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Sinusoidal Obstruction Syndrome Among Pediatric Hematopoietic Stem Cell Transplant Patients

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy in Nursing

by

Tracy Ono

2024

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ABSTRACT OF THE DISSERTATION

Sinusoidal Obstruction Syndrome Among

Pediatric Hematopoietic Stem Cell Transplant Patients

by

Tracy Ono

Doctor of Philosophy in Nursing

University of California, Los Angeles, 2024

Professor Dorothy J. Wiley, Chair

Evidence strongly supports hematopoietic stem cell transplants (HSCTs) for the treatment of malignancy. HSCT carries risks, including fatality, that are associated with intensive conditioning radiation and chemotherapy that optimize the bone marrow for stem-cell implantation. Hepatic *sinusoidal obstruction syndrome* (SOS) is a rare complication that disproportionately affects children where progression to severe SOS requires advanced life support and carries high mortality (>80%). A historical literature review and two quantitative studies explored nurse-sensitive predictors for SOS and the association between SOS and malignancy relapse.

The literature review targeted people aged 19 and younger receiving HSCT treatment. Five themes emerged: diagnostic and severity grading; pharmacotherapy, primarily concentrated on defibrotide; biologic indicators; advances in diagnostic imaging; and clinical SOS treatment and management variability.

We evaluated the **associations between heart rate patterns and SOS** using routine, clinically recorded electronically-measured heart rates for 0.5 to 19-year-olds following HSCT. While SOS-affected youth consistently showed increasing mean heart rates across 14 and 28 days following HSCT, unaffected minors showed flat patterns. For example, among 0.5 to 2.5-year-olds, mean heart rates increased 1.37-fold over the first 14 days, compared to no change observed among unaffected same-aged children. These and other acute changes in heart rate patterns surrounding HSCT may be new biomarkers for SOS.

The **associations between SOS and malignancy relapse following HSCT** evaluated follow-up data for 180 pediatric HSCT recipients, 0.5 to 19 years of age. Twenty-eight diagnosed with SOS showed a shorter time to relapse in bivariate analysis. Multivariable adjusted models showed SOS was associated with a 3.2-fold higher odds of relapse than observed among youth without SOS. Alkylating chemotherapy was independently associated with lower odds of relapse in these analyses.

These analyses underscore a critical need to evaluate routinely collected EMR data, especially data electronically evaluated (vs. counts by many personnel), as risk factors for disease outcomes that drive care and prescriptive interventions among people treated with HSCT. Evaluating nurse-sensitive indicators for early diagnosis of SOS and malignancy relapse prevention may improve patient care, survival, and quality of life.

The dissertation of Tracy Ono is approved.

Barbara Mae Bates-Jensen

David Elashoff

Rita Lynne Secola

Kristi Karin Westphaln

Dorothy J. Wiley, Committee Chair

University of California, Los Angeles

2024

DEDICATION

To my husband Maikol, for your love and support through the years; without you, I could never have accomplished this goal.

To my children, Eaton and Mia, may you always reach for the stars and strive to fulfill all your dreams.

and

To all the children and adolescents affected by sinusoidal obstruction syndrome following hematopoietic stem cell transplant, the strength you and your parents show has been an inspiration.

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love and patience. Maikol, your love and support along this journey were nothing short of amazing. You were indispensable to my success. We made it!

CURRICULUM VITAE

Education

Master of Science in Nursing	University of California, Los Angeles	2008
Bachelor of Arts, History & Theater	Beloit College	2003

License and Certification

California States RN License, License Number: 738642	2008-current
Public Health Nurse License, License Number: 74605	2008-current
Pediatric Critical Care RN, Certified	2018-current
American Heart Association PALS Certified	2011-current
American Heart Association ACLS Certified	2020-current
American Heart Association BLS Certified	2008-current

Professional Experience

Research Assistant *University of California, Los Angeles*	2006-2008
Patient Care Service Aide *Children's Hospital Los Angeles*	2008-2009
Clinical Nurse I & II, Medical-surgical *Children's Hospital Los Angeles*	2009-2011
Teaching Assistant *University of California, Los Angeles*	2017-2022
Clinical Nurse II & III, Pediatric Intensive Care Unit *Children's Hospital Los Angeles*	2011-current

Presentations

Ono, T., Gleason, K., Attanasio, D. (2018, April) *Nurse-Led Bedside Rounds in the Pediatric Intensive Care Unit: Best Practice for Interdisciplinary Teams*. Poster presented at Society of Pediatric Nurses 28th Annual Conference: The Pinnacle of Pediatric Care, Denver, CO**.**

Wiley, D.J., Wiesmeier, E., **Ono, T.**, Larson, L., Masongsong, E., Fitzgerald, L. (2008, April) *Characteristics of urinary urgency among college-age women who are asymptomatic of pain: lessons for identifying urinary urgency risk factors.* Poster presented at: University of California, Los Angeles. 7th Annual Research and Evidence-Based Practice Conference, Los Angeles, CA**.**

Honors and Awards

Kaiser Permanente Deloras Jones RN Scholarship	2016
Dr. Linda Sarna Doctoral Fellowship	2019
Linda Burnes Bolton Emerging Leader Scholarship	2020
Dean Linda Sarna Endowed Doctoral Fellowship	2022

CHAPTER ONE: INTRODUCTION TO THE DISSERTATION

Background and Significance

Hematopoietic stem cell transplants (HSCT) are performed to treat a wide range of diseases, including malignancies, anemias, and genetic disorders (U.S. Department of Health and Human Services, 2023a). In 2020, 22,000 HSCT procedures were performed in the United States, of which 11% of the recipients were children and adolescents under 18 years of age (U.S. Department of Health and Human Services, 2023b). For some diagnoses, such as chronic myeloid leukemia, HSCT may be the only chance of cure (Cant et al., 2007). Nonetheless, preconditioning regimens that prepare the bone marrow to engraft new cells, with radiation and chemotherapies predispose patients, particularly children, to post-HSCT complications such as sinusoidal obstruction syndrome (SOS), which may carry a high mortality rate (Mohty et al., 2015).

Sinusoidal obstruction syndrome (SOS) is a complication that results from radiation and chemotherapy-induced damage to the hepatic endothelium and sinusoidal barrier (Corbacioglu et al., 2018; Mohty et al., 2015). Usually, SOS develops in the first few weeks following HSCT, with children 2 to 6 times more likely to develop SOS than adults (Corbacioglu et al., 2018). Among them, 30-60% advance to severe SOS, presenting with symptoms of multi-organ dysfunctions that require aggressive life support measures (Corbacioglu et al., 2018). Nearly 80% of people with severe SOS die from the disease (Corbacioglu et al., 2019; Yakushijin et al., 2016). SOS diagnosis is driven by clinical presentation reflecting liver dysfunction: hyperbilirubinemia, refractory thrombocytopenia, weight gain, and increased abdominal girth (Cairo et al., 2020; Corbacioglu et al., 2018). Interestingly, recent evidence suggests that 20% of children present later than expected, diagnosed after 21 days, and 30% will not display

hyperbilirubinemia, each a classic symptom of SOS (Cairo et al., 2020; Corbacioglu et al., 2020). Diagnostic and severity criteria have been updated repeatedly to reflect evolving information that includes the value of ultrasound imaging to confirm disease and approval of medication treatment (for SOS) where there is pulmonary or renal involvement, Defibrotide (Defitelio, Jazz Pharmaceuticals, Palo Alto, CA). Prophylactic treatment using Defibrotide is currently under investigation (Corbacioglu et al., 2015; Roh et al., 2021).

Early identification and treatment initiation are paramount to improving patient care and outcomes in children affected by SOS following HSCT. Published literature for pediatric HSCT recipients evaluates associations between biological risk factors for disease, innovative diagnostic technologies, and treatment and SOS. Although nurses have been described in the literature as paramount players in symptom recognition, bedside nurse involvement is varied and minimally included in discussions at the time of diagnosis. While substantial literature examines associations between complications such as graft-versus-host disease and relapse and overall survival, there is a paucity of research evaluating relationships between SOS and malignancy relapse (Barrett & Battiwalla, 2010; Kreidieh et al., 2022; Sharma et al., 2021). Therefore, this dissertation strives to address these areas by evaluating potential nurse-sensitive indicators of disease and exploring the association between SOS and malignancy relapse using data routinely collected by nurses and recorded in the electronic medical record (EMR).

Purpose of the Study

This dissertation focuses on nurse-sensitive indicators that may improve the timely diagnosis of SOS at the bedside and the association between SOS and malignancy relapse. Specifically, I evaluated real-time heart rate patterns from data collected in the inpatient (hospital) setting and examined differences between SOS-affected children and unaffected youth.

An earlier diagnosis may be prompted by the use of routine periodic heart rate monitoring as well as other routine measurements to identify nurse-sensitive biomarkers of SOS. Early SOS diagnosis would likely improve survival.

Malignancy relapse following HSCT significantly risks premature death, especially among patients who suffer SOS complications (Faraci et al., 2019; Kreidieh et al., 2022) Identifying risk factors for relapse holds great promise for increasing the length and quality of life for children treated using HSCT. The second phase of this research plan evaluated the associations between SOS and malignancy relapse, an understudied area in healthcare.

Dissertation Overview: Three Manuscripts

This dissertation consists of three manuscripts. The first manuscript is a historical review of the literature surrounding SOS in pediatric patients who were treated with an HSCT. Five themes best describe the published literature for SOS: diagnosis and severity, pharmacotherapy, biomarkers of disease, diagnostic technologies, and practice variability across provider groups.

Diagnosis and severity criteria are built upon the presence of liver dysfunction symptomology (Cairo et al., 2020; Corbacioglu et al., 2018; Jones et al., 1987; McDonald et al., 1984). The literature review describes the natural history of the disease, especially the impact natural history studies have on overall treatment and clinical recommendations for patients, particularly among children, without hyperbilirubinemia.

Pharmacotherapy studies largely focus on clinical studies data for defibrotide (Richardson et al., 2016; Triplett et al., 2015). These include dose-ranging studies and administration-timing studies relative to SOS severity. Recently published studies testing defibrotide as prophylaxis for SOS disease are explored, possibly representing a highly productive area of clinical research.

Studies evaluating **biomarkers** (of SOS) largely rest on analysis of the disease's incidence and prevalence. Additionally, studies evaluating **diagnostic technologies** for SOS disease seek to identify early markers that combine with clinical SOS symptoms to identify early disease. Last, **clinical practice variations** in SOS care management and treatment may strongly impact diagnosis and treatment. While each thematic area expands our understanding of SOS, a paucity of literature explores changes in routinely monitored physiologic characteristics that may predict SOS disease at an earlier time, all of which may improve survival. Preventing SOS as an outcome may similarly improve the risk of malignancy relapse.

The second manuscript evaluates heart rate data routinely collected at the bedside for 180 pediatric HSCT recipients aged 6 months to 19 years. Using multivariable linear regression analyses, we evaluated the association between SOS and heart rate measurements over two time periods, controlling for the effects confounders and effect modifiers. We explored these relationships between HSCT and day 14 as well as between transplant and day 28 or SOS diagnosis.

Little is known about the association between SOS and the risk of malignancy relapse following HSCT. Our third manuscript explores this relationship for youth aged 6 months to 19 years. Cox proportional hazard, and unadjusted and multivariable-adjusted logistic regression analyses each explored the association between SOS and relapse, controlling for the effects of confounders and effect modifiers.

Conclusion

Collectively, these manuscripts elucidate previously unexplored areas of nursing science research using clinical data routinely collected as part of routine bedside care. Studying possible associations between SOS and malignancy relapse may lead to improvements that positively

affect the quality and quantity of life. This nurse-sensitive indicator may predict risk for SOS and, in turn, associations between SOS and malignancy relapse among youth treated with HSCT.

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CHAPTER TWO: MANUSCRIPT ONE

Pediatric Sinusoidal Obstruction Syndrome: A Historical Review of Literature

Tracy Ono MSN RN CCRN[1,2*], Rita Secola PhD RN CPON NEA-BC FAAN[1,2], Barbara Bates-Jensen PhD RN FAAN[1], Kristi K. Westphaln PhD RN CPNP-PC[1,2], David Elashoff PhD[3], Dorothy J. Wiley PhD RN FAAN[1]

[1]University of California Los Angeles School of Nursing, Los Angeles, California, United States
[2]Children's Hospital of Los Angeles, Los Angeles, California, United States
[3] David Geffen School of Medicine at UCLA, Department of Medicine Statistics Core, University of California, Los Angeles, California, United States

*Corresponding Author:
Tracy Ono

Email: tkono@ucla.edu

Abstract

Background Hematopoietic stem cell transplants (HSCTs) are performed to treat a wide range of diseases among children and adolescents. Conditioning for HSCT includes intensive chemo- and radiation therapy to allow the highest success of engraftment and subsequent cure. The intensity of conditioning and treatment predisposes patients to potentially fatal post-HSCT complications such as sinusoidal obstruction syndrome (SOS). This historical review describes the current literature surrounding SOS among pediatric HSCT patients.

Methods A literature search of health-related databases, PubMed, CINAHL, and Web of Science for works published between 2013-2023. Inclusion criteria limited the articles to English, included pediatric patients, and were SOS-focused following HSCT, where SOS was the primary outcome. Diagnostic and severity criteria, Defibrotide use, biological SOS indicators, innovative diagnostic approaches, and provider variability surrounding SOS will be synthesized.

Results Among 1657 articles from initial searches, 56 were assessed for statistical methods, and 24 were included in a historical review of the literature. Three historically pivotal articles and two expert panel assessments critical to the foundation for clinical guidelines and practice are included.

Discussion The literature base surrounding pediatric SOS may be broadly categorized into five thematic areas: diagnostic and severity grading, pharmacotherapy primarily focused on defibrotide, biologic indicators, diagnostic imaging, and clinical variability. Varying methods and focus areas of study make it challenging to validate results across studies. Additional research evaluating possible changes that occur prior to diagnosis may provide light on preemptive interventions that may be employed for earlier identification of at-risk children.

Keywords: Hematopoietic stem cell transplant, sinusoidal obstruction syndrome, pediatric stem cell transplant

Introduction

Potentially fatal, Sinusoidal obstruction syndrome (SOS) is a rare complication of hematopoietic stem cell transplants (HSCT) that usually manifests within 21 days of transplant (Richardson et al., 2013). The prevalence of SOS among children 18 years and younger is 2- to 6-fold higher than adult HSCT recipients, 20-60% vs 10%, respectively (Carreras et al., 2011; Corbacioglu et al., 2018; Mohty et al., 2015). Nearly 30 to 60% of the affected develop severe SOS with multiorgan failure, of whom more than 80% succumb to the disease (Corbacioglu et al., 2016; Yakushijin et al., 2018). To date, there is a singular Food and Drug Administration-approved treatment for SOS with renal or pulmonary involvement, Defibrotide (DF) (Defitelio, Jazz Pharmaceuticals, Palo Alto, CA).

Early HSCT and SOS studies were observational and focused on the pathophysiology of the disease, treatment, diagnostic imaging, and laboratory and genomic risk factors for the disease (Cheuk, 2012; DiCarlo et al., 2014; Piao et al., 2016; Reiss et al., 2002; Sartori et al., 2012). Three historically pivotal studies developed SOS diagnostic and severity grading criteria that are still applied in practice today among pediatric and adult settings (Jones et al., 1987; McDonald et al., 1993; McDonald et al., 1984). Current literature, primarily focused on SOS in children, shows that pediatric HSCT populations differ from adults in terms of the clinical presentation of SOS. Fifteen to 20% of SOS cases in children present after day 30 (Corbacioglu et al., 2018). Additionally, key diagnostic symptoms such as weight gain and pain are less reliable in younger children due to variability in measurement and the effect of external factors.

Evidence has shown that early identification and initiation of DF are crucial to improving outcomes. Thus, current research centers on biological and physiologic disease markers, technological advances in diagnostics, and treatment effectiveness across all SOS severities.

While these studies overrepresent populations treated in major medical centers (e.g., comprehensive cancer centers), they may broadly represent the experiences of children treated for hematologic and solid tumor malignancies. This historical review of the literature aims to discuss the current themes found in pediatric SOS literature and highlight areas for future research.

Methods

A literature search of health-related databases, PubMed, CINAHL, and Web of Science, was performed for peer-reviewed data-based articles published between 2013 and 2023. Key search terms included bone marrow transplant, veno-occlusive disease, hematopoietic stem cell transplant, pediatrics, and sinusoidal obstruction syndrome. A total of 1657 articles resulted. The PRISMA diagram is shown in Supplemental Figure 1. Filters applied to the search results included publication date (2013-2023), humans, age criteria (birth to 18 years), and English language. The application of filters and removal of duplicates and non-empirical studies narrowed the results to 114 articles. Abstracts were further evaluated for pertinence to SOS, specifically treatment and diagnostic techniques. Fifty-eight articles in which SOS was one of many outcomes for a single exposure were excluded from this review. Fifty-six articles were evaluated in detail for statistical methods, applicability to new contributions to understanding disease, and updated approaches to SOS diagnosis. Six studies that included sample sizes under 50 or cohort populations composed of adults and children were retained for the importance of contribution to understanding the disease, the effectiveness of treatment in advanced SOS disease, or innovative diagnostic approaches.

Results

This review includes twenty-four articles (see Table 1). Three historically pivotal articles published before 2013 were retained in this review due to their importance to the foundation of SOS literature. Two expert panels deliberated on practice and evidence to update diagnostic criteria, including illness severity, to propose treatment guidelines (Cairo et al., 2020; Corbacioglu et al., 2018). Nineteen articles reflect the contemporary state of SOS science; among these, 16 enrolled children exclusively, and 16 reported findings from studies comprising more than 50 patients (Akil et al., 2015; Corbacioglu, 2020; Doring et al., 2016; Doring et al., 2015; Faraci et al., 2019; Füssiová et al., 2023; Han et al., 2023; Naples et al., 2016; Nishida et al., 2018; Park et al., 2018; Piao et al., 2016; Reddivalla et al., 2020; Richardson et al., 2019; Richardson et al., 2016; Roh et al., 2021; Seifert et al., 2015; Skeens et al., 2016; Strouse et al., 2016; Triplett et al., 2015; Visal Okur et al., 2021).

Diagnostic Criteria

Sinusoidal obstructive syndrome is a clinically identified and diagnosed complication of HSCTs. Two diagnostic criteria originating in the 1980s, the Baltimore criterion created by Jones et al. (1987) and the Seattle criterion by McDonald et al. (1984), have guided clinicians for decades (Table 2.a and 2.b). While the studies leading to these guidelines included adults and children, no guidelines applied solely to the pediatric HSCT population. In both studies, histological samples were compared to clinical symptom observation and diagnosis to develop the criteria for SOS. The Seattle criterion identified painful hepatomegaly, with or without an increase in weight, ascites, and jaundice as primary signs of SOS (Table 2.a) (McDonald et al., 1984). Early data on these signs and symptoms showed high sensitivity and specificity: 88% (23/26) and 92% (35/38). Young age (p=0.020), malignancy (p=0.030), and elevated serum

aspartate aminotransferase (p=0.0004) were statistically significantly associated with SOS (McDonald et al., 1984). Modifications to the criterion and SOS severity scale developed in 1993 included symptom onset within 20 days following HSCT, hyperbilirubinemia (>2mg/dL), and body weight gain >2% above pre-transplant baseline (McDonald et al., 1993).

The Baltimore criterion defined SOS as hyperbilirubinemia (98%) and at least two other symptoms - weight gain >5% above pre-transplant baseline (92%), ascites (85%), and painful hepatomegaly (90%) (Table 2.b) (Jones et al., 1987). Sensitivity and specificity were 95% (20/21) and 93% (25/27). Evidence showed temporal symptom appearance following HSCT: weight gain around day eight, hyperbilirubinemia two days after weight gain, and elevated serum aspartate aminotransferase three days after hyperbilirubinemia develops. Studies identified serum aspartate aminotransferase as an independent risk factor and hyperbilirubinemia as statically significantly associated with outcome (Jones et al., 1987). Despite statistical significance, serum aspartate aminotransferase was omitted from both criteria due to a high correlation with a history of liver disease (McDonald et al., 1984).

