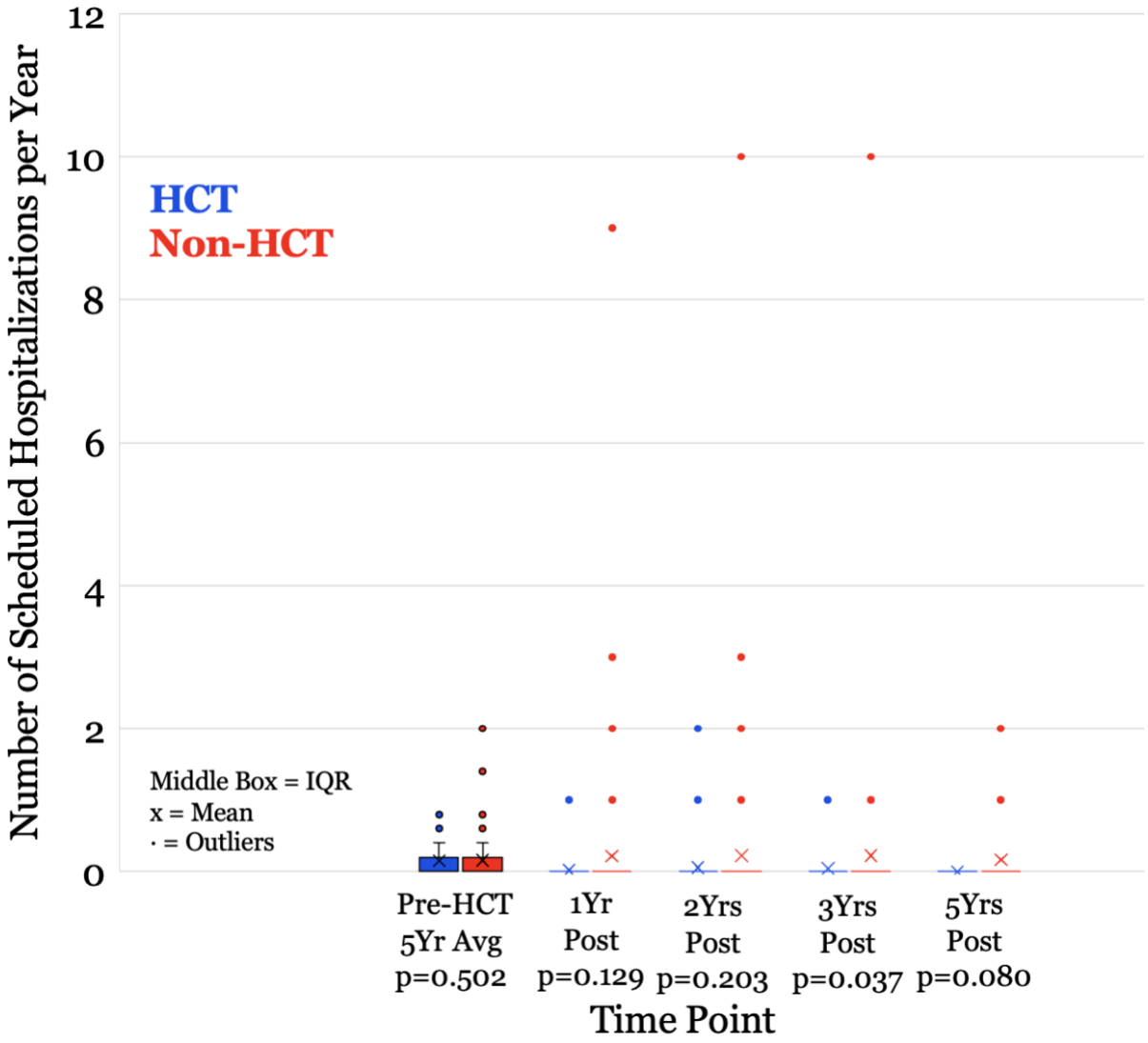