In recent years, evidence suggests a fraction of SOS-affected patients develop disease in the absence of hyperbilirubinemia, anicteric SOS (aSOS). One of the first studies to examine pediatric HSCT patients who develop aSOS (30%) showed that affected patients still had positive hepatic portal flow reversal on ultrasound (Naples et al., 2016). Affected patients also suffered from SOS progression and mortality. While aSOS is seen in HSCT patients of all ages, an analysis of a randomized control DF clinical trial showed that aSOS is twice as common among children than adults, 29% versus 15%, respectively (Corbacioglu et al., 2020). One study of over 4000 HSCT-treated children reported 103 cases of SOS, among whom 28 (27%) displayed aSOS (Faraci et al., 2019). However, their data suggested that aSOS-affected youth

were at least as likely to resolve disease as youth showing icteric SOS symptoms (96% vs. 80%) (Faraci et al., 2019). Nonetheless, experts suggest that the absence of hyperbilirubinemia may delay diagnosis and treatment initiation from 1 to 11 days (Naples et al., 2016).

Other characteristic developments include the possibility of late-onset SOS and prolonged refractory thrombocytopenia. Data indicates that 20% of SOS-affected pediatric patients may develop late-onset SOS on or after day 21 post-HSCT (Corbacioglu et al., 2020). Refractory thrombocytopenia is believed to be due to the uninhibited endothelial activation of the SOS disease process and requires multiple daily platelet transfusions in SOS patients. This observation has been seen from early studies in the 1980s and continues through today (Corbacioglu et al., 2018). However, thrombocytopenia has previously been omitted from diagnostic criteria due to the expected pancytopenia phase, which occurs during the first two weeks of transplant and coincides with the primary diagnostic period for SOS (Hod & Schwartz, 2008; Léger & Nevill, 2004; Mohty et al., 2016). A recent investigation found refractory thrombocytopenia present in all of the SOS children in a case-control study at a median of eight days before diagnosis ($p<0.0001$) (Embaby et al., 2020).

To address the differences between the adult and pediatric populations, the European Society for Blood and Marrow Transplantation (EBMT) published updated SOS diagnosis recommendations specific to children in 2018 (see Table 2.c) (Corbacioglu et al., 2018). Primarily, the EBMT updates removed the diagnosis time constraint, considered overall trends of serum bilirubin levels rather than an absolute level, and included the predictive factor of refractory thrombocytopenia. A study by Fussiova et al. (2023) comparing the Seattle, Baltimore, and new EBMT criteria among pediatric SOS patients found the increased incidence of aSOS to be statistically significant in the EBMT group than the modified Seattle group (87.5% versus

50%, p=0.040). Refractory thrombocytopenia was frequently the first symptom observed in 90% of patients (Füssiová et al., 2023). In a large historical cohort study, using repeated measures for 4021 children (5072 HSCTs), investigators reclassified cases to EBMT SOS criteria (2000-2016) using data from an extensive multi-center database (Faraci et al., 2019). Therein, the incidence of severe SOS was 2% (n=103); among these, 61% of SOS-affected and 77% of unaffected controls survived to one year, respectively (p=0.003) (Faraci et al., 2019). Mortality attributable to causes other than relapse among SOS-affected youth was 2.12-fold higher than found among unaffected controls (p<0.001) (Faraci et al., 2019).

The 2020 SOS guidelines combined the Seattle and Baltimore criteria, the EBMT recommendations, and new technological diagnostics available for patients of all ages to define case criteria (Table 2.e). Two diagnostic procedures were proposed as independent predictors for improved care: unexplained increased portal wedge pressures or liver biopsy showing histological evidence of SOS (Cairo et al., 2020). Additionally, in the absence of portal wedge pressure or histological findings, the presence of at least two clinical symptoms confirm SOS diagnosis following HSCT: refractory thrombocytopenia, at least 5% weight gain over baseline, right upper quadrant abdominal pain, ultrasound-confirmed ascites, age-specific presence of hepatomegaly or greater than baseline measures, or ultrasound-confirmed reversal of portal venous flow, or last, bilirubin ≥2 mg/dL or values greater than the upper limit of the institutional maximum *normal* cut point value (Cairo et al., 2020).

Severity Grading

Similar to the diagnostic criteria, the SOS severity scale, which has driven practice, was implemented in the 1990s by McDonald et al. The severity of SOS was determined using a scale ranging from mild to severe, correlating with the extent of supportive care needed to address pain

management, fluid retention and overload, laboratory irregularities, and the potential of reversing liver disease. McDonald et al. (1993) examined SOS severity in relation to pre-transplant, transplant, and clinical factors, including multiorgan failure. Hyperbilirubinemia and weight gain >2% were significantly associated with cardiac and respiratory organ involvement ($p<0.001$) (McDonald et al., 1993). Hyperbilirubinemia was also a predictor of renal insufficiency, with a relative risk of 4.9. A positive correlation was found between SOS severity and the increased need for supportive care, which resulted in multiorgan failure (McDonald et al., 1993).

Efforts have been made to quantify SOS severity. Among SOS-affected adults, reports that reflected the practices of individual providers introduced a new grading system utilizing the Common Terminology Criteria for Adverse Events (CTCAE) that ranked SOS patients on a 1-5 (mild to death) grading scale (Carreras, 2015; Chao, 2014). The scales factored in variables such as bilirubin, liver and renal function, and rate of weight change. CTCAE SOS severity guidelines were adopted mainly in adults. However, pediatric SOS grading was not updated until 2018 by Corbacioglu et al. (Table 2.d). The updated pediatric SOS severity recommendations include specifications for trending liver enzymes such as bilirubin, and renal, pulmonary, and mentation function changes, worsening ascites, and persistent refractory thrombocytopenia (Corbacioglu et al., 2018).

The three-point SOS severity scale was modified in 2020 to include an unaffected state (0) and death (V), with four intermediate grades of disease (I-IV) that were applied across all age groups (Cairo et al., 2020). This system incorporates cardiac, neurological, respiratory, renal, fluid homeostasis, and hepatic signs and symptoms of disease (I-IV) (Table 2.f) (Cairo et al., 2020). In research, youth affected by Grades I to V SOS symptoms are compared to otherwise similar youth evaluated as Grade 0 in most study designs.

Pharmacotherapy: Defibrotide

A single *on-label* preventive *treatment* for SOS with renal or pulmonary involvement, Defibrotide (DF), was approved by the Food and Drug Administration in 2016 (Defitelio, *Jazz* Pharmaceuticals, Palo Alto, CA). Nonetheless, DF for prophylaxis is not approved. Pathogenesis of SOS leads to a prothrombotic-hypofibrinolytic state caused by damage inflicted on the hepatic endothelium, specifically at the sinusoids, by pre-HSCT conditioning, specifically myeloablative chemotherapy and total body irradiation (Mohty et al., 2015). Despite practice changes to reduced-intensity conditioning, the incidence of SOS among allogeneic HSCT patients remains roughly nine percent (Richardson et al., 2017). DF acts as a primary antithrombotic agent in the plasmin pathway with minimal bleeding risks (Corbacioglu et al., 2012). A phase 3 clinical trial evaluating the efficacy of DF in SOS patients with multiorgan failure showed improved 100-day survival among DF recipients, 38.2% versus 25% in controls, p=0.011 (Richardson et al., 2016). Adverse events (AE) such as bleeding or hypotension remained comparable between cases and controls. However, DF recipients reported better 100-day complete response rates, 25.5% to 12.5%, than controls, p=0.016 (Richardson et al., 2016).

Continued SOS progression despite DF administration has led to further research into the effectiveness of different DF doses. High-dose DF was evaluated in patients with persistent or worsening SOS on standard 60mg/kg/day dosing (Triplett et al., 2015). DF was increased by 10mg/kg/day to a maximum dose of 110mg/kg/day in affected patients. DF doses greater than 100mg/kg/day were statistically significantly associated with 4-fold more bleeding events than patients receiving standard doses, 13% versus 3%, p=0.008 (Triplett et al., 2015). DF cost may limit administration initiation until diagnosis confirmation is obtained by evidence of hepatic reversal of portal flow on ultrasound. Strouse et al. (2016) evaluated DF treatment's impact on

severe SOS in pediatric and adult patients. Among the pediatric (<16 years, n=36) HSCT patients enrolled in the study, 100-day SOS resolution between DF (n=25) and non-DF (n=11) was 56% versus 45.5% (10.5% difference, 95% CI: -24.8, 45.8). However, 100-day survival was not improved for SOS-affected patients <16 years who received DF, 40% and 45.5%, respectively, in the DF and non-DF groups (-5.5% difference, 95% CI: -40.7-29.7). Overall 100-day SOS resolution and survival were improved when looking at the total study population (n=96), 8.1% (95% CI: -11.2-27.4) and 22.1% (95% CI: 2.6-41.6) absolute differences, respectively (Strouse et al., 2016).

Prophylactic use of DF continues to be under investigation. Roh et al. (2021) evaluated low-dose DF as prophylaxis, administering DF from days -3 to 10 (HSCT = day 0). This case-control study separated the children into two groups: 1) first-round HSCT and 2) second-round HSCT of tandem (two within a period of no more than six months) treatment. Although incidence in the total cohort was lower in the prophylactic DF group, 4.3% (n=3) versus 12.8% (n=10), the difference did not show statistical significance, p=0.071. Prophylactic DF was only shown to be statistically significant among the second group, 2.9% (n=1) versus 28.6% (n=6), p=0.005 (Roh et al., 2021). Although prophylactic DF demonstrated statistical significance only among patients receiving the second part of tandem treatment, some power may have been lost due to the small SOS sample size. Mixed results have been seen when evaluating high-dose DF in patients who have already progressed to severe SOS. However, DF has improved overall outcomes and mortality among SOS-affected pediatric HSCT patients. Further large-scale studies assessing the prophylactic use of DF are necessary to support its adoption as a standard SOS prophylaxis.

Biologic Indicators

Continued poor outcomes among SOS-afflicted pediatric HSCT patients necessitate early diagnosis and accurate risk identification, prompting research into biological studies as possible indicators of patients considered at high risk of developing SOS. Biomarkers with known inflammatory properties have become a high area of SOS research (Akil et al., 2015; Doring et al., 2015; Han et al., 2023; Piao et al., 2016; Seifert et al., 2015). Assault on the tissues caused by malignancy and HSCT conditioning alters levels of related biomarkers; however, to date, biomarkers are not utilized as tools for SOS risk stratification. Biomarkers associated with inflammation may include interleukin (IL)-β, IL-2, IL-4, IL-6, IL-8, and tumor necrosis factor (TNF)-α and TNF-β (Brenner et al., 2014; Jones et al., 1987). IL-6, IL-8, and TNF-α measured shortly before SOS diagnosis are more predictive of disease than baseline measurements. Specifically, when compared to the pre-conditioning baseline measurements, the levels of IL-6, IL-8, and TNF- α were 23-, 5-, and 3-fold higher one to three days before diagnosis (p-values≤0.031) (Doring et al., 2015).

Akil et al. (2015) examined and stratified biomarkers to create a prognostic and diagnostic SOS screening panel that evaluated areas under the curve (AUC) for each targeted marker. L-Ficolin (AUC 0.84, $p<0.001$), hyaluronic acid (AUC: 0.88, $p<0.001$)), and vascular cell adhesion molecule-1 (AUC: 0.70, $p=0.001$) showed promise as an SOS prognostic panel, identifying 70% (n=32) of SOS-affected patients in comparison to 45 patients identified using the Seattle and Baltimore criteria. When applied with clinical SOS characteristics, 83.3% (n=37) of SOS-affected patients were accurately identified (Akil et al., 2015). Research group Han et al. (2023) prospectively evaluated L-ficolin, hyaluronic acid, and stimulation 2 as risk markers for SOS among pediatric HSCT patients at four transplant centers. Elevated levels of hyaluronic acid

(>200ng/ml) and stimulation 2 (>45ng/ml) proved a statistically significant association with SOS incidence, p=0.002 and p<0.0001, respectively (Han et al., 2023). Patients with low L-Ficolin (<1100ng/ml) at day three post-HSCT had a nine times higher risk of SOS (p=0.0003) (Han et al., 2023).

Heparanase is related to inflammation, angiogenesis, and tissue repair. In patients with malignancies, heparanase is intimately correlated to tumor growth, metastases, and reduced survival time (Arvatz et al., 2016). Specifically, heparanase rs436254 is shown to have high gene expression in acute myeloid leukemia patients, thus promoting cancer cell proliferation (Ostrovsky et al., 2007). Seifert et al. (2015) compared heparanase rs4693608 genotypes A to G and rs436254 genotypes C to T as SOS risk factors. Polymorphism heparanase rs4693608 AA (14.3%) was shown to have a three times higher prevalence of SOS compared to AG (4.7%, p=0.038) (Seifert et al., 2015). Similarly, genotype TC rs4364254 (2.9%) was associated with a 5-fold lower SOS incidence than genotype TT (14.7%, p=0.015). Multivariate analyses showed a statistically significant proportional hazard for AA-TT as an independent SOS risk factor, with a hazard ratio of 4.055 (p=0.030) (Seifert et al., 2015).

Previous studies have linked polymorphism FOXP3 rs3761548 to autoimmune diseases and some cancers. Researchers have also begun investigating FOXP3 rs3761548 for an association with SOS. HSCT-treated patients with genotype AA or AC donors were shown to have a decreased incidence of SOS (8.6% versus 24.9%, p=0.011) and marginally lower overall survival (63.5% versus 65.7%, p=0.043) (Piao et al., 2016). Biologic markers show potential as prognostic and diagnostic indicators of SOS risk. Key genotypes may hold promise in identifying patients at increased risk of SOS, thus improving survival. Further research is needed to

corroborate existing correlations and eliminate the possibility of confounding by other post-HSCT complications.

The impact of SOS also includes evaluating systems affected by the physiological changes brought about through the SOS disease process. Physiologic changes and SOS-induced cell injury influence related markers such as iron levels and uric acid (El Ridi & Tallima, 2017; Visal Okur et al., 2021). Studies in this area remain limited. An elevated iron burden prior to HSCT has been associated with hepatic damage, SOS, and decreased overall survival following transplant (Yan et al., 2018). A standard method for measuring iron stores is to evaluate serum ferritin levels (Doring et al., 2016). Consequently, research has evaluated ferritin's prognostic and diagnostic capabilities in pediatric HSCT patients. Evidence has shown that SOS-affected children displayed 18.8 times higher ferritin levels at diagnosis than unaffected controls (p=0.007) (Doring et al., 2016).

SOS occurs due to damage to the hepatic endothelium from pre-transplant myeloablative chemotherapy and total body irradiation (Mohty et al., 2015). Uric acid is a known by-product of injured endothelial cells, particularly in the liver (El Ridi & Tallima, 2017). Okur et al. (2021) examined uric acid levels before conditioning (day -9, HSCT=day 0) to indicate pre-existing endothelial injury and inflammation in allogeneic HSCT children. Data showed that children with elevated pre-conditioning UA uric acid levels (>3.32 mg/dL) had a higher incidence of SOS. The receiver operator curve determined a uric acid reference level of 3.32ml/dL, with the area under the curve at 62.4% (sensitivity 62%, specificity 61%). Pre-conditioning uric acid continued to show significance as an SOS risk factor in the multivariate model with an odds ratio of 2.54 (95% CI: 1.26-5.12, p=0.009) (Visal Okur et al., 2021).

Diagnostic Imaging

In clinical practice, conventional ultrasound (US) is commonly utilized for SOS confirmation following clinical diagnosis. In recent years, researchers have worked to develop additional ways to employ US images as a predictive aid during the immediate post-HSCT period. Nishida et al. (2018) tested a 10-point US, HokUS-10, a scoring tool that evaluated portal blood flow, hepatic vein diameters, and gallbladder wall thickening to predict changes brought about by SOS. HokUS-10 allocated points to patients based on positive findings in 10 areas reliant on US imaging. The median score of SOS-affected patients was seven compared to two in unaffected controls, $p<0.0001$. HokUS-10 predicted SOS before clinical diagnosis in 40% of SOS-affected patients. Sensitivity, specificity, positive predictive value, and negative predictive value, were 80%, 96.9%, 95.3%, and 72.7%, respectively (Nishida et al., 2018).

Evidence has shown that US imagery is promising to improve SOS outcomes through early recognition and the ability to predict SOS. Park et al. (2018) examined the possibility of using US images to identify children progressing to SOS when only one symptom was present and, therefore, did not meet diagnostic criteria. Findings in the SOS group compared to other diagnoses were statistically significant for gallbladder wall edema, ascites, and hepatomegaly, $p<0.001$, $p<0.001$, and $p=0.001$, respectively (Park et al., 2018)

Advances in US technology allow the use of shear-wave and transient elastography to evaluate morphologic liver characteristics and stiffness through velocity measurements of low-frequency vibrations that radiate through hepatic tissues (Jung & Kim, 2012; Reddivalla et al., 2020). Transient elastography evaluation has shown liver stiffness spikes three to six days (average 4.5 days) before SOS diagnosis by Seattle or Baltimore criteria (Colecchia et al., 2017). In a study comparing shear-wave elastography to traditional US, shear-wave elastography

resulted in significant velocity differences between SOS and non-SOS-affected HSCT children in pre-conditioning (baseline) measurements and changes from baseline to day five post-HSCT (0.24 vs. 0.02, p=0.020) and day 14 (0.91 vs 0.03, p=0.010) (Reddivalla et al., 2020). The main hepatic artery resistive index and velocity of the main portal vein measured by traditional US were not statistically significant when compared at baseline, day 5, and day 14. Shear-wave elastography shows promise as a predictive tool for SOS (Reddivalla et al., 2020). SOS was diagnosed by shear-wave elastography at a median of 9.2 prior to clinical diagnosis and 11 days before traditional US imaging, p=0.023 and p=0.009, respectively (Reddivalla et al., 2020). New diagnostic methods promise improved survival and quicker interventions to minimize morbidity. Future studies validating US methods may support utilization as a standard diagnostic.

Clinical Variability

Despite the shift from myeloablative chemotherapy to reduced intensity conditioning utilizing lower-dose total body irradiation, SOS supportive care and treatment have remained unchanged (Johnson & Savani, 2012). The continued high incidence and mortality rate seen in afflicted HSCT patients may be due to a lack of standardization in approaches to SOS diagnosis, management, and treatment. Survey data for 155 critical care and HSCT providers at 74 medical centers in four countries (United States, Canada, Australia, and England) suggested that providers show incomplete agreement for SOS diagnosis, management, and treatment (Skeens et al., 2016). For example, 40% of providers reported hyperbilirubinemia is necessary, but alone insufficient, for SOS diagnosis. Providers generally agreed on continued monitoring of daily fluid intake in affected patients with a strong emphasis on using diuretics and albumin for ongoing diuresis (95%); however, inconsistency was seen in fluid restriction. Fifty percent of providers agreed on restricting fluids to 75% of average daily requirements, while 21% did not

view fluid restriction as necessary. Overall, respondents (92%) reported utilizing DF for treatment. However, only 75% initiated DF at the time of SOS diagnosis. Other providers (14%) awaited hepatic ultrasound to detect reversal of venous portal flow, and the remaining waited for evidence of pulmonary or renal involvement to start DF (Skeens et al., 2016). Widespread variability in SOS management may impact patient outcomes.

In the absence of empirical studies and in nursing, expert opinions often inform care practices for people undergoing HSCT. Although nurses routinely report fluid balance metrics, body weight, abdominal girth, pain, and skin color, few empirical studies strongly support the importance of nursing care in quality outcomes. The Italian Group for Bone Marrow Transplantation (GITMO) expert panel of nurses conducted a literature review, disseminated a survey to GITMO HSCT centers, and analyzed (transplant) procedures and protocols for SOS monitoring, training, and management (Botti et al., 2016). Although practices varied across all care features, most HSCT centers reported the adoption of standardized monitoring protocols (95%) with evidence-based patient-care checklists (82.5%) (Botti et al., 2016). Nonetheless, only 40% reported instituting guidelines to notify providers of physiological change. Less than half (40%) reported in-house education programs to identify hepatic HSCT complications, and less than 60% of nurses attended (Botti et al., 2016). GITMO has since developed ‘golden points of care’ recommendations that identify nursing responsibilities for managing HSCT patients to efficiently detect signs and symptoms of SOS (Botti et al., 2020). Assessing the relationship between standard protocol components, morbidity, and mortality is essential to advancing patient safety. Overall, empirical studies that systematically evaluate predictors of SOS may identify modifiable factors that advance nursing care and improve patient survival.