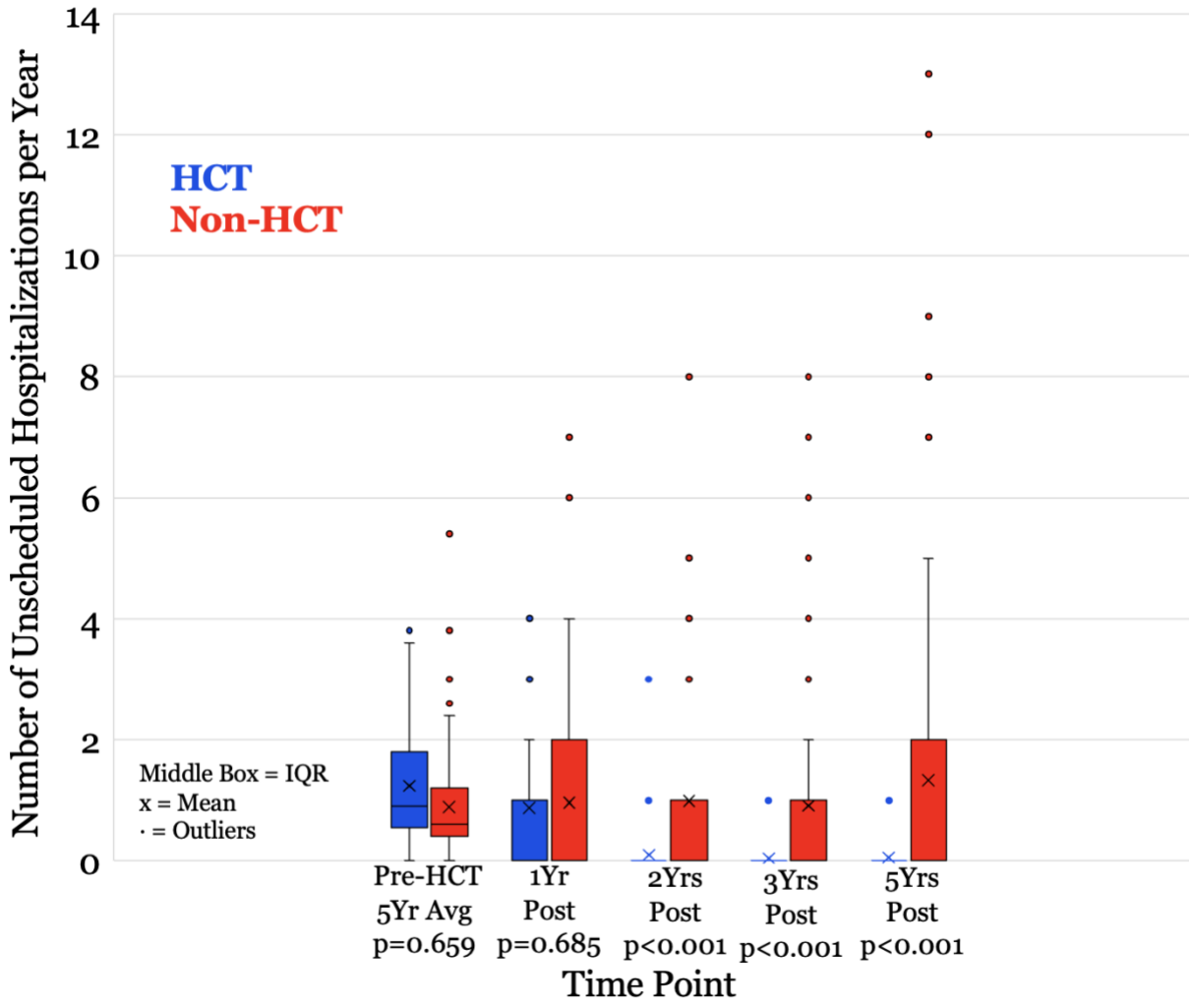


Figure 2: Longitudinal Number of Scheduled Hospitalizations in Pediatric Patients with SCD by HCT Versus Medical Treatment



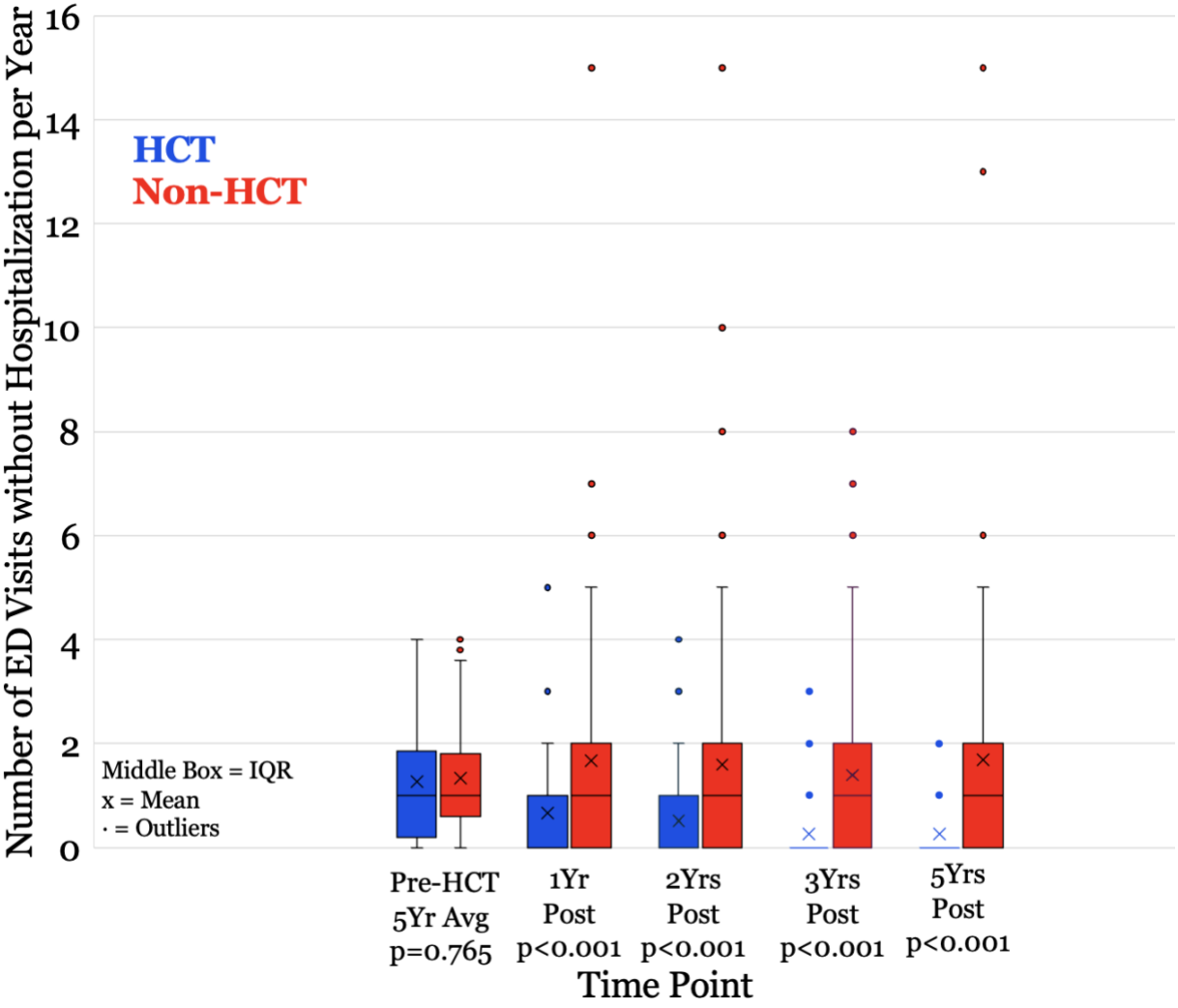
The number of scheduled hospitalizations per year pre-HCT (which is the average of a 5-year total to normalize the data) was similar between the two groups with a median of 0 and a range of 0-2 in the non-HCT group and 0-0.8 in the HCT group. Post-HCT, the median number remained 0 at all time points for both groups. The range for the non-HCT group was, as evidenced in the Box and Whisker plot, much larger than in the HCT group, particularly at the 1-year, 2-years, and 3-years post-HCT time points when there were up to 10 scheduled hospitalizations for some patients in the non-HCT group compared to a maximum number of 2 scheduled hospitalizations in the HCT group. At 3-years post-HCT, the difference between the groups was statistically significant with a p-value of 0.037. At 5-years post-HCT, there were no scheduled hospitalizations for the HCT group compared to a median of 0 and a range of 0-2 for the non-HCT group.