Discussion

Research advancing knowledge of the pathophysiology of SOS allowed for the development of DF and informed new approaches to risk assessment and diagnosis identification. While much promise has been shown in predictive biomarkers and diagnostic imaging techniques, inconsistency across the types of indicators examined and variation across methodological approaches make generalization of findings challenging (Figure 1). Thus, additional prospective studies are needed to validate these findings and promote their widespread application in practice. Future research exploring aSOS on a large scale will provide an increased understanding of the differences between those affected with aSOS and patients who present with traditional SOS, allowing for improved disease identification.

Despite a better understanding of SOS disease progression and the shift to reduced intensity chemotherapy and decreased total body irradiation, SOS practice approaches remain primarily focused on diagnosis forward instead of preemptive interventions from the time of conditioning (Johnson & Savani, 2012). Furthermore, clinical practice variability continues to be seen among providers and nurses alike. These practice differences contribute largely to the lack of standardization in the treatment and management approach reflected in patient outcomes. Research that identifies early SOS recognition difficulties and clinical changes in characteristics and physiological measures of systems affected by hepatic function may hold predictive qualities for patients at the earliest stages of SOS.

Additionally, although nurses have been highlighted as key contributors necessary in identifying patient changes and recognizing the signs and symptoms of SOS, multidisciplinary involvement, like other SOS approaches, varies widely between institutions and remains primarily physician-led. Nursing-specific data showed that 85% of physicians performed

assessments without bedside nurses present, and 35% of nurses were not informed of the assessment results (Botti et al., 2016b). Thus, further research in this area may enhance nurse-physician partnerships within the care team and allow for the joint development of SOS risk protocols and assessment standards. Data surrounding patients afflicted with aSOS may underscore ways to improve the care provided to pediatric HSCT patients throughout the care continuum. Educating HSCT care teams about the significance of nurse observations in the recognition of SOS signs and symptoms will contribute to transforming nursing practice and emphasizing the pivotal role of nurses as primary identifiers of a critical post-HCST complication.

Table 1. Studies of Sinusoidal Obstruction Syndrome in Pediatric HSCT Patients

Citation	Study Design	Sample Size & Population	Aim	Results		
SOS Diagnostic and Severity Criteria						
ALL acute lymphoblastic leukemia, SGOT serum aspartate aminotransferase, MOF multi-organ failure, aSOS anicteric SOS, HR hazard ratio, EBMT European Society for Blood and Marrow Transplantation						
McDonald et al. (1984)*	Prospective single-center study	255 HSCT children and adults	SOS risk factors for disease	Multivariate Analyses		
				Age >15yrs vs less	RR 3.6 (1.19, 11.0),	*p*=0.02
				Other malignancies vs. ALL	RR 2.4 (1.09, 5.30),	*p*=0.03
				Increased SGOT vs. not	RR 3.4 (1.73, 6.74),	*p*=0.0004
				Prior liver disease vs. not	RR 1.7 (0.76, 3.62),	*p*=0.20
				Histological vs. Clinical Diagnosis		
				+ SOS	23 vs 26,	sensitivity 88.5%
				- SOS	35 vs 38,	specificity 92%
Jones et al. (1987)*	Retrospective single-center study	235 HSCT children and adults	Define characteristics of SOS	Pre-HSCT characteristics		
				Increased SGOT vs. not	48% vs 16%,	*p*=0.000007
				Multiple ALL relapses vs singular	30% vs 12%,	*p*=0.03
				Histological vs. Clinical Diagnosis		
				+ SOS	20 vs 21,	specificity 95%
				- SOS	25 vs 27,	sensitivity 93%
				Observational sequencing of clinical symptoms (% incidence)		
				Weight gain (92%)	Avg 8.6 days	
				Bilirubin >2mg/dL (98%)	2 days after weight gain	
				Increased SGOT (83%)	Avg 2-3 days after bilirubin spike	
				Ascites (85%)	1-2 weeks of diagnosis	
				Hepatomegaly (90%)	1-2 weeks of diagnosis	
McDonald et al. (1993)*	Prospective single-center study	355 HSCT children and adults	Association between SOS severity and multi-organ failure	SOS vs. no SOS		
				Renal insufficiency	38% vs 13%,	*p*<0.001
				Need for oxygen	31% vs 9%,	*p*<0.001
				Pulmonary infiltrates	36% vs 16%,	*p*<0.001
				Transfusions required	13% vs 3%,	*p*<0.001
				Mild/Moderate SOS vs Severe		
				Renal failure	54% vs 10%,	*p*<0.001
				Cardiac failure	63% vs 26%,	*p*<0.001
				Ventilatory support	43% vs 4%,	*p*<0.001
				Neurologic changes	78% vs 41%,	*p*<0.001

				Transfusions required	39% vs 13%,	p<0.001
Naples et al. (2016)	Retrospective single-center study	30 HSCT children	Early identifier of anicteric SOS (aSOS)	SOS vs. aSOS Total bilirubin (median) PICU (2 MOF, SOS) vs ward (aSOS)	 10.3 vs 1.1, 2 vs 1,	 p<0.0001 p=0.007
Corbacioglu et al. (2020)	Retrospective single-center study	803 HSCT patients, 460 children	Evaluate the incidence of aSOS and late-onset SOS	Incidences Among Children SOS: aSOS aSOS with multiorgan failure SOS after day +21 100-day post-HSCT survival SOS aSOS	 71% : 29% 26% 20% 64% (CI 58-69%) 91% (84-95%	
Faraci et al. (2020)	Retrospective multi-center	4021 HSCT children	Define SOS patient characteristics, evaluate risk factors and outcomes when EBMT criteria applied	Incidence Among Children SOS (overall) aSOS (bilirubin<2mg/dL) Incidence Complete SOS resolution SOS vs. aSOS 1-year overall survival SOS vs no SOS Non-relapse mortality SOS vs no SOS	 2% 27% 80% vs. 96% 61% vs 77% HR 2.12 (1.45, 3.08)	 p=0.0033 p<0.001
Fussiova et al. (2023)	Retrospective single-center study	179 HSCT children	Compare SOS incidence between historical (Seattle/Baltimore) and updated EBMT criteria.	Historical vs. EBMT criteria Overall incidence aSOS incidence Median bilirubin	 Chi-square 0.55, Chi-square 4.40, 3.4 vs 1.23,	 p=0.46 p=0.04 p=0.045
Pharmacotherapy: Defibrotide (DF) Studies						
Triplett et al (2015)	Prospective single-center study	34 HSCT children	Safety and efficacy of high-dose DF	DF increased risk of hemorrhage	13% vs 3%,	p=0.008
Richardson et al. (2016)	Prospective multi-center study	102 HSCT children and adults	DF efficacy among SOS patients with multiorgan failure	DF vs. no DF 100-day complete response to HSCT 100-day post-HSCT survival	 25.5% vs 12.5%, 38.2% vs 25%,	 p=0.0160 p=0.0109
Strouse et al (2016)	Retrospective clinical database study	96 HSCT children and adults	DF efficacy among severe SOS	100-day SOS resolution Absolute Differences Overall cohort <16 years	 22.1% (CI 2.6-41.6) 10.5% (CI -24.8-45.8)	

				100-day Post-HSCT Survival Absolute Differences		
				Overall cohort	8.1% (CI -11.2-27.4)	
				<16 years	-5.5% (CI -40.7-29.7)	
Roh et al (2021)	Retrospective single-center study	147 HSCT children	Prophylactic low-dose DF efficacy	SOS incidence, DF vs not		
				Overall cohort	4.3% vs 12.8%,	*p*=0.071
				1st HSCT	5.9% vs 7.0%,	*p*=0.833
				2nd HSCT of tandem	2.9% vs 28.6%,	*p*=0.005
Biologic Indicators AUC area under the curve, IL interleukin, TNF tumor necrosis factor, HPSE heparinase, UA uric acid, HA hyaluronic acid, ST2 stimulation 2						
Akil et al (2015)	Prospective multi-center study	120 HSCT patients	Develop biomarker prognostic screening panel for SOS	Prognostic AUC SOS vs no SOS		
				L-Ficolin	AUC 0.88,	*p*<0.001
				Hyaluronic acid	AUC 0.81,	*p*<0.001
				Vascular cell adhesion molecule-1	AUC 0.81,	*p*=0.001
Doring et al (2015)	Retrospective single-center study	61 HSCT children	Acute changes in IL-6, IL-8, TNF-α levels at SOS onset	Median levels pre-SOS vs. 1st symptom presence		
				IL-6	3.150 vs 69.850,	*p*=0.0313
				IL-8	18.4 vs 105,	*p*=0.0156
				TNF-α	8 vs 22.30,	*p*=0.0313
Seifert et al (2015)	Retrospective single-center study	160 donors and HSCT children	Cumulative incidence and risk for SOS	Univariate Cumulative SOS Incidence		
				rs4693608 AG and GG vs AA	4.7% vs 14.3%,	*p*=0.038
				rs4364254 TC vs TT	2.9% vs 14.7%,	*p*=0.015
				Multivariate Risk for SOS		
				Pre-HSCT ferritin	HR 1.097 (1.010, 1.190)	*p*=0.028
				HPSE AA-TT	HR 4.055 (1.142, 14.390)	*p*=0.030
Doring et al (2016)	Retrospective single-center study	138 HSCT children	Ferritin as a SOS predictor	Median ferritin levels		
				Pre-SOS vs. at diagnosis	0.1 vs 2.8,	*p*=0.0078
Piao et al (2016)	Retrospective single-center study	171 HSCT children	FOXP3 rs3761548 effect on SOS	SOS Cumulative Incidence		
				AA or AC genotype vs CC	8.5% vs 24.9%,	*p*=0.011
				SOS Risk Predictor		
				CC genotype	HR 3.97 (1.47-10.74)	
Visal Okur et al (2021)	Retrospective single-center study	222 HSCT children	Risk association of pre-conditioning uric acid (UA) levels	Pre-SOS levels vs. at diagnosis		
				UA	OR: 2.54 (1.26, 5.12),	*p*=0.009
				Serum albumin	OR: 0.45 (0.22, 0.95),	*p*=0.037

Han et al (2023)	Prospective multi-center study	80 HCST children	Evaluated L-ficolin, HA, and ST2 as possible SOS risk identifiers	Multivariate Hazard Ratio L-ficolin (low vs high) HA (high vs low) ST2 (high vs low) +SOS vs -SOS Combined: ↑HA, ↑ ST2, ↓L-ficolin	 21.3 (1.5-295.0), 10.4 (0.8-134.7), 284.9 (4.3-1.9x10^4), 9.30 (2.07-41,75),	 *p*=0.0225 *p*=0.0741 *p*=0.0084 *p*=0.0008
Diagnostic Imaging PUV paraumbilical vein, HRL hepatic right lobe, HLL hepatic left lobe, PV portal vein, HA hepatic artery, MHA RI main hepatic artery resistive index, MPV main portal vein						
Nishida et al (2018)	Prospective single-center study	105 HSCT adults	Evaluate characteristics associated with SOS	Median HokUS-10 Score SOS diagnosis vs day +14 no SOS HokUS-10 Elements (score points) Ascites (1-2) Gallbladder thickening (1) PUV blood flow signal (2) PUV diameter (2) HRL vertical diameter (1) HLL vertical diameter (1) PV diameter (1) PV flow direction (1) PV mean velocity (1) Resistive index HA (1)	 7 vs 2, OR (95% CI) 32.309 (6.202, 168.314), 1.540 (1.247, 1.902), 27.300 (5.778, 128.981), 7.337 (2.290, 23.505), 1.084 (1.030, 1.141), 1.016 (0.961, 1.073), 1.425 (1.045, 1.942), Congestion vs hepatofugal 0.917 (.0836, 1.006), 1898.384 (0.544, 6626616.11),	 *p*<0.0001 *p*<0.001 *p*<0.001 *p*<0.001 *p*=0.001 *p*=0.002 *p*=0.581 *p*=0.025 *p*=0.67 *p*=0.70
Park et al (2018)	Prospective single-center study	59 HSCT children	Predict SOS using clinical characteristics	Characteristics of SOS vs no SOS Gallbladder wall edema Ascites Hepatomegaly Reversed portal flow	 OR: 35.370 (0-0.538), OR: 56.393 (0.001-0.394), 60% vs 15%, 20% vs 0%,	 *p*=0.028 *p*=0.011 *p*=0.001 *p*=0.011
Reddivalla et al (2020)	Prospective single-center study	25 HSCT children	Shear wave elastography (SWE) will have earlier and more accurate detection of SOS compared to traditional US.	Characteristics of SOS vs no SOS Traditional ultrasound (US) Baseline MHA RI Day +5 MHA RI Day +14 MHA RI Baseline MPV velocity Day + 5 MPV velocity Day +14 MPV velocity SWE US Baseline (preconditioning)	 0.79 vs 0.71, -0.00 vs 0.01, 0.08 vs 0.02, 34.06 vs 35.7, 5.25 vs 7.02, -15.25 vs 0.95, 1.24 vs 1.41,	 *p*=0.089 *p*=0.774 *p*=0.508 *p*=0.772 *p*=0.791 *p*=0.071 *p*=0.06

				Change baseline to day +5	0.24 vs 0.02,	*p*=0.02
				Change baseline to day +14	0.91 vs 0.03,	*p*=0.01
				Days to SOS diagnosis		
				SWE before clinical	9.2 (2.1, 16.3),	*p*=0.0228
				SWE before traditional US	11 (4.5, 17.5),	*p*=0.0094
Clinical Variability CC critical care, RPVF reverse portal venous flow, aSOS anicteric SOS						
Skeens et al (2016)	Observational electronic multi-center study	155 HSCT or critical care providers	SOS diagnosis, treatment, care management	Provider Variability (% respondents, HSCT vs. CC providers)		
				Diagnosis		
				Modified Seattle	70%, 104 vs. 4,	*p*<0.0001
				Baltimore	65%, 95 vs. 4,	*p*<0.0001
				Diagnose aSOS	60%, 88 vs 6,	*p*=0.0023
				Treatment		
				Prophylaxis used	66%, 97 vs. 4,	*p*<0.0001
				DF initiated at diagnosis	75%, 109 vs. 7,	*p*<0.0001
				Initiate after reverse RPVF	14%, 12 vs 10,	*p*<0.0001
				With evidence of pulmonary dysfunction	6%, 5 vs 4,	*p*=0.0208
				Supportive care		
				Fluid restriction	50%, 24 vs 9,	*p*=0.0189
				Paracentesis for decreased urine output	36%, 4 vs 14,	*p*=0.0042

*Historically pivotal articles

Table 2. SOS Diagnostic and Severity Criteria

a. Modified Seattle Criterion[1]

Presentation of at least 2 symptoms within 20 days post-HSCT

- Hyperbilirubinemia
- >2% weight gain above baseline
- Ascites
- Jaundice
- Painful hepatomegaly

b. Baltimore Criterion[2]

Presentation of hyperbilirubinemia and at least 2 symptoms

- Ascites
- Painful hepatomegaly
- Unexplained weight gain >5% above baseline

c. 2018 EBMT Updated Recommendations for Pediatric SOS Criteria[3]

Presence of ≥2 symptoms following HSCT unexplained by other means, occurring at any point following HSCT

- 3 consecutive days of weight gain with diuretic administration or ≥5% weight gain above baseline
- Hepatomegaly (best practice, identification by imaging)
- Ascites (best practice, identification by imaging)
- Consumptive thrombocytopenia refractory to transfusions
- 3 consecutive days of increasing bilirubin levels above baseline or hyperbilirubinemia (≥2mg/dL) in 72 hours

d. 2018 EBMT Updated Recommendations for Classifying Pediatric SOS Severity[3]

	Mild	Moderate	Severe	Very Severe
Ascites	Minimal	Moderate	Severe ascites requiring drainage	
Neurologic status	Normal	Normal	Normal	Cognitive Impairment
Pulmonary function	0-2L O2	> 2L O2	Positive pressure assistance	
Refractory thrombocytopenia	< 3 days	3-7 days	>7days	
Bilirubin	< 2mg/dL		≥2 mg/dL	
Liver function (AST, ALT)*	≤ 2 x normal	3-5 x normal	>5 x normal	
Coagulation	Normal	Normal	Impaired	Impaired, replacement required
Renal function (GFR)*	89-60 mL/min	59-30 mL/min	29-15 mL/min	<15 mL/min

e. 2020 Proposed SOS Diagnostic Criteria Recommendations[4]

Any two of the following elements

- Bilirubin ≥2mg/dL or above institution-specific limits
- Hepatomegaly
- Confirmed ascites
- Right upper quadrant abdominal pain
- Unexplained weight gain ≥5% above baseline
- Confirmed reversal of portal venous blood flow
- Post-HSCT refractory thrombocytopenia

OR one of the following

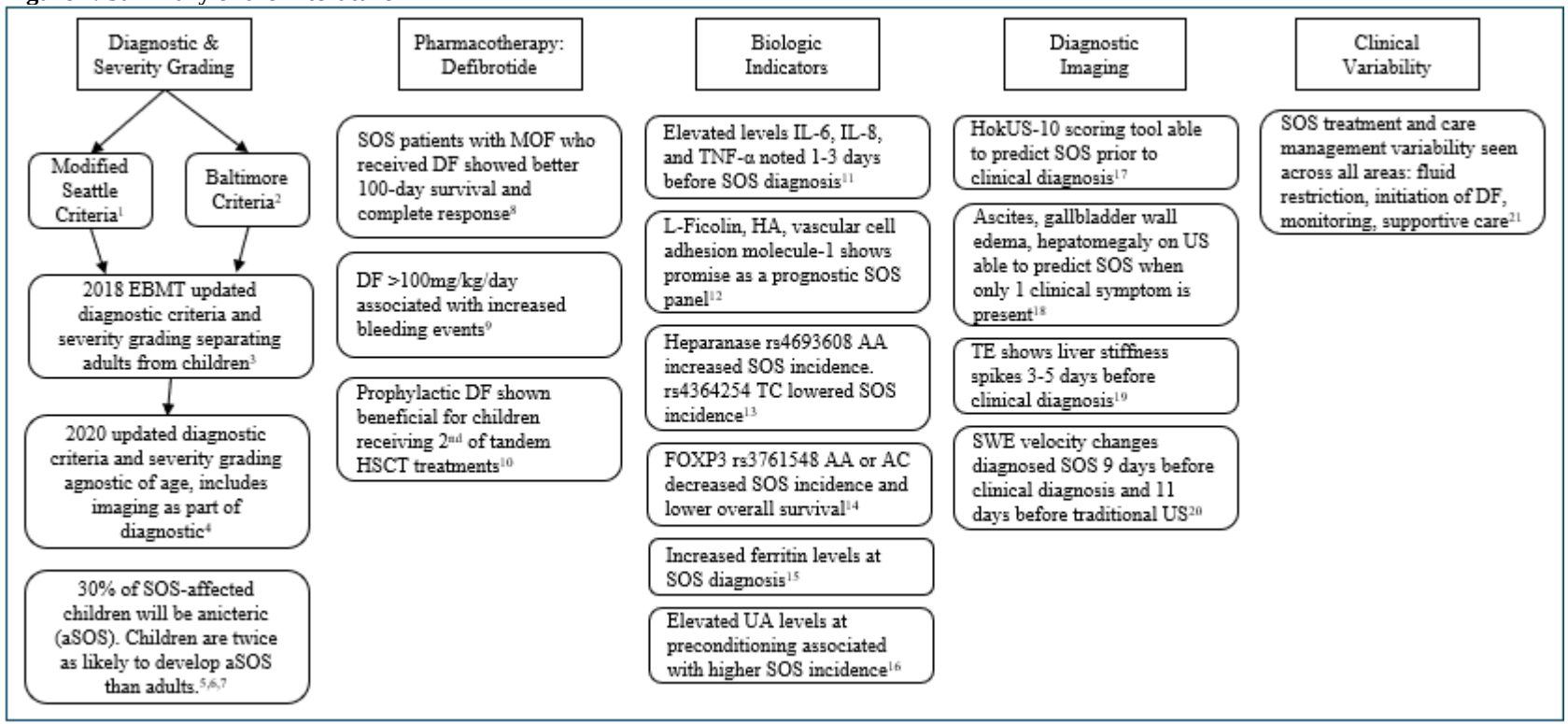
- Increased portal venous wedge pressure
- Confirmed SOS by hepatic biopsy

f. 2020 Proposed Updated SOS Grading System[4] (Grade 0 = No SOS, Grade V = Death for all systems)