Figure 3: Longitudinal Number of Unscheduled Hospitalizations in Pediatric Patients with SCD by HCT Versus Medical Treatment



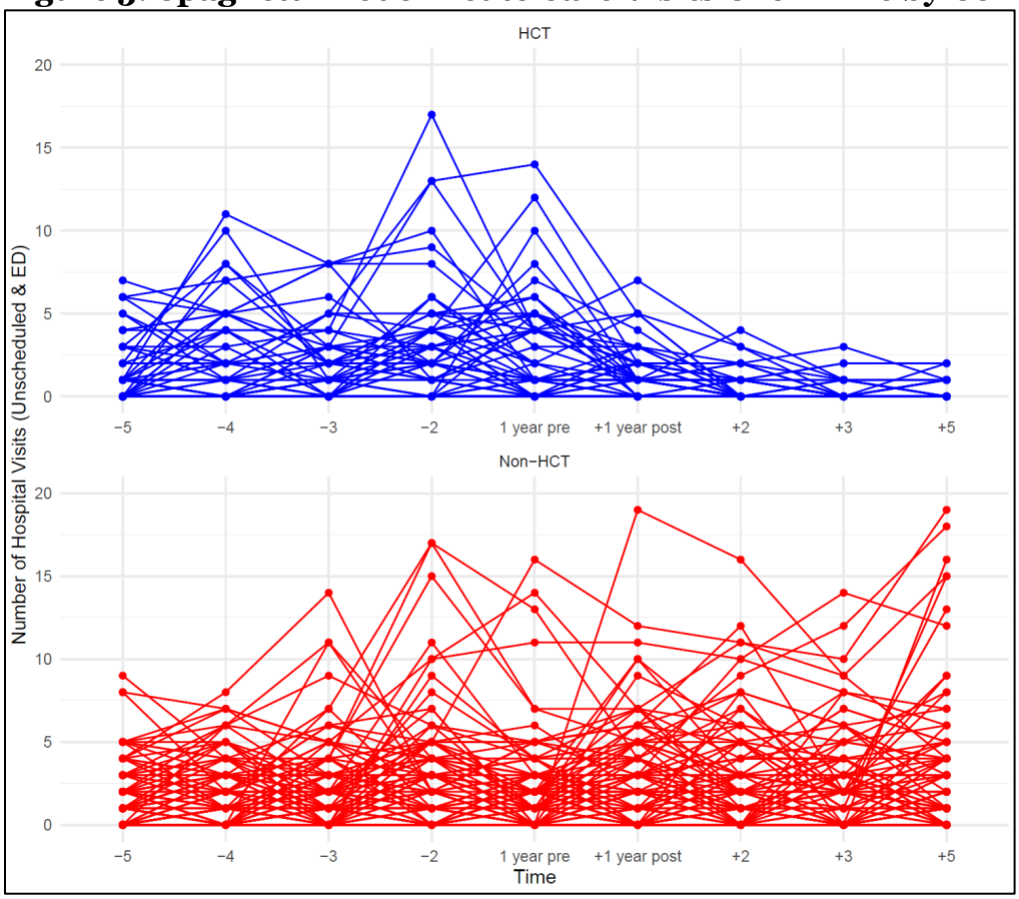
The number of unscheduled hospitalizations per year between the HCT and non-HCT groups was similar pre-HCT (an average of the 5-year pre-HCT total to normalize the data) with a median of 0.9 (range 0-3.8) and 0.6 (range 0-5.4) respectively.. The number of hospitalizations per year for the HCT group remained largely unchanged in the 1st year post-HCT with a median of 1 and a range of 0-4, however at all time points post-HCT the HCT group had significantly fewer hospitalizations per year than the non-HCT group with a median of 0 and a range of 0-3 at 2-years post-HCT and 0-1 at 3-years and 5-years post-HCT ($p<0.001$ for all time points >1 year post-HCT). As demonstrated in the Box and Whisker plot, the range of the number of hospitalizations per year in the non-HCT group remained relatively similar over time.