	Grade I	Grade II	Grade III	Grade IV
Cardiac function	Noted laboratory changes but asymptomatic	Activity induced symptoms	Symptoms noted with minimal activity	Vasoactive medications or mechanical support required
Fluid status	Increased weight or ascites noted as 5-10% above baseline. No intervention required	Increased weight or ascites noted as 10-20% above baseline. Intervention indicated	Increased weight or ascites noted as >20% above baseline. Invasive intervention required	Emergent operative intervention required
Hepatic function				
Bilirubin	Above ULN-1.5*ULN if normal at baseline; otherwise >1-1.5*baseline measurement	Above 1.5-3*ULN if normal at baseline; otherwise >1.5*3 baseline measurement	Above 3-10*ULN if normal at baseline; otherwise >3*10 baseline measurement	Above 10*ULN if normal at baseline; otherwise >10*baseline measurement
Transaminase	Above ULN-3*ULN if normal at baseline; otherwise >1.5-3*baseline	Above 3-5*ULN if normal at baseline; otherwise >3-5*baseline	Above 5-20*ULN if normal at baseline; otherwise >5-20*baseline	Above 20*ULN if normal at baseline; otherwise >20*baseline
Portal hypertension	-	↓ PV flow	reversed PV flow, ascites	Necessitates urgent intervention
Neurologic function	Mildly symptomatic	Symptoms limits ADL	Severe, disrupts ADL	Necessitates urgent intervention
Pulmonary function	-	O_2<88% with exertion, requires intermittent oxygen	O_2<88% at rest	Necessitates urgent intervention
Renal function	Cr>ULN-(1.5*ULN)	Cr>1.5-3*baseline or ULN	Cr>3*baseline or >3-6*ULN	>6*ULN

AST: aspartate transaminase, ALT: alanine transaminase, GFR: glomerular filtration rate, ULN upper limit of normal, PV portal vain, ADL activities of daily living, Cr creatinine
[1] (McDonald et al., 1993) [2] (Jones et al., 1987) [3](Corbacioglu et al., 2018) [4](Cairo et al., 2020)

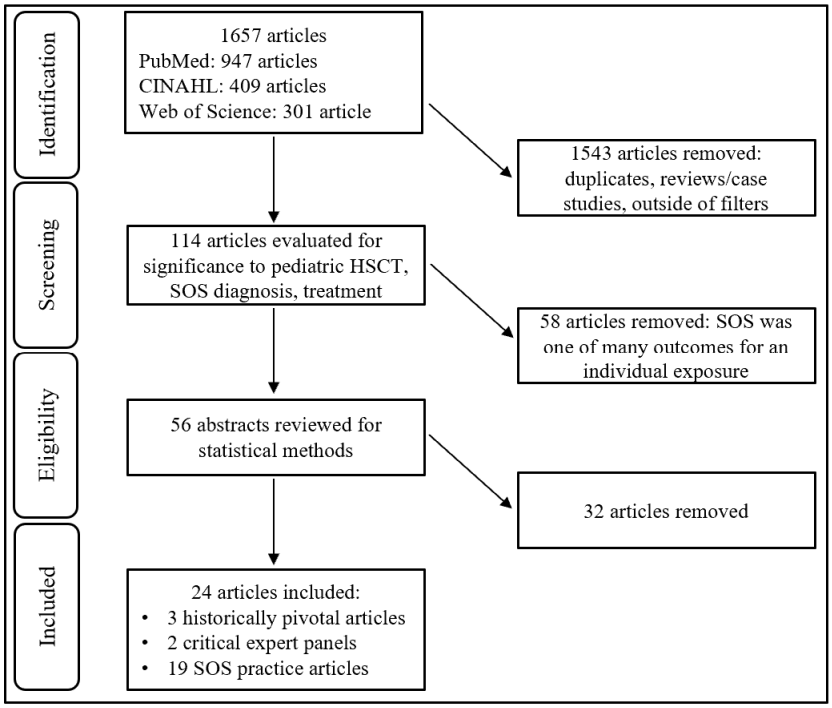
Figure 1. Summary of the Literature



EBMT European Society of Bone and Marrow Transplantation, DF defibrotide, MOF multi-organ failure, IL interleukin, TNF tumor necrosis factor, HA hyaluronic acid, UA uric acid, US ultrasound, TE transient elastography, SWE shear-wave elastography

[1](McDonald et al., 1984) [2](Jones et al., 1987) [3](Corbacioglu et al., 2018) [4](Cairo et al., 2020) [5-7](Corbacioglu et al., 2019; Faraci et al., 2019; Naples et al., 2016) [8](Richardson et al., 2016) [9](Triplett et al., 2015) [10](Roh et al., 2021) [11](Doring et al., 2015) [12](Akil et al., 2015) [13](Seifert et al., 2015) [14](Piao et al., 2016) [15](Doring et al., 2016) [16](Visal Okur et al., 2021) [17](Nishida et al., 2018) [18](Park et al., 2018) [19](Colecchia et al., 2017) [20](Reddivalla et al., 2020) [21](Skeens et al., 2016)

Supplemental Figure 1. PRISMA diagram



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CHAPTER 3: MANUSCRIPT TWO

Heart Rate Changes in Pediatric Patients with Sinusoidal Obstruction Syndrome Following Hematopoietic Stem Cell Transplant

Tracy Ono MSN RN CCRN[1,2*], Jenny Brook MS[3], David Elashoff PhD[3], Rita Secola PhD RN CPON NEA-BC FAAN[1,2], Barbara Bates-Jensen PhD RN FAAN[1], Kristi K. Westphaln PhD RN CPNP-PC[1,2], Dorothy J. Wiley PhD RN FAAN[1]

[1]University of California Los Angeles School of Nursing, Los Angeles, California, United States
[2]Children's Hospital of Los Angeles, Los Angeles, California, United States
[3] David Geffen School of Medicine at UCLA, Department of Medicine Statistics Core, University of California, Los Angeles, California, United States

*Corresponding Author:
Tracy Ono

Email: tkono@ucla.edu

Abstract

Background Preconditioning radiation and chemotherapy that patients receive prior to hematopoietic stem cell transplant (HSCT) places them at high risk of complications, including sinusoidal obstruction syndrome (SOS). SOS increases a patient's risk of multi-organ dysfunction and failure. This paper compares heart rate patterns for pediatric patients with SOS and unaffected youth following HSCT.

Methods Heart rate, transplant characteristics, medication, and sociodemographic data gathered from electronic medical records for 180 pediatric patients undergoing HSCT as a treatment for malignancy between January 1, 2015, and January 1, 2019, were evaluated. Real-time heart rate measurements were examined from HSCT to days 14 and 28. Effects of age were assessed by quartiles (6 months-2.5 years, 2.5-6 years, 6-11 years, and 11+ years) for pattern changes comparing SOS-affected children to unaffected children. Multivariable linear regression analysis estimated heart rate, controlling for the effects of SOS, age, time on study, malignancy type, and sociodemographic characteristics.

Results The incidence of SOS was 15.6% (28/180), and diagnosis was made on average at 14.5 days following HSCT. Fully-adjusted linear regression models suggested SOS increased heart rate 1.24- to 1.37-fold over the first 14 days following HSCT across all age quartiles. However, heart rate over the risk period for unaffected children across age quartiles increased at most 1.15-fold. Heart rate patterns were similar when 28 days of data were evaluated. Additionally, hematologic malignancy reflected a statistically significant effect on heart rate estimates in the 14 and 28-day fully adjusted models.

Discussion Day-to-day trends in heart rate patterns following HSCT should be evaluated more closely to improve patient safety. Increasingly greater heart rate, measured routinely in the post-

HSCT period, may be a risk factor for SOS. Earlier detection with prompt treatment may decrease SOS-related morbidity and mortality.

Introduction

Sinusoidal Obstruction Syndrome (SOS) is a severe complication of hematopoietic stem cell transplants (HSCT) with life-threatening implications. Acute injury to the hepatic endothelium triggers a cascade of events that may result in multiorgan dysfunction or failure. SOS usually manifests within 21 days post-HSCT (Cairo et al., 2020). Children are disproportionately at risk of developing SOS than adults, 20-60% vs. 10% (Corbacioglu et al., 2018; Mahadeo et al., 2020). Thirty to 60% of SOS-affected patients will require advanced life support measures to treat severe SOS-induced multi-organ dysfunction (Corbacioglu et al., 2018). Despite advanced support efforts, mortality among patients who progress to severe SOS with multi-organ failure is >80% (Corbacioglu et al., 2019; Yakushijin et al., 2016).

The five aims of quality healthcare are patient safety, cost reduction, health equity, provider well-being, and customer satisfaction (Berwick et al., 2008; Itchhaporia, 2021; Rishi et al., 2015). SOS increases morbidity and mortality among affected children (Faraci et al., 2019). Morbidity and hospital length of stay are positively associated with hospital costs (r=0.77, p<0.0001) (Godara et al., 2020). Earlier detection of SOS in children rendered vulnerable by cancer treatment maximizes the achievement of all five aims.

Background

Pre-transplant conditioning with myeloablative chemotherapy and total body irradiation may damage hepatic endothelium, leading to venous narrowing, sclerosis, and fibrin deposits into hepatic sinusoids (Mohty et al., 2015). Fenestrations in the sinusoidal barrier allow red blood cells and detaching endothelial cells to migrate and obstruct hepatic sinusoidal blood flow (Carreras & Diaz-Ricart, 2011). Progressive obstruction causes fluid retention, overload, and portal venous blood shunting to the abdominal cavity, preceding multi-organ dysfunction (Mohty

et al., 2015; Triplett et al., 2015). Treating severe SOS-associated sequelae often requires advanced support of multiple organs, including vasoactive medications, mechanical ventilatory support (62%), and continuous renal replacement therapy (46%), or death may result (Reiss et al., 2002).

The diagnosis of SOS relies on the identification of a cluster of clinical symptoms. Historically, diagnosis was made based on two diagnostic models. The Baltimore Criteria included hyperbilirubinemia (>2mg/dL) and two or more signs of poor liver function, such as >5% weight gain over the pre-HSCT measure, ascites, or hepatomegaly (Jones et al., 1987). The modified Seattle criterion required evidence of two of five liver failure signs or symptoms within 20 days of HSCT: right upper quadrant pain associated with hepatomegaly, >2% weight gain above the pre-HSCT measure, jaundice, hyperbilirubinemia, and ascites (McDonald et al., 1984; Skeens et al., 2016).

Newer diagnostic strategies rely upon new technologies and newly discovered features of SOS. Some data suggest that 30% of SOS-affected youth do not show higher bilirubinemia measures, and 20% develop SOS 21 or more days after HSCT (Corbacioglu et al., 2020; Faraci et al., 2019). Additionally, some children and adults with SOS develop post-HSCT refractory thrombocytopenia as much as eight days before diagnosis (Embaby et al., 2020). Newer recommendations rely upon single procedures *or* multiple symptom clusters. Histological diagnosis of SOS or increased portal venous wedge pressure are signs supporting the (SOS) diagnosis (Cairo et al., 2020). Similarly, the clinical presence of *any* two symptoms following HSCT supports an SOS diagnosis: hyperbilirubinemia ≥2mg/L, refractory thrombocytopenia, hepatomegaly compared to baseline, unexplained ≥5% weight gain above baseline, ultrasound confirmation of ascites or reversed portal venous flow, and right upper quadrant pain (Cairo et

al., 2020). SOS disease severity, formerly classified as mild to severe, has been transformed to a five-point scale based on the progressive level of multi-organ involvement (Cairo et al., 2020).

Biomarkers, improved diagnostic tools, and innovative treatments comprise the most recent SOS research efforts. Only one medication, defibrotide (DF), has gained approval from the U.S. Food and Drug Administration (FDA) for treating SOS accompanied by renal and pulmonary dysfunction as per its labeled indication (Defitelio, Jazz Pharmaceuticals, Palo Alto, CA). DF as prophylaxis is under investigation. The paucity of effective preventative treatments makes early disease recognition and diagnosis essential to improving patient care and outcomes. Earlier treatment and supportive care may significantly decrease SOS-associated morbidity and mortality, especially if overlooked nurse-sensitive indicators are explored as possible predictors of disease. This paper evaluates heart rate changes in pediatric patients with SOS following HSCT relative to patterns seen in unaffected, otherwise similar youth. Longitudinal changes in heart rate patterns in two premorbid periods, 14 and 28 days following HSCT, were evaluated as risk periods for young patients at risk for SOS.

Methods

Subjects and Setting

A cohort of 180 youth was identified by electronic medical record (EMR) data for children and adolescents, six months to 19 years of age, with underlying malignancy diagnoses, and complete data for their first HSCT performed between January 1, 2015, and January 1, 2019 (Table 1). The cohort was treated at a single pediatric tertiary-care hospital, serving many low socioeconomic households. Institutional Review Board exemption was obtained from Children's Hospital Los Angeles (2020: IRB# CHLA-20-00081) and the University of California, Los Angeles (2020: IRB# 20-000740).

One hundred thirty-five International Classification of Disease codes, version 9 or 10, were used to identify cases of youth treated with HSCT, the underlying diagnosis of malignancy, and the differentiation between youth with SOS or not (Supplemental Table 1). Eligible cases identified from the EMR search were cross-checked against the HSCT provider-team records to verify final inclusion in the study.

Variables

Data from the EMR were obtained for information on demographics, transplant characteristics, vital statistics, and medications. Records dating from admission to discharge or death were evaluated. The exposure of interest was SOS following HSCT, and the outcome of interest was heart rate. Real-time heart rate measurements from the entirety of each child's inpatient clinical care at the time of HSCT were used in these analyses. While exploratory descriptive statistics evaluated a variety of periods, the final analysis focused on the day of transplant (day 0) through the first 14 to 28 days following HSCT. SOS diagnosis is a time-dependent variable that follows HSCT. Thus, we justified each patient's clinical data to their corresponding HSCT date (*zero time*) and evaluated the effect of other time-dependent variables relative to this point (e.g., heart rate).

Confounders and Effect Modifiers

Several variables appeared to be confounders or effect modifiers. Traditional confounders included race (non-White vs. White), sex (male vs. female), age (in quartiles), and ethnicity (non-Hispanic vs. Hispanic). In children, age impacts the expected values of vital statistics such as heart rate. Heart rate is inversely associated with chronological age, and the children were grouped in (age) quartiles: 6 months to 2.5 years, 2.5 to 6 years, 6 to 11 years, and 11 years and above. Poverty was the proxy indicator for socio-economic status (SES) and was based on Los

Angeles County (LAC) Service Planning Areas (SPA). The national prevalence of poverty (15.5%) determined low vs. high SES for this study. Relevant to our study period, SPAs where the prevalence of poverty was below the U.S. Federal Poverty Level in 2017 (i.e., higher income areas, SPAS 2, 3, 5) were compared to those that measured at or above the national level of poverty (i.e., low-income areas, SPAs 1, 4, 6, 7, 8) (LAC Department of Public Health, 2017). Children residing in zip codes outside of LAC were grouped and compared to the LAC high SES SPAs.

Exploratory Characteristics

Conditioning chemotherapy medications were organized and analyzed by class due to the number of medications and the resulting small cell sizes when evaluated individually. Chemotherapy medications were categorized into alkylating agents, purines, and monoclonal antibodies. Medications in each class were alkylating agents – Cyclophosphamide, Carmustine, Busulfan, Thiotepa, and Melphalan. Purine agents included Clofarabine and Fludarabine, and three monoclonal antibodies included Campath, Anti-thymocyte globulin, and Rituximab. In the analysis, purines and monoclonal antibodies were grouped together and compared to the alkylating agents.

Similar to chemotherapy medications, specific malignancies could not explore primary malignant diagnosis due to small sample sizes at that level of specificity. Thus, malignancies were categorized as hematologic malignancies and solid tumors. Hematologic malignancies included leukemias, lymphomas, and myelodysplastic syndromes, while solid tumors were predominantly intracranial tumors but also included germ cell, rhabdoid, Wilms, yolk sac tumors, and retinoblastoma. HSCT type was classified as autologous or allogenic.

Statistical analysis

Descriptive, tabular, and graphical analyses exploring the heart rate patterns among the SOS-affected and unaffected controls were conducted using Statistical Analysis System (SAS) 9.4. Heart rate trends and regression lines were plotted over the first 14 and 28 days following HSCT. In addition, heart rate measurements for affected children were truncated on the day of SOS diagnosis for the 28-day plots (Figures 1 and 2). A sharp, positive slope observed among SOS-affected patients, individually and as age groups, compared to the controls in each age quartile guided the multivariable analyses (Figures 1 and 2, and Supplemental Figures 1 and 2). The effect of SOS on heart rate was time-dependent. SOS (vs. not), time (days) following HSCT infusion, and their interaction were forced into each model as a multivariable model was constructed to predict heart rate over time. Otherwise, covariates were explored stepwise (Table 2.a. and Supplemental Table 2.a.) to predict heart rate. A mixed linear regression model allowed the evaluation of fixed and random effects on heart rate. Variables included in the model were assessed for statistical significance using a p-value ≤ 0.05.

The diagnosis of SOS was the exposure of interest. Risk for SOS is time-dependent, usually within 14 to 28 days following HCST, and younger children are at an increased risk for SOS than older youth (Cairo et al., 2020). The initial multivariable model included SOS, *zero time*, the interaction of SOS with *zero time*, and age quartile. Adding malignancy type alone improved the fit of the model (Table 2.a). Younger age groups were compared to the oldest quartile (referent) for these analyses. Race was categorized as non-White versus White (referent), and findings for non-Hispanic youth were compared to those with Hispanic ethnicity (referent). Poverty was evaluated as LAC low SES and outside LAC, which were explored separately compared to LAC high SES (referent). While the sociodemographic variables did not improve

fit, they were forced into the model to control for possible residual confounding (Table 2.a.) (Gustafson & Greenland, 2006).

We evaluated two- and three-way statistical interaction terms between SOS, age, and *zero time* in the analyses. The deviance statistic suggested these features improved the fit of the model (*fully-adjusted model,* Table 2.b. and Supplemental Table 2.b.). To further validate the heart rate differences between affected and unaffected children within the first 14 days post-HSCT, the same fully-adjusted model was applied to the cohort, analyzing the data through day 28 or SOS diagnosis (Supplemental Table 2). The effect of the two- and three-way interactions on heart rates were applied to the mean heart rate intercept to determine the heart rate trajectories for each age quartile over 14 days and 28 days (Tables 3.a and 3.b). Figures 3.a. and 3.b show the resulting heart rate trajectories. To estimate mean heart rates using model-derived coefficients, including the intercept and two- and three-way statistical interactions, we limited our predictions to reflect the availability of real-time data for each age quartile. For example, for 6 months to 2.5 years old, 9 of 10 children were diagnosed with SOS within the first 14 days after HSCT – limiting our estimates to day 1, day 7, and day 14. In summary, this study evaluated heart rate changes in SOS-affected HSCT children seen over the first 14 days post-HSCT and compared the trajectory to observations when extended to day 28 post-HSCT.

Results

Descriptive analyses for demographic characteristics are shown in Table 1. Ninety-three patients received autologous HSCT (51.7%), and 87 were allogeneic recipients (48.3%). Underlying diagnoses were evaluated in two categories: hematologic malignancies (n=93, 51.7%) and solid tumors (n=87, 48.3%). All patients treated for a solid tumor underwent an

autologous transplant versus 6 (6.5%) and 87 (93.5%) hematologic malignancy patients who were treated with autologous or allogeneic transplants, respectively.

Using the modified Seattle criterion to diagnose SOS, 28 (15.6%) patients, most of whom received an allogeneic HSCT to treat a hematologic malignancy (n=26, 92.8%), were identified (McDonald et al., 1984). SOS was only present in two patients who received an autologous HSCT. The median time to SOS diagnosis was 14.5 days, ranging from four to 41 days. Thirteen patients had mild SOS, 11 were classified as moderate, and four progressed to severe SOS, requiring a transfer to the Pediatric Intensive Care Unit for Continuous Veno-Venous Hemofiltration. Hematologic cancers (28% vs. 2.3%) and allogenic HSCTs (30% vs. 2.2%) were statistically significantly over-represented among children with SOS (p-values<0.0001).

The whole cohort, on average, showed 131 heart rate measurements recorded at a mean interval of 2.7 hours ranging from less than 1 minute to 6.7 hours over 14 days following HSCT. As expected, SOS-affected children had a higher average number of measurements (146 vs. 128 measures) and a slightly shorter average time interval (2.4 vs. 2.7 hours) than controls, likely due to the need for more frequent monitoring as SOS was diagnosed. When the observation period was expanded to 28 days, the cohort recorded an average of 185 heart rate measurements at a mean time interval of 2.8 hours, and children developing SOS similarly showed fewer measurements and shorter intervals between than unaffected controls: (μ) 145 vs. 192, and 2.5 vs. 2.9 hours, respectively. For these estimates, the effect of early diagnosis truncated heart rate measurement frequency and intervals for the analysis, especially among younger children, who were often diagnosed in the first 14 days of observation.

SOS-affected children showed a sharp increase in heart rate following HSCT when compared to unaffected controls during the first 14 days. Stratified linear regression lines

supported this observation, with the effect greatest among the youngest children (Figure 1, Panels A-H). This pattern was reflected in individual (Figures 1 and 2) for 14- and 28-day plots as well as the overall effect on heart rate for each age (quartile) group (Supplemental Figures 1 and 2). Interestingly, the trajectory of heart rate for youth who developed SOS later showed a shallower slope compared to those who developed SOS closer to 14 days following HSCT (Figure 2, Panels A-H).

Multivariable models showed the effect of SOS and other covariates on patient heart rates (Table 2.a). SOS (p=0.0026), *zero time* (p<0.0001), and the interaction (p<0.0001) between the two covariates were shown to have a strong statistically significant impact on heart rates over the first 14 days following HSCT. Age was also statistically significant across all age quartiles, p<0.0001. The strength of these associations formed the initial model to which all other covariates were included. Similar to the univariate analyses, hematologic malignancy and allogenic HSCTs independently displayed a statistically significant impact on heart rates over 14 days, p=0.001 and p=0.010. However, when placed in the multivariable model together, only hematologic malignancy remained statistically significant, p=0.030. This result is likely due to the high correlation between the malignancy and HSCT type covariates. Finally, chemotherapy class and traditional confounders (age, sex, race, ethnicity) and effect modifiers (poverty) did not reflect a statistically significant contribution.

The **fully-adjusted multivariable model** included two- and three-way interactions between SOS, zero time, and age (Table 2.b). The importance of the interactions between SOS, age (quartiles), and zero time on heart rate were reflected in the statistically significant p-values noted in this model. Children under six years of age showed more statistical significance than their older counterparts. This may be reflective of the increased SOS risk among younger

children or due to their shorter periods before diagnosis. Malignancy remained a statistically significant predictor of heart rate in the fully-adjusted model (p=0.003). As seen in the base model, the demographic confounders (sex, race, ethnicity) and effect modifier (poverty) were not statistically significant predictors of heart rate (p-values> 0.05).

From the fully-adjusted model, we estimated heart rates for 14- and 28-day intervals, controlling for malignancy, race, ethnicity, sex, and poverty, among SOS-affected and unaffected children in each age quartile at seven-day intervals beginning at HSCT-day 1. Over 14 days, all patients saw an increase in heart rates over time, and the change among SOS-affected patients was significantly higher than that of their unaffected counterparts (Table 3.a). Among the youngest children, there was a 1.37-fold increase in heart rate for children that developed SOS compared to a 1.03-fold increase among the unaffected over the first 14 days. Although the older children also displayed a change, increases in other (age) quartiles were less stark. Age quartile two (Q2) saw a 1.27-fold increase among the affected versus a 1.14-fold increase in the unaffected (Figure 3.a). Likewise, heart rates in SOS-affected children 6 to 11 years (age, Q3) and 11+ years (age, Q4) showed similar increases when compared to youth unaffected by SOS, 1.30- vs. 1.15-fold (Q3) and 1.24- vs. 1.1-fold (Q4) (Figure 3.a).

The effect of SOS on the 28-day heart rate trajectory mirrored increases seen over the first 14 days of observation. In the SOS-affected group, the trajectory time period of each age quartile differs to reflect the number of days premorbid real-time heart rate data was available. The youngest children (age quartile 1) had the shortest time to diagnosis period (14 days) and showed a 1.36-fold increase in heart rates between days 1 and 14. The premorbid phase for affected children in age quartiles two and four was 21 days; each (quartile) displayed a 1.15- and 1.35-fold increase between days 1 and 21. Quartile three was the sole age group (6-11 years)

whose premorbid phase spanned all 28 days. Heart rates for SOS-affected children in (age) quartile three reflected a 1.31-fold increase between days 1 and 28. There was a minimal change to the heart rates for unaffected children through day 28, albeit point estimates suggested a slightly lower heart rate on day 28 than on day one (Table 3.b and Figure 3.b). Of note, lower heart rates were observed among the SOS-affected children on day one across all age groups in both the 14- and 28-day trajectories compared to their unaffected counterparts.

Discussion

This may be the first study to find heart rate patterns associated with SOS, using data routinely collected in clinical settings for youth under 19 years of age undergoing HSCT treatments, of whom 15.6% developed SOS. While heart rate may be responsive to clinical therapies and ambient conditions, including auditory and physical stimulation, measurements evaluated were collected at expected routine intervals in an acute care setting. Through this study, we discovered that heart rate changes among children who developed SOS were early and routinely evaluated by nurses (nurse-sensitive predictor).

Previous research supports that routine vital sign surveillance per the Pediatric Early Warning System (PEWS) score predicts acute clinical deterioration that may lead to advanced life support measures following HSCT (Agulnik et al., 2020). Ahmad and Mahadeo (2021) discussed multiorgan dysfunction among HSCT patients during the post-transplant period and described the absence of a screening tool for patients who suffer mild effects of complications to HSCT treatment who may not require transfer to the Intensive Care Unit. Consequently, they noted that further study into different ways to assess hemodynamic alterations may assist in creating new monitoring approaches for HSCT patients (Ahmad & Mahadeo, 2021).

Some investigations report findings that support cardiac effects following HSCT (Kobayashi et al., 2020; Moriyama et al., 2022). For example, children treated with allogenic HSCTs who received cumulatively high doses of anthracyclines or who developed graft versus host disease (GVHD) showed 4% and 87% higher odds of cardiac dysfunction within 9 to 35 days of HSCT than unexposed comparators (Moriyama et al., 2022). Additionally, cardiac autonomic nervous system dysfunction was identified in 24-hour Holter monitoring of low-frequency power was lower following HSCT (445.7 ms) than before chemotherapy conditioning (773.4 ms, p=0.030) (Kobayashi et al., 2020). Our findings may be the first report evaluating routinely collected heart rate monitoring for patterns specifically preceding SOS diagnosis following HSCT.

A limitation of this approach is its focus on heart rates as an association with children who developed SOS during the first 28 days of care following HSCT. However, this stresses the importance of a nurse-sensitive measure that focuses on patient care and may predict the progression to SOS. These analyses may trigger provider suspicions for patients at risk of developing SOS. Another limitation was that this study took place at a single tertiary specialty hospital for children with many pediatric patients who receive HSCT as a treatment for malignancy. Nonetheless, all subjects in this sample received their first HSCT. Future studies across all diagnoses treated with HSCT and among patients who experienced multiple transplants will further evaluate the relationship of heart rate patterns among SOS-affected children. Sources of misclassification bias may be important to this study. Most data that predicted heart rate patterns associated with SOS were recorded electronically and sent directly to the EMR. Additionally, dichotomous and polychotomous variables, such as sex and age, are redundantly self-reported and recorded across many visits, and discrepancies would likely be found and

corrected. Thus, misclassification may be infrequent, and bias may be small. Nonetheless, misclassification is often associated with self-report data, and bias introduced into the analysis may be difficult to predict (Alexander, 2015).

Conclusion

Early identification and treatment are paramount for improving outcomes among patients who develop SOS. Future research to assess heart rate patterns using standardized protocols before and during preconditioning and after HSCT, possibly using Holter monitoring, may better contextualize post-HSCT changes associated with risk for SOS. Early recognition that improves detection and treatment or supports prophylactic treatment may improve survival and diminish disease among children treated using HSCT. Currently, DF treatment is limited to SOS with renal or pulmonary involvement (Defitelio, Jazz Pharmaceuticals, Palo Alto, CA).

Scrutiny of heart rate pattern changes from HSCT patients' baselines should not be overlooked. This study identified acute increases in heart rate values among SOS-affected HCST patients that were not observed in unaffected children. Using this data to identify patients with an acute change from their pre-HSCT baseline may assist in earlier SOS diagnosis. The importance of this work may improve the quality and quantity of life, especially for the very youngest children affected by cancer and treated using HSCT (Sikka et al., 2015). If sustained over time and study groups, these findings will improve patient safety, customer satisfaction, cost reduction, provider well-being, and health equity.

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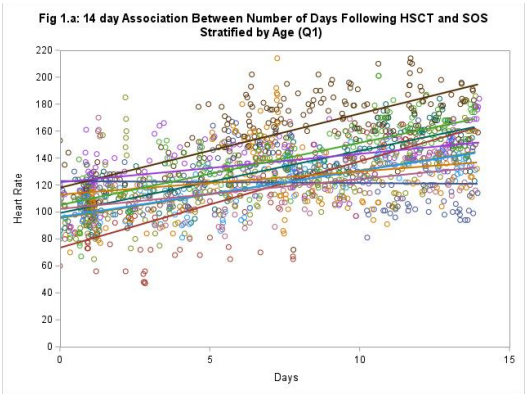
Angeles Department of Medicine Statistics Core, and the Office of Advanced Research Computing, Statistical Methods, and Data Analytics.

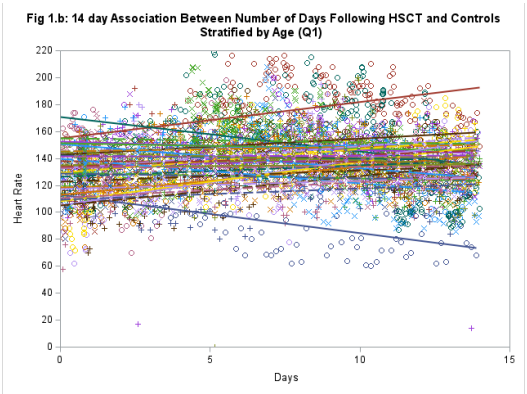
Table 1. Study Cohort Demographics

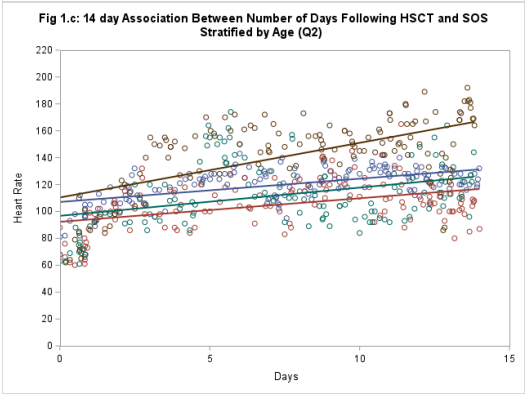
	Total Sample (n=180)		SOS (n=28)		Not SOS (n=152)		
	n	%	n	%	n	%	*p*-value
Age (Quartiles)							
6 months – 2.5 years (Q1)	45	25.0	10	22.2	35	77.8	0.3655
2.5 years – 6 years (Q2)	46	25.6	4	8.7	42	91.3	
6 years – 11 years (Q3)	44	24.4	7	15.9	37	84.1	
11 years – 19 years (Q4)	45	25.0	7	15.6	38	84.4	
Race							
White	78	43.3	15	19.2	63	80.8	0.2342
Non-White	102	56.7	13	12.7	89	87.3	
Ethnicity							
Hispanic	77	42.8	14	18.2	63	81.8	0.4006
Non-Hispanic	103	57.2	14	13.6	89	86.4	
Sex							
Male	89	49.4	15	16.9	74	83.1	0.6346
Female	91	50.6	13	14.3	78	85.7	
HSCT Type							
Autologous	93	51.7	2	2.2	91	97.8	<0.0001*
Allogeneic	87	48.3	26	30.0	61	70.0	
Malignancy Type							
Hematologic	93	51.7	26	28.0	67	72.0	<0.0001*
Solid Tumor	87	48.3	2	2.3	85	97.7	
Chemotherapy Class							
Alkylating Agents	162	90.0	25	15.4	137	84.6	0.8910
Purines/ monoclonal antibodies	18	10.0	3	16.7	15	83.3	
Poverty							
LAC low SES	72	40.0	8	11.1	64	88.9	0.3523
LAC high SES	54	30.0	11	20.4	43	79.6	
Outside LAC	54	30.0	9	16.7	45	83.3	

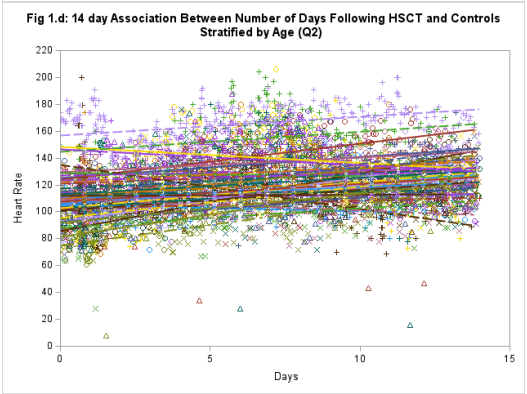
* $p \leq 0.05$ LAC=Los Angeles County, SES=socioeconomic status

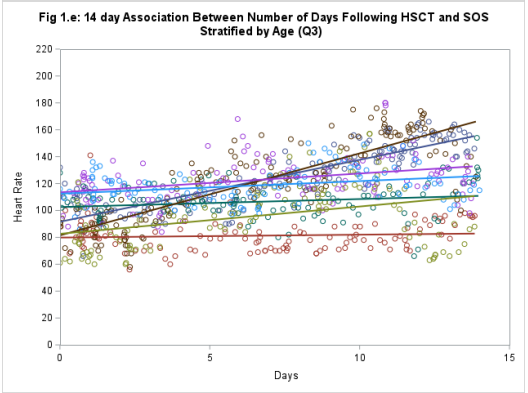
Figure 1. Heart Rate Scatter Plot to Day 14 by Age Quartile

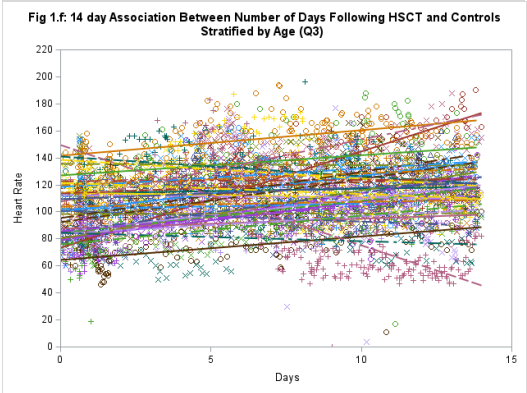


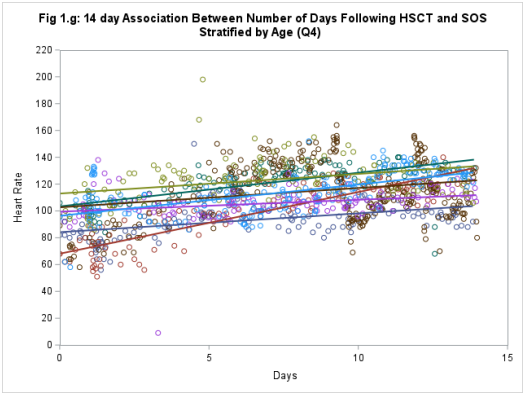












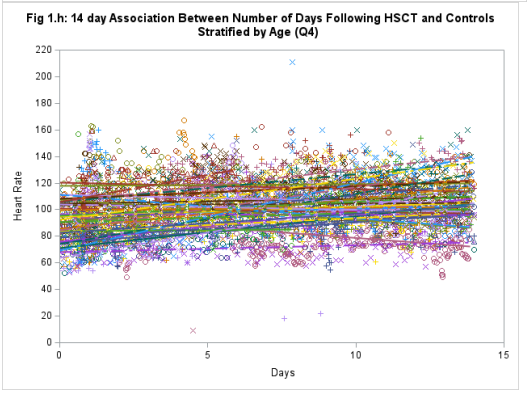
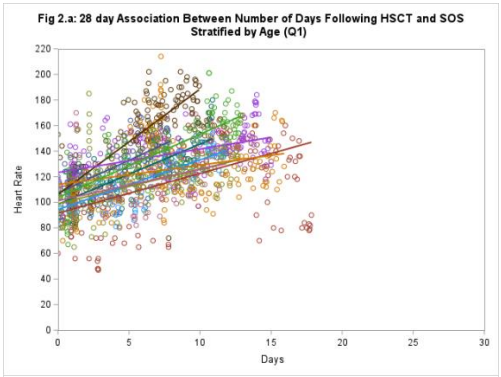
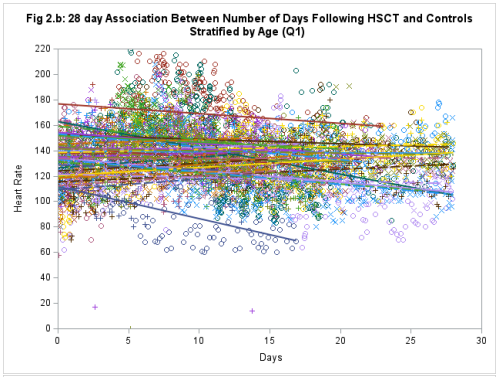
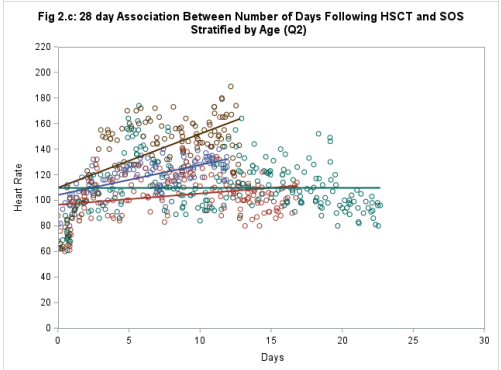
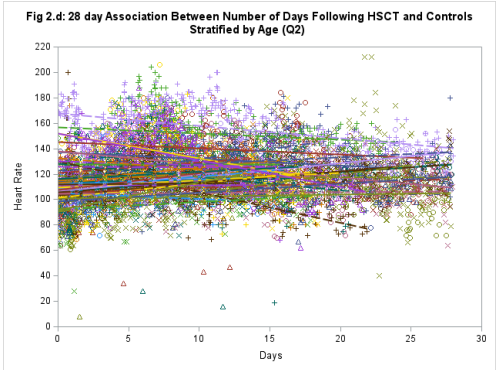


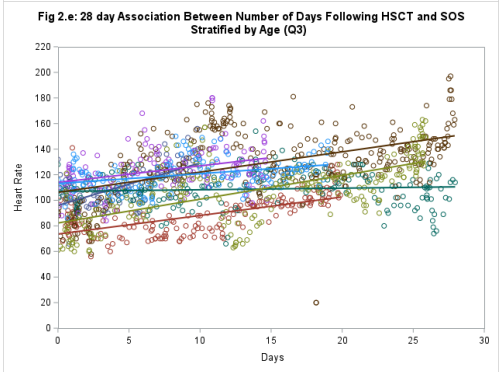
Figure 2. Heart Rate Scatter Plot to SOS Diagnosis or Day 28 by Age Quartile