Figure 4: Longitudinal Number of ED Visits without Hospitalization in Pediatric Patients with SCD by HCT Versus Medical Treatment



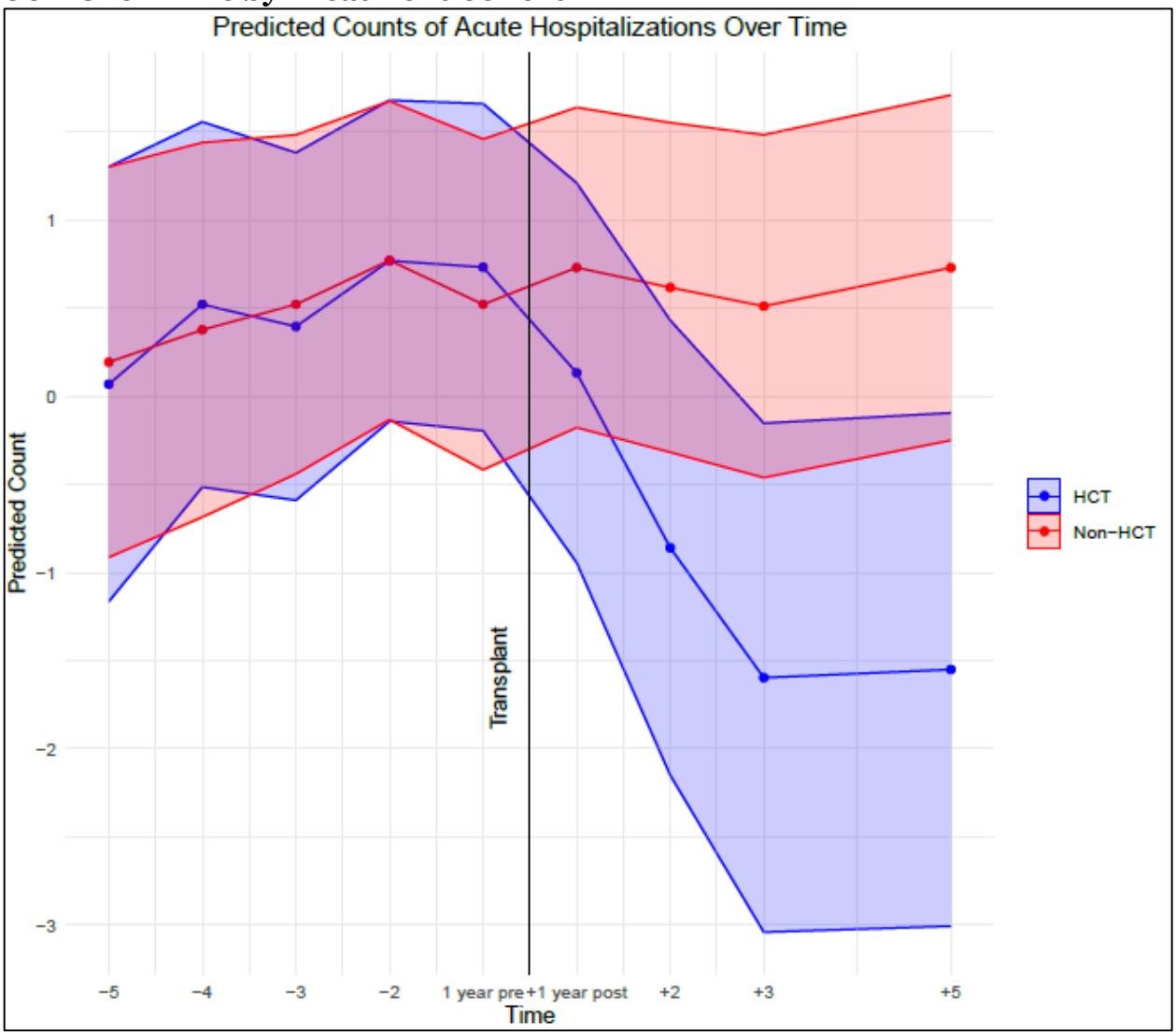
Pre-HCT, which is an average of the 5-year total to normalize the data, the two groups have similar rates of ED visits without hospitalization per year with a median of 1 for both the HCT (range 0-4) and non-HCT (range 0-4) groups. Post-HCT, the HCT group has significantly less ED visits per year with a median that is consistently 0 and an interquartile range (IQR) that get smaller each year. The non-HCT group remains relatively stable in their number of ED visits per year post-match timepoint with a median of 1 at 1-, 2-, 3-, and 5-years post HCT> The IQR remains 0-2 for all time points post-HCT with a few outliers have more frequent ED visits (range 0-15 at 1-, 2-, and 5-years post-HCT and 0-8 at 3-years post-HCT).