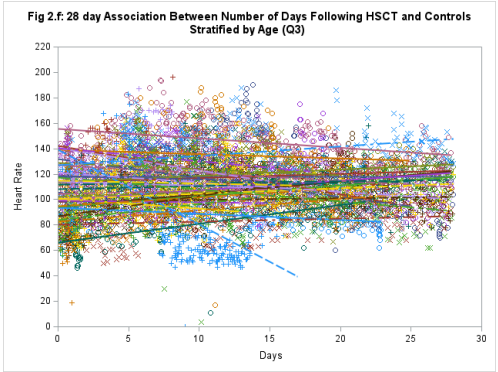


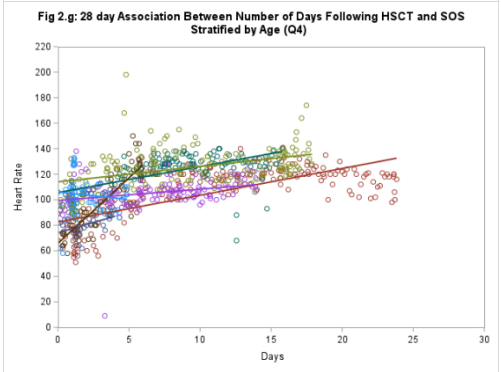












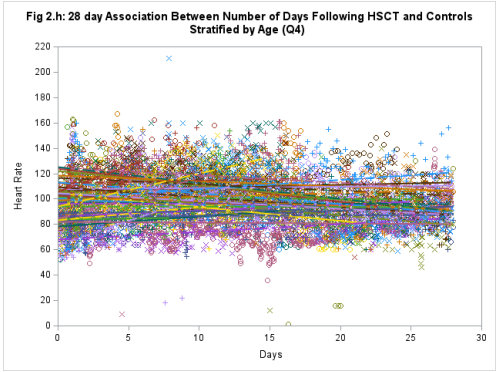


Table 2.a. 14-Day Multivariable Regression Models

Covariates	Mean Heart Rate, (Standard Error) (*p*-value)										
	Model 1	**INITIAL MODEL**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**	**Model 8**	**Model 9**	**Model 10**	**BASE MODEL**
HR Intercept	110.75	96.6420	96.0581	102.39	100.28	97.5248	97.7083	96.4169	98.5641	103.03	106.12
SOS											
SOS-Affected (vs. unaffected)	-11.5227, (3.8201) (0.0026)*	-13.2153, (3.0231) (<0.0001)*	-13.2104, (3.0313) (<0.0001)*	-9.3938, (3.1741) (0.0031)*	-9.9761, (3.2292) (0.002)*	-13.0942, (3.0296) (<0.0001)*	-13.4024, (3.0422) (<0.0001)*	-13.1870, (3.0346) (<0.0001)*	-13.2918, (3.0408) (<0.0001)*	-9.7942, (3.1997) (0.0022)*	-9.1069, (3.2468) (0.0050)*
Zero time (continuous)	0.9049, (0.03230) (<0.0001)*	0.9043, (0.0323) (<0.0001)*	0.9043, (0.0313) (<0.0001)*	0.9045, (0.03230) (<0.0001)*	0.9045, (0.03230) (<0.0001)*	0.9042, (0.03230) (<0.0001)*	0.9042, (0.03230) (<0.0001)*	0.9043, (0.03230) (<0.0001)*	0.9041, (0.03230) (<0.0001)*	0.9045, (0.03230) (<0.0001)*	0.9043, (0.03230) (<0.0001)*
SOS*Zero time* (interaction)	1.8103, (0.07582) (<0.0001)*	1.8109, (0.07582) (<0.0001)*	1.8109, (0.07582) (<0.0001)*	1.8106, (0.07582) (<0.0001)*	1.8106, (0.07582) (<0.0001)*	1.8109, (0.07582) (<0.0001)*	1.8109, (0.07582) (<0.0001)*	1.8109, (0.07582) (<0.0001)*	1.8111, (0.07582) (<0.0001)*	1.8107, (0.07582) (<0.0001)*	1.8108, (0.07582) (<0.0001)*
Age quartile											
Quartile 1 (6 months - 2.5 years)		31.3475, (3.0296) (<0.0001)*	31.2175, (3.1092) (<0.0001)*	27.7458, (3.1531) (<0.0001)*	29.3394, (3.0795) (<0.0001)*	31.1434, (3.0428) (<0.0001)*	31.0463, (3.0713) (<0.0001)*	31.3360, (3.0385) (<0.0001)*	31.0428, (3.0381) (<0.0001)*	27.0819, (3.2228) (<0.0001)*	26.6841, (3.2201) (<0.0001)*
Quartile 2 (2.6 - 6 years)		17.3474, (3.0145) (<0.0001)*	17.2177, (3.0941) (<0.0001)*	13.6777, (3.1470) (<0.0001)*	15.3200, (3.0671) (<0.0001)*	17.3744, (3.0176) (<0.0001)*	16.9741, (3.0759) (<0.0001)*	17.2788, (3.0427) (<0.0001)*	17.2187, (3.0169) (<0.0001)*	12.9829, (3.2234) (<0.0001)*	13.0485, (3.2086) (<0.0001)*
Quartile 3 (6.1 - 11 years)		8.4995, (3.0589) (<0.0001)*	8.4723, (3.0705) (0.0058)*	6.9230, (3.0181) (0.0218)*	8.0907, (3.0122) (0.0072)*	8.5405, (3.0623) (0.0053)*	8.2535, (3.0883) (0.0075)*	8.4789, (3.0692) (0.0057)*	8.2101, (3.0684) (0.0075)*	6.1846, (6.2010) (0.3186)*	6.2835, (3.0612) (0.0401)*
Quartile 4 [reference group 0] (11.1 years +)		0	0	0	0	0	0	0	0	0	0
Chemotherapy Class											
Alkylating (vs. purines/monoclonal antibodies)			0.7289, (3.7124) (0.8444)								
Malignancy Type											
Hematologic (vs. Solid tumors)				-7.9344, (2.4531) (0.0012)*						-13.8047, (6.3766) (0.0304)*	-8.3114, (2.4978) (0.0009)*
HSCT Type											
Allogenic (vs. Autologous)					-6.2065, (2.4092) (0.0100)*					6.1846, (6.2010) (0.3186)	
Sex											
Male (vs. Female)						-1.7635, (2.1617) 0.4146					-2.2422, (2.1323) (0.2930)
Race											
Non-white (vs. White)							-1.4151, (2.2241) (0.5246)				-1.1450, (2.2108) (0.6045)
Ethnicity											
Non-Hispanic (vs. Hispanic)								0.4319, (2.1917) (0.8438)			0.4062, (2.2027) (0.8537)
Poverty											
LAC low SES (vs. LAC < national poverty prevalence (15.2%)									-1.4422, (2.6060) (0.5800)		-0.4473, (2.5962) (0.8632)
Outside LAC (vs. LAC < national poverty prevalence (15.2%)									-3.8417, (2.7714) (0.1657)		-4.2913, (2.7114) (0.1135)
Deviance Statistic Model Comparison	NS	<0.0001* (1 vs INITIAL)	NS	0.0002* (INITIAL vs 4)	0.00148* (INITIAL vs 5)	NS	NS	NS	NS	NS	1.0E-5* (INITIAL vs BASE)

*$p < 0.05$ HR heart rate, LAC Los Angeles County, SES socio-economic status

Table 2.b. 14-Day Multivariable Interaction Model

Covariate	FULLY ADJUSTED MODEL Mean HR, (Standard Error) (p-value)
HR Intercept	104.84
SOS	
Affected (vs. unaffected)	1.3963, (5.9925) (0.8158)
Zero time (continuous)	0.8828, (0.06168) (<0.0001)*
SOS*Zero time (interaction)	1.1465, (0.1501) (<0.0001)*
Age	
Quartile 1 (6 months - 2.5 years)	32.3718, (3.7235) (<0.0001)*
Quartile 2 (2.6 - 6 years)	11.7986, (3.4946) (0.0007)*
Quartile 3 (6.1 - 11 years)	5.9382, (3.4406) (0.0844)
Quartile 4 (11.1 years +) [reference group 0]	0
Interaction of SOS by Age Quartile	
SOS*Age quartile 1	-22.9501, (7.9692) (0.0040)*
SOS*Age quartile 2	-9.0913, (9.6046) (0.3439)
SOS*Age quartile 3	-7.3832, (8.4653) (0.3831)
SOS*Age quartile 4	0
Interaction of Time by Age Quartile	
*Zero time*Age quartile 1	-0.5568, (0.09035) (<0.0001)*
*Zero time*Age quartile 2	0.4166, (0.08862) (<0.0001)*
*Zero time*Age quartile 3	0.2001, (0.09058) (0.0272)*
*Zero time*Age quartile 4	0
3-way Interaction of SOS, Time by Age Quartile	
SOS*Zero time*Age quartile 1	1.9545, (0.1975) (<0.0001)*
SOS*Zero time*Age quartile 2	-0.08154, (0.2431) (0.7373)
SOS*Zero time*Age quartile 3	0.2490, (0.2190) (0.2554)
SOS*Zero time*Age quartile 4	0
Malignancy Type	
Hematologic (vs. Solid tumors)	-7.9220, (2.5754) (0.0021)*
Sex	
Male (vs. Female)	-2.1519, (2.1568) (0.3184)
Race	
Non-white (vs. White)	-0.9801, (2.2355) (0.6611)
Ethnicity	
Non-Hispanic (vs. Hispanic)	0.3251, (2.2348) (0.8844)
Poverty	
LAC low SES (vs. LAC <_national poverty prevalence (15.2%)	-0.3946, (2.6186) (0.8802)
Outside LAC (vs. LAC <_national poverty prevalence (15.2%)	-4.1178, (2.7308) (0.1316)
Deviance Statistic Model Comparison	<0.0001* (BASE vs FULLY ADJUSTED)

*$p \leq 0.05$ LAC Los Angeles County, SES socio-economic status, HR heart rate

Table 3.a. 14-Day Heart Rate Trajectory															
SOS Affected															
Age Quartile 1	**Day 1**	**Day 7**	**Day 14**	**Age Quartile 2**	**Day 1**	**Day 7**	**Day 14**	**Age Quartile 3**	**Day 1**	**Day 7**	**Day 14**	**Age Quartile 4**	**Day 1**	**Day 7**	**Day 14**
Intercept	104.84	104.84	104.84		104.84	104.84	104.84		104.84	104.84	104.84		104.84	104.84	104.84
SOS Affected	1.3963	1.3963	1.3963		1.3963	1.3963	1.3963		1.3963	1.3963	1.3963		1.3963	1.3963	1.3963
Zero time	0.8828	6.1796	12.3592		0.8828	6.1796	12.3592		0.8828	6.1796	12.3592		0.8828	6.1796	12.3592
SOS*Zero time	1.1465	8.0255	16.051		1.1465	8.0255	16.051		1.1465	8.0255	16.051		1.1465	8.0255	16.051
SOS*Age	-22.9501	-22.9501	-22.9501		-9.0913	-9.0913	-9.0913		-7.3832	-7.3832	-7.3832		0	0	0
Zero time*Age	-0.5568	-3.8976	-7.7952		0.4166	2.9162	5.8324		0.2001	1.4007	2.8014		0	0	0
SOS*Zero time*Age	1.9545	13.6815	27.363		-0.08154	-0.57078	-1.14156		0.249	1.743	3.486		0	0	0
Age: 0.6-2.5 years	32.3718	32.3718	32.3718	**Age: 2.6-6 years**	11.7986	11.7986	11.7986	**Age: 6.1-11 years**	5.9382	5.9382	5.9382	**Age: 11-19 years**	0	0	0
Predicted Heart Rate	**119.085**	**139.647**	**163.636**		**111.308**	**125.4941**	**142.0446**		**107.2697**	**122.1401**	**139.4889**		**108.2656**	**120.4414**	**134.6465**
Unaffected															
Age Quartile 1	**Day 1**	**Day 7**	**Day 14**	**Age Quartile 2**	**Day 1**	**Day 7**	**Day 14**	**Age Quartile 3**	**Day 1**	**Day 7**	**Day 14**	**Age Quartile 4**	**Day 1**	**Day 7**	**Day 14**
Intercept	104.84	104.84	104.84		104.84	104.84	104.84		104.84	104.84	104.84		104.84	104.84	104.84
SOS Affected	0	0	0		0	0	0		0	0	0		0	0	0
Zero time	0.8828	6.1796	12.3592		0.8828	6.1796	12.3592		0.8828	6.1796	12.3592		0.8828	6.1796	12.3592
SOS*Zero time	0	0	0		0	0	0		0	0	0		0	0	0
SOS*Age	0	0	0		0	0	0		0	0	0		0	0	0
Zero time*Age	-0.5568	-3.8976	-7.7952		0.4166	2.9162	5.8324		0.2001	1.4007	2.8014		0	0	0
SOS*Zero time*Age	0	0	0		0	0	0		0	0	0		0	0	0
Age: 0.6-2.5 years	32.3718	32.3718	32.3718	**Age: 2.6-6 years**	11.7986	11.7986	11.7986	**Age: 6.1-11 years**	5.9382	5.9382	5.9382	**Age: 11-19 years**	0	0	0
Predicted Heart Rate	**137.5378**	**139.4938**	**141.7758**		**117.938**	**125.7344**	**134.8302**		**111.8611**	**118.3585**	**125.9388**		**105.7228**	**111.0196**	**117.1992**

Figure 3.a. 14-Day Heart Rate Trajectory

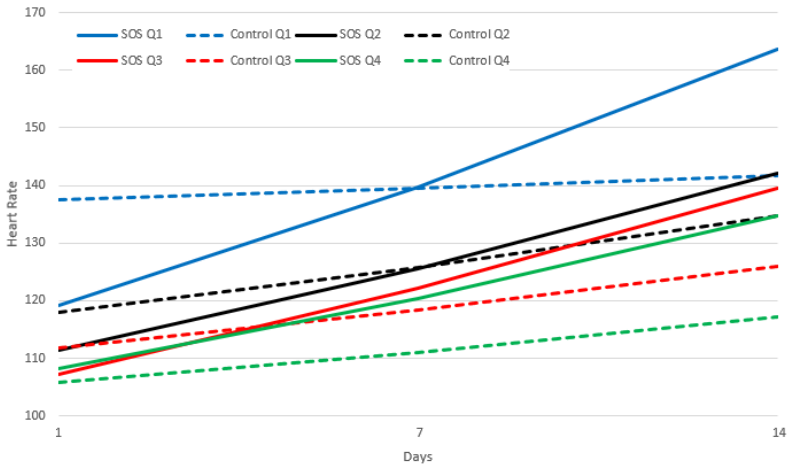


Table 3.b.28-Day Heart Rate Trajectory

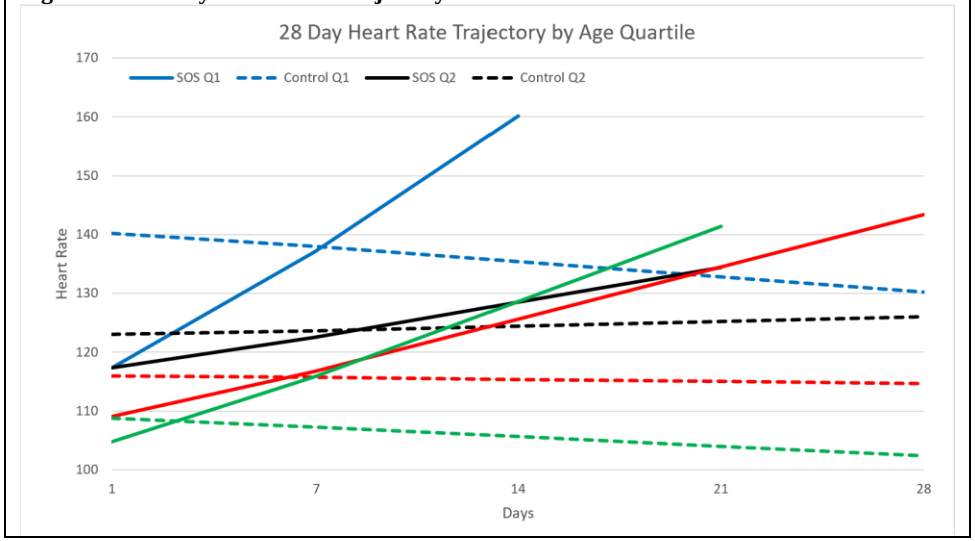
SOS Affected

Age Quartile 1	Day 1	Day 7	Day 14	Age Quartile 2	Day 1	Day 7	Day 14	Day 21	Age Quartile 3	Day 1	Day 7	Day 14	Day 21	Day 28	Age Quartile 4	Day 1	Day 7	Day 14	Day 21
Intercept	108.96	108.96	108.96		108.96	108.96	108.96	108.96		108.96	108.96	108.96	108.96	108.96		108.96	108.96	108.96	108.96
SOS Affected	-5.9802	-5.9802	-5.9802		-5.9802	-5.9802	-5.9802	-5.9802		-5.9802	-5.9802	-5.9802	-5.9802	-5.9802		-5.9802	-5.9802	-5.9802	-5.9802
Zero time	-0.236	-1.652	-3.304		-0.236	-1.652	-3.304	-4.956		-0.236	-1.652	-3.304	-4.956	-6.608		-0.236	-1.652	-3.304	-4.956
SOS*Zero time	2.0669	14.4683	28.9366		2.0669	14.4683	28.9366	43.4049		2.0669	14.4683	28.9366	43.4049	57.8732		2.0669	14.4683	28.9366	43.4049
SOS*Age	-20.5769	-20.5769	-20.5769		-0.3576	-0.3576	-0.3576	-0.3576		-2.2589	-2.2589	-2.2589	-2.2589	-2.2589		0	0	0	0
Zero time*Age	-0.1352	-0.9464	-1.8928		0.3471	2.4297	4.8594	7.2891		0.1874	1.3118	2.6236	3.9354	5.2472		0	0	0	0
SOS*Zero time*Age	1.5949	11.1643	22.3286		-1.3254	-9.2778	-18.5556	-27.8334		-0.7477	-5.2339	-10.4678	-15.7017	-20.9356		0	0	0	0
Age: 0.6-2.5 years	31.6299	31.6299	31.6299	**Age: 2.6-6 years**	13.9225	13.9225	13.9225	13.9225	**Age: 6.1-11 years**	7.0879	7.0879	7.0879	7.0879	7.0879	**Age: 11-19 years**	0	0	0	0
Predicted Heart Rate	**117.3234**	**137.067**	**160.1012**		**117.3973**	**122.5129**	**128.4811**	**134.4493**		**109.0794**	**116.703**	**125.5972**	**134.4914**	**143.3856**		**104.8107**	**115.7961**	**128.6124**	**141.4287**

Unaffected

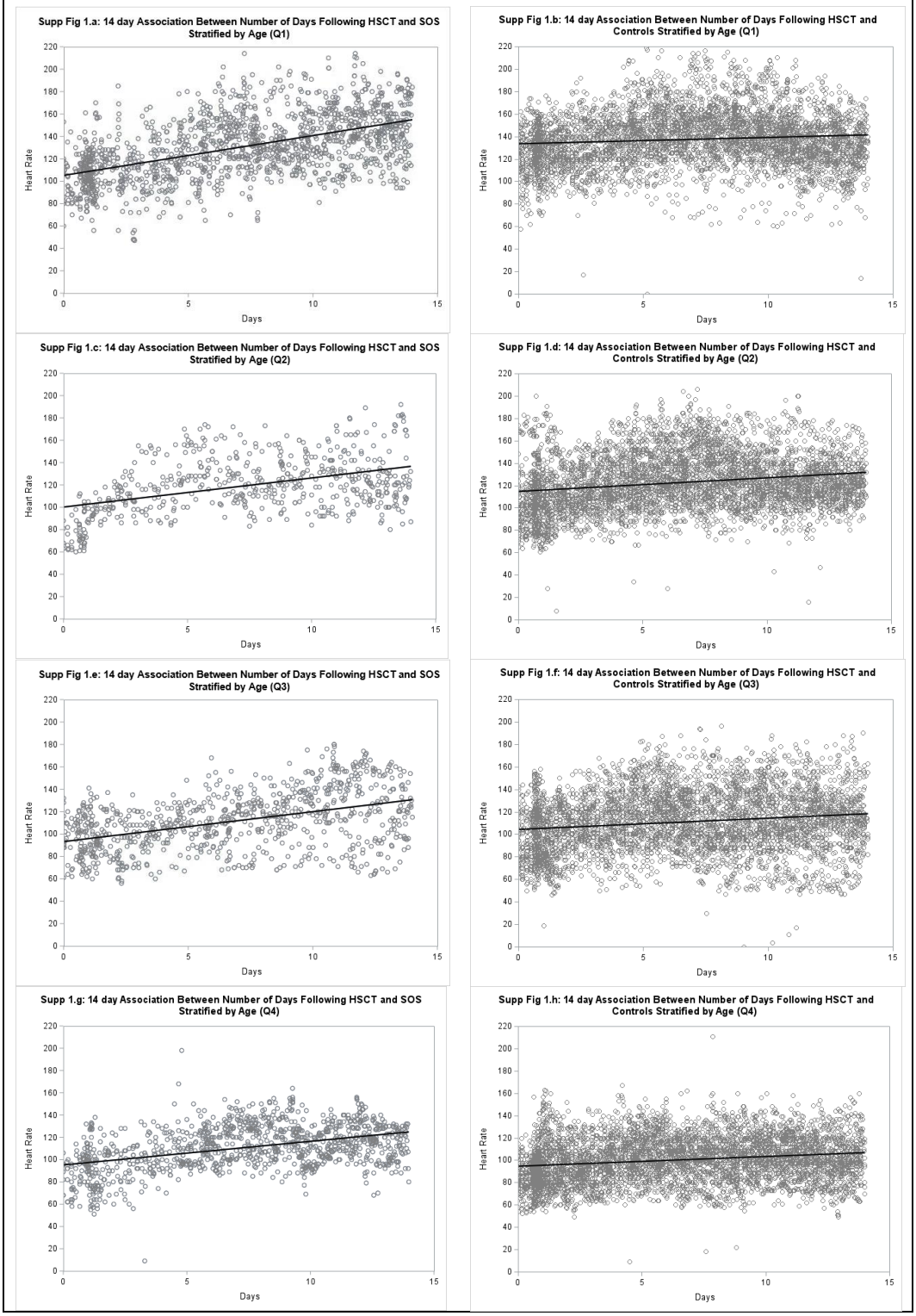
Age Quartile 1	Day 1	Day 7	Day 14	Day 21	Day 28	Age Quartile 2	Day 1	Day 7	Day 14	Day 21	Day 28	Age Quartile 3	Day 1	Day 7	Day 14	Day 21	Day 28	Age Quartile 4	Day 1	Day 7	Day 14	Day 21	Day 28
Intercept	108.96	108.96	108.96	108.96	108.96		108.96	108.96	108.96	108.96	108.96		108.96	108.96	108.96	108.96	108.96		108.96	108.96	108.96	108.96	108.96
SOS Affected	0	0	0	0	0		0	0	0	0	0		0	0	0	0	0		0	0	0	0	0
Zero time	-0.236	-1.652	-3.304	-4.956	-6.608		-0.236	-1.652	-3.304	-4.956	-6.608		-0.236	-1.652	-3.304	-4.956	-6.608		-0.236	-1.652	-3.304	-4.956	-6.608
SOS*Zero time	0	0	0	0	0		0	0	0	0	0		0	0	0	0	0		0	0	0	0	0
SOS*Age	0	0	0	0	0		0	0	0	0	0		0	0	0	0	0		0	0	0	0	0
Zero time*Age	-0.1352	-0.9464	-1.8928	-2.8392	-3.7856		0.3471	2.4297	4.8594	7.2891	9.7188		0.1874	1.3118	2.6236	3.9354	5.2472		0	0	0	0	0
SOS*Zero time*Age	0	0	0	0	0		0	0	0	0	0		0	0	0	0	0		0	0	0	0	0
Age: 0.6-2.5 years	31.6299	31.6299	31.6299	31.6299	31.6299	**Age: 2.6-6 years**	13.9225	13.9225	13.9225	13.9225	13.9225	**Age: 6.1-11 years**	7.0879	7.0879	7.0879	7.0879	7.0879	**Age: 11-19 years**	0	0	0	0	0
Predicted Heart Rate	**140.2187**	**137.9915**	**135.3931**	**132.7947**	**130.1963**		**122.9936**	**123.6602**	**124.4379**	**125.2156**	**125.9933**		**115.9993**	**115.7077**	**115.3675**	**115.0273**	**114.6871**		**108.724**	**107.308**	**105.656**	**104.004**	**102.352**

Figure 3.b. 28-Day Heart Rate Trajectory

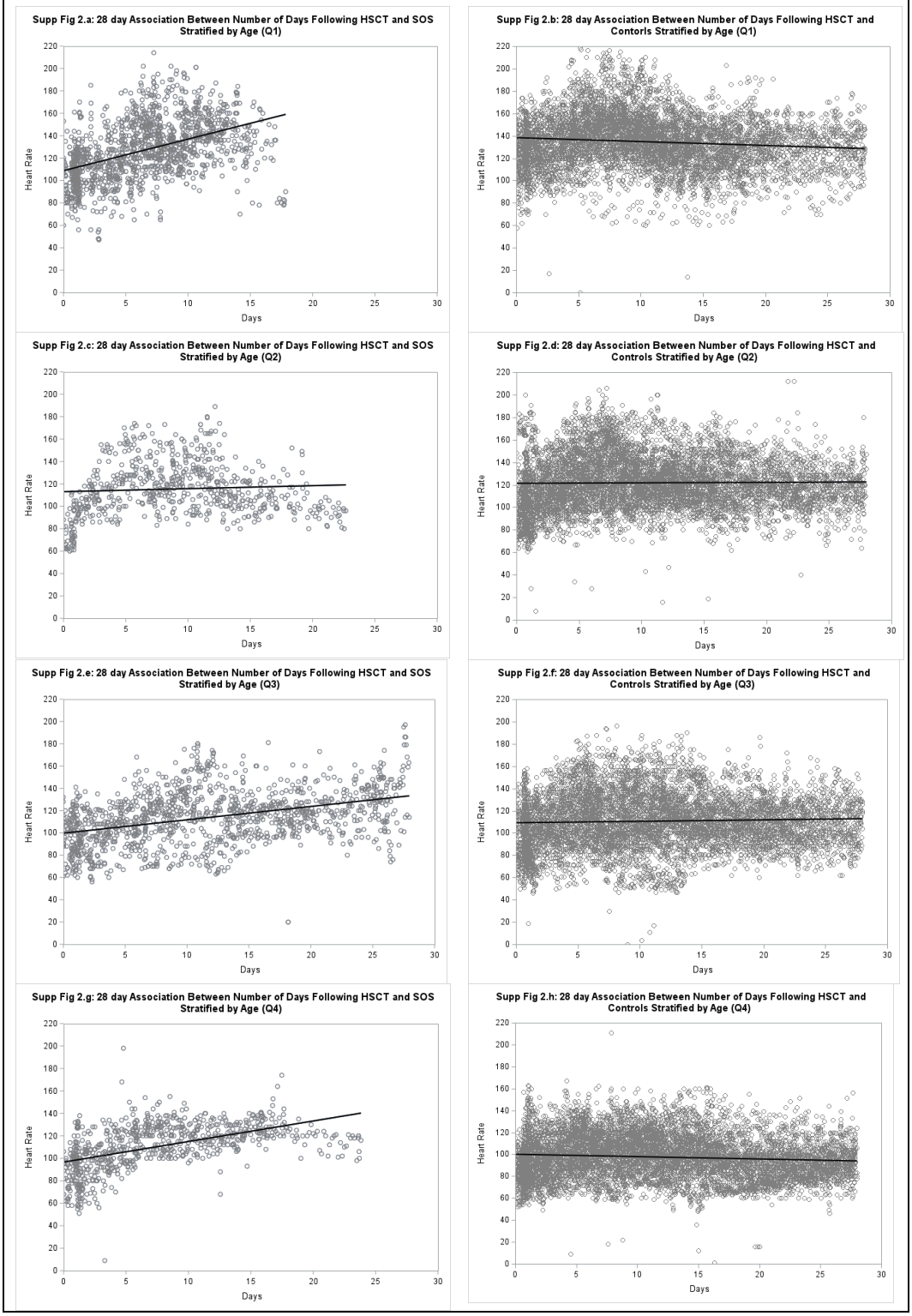


Supplemental Table 1. ICD 9 and 10 Codes				
Code Type	**ICD 9**		**ICD 10**	
	Code	Description	Code	Description
Malignant Neoplasms	176-189	Malignant neoplasms of genitourinary organs	C51-68	Malignant neoplasms of genitourinary organs
	190-199	Malignant neoplasm of other and unspecified sites	C69-72	Malignant neoplasms of eye, brain, and other parts of central nervous system
	200-209	Malignant neoplasm of lymphatic and hematopoietic tissue	C81-96	Malignant neoplasms of lymphoid, hematopoietic, and related tissue
	235-239	Neoplasms of uncertain behavior or nature	D37-48	Neoplasms of uncertain behavior, polycythemia vera, and myelodysplastic syndromes
SOS	573	Other disorders of the liver	K71-77	Diseases of liver
HSCT	v42.8-42.9	Organ and tissue replaced by transplant	Z94	Bone marrow and stem cell transplant status
			PCS 3023X0 30240X0, 0250X0, 30260X0, 0233X0, 30243X0, 0253X0, 30260X0, 30263X0	Autologous cord blood stem cells
			PCS 30250G1, X1, Y1 30253G1, X1, Y1 30260G1, X1, Y1 30263G1, X1, Y1	Non-autologous bone marrow, cord blood, stem cells, hematopoietic stem cells
			PCS 30230G2, X2, Y2 30233G2, X2, Y2 30240G2, X2, Y2 30243G2, X2, Y2	Allogeneic related bone marrow, cord blood stem cells, hematopoietic stem cells
			PCS 30230G3, X3, Y3 30233G3, X3, Y3 30240G3, X3, Y3 30243G3, X3, Y3	Allogeneic unrelated bone marrow, cord blood stem cells, hematopoietic stem cells
			PCS 30230G4, X4, Y4 30233G4, X4, Y4 30240G4, X4, Y4 30243G4, X4, Y4	Allogeneic unspecified bone marrow, cord blood stem cells, hematopoietic stem cells

Supplemental Figure 1. Heart Rate Scatter Plot to Day 14 by Age Quartile



Supplemental Figure 2. Heart Rate Scatter Plot to SOS Diagnosis or Day 28 by Age Quartile



Supplemental Table 2.a. 28-Day Multivariable Regression Models

Covariates	Mean Heart Rate, (Standard Error) (*p*-value)									
	Model 1	**INITIAL MODEL**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**	**Model 8**	**Model 9**	**BASE MODEL**
HR Intercept	116.70	101.80	102.58	105.65	104.06	102.52	103.29	101.44	103.80	109.61
SOS										
SOS-Affected (vs. unaffected)	-12.2309, 3.6526 (0.0008)*	-13.8152, 2.7495 (<0.0001)*	-13.8220, 2.7566 (<0.0001)*	-11.2433, 2.9245 (0.0001)*	11.7886, 2.9710 (<0.0001)*	-13.7167, 2.7565 (<0.0001)*	-14.0777, 2.7639 (<0.0001)*	-13.7712, 2.7594 (<0.0001)*	-13.8840, 2.7606 (<0.0001)*	-11.1247, 2.9845 (<0.0001)*
Zero time (continuous)	-0.1365, 0.01551 (<0.0001)*	-0.1356, 0.01551 (<0.0001)*	-0.1356, 0.01551 (<0.0001)*	-0.1345, 0.01551 (<0.0001)*	-0.1347, 0.01551 (<0.0001)*	-0.1355, 0.01551 (<0.0001)*	-0.1355, 0.01551 (<0.0001)*	-0.1355, 0.01551 (<0.0001)*	-0.1358, 0.01551 (<0.0001)*	-0.1346, 0.01551 (<0.0001)*
SOS**Zero time* (interaction)	1.7737, 0.05349 (<0.0001)*	1.7721, 0.05344 (<0.0001)*	1.7723, 0.05345 (<0.0001)*	1.7711, 0.05344 (<0.0001)*	1.7712, 0.05344 (<0.0001)*	1.7720, 0.05344 (<0.0001)*	1.7724, 0.05344 (<0.0001)*	1.7722, 0.05344 (<0.0001)*	1.7728, 0.05344 (<0.0001)*	1.7720, 0.05344 (<0.0001)*
Age quartile										
Quartile 1 (6 months - 2.5 years)		32.0513, 2.7614 (<0.0001)*	32.2249, 2.8332 (<0.0001)*	29.6306, 2.9112 (<0.0001)*	30.7948, 2.8390 (<0.0001)*	31.8848, 2.7745 (<0.0001)*	31.6299, 2.7962 (<0.0001)*	32.0333, 2.7689 (<0.0001)*	31.7242, 2.7640 (<0.0001)*	28.4965, 2.9658 (<0.0001)*
Quartile 2 (2.6 - 6 years)		18.9069, 2.7464 (<0.0001)*	19.0804, 2.8183 (<0.0001)*	16.4457, 2.9035 (<0.0001)*	17.6418, 2.8258 (<0.0001)*	18.9293, 2.7503 (<0.0001)*	18.3842, 2.7993 (<0.0001)*	18.7991, 2.7715 (<0.0001)*	18.7724, 2.7435 (<0.0001)*	15.6316, 2.9533 (<0.0001)*
Quartile 3 (6.1 - 11 years)		9.3043, 2.7866 (0.0008)*	9.3404, 2.7967 (0.0008)*	8.2463, 2.7847 (0.0031)*	9.0483, 2.7752 (0.0011)*	9.3369, 2.7907 (0.0008)*	8.9594, 2.8102 (0.0014)*	9.2719, 2.7953 (0.0009)*	8.9900, 2.7901 (<0.0013)*	7.4866, 2.8178 (0.0079)*
Quartile 4 [reference group 0] (11.1 years +)		0	0	0	0	0	0	0	0	0
Chemotherapy Class										
Alkylating (vs. purines/monoclonal antibodies)			-0.9761, 3.3802 (0.7728)							
Malignancy Type										
Hematologic (vs. Solid tumors)				-5.3255, 2.2631 (0.0186)*						-5.5833, 2.2988 (0.0152)*
HSCT Type										
Allogenic (vs. Autologous)					-3.8740, 2.2192 (0.0809)					
Sex										
Male (vs. Female)						-1.4356, 1.9701 (0.4662)				-1.9535, 1.9628 (0.3196)
Race										
Non-white (vs. White)							-1.9783, 2.0241 (0.3284)			-1.8301, 2.0352 (0.3685)
Ethnicity										
Non-Hispanic (vs. Hispanic)								0.6779, 1.9963 (0.7334)		0.7207, 2.0275 (0.7222)
Poverty										
LAC low SES (vs. LAC < national poverty prevalence (15.2%)									-1.4383, 2.3693 (0.5438)	-0.6079, 2.3893 (0.7992)
Outside LAC (vs. LAC < national poverty prevalence (15.2%)									-4.0752, 2.5210 (0.1060)	-4.3980, 2.4967 (0.0782)
Deviance Statistic Model Comparison	NS	<0.0001* (1 vs INITIAL)	NS	0.0027* (INITIAL vs 4)	NS	NS	NS	NS	NS	0.00001* (INITIAL vs BASE)

*$p < 0.05$ LAC Los Angeles County, SES socio-economic status

Supplemental Table 2.b. 28-Day Multivariable Interaction Model

Covariates	FULLY ADJUSTED Mean HR, (Standard Error) (*p*-value)
HR Intercept	108.96
SOS	
SOS-Affected (vs. unaffected)	-5.9802, (5.4973) (0.2767)
Zero time (continuous)	-0.2360, (0.02690) (<0.0001)*
SOS*Zero time* (interaction)	2.0669, (0.1333) (<0.0001)*
Age quartile	
Quartile 1 (6 months - 2.5 years)	31.6299, (3.3957) (<0.0001)*
Quartile 2 (2.6 - 6 years)	13.9225, (3.1857) (<0.0001)*
Quartile 3 (6.1 - 11 years)	7.0879, (3.1341) (0.0237)*
Quartile 4 (11.1 years +) [reference group 0]	0
Interaction of SOS by Age Quartile	
SOS*Age quartile 1	-20.5769, (7.3164) (0.0049)*
SOS*Age quartile 2	-0.3576, (8.7968) (0.9676)
SOS*Age quartile 3	-2.2589 (7.7371) (0.7703)
SOS*Age quartile 4	0
Interaction of Time by Age Quartile	
*Zero time**Age quartile 1	-0.1352, (0.04438) (0.0023)*
*Zero time**Age quartile 2	0.3471, (0.04178) (<0.0001)*
*Zero time**Age quartile 3	0.1874, (0.04103) (<0.0001)*
*Zero time**Age quartile 4	0
3-way Interaction of SOS, Time by Age Quartile	
SOS**Zero time**Age quartile 1	1.5949, (0.1855) (<0.0001)*
SOS**Zero time**Age quartile 2	-1.3254, (0.1944) (<0.0001)*
SOS**Zero time**Age quartile 1	-0.7477, (0.1533) (<0.0001)*
SOS**Zero time**Age quartile 4	0
Malignancy Type	
Hematologic (vs solid tumors)	-5.3039, (2.3583) (0.0245)*
Sex	
Male (vs female)	-1.7163, (1.9756) (0.3850)
Race	
Non-white (vs. White)	-1.4468, (2.0477) (0.4799)
Ethnicity	
Non-Hispanic (vs Hispanic)	0.7233, (2.0470) (0.72.38)
Poverty	
LAC low SES (vs. LAC < national poverty prevalence (15.2%)	-0.7839, (2.3982) (0.7438
Outside LAC (vs. LAC < national poverty prevalence (15.2%)	-4.3650, (2.5020) (0.0811)

*$p \leq 0.05$ LAC Los Angeles County, SES socio-economic status, HR heart rate

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CHAPTER FOUR: MANUSCRIPT THREE

Association Between Sinusoidal Obstruction Syndrome and Relapse Among Pediatric Hematopoietic Stem Cell Transplant Patients

Tracy Ono MSN RN CCRN[1,2*], Jenny Brook MS[3], David Elashoff PhD[3], Rita Secola PhD RN CPON NEA-BC FAAN[1,2], Barbara Bates-Jensen PhD RN FAAN[1], Kristi K. Westphaln PhD RN CPNP-PC[1,2], Dorothy J. Wiley PhD RN FAAN[1]

[1]University of California Los Angeles School of Nursing, Los Angeles, California, United States
[2]Children's Hospital of Los Angeles, Los Angeles, California, United States
[3] David Geffen School of Medicine at UCLA, Department of Medicine Statistics Core, University of California, Los Angeles, California, United States

*Corresponding Author:
Tracy Ono

Email: tkono@ucla.edu

Abstract

Background Hematopoietic stem cell transplants (HSCT) treat a range of malignancies. Preparative chemotherapy and radiation therapy predispose patients to transplant complications, including Sinusoidal Obstruction Syndrome (SOS). While HSCTs may cure disease, 20% of patients with hematological malignancy experience a relapse, with the incidence varying across tumor types. Little is known about the association between SOS and relapse. This study explores the relationship between SOS and relapse among pediatric HSCT recipients.

Methods Electronic medical record data for 180 pediatric HSCT patients transplanted for malignancy between January 1, 2015, and January 1, 2019, evaluated the association between SOS and relapse. Associations between ordinal and nominal categorical variables and between SOS and other covariates and time to relapse were evaluated Cox proportional hazard (CPH) survival curves and Chi-square statistics (-2log(likelihood ratio)). Multivariable logistic regression models compared the odds of relapse for children with and without SOS, controlling for the effect of age, chemotherapy, and sociodemographic characteristics. Model fit was evaluated using the deviance statistic.

Results CPH analyses suggested SOS was associated with a shorter time to relapse (p=0.005), and alkylating chemotherapy as pre-conditioning was protective against relapse among children without SOS (p=0.032) but not among children with SOS (p=0.7). Multivariable analyses suggested SOS-affected children show a 3.2-fold higher odds (95% CI: 1.292, 7.938) of relapse than unaffected youth. Overall, the independent effect of receiving an alkylating agent as pre-conditioning showed a 4.2-fold lower risk of relapse (OR=0.235, 95% CI: 0.078, 0.710).

Discussion These data suggest SOS increases the risk of malignancy relapse. Identifying the physiological features or SOS treatment characteristics that enhance the risk for relapse may improve survival in pediatric HSCT patients.

Introduction

Hematopoietic stem cell transplants (HSCT) treat a range of diseases afflicting infants, children, and adolescents. While the goal is cure, 20% of allogeneic HSCT patients treated for a hematologic malignancy will experience a relapse of their cancer (Barrett & Battiwalla, 2010). For those with "high risk" malignancy, relapse risk is 2- to 4-fold higher (Barrett & Battiwalla, 2010). Malignant types, specific chemotherapies and other treatments, and GVHD are risk factors for relapse following HSCT (McDonald et al., 2020; Sharma et al., 2021; Yalçin et al., 2015). However, sinusoidal obstruction syndrome (SOS) is independently associated with a higher risk for mortality following HSCT (Faraci et al., 2019).