Figure 5: Spaghetti Plot of Acute Care Visits Over Time by Cohort



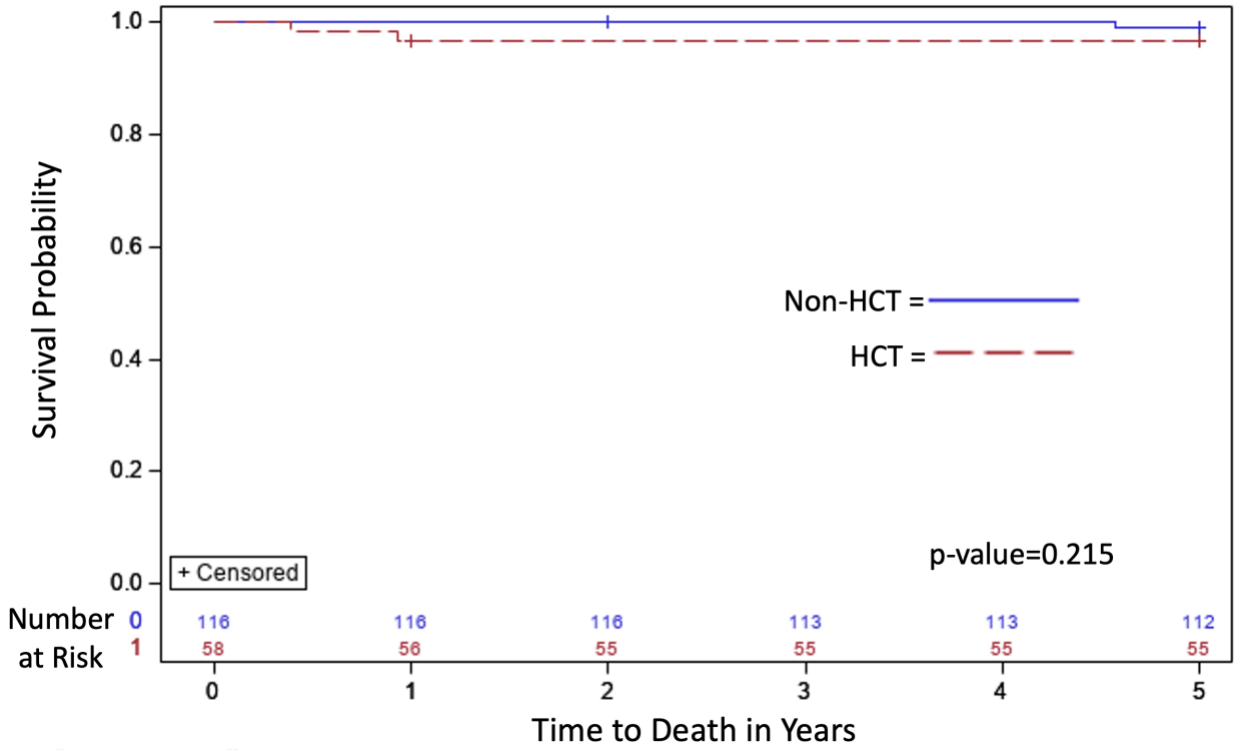
Individual patient's acute care visits over time are plotted at yearly intervals pre-HCT and at 1-, 2-, 3-, and 5-years post-HCT. While the majority of the HCT group's lines fall between between 0 and 2.5 acute care visits per year for the time points post-HCT, most of the non-HCT groups lines are between 0 and 5 acute care visits per year with another group between 0 and 10acute care visits per year and some outliers with as many as 19 acute care visits per year.

Figure 6: Predicted Counts of Acute Care Visits in Pediatric Patients with SCD Over Time by Treatment Cohort



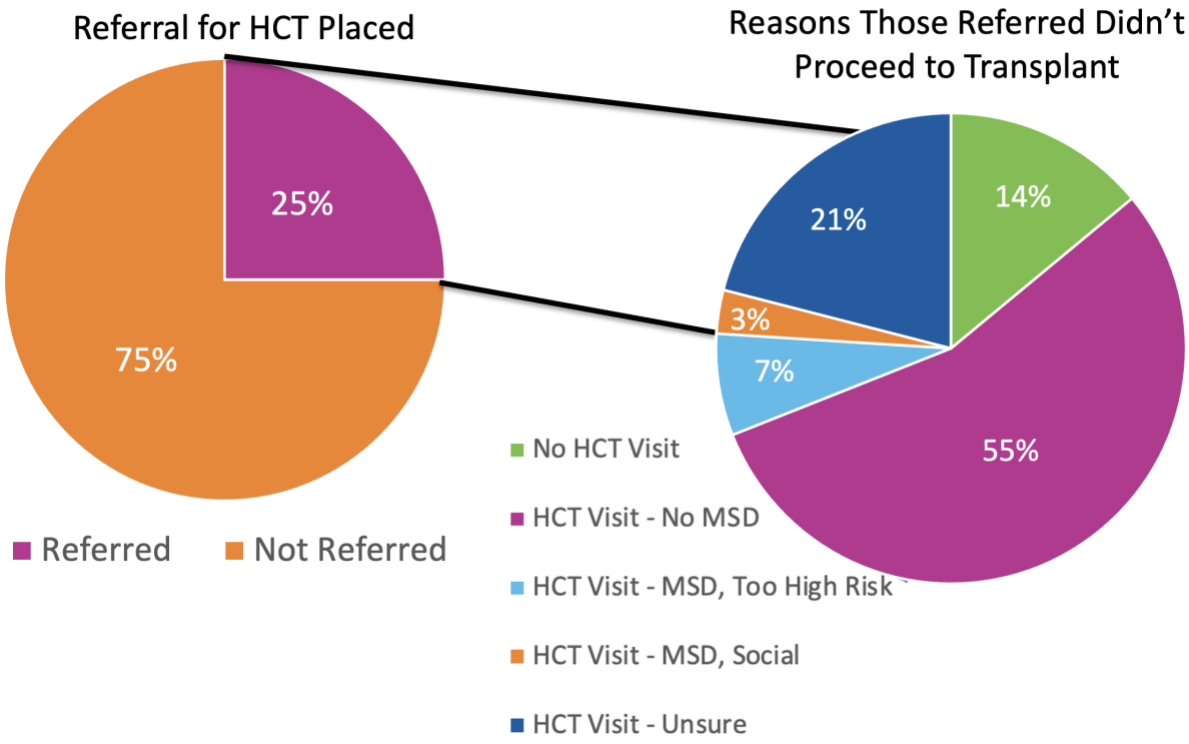
In a model adjusted for insurance status and absolute reticulocyte count, the predicted number of acute care visits per year decreases in the HCT group post-HCT while remaining largely unchanged in the non-HCT group. The 95% confidence intervals (CI) – depicted here as the shaded portions of the graphic – overlap for most of the pre-HCT time points, but post-HCT we see the HCT group's 95% CI decrease with little overlap noted by 5-years post-HCT. At 1-year post-HCT and beyond, the number of acute care visits was predicted to be lower in the HCT cohort by about 1 visit per year (LS mean difference -0.61, 95% CI: -1.03—1.19, p=0.004). This trend continues and by 5-years post-HCT, the predicted difference in acute care visits per year between the two groups is approximately 2 visits per year (LS mean difference -2.28, 95% CI: -2.96, -1.60, p<0.001)

Figure 7: Overall Survival of Pediatric Patients with SCD by Treatment Cohort



Overall survival between the two groups did not differ at 5-years post-HCT (p=0.215). The timing and causes of death did differ however: the 2 deaths in the HCT cohort occurred in the 1st year post-HCT one from GVHD and one from sepsis while the one death in the non-HCT cohort occurred at 5-years post-match timepoint from cardiac arrest. Patients with SCD are expected to live into adulthood but have a known decreased life expectancy compared to unaffected peers. Our cohort's mean age at the end of follow-up is 14 years meaning that longer follow-up is likely needed to potentially see a survival advantage of HCT

Figure 8: Trends in HCT Referral Within the Non-HCT Pediatric SCD Cohort



The majority (N=87, 75%) of patients in our non-HCT cohort were not referred for a consultation with the HCT team. Of the 25% who were referred, 86% (N=25) went for a consultation visit. The most common reason noted in the EMR for not proceeding to HCT was lack of a MSD (N=16, 55%). Three patients were known to have MSDs. Two of those patients and their families decided that HCT was too high risk a therapy. The other plans to go for HCT but has had social barriers that have prevented them from doing so.