Background

SOS is a complication that results from severe damage to the hepatic endothelium that occurs during preconditioning radiation and chemotherapy in which a cascade of events is triggered that may lead to multi-organ dysfunction, failure, or death (Mohty et al., 2015). Practice changes from myeloablative to reduced-intensity conditioning regimens have decreased overall SOS incidence (mean=13.7%) (Corbacioglu et al., 2019). Children have a 20% to 60% greater likelihood of developing SOS when compared to the adult population (Corbacioglu et al., 2019; Mahadeo et al., 2020). Nearly 30% to 60% of children who develop SOS progress to severe SOS that requires advanced life support, and of these, more than 80% will die (Cairo et al., 2020; Reiss et al., 2002). Additionally, SOS-affected children have shown lower overall one-year survival than their unaffected counterparts (61% vs. 77%, p=0.003) (Faraci et al., 2019). However, SOS-affected children have a higher incidence of non-relapse mortality following HSCT than unaffected youth: i.e., at 100 days, 22% vs. 6%; at one year, 30% vs. 12%; and at five years, 23% vs. 5% (p-values<0.0001) (Faraci et al., 2019).

SOS diagnostic criteria were defined by the Baltimore and modified Seattle criteria to guide clinical practice and research (Jones et al., 1987; McDonald et al., 1984). In 2018, the European Society for Bone Marrow Transplantation (EBMT) updated the guidelines to improve diagnosis and severity classifications and differentiate between disease affecting children and adults (Corbacioglu et al., 2018). In 2020, Cairo and colleagues (2020) published additional SOS diagnostic criteria that realigned severity across the age spectrum. If deemed medically necessary, data from two procedures coincidentally performed may be helpful in diagnosing SOS: increased portal venous wedge pressure or biopsy results positive for SOS (Cairo et al., 2020). Overall, signs and symptoms of the disease remain the most frequent criteria for diagnosing SOS, especially in the presence of two or more of the following symptoms: hyperbilirubinemia (>2mg/dL), refractory thrombocytopenia, weight gain >5% above baseline, ascites or reversed portal venous flow confirmed by ultrasound imaging, hepatomegaly above baseline, or right upper quadrant pain (Cairo et al., 2020).

There is currently no approved prophylaxis for SOS. However, one medication is approved for on-label treatment of SOS where pulmonary and renal systems are involved: Defibrotide (DF) (Jazz Pharmaceuticals, 2016).

While potentially curative, HSCTs are not an assurance to eliminate disease and come with additional risks. Chemoradiation therapy-induced hepatic endothelial damage causes SOS and increases the risk for mortality among HSCT-treated children (Faraci et al., 2019). Nonetheless, little is known about the impact that SOS has on malignancy relapse alone. Thus, to explore associations between SOS and malignancy relapse among pediatric HSCT patients, controlling for the effects of treatment and sociodemographic characteristics, we studied 180 children treated at a single tertiary care children's hospital.

Methods

Subjects and Setting

Eligible subjects were identified from the electronic medical records (EMR) at a single pediatric tertiary care facility that provides specialty services to children, often from underprivileged households. The study cohort comprised 180 children who met inclusion criteria: 6 months to 19 years old and received their first HSCT as a treatment for a primary malignancy between January 1, 2015, and January 1, 2019. To identify eligible patients with a primary malignant neoplasm who underwent an HSCT and those who developed SOS, we employed a specific cluster of 135 International Classification of Disease Codes (ICD) 9 and 10, explicated in a table (Supplemental Table 1). The Institutional Review Boards (IRB) at Children's Hospital Los Angeles (2020: IRB# CHLA-20-00081) and the University of California, Los Angeles (2020: IRB# 20-000740) reviewed and approved this secondary data analysis protocol as exempt.

Variables

In this study, the exposure of interest was SOS. Patients diagnosed with SOS were initially identified using ICD 9 and 10 codes, and cases were confirmed by using a separate database managed by the HSCT provider team. HSCT providers employed the modified Seattle criterion for SOS diagnosis (S. Jodele, personal communication, October 2017). Relapse, the exposure of interest, and the last date of contact following HSCT were similarly confirmed through documentation by the HSCT providers in the transplant database. The last date of contact was defined by the date of death, as documented in the EMR from an inpatient admission or per a report from a referring physician's office, or the last contact between the transplant team providers and the patient or family, usually a parent, following HSCT.

Other covariates of interest were extracted from the EMR, including medications, sociodemographic and transplant-related characteristics. Categorical variables were sex (male, female), HSCT type (allogenic, autologous), race (White, non-White), and ethnicity (Hispanic, non-Hispanic). Age was evaluated as quartiles (ordinal) and, in the final model, was centered around the population's mean and treated as a continuous variable. Additionally, we evaluated malignancy type (hematologic, solid tumor), chemotherapy agents (alkylating, purines/monoclonal antibodies), and socioeconomic characteristics measured by residence in Service Planning Areas (SPAs) with or without poverty prevalence greater than the national prevalence of households with incomes ≤100% Federal Poverty Level (15.2%) in 2017 (Los Angeles County [LAC] Department of Public Health, 2017). Children in high-poverty areas were compared to children living in SPAs with low poverty prevalence and children who lived outside of LAC at the time of their admission to the index hospital (i.e., higher prevalence of higher income households) (LAC Department of Public Health, 2017).

Statistical Analysis

Statistical Analysis System (SAS) 9.4 was used to conduct descriptive, tabular, and graphical analyses evaluating the association between SOS and relapse among HSCT pediatric patients treated for malignancy. Chemotherapies were grouped by drug class: alkylating agents versus purines or monoclonal antibodies (referent). Data for children with hematologic malignancies were compared to youth with solid tumors (referent); additionally, data for non-White youth were compared to children reported as White race (referent) and Hispanic (referent), and non-Hispanic ethnic groups were compared. Data for children reported to reside in low-income LAC SPAs, and youth living outside of the County, were compared to data from children living in high-income (LAC) SPAs (referent). The mean age (7.2 years) served as the referent in

multivariable analyses. **Bivariate analyses** examined each covariate's effect on the risk of relapse.

Cox proportional hazard (CPH) survival curves evaluated associations between SOS, alkylating chemotherapy agents, age in quartiles, and recurrent malignancy following primary HSCT treatment. For CPH analyses, patients were censored at malignancy relapse or the last date of contact. A SAS procedure, PROC LIFETEST, assesses survival differences between levels of covariates using the likelihood ratio test that yielded p-values for individual Chi-square statistics with corresponding degrees of freedom ("SAS/STAT 12.1 User's Guide: The LIFETEST Procedure," 2012, p. 4007). Initial CPH models contrasted four age groups (quartiles) for survival: 6 months to 2.5 years, 2.5 to <6, 6 to <11 years, and 11 to <19 years of age. The final CPH models evaluated the risk of relapse for two age groups: 6 months to 2.5 years and >2.5 years to 19 years (Supplemental Figures 1 and 2).

Bivariate analyses and CPH survival curves informed our series of **multivariable logistic regression models**. The base model's variables included SOS and age, measured as the difference between each child's age and the mean for the sample (Table 2). A p-value level ≤ 0.05 determined the statistical significance of the variables. Treatment characteristics (chemotherapy, malignancy, and transplant type) were added stepwise and retained where the deviance statistic showed an improved model fit. While each sociodemographic characteristic was similarly evaluated using the deviance statistic, we elected to force sex, race, ethnicity, and poverty into the final model to control for possible residual confounding (Gustafson & Greenland, 2006). The fully adjusted final model included SOS, age (difference from the mean), chemotherapy class, and sociodemographic covariates.

Results

The demographic and treatment characteristics of the study cohort are shown in Table 1. On average, the sample is best described as 7.2 years of age (standard deviation: 5.33), non-White (56.7%), and non-Hispanics (57.2%). Males (49.4%) and females (50.6%) were near-equally represented. While 51.7% of youth were treated for hematologic malignancies, 90% received at least one alkylating agent as myeloablative therapy. Overall, hematologic malignancy was highly correlated with allogenic transplant (r=0.94, p<0.0001)

Twenty-five percent (45/180) of children experienced a relapse of their malignancy, and among them, the median follow-up time was 3.75 months, with a range from 14 days to 4 years. For youth who did not relapse following HSCT, the median follow-up time was 1.2 years, with a range from 29 days to 7 years. The correlation between HSCT type and malignancy type was high across children with (r=1.0) and without (r=0.91) relapse (p-values<0.0001).

The incidence of relapse among the SOS affected (42.9%, 12/28) and unaffected (21.7%, 33/152) differed significantly (p=0.0176). Among the SOS-affected youth who relapsed, the majority (83.3%, 10/12) received an alkylating chemotherapy agent during the HSCT preconditioning phase. Relapse rates were statistically significantly higher among allogeneic recipients than autologous recipients: 33.3% vs 17.2% (p=0.0125). Children conditioned using purines and monoclonal antibodies were nearly twice as likely to relapse (50% vs 22.2%, p=0.0098). Last, mortality among children who relapsed was statistically significantly higher than those who did not, 72.3% vs 27.7%, p<0.0001.

Most children diagnosed with SOS received allogeneic HSCTs for hematologic malignancies (92.8%, 26/28). Across the four age strata, SOS disproportionately affected children under 2.5 years of age (35%, 10/28) versus 14% to 25% among older age groups (Table

1). Overall, the time to SOS diagnosis ranged between 4 and 41 days (median=14.5 days), and SOS severity was highest among mild cases (46.4%, 13/28) and lowest among severe cases with multiorgan failure (14.3%, 4/28) when admitted to the Pediatric Intensive Care Unit (PICU) for advanced supportive care. Hematologic malignancy and allogenic HSCT were highly correlated, and each was statistically significantly associated with developing SOS (p-values <0.0001).

The initial **Cox Proportional Hazards (CPH)** suggested the time to relapse for SOS-affected children was shorter than (SOS) unaffected youth (p=0.005, Figure 1). A series of statistical contrasts suggested that the association of SOS with relapse was modified across age (Figure 2, Panels A-D and Supplemental Figures 1 and 2), with infants and toddlers (6 months to 2.5 years) with SOS showing a shorter time to relapse than similarly aged children without SOS (p=0.029, Figure 2, Panel A). Additionally, among children receiving alkylating preconditioning agents, children with SOS showed a shorter time to relapse than unaffected youth (p=0.006), but we found no association between SOS and relapse among the small group of youth that received purines or monoclonal antibodies as preconditioning (Figure 3, Panels A and B)

We explored bivariate associations between other covariates of interest and relapse using a series of CPH models. Children who received alkylating agents as preconditioning therapy for HSCT showed a longer time to relapse than children receiving purines or monoclonal antibodies using CPH models (p=0.029) (Figure 4).

In the **bivariate tabular analyses**, youth experiencing SOS showed 2.7-fold higher odds of relapse than unaffected youth (OR=2.705, 95% CI: 1.165, 6.277, p=0.021) (Table 2). Similarly, those who received allogenic human stem cells showed a 2.4-fold higher odds of relapse than autologous HSCT recipients (OR=2.406, 95% CI: 1.196, 4.841, p=0.014). Treatment

agents affected the risk for relapse. Children preconditioned with alkylating agents showed a 3.5-fold lower odds of relapse (OR=0.286, 95% CI: 0.106, 0.773, p=0.014).

A series of **multivariable models** systematically evaluated associations between the base model of SOS and age, measured as the difference (years) between the child's age and the mean for the sample and individual covariates. When treatment and sociodemographic covariates were added to the base model individually, only chemotherapy class, alkylating agents, showed statistical significance added to the model fit. Children who received an alkylating agent were shown to have a 3.58-fold lower risk of relapse than those receiving purines or monoclonal antibodies (OR=0.279, 95% CI: 0.098, 0.796 p=0.017). The models that included the main effects (SOS and age) and individually evaluated the effect of adding malignancy type, HSCT type, and each of four sociodemographic characteristics to the model suggested their addition did not improve the fit of the model, using the deviance statistic.

The **fully-adjusted multivariable model** included SOS, age, chemotherapies as preconditioning therapy, race, sex, ethnicity, and poverty measures. These analyses suggested that children with SOS showed a 3.2-fold higher risk for malignancy relapse (OR=3.203, 95% CI: 1.292, 7.938, p=0.012) (Table 2), even after controlling for chemotherapy agents' effects and sociodemographic characteristics. Independently, alkylating agents continued to be associated with a decreased risk for relapse when compared to purine or monoclonal antibody conditioning regimens (OR=0.235, 95% CI: 0.078, 0.710 p=0.010). Sociodemographic variables were not statistically significantly associated with the risk for relapse in the fully-adjusted model.

Discussion

This study examined the relationship between SOS and risk for relapse following HSCT. To our knowledge, our study was the first to assess the impact of SOS on the relationship

between alkylating medications and relapse. Children who were affected by SOS showed an earlier time to relapse. Our findings suggest that SOS-affected patients are at increased risk of developing disease recurrence. A series of CPH models demonstrated that SOS-affected children are more likely to experience a malignancy relapse in slightly less than two years, consistent with the findings of the fully adjusted model. While sociodemographic variables were not statistically significant to the risk of SOS in this study, research conducted by Faraci et al. (2019) reported that female children show an increased risk of SOS (hazard ratio (HR) 1.62, p=0.018). Although age was not statistically significant in our multivariable models, CPH survival analyses suggested that the very youngest age group might be at higher risk for relapse among those with SOS. Other researchers have reported that younger age was more often associated with a shorter time to relapse (p=0.020) (Versluys et al., 2021).

Hematologic malignancies are strongly tied to allogenic HSCTs and conditioning regimens that include medication such as Busulfan, Melphalan, and Cyclophosphamide, myeloablative chemotherapy (Fraint et al., 2020; Sharma et al., 2021; Willasch et al., 2020). These medications are also known risk factors for SOS (Cairo et al., 2020; Mahadeo et al., 2020). Previous studies have resulted in varying associations between myeloablative chemotherapy and relapse risk. In a study comparing different conditioning regimens, combined treatment consisting of Busulfan and Cyclophosphamide was found to be statistically significantly associated with a 2.4-fold higher incidence of relapse when compared to a triple regimen including Clofarabine, Fludarabine, and Busulfan (p=0.060) (Versluys et al., 2021). However, other researchers found myeloablative conditioning regimens to lower the risk of relapse 1.3-fold when compared to conventional therapy (p=0.001) (Yalçin et al., 2015).

Our analyses may be limited. Studies using large databases have evaluated associations between SOS and mortality across many covariates included in this study (Faraci et al., 2019; Versluys et al., 2021). However, our analysis evaluated data from a single tertiary pediatric specialty hospital. Eligibility limited participant data to first-time HSCTs, excluding additional data for seven individuals. Thus, our sample size may limit our ability to detect some sociodemographic variables' effect on relapse. Some larger studies elected to reclassify SOS diagnosis using more contemporary, updated diagnostic guidelines. We analyzed the data employing definitions used at the time of diagnosis rather than reclassifying individual cases based on updated criteria. These cases were treated at a referral center in a large urban area, for which follow-up times may differ from non-referral medical centers. Interestingly, our sensitivity analysis showed little difference in point estimates for SOS or poverty parameters when we examined models based on children living in or outside LAC. Inconsistencies among self-reported variables, such as age and sex, documented across multiple visits and diagnostic algorithms also introduced possible misclassification bias into our analyses and limited interpretation of the directionality of our findings (Rosenman et al., 2011; Wacholder et al., 1995).

Conclusion

Malignancy relapse is a crucial characteristic of the natural history of disease that strongly affects survival in children with cancer. Among allogeneic HSCT-treated children and adults who suffer a relapse, the two-year survival is 20% (Barrett & Battiwalla, 2010; Kreidieh et al., 2022). This study explored previously unexamined relationships between SOS, a potentially fatal HSCT complication, and malignancy relapse following transplant among children. Additional study in this area will help build an extensive understanding of factors that may

influence patients' risk of relapse and possibly decrease premature mortality. Our study detected an association between SOS-affected HSCT children and an increased risk of relapse, which may also contribute to lower survival.

Acknowledgments

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Table 1. Study Cohort Demographics

	Total Sample (n=180)		SOS (n=28)		Not SOS (n=152)			Relapse (n= 45)		No Relapse (n=135)			Alive (n=133)		Deceased (n=47)		
	n	%	n	%	n	%	*p*-value	n	%	n	%	*p*-value	n	%	n	%	*p*-value
Age (Quartiles)																	
6 months – 2.5 years (Q1)	45	25.0	10	22.2	35	77.8	0.3655	14	31.1	31	68.9	0.2960	31	68.9	14	31.1	0.1848
2.5 years – 6 years (Q2)	46	25.6	4	8.7	42	91.3		8	17.4	38	82.6		41	89.1	5	10.9	
6 years – 11 years (Q3)	44	24.4	7	16	37	84		9	20.5	35	79.5		34	77.3	10	22.7	
11 years – 19 years (Q4)	45	25.0	7	15.6	38	84.4		14	31.1	31	68.9		27	60.0	18	40.0	
Race																	
White	78	43.3	15	19.2	63	80.8	0.2342	17	21.8	61	78.2	0.3852	60	76.9	18	23.1	0.4190
Non-White	102	56.7	13	12.7	89	87.3		28	27.5	74	72.5		73	71.6	29	28.4	
Ethnicity																	
Hispanic	77	42.8	14	18.1	63	81.9	0.4006	23	30.0	54	70.0	0.1920	51	22.2	26	33.8	0.0438*
Non-Hispanic	103	57.2	14	13.6	89	86.4		22	21.4	81	78.6		82	79.6	21	20.4	
Sex																	
Male	89	49.4	15	16.9	74	83.1	0.6346	22	24.7	67	75.3	0.9314	66	74.2	23	25.8	0.9356
Female	91	50.6	13	14.3	78	85.7		23	25.3	68	74.7		67	73.6	24	26.4	
HSCT Type																	
Autologous	93	51.7	2	2.2	91	97.8	<.0001*	16	17.2	77	82.8	0.0125*	76	81.7	17	18.3	0.0137*
Allogeneic	87	48.3	26	29.9	61	70.1		29	33.3	58	66.7		58	66.7	30	33.3	
Malignancy Type																	
Hematologic	93	51.7	26	28.0	67	72.0	<.0001*	29	31.1	64	68.9	0.0476	63	67.7	30	32.3	0.0529
Solid Tumor	87	48.3	2	2.3	85	97.7		16	18.4	71	81.6		70	80.5	17	19.5	
Chemotherapy Class																	
Alkylating Agents	162	90.0	25	15.4	137	84.6	0.8910	36	22.2	126	77.8	0.0098*	121	74.7	41	25.3	0.4621
Purines/ Monoclonal antibodies	18	10.0	3	16.7	15	83.3		9	50.0	9	50.0		12	66.7	6	33.3	
Poverty																	
LAC low SES	72	40.0	8	11.1	64	88.9	0.3523	22	30.6	50	69.4	0.2982	49	68.1	23	31.9	0.3153
LAC high SES	54	30.0	11	20.4	43	79.6		10	18.5	44	81.5		43	79.6	11	20.4	
Outside LAC	54	30.0	9	16.7	45	83.3		13	24.1	41	75.9		41	75.9	13	24.1	
SOS																	
SOS affected	28	15.6	-	-	-	-	-	12	42.9	16	57.1	0.0176*	15	53.6	13	46.4	0.0077*
Unaffected	152	84.4	-	-	-	-		33	21.7	119	78.3		118	77.6	34	22.4	
Relapse																	
Yes	45	25.0	-	-	-	-	-	-	-	-	-	-	11	24.4	34	75.6	<.0001*
No	135	75.0	-	-	-	-		-	-	-	-		122	90.4	13	9.6	

* $p \leq 0.05$ LAC Los Angeles County, SES socioeconomic status

Figure 1: Association of SOS and Relapse Risk

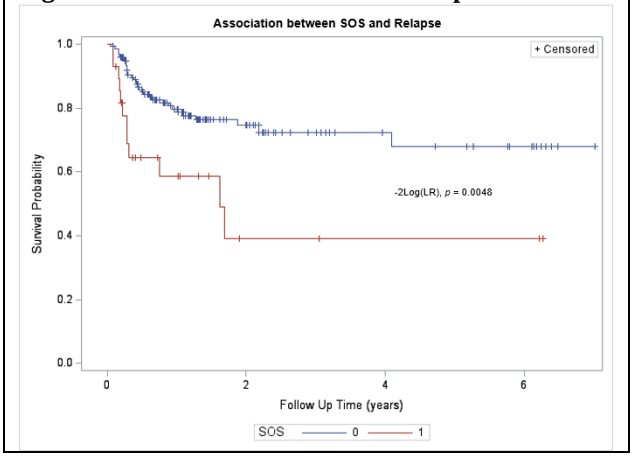


Figure 2: Contrast of the Effect of Age (in quartiles) on the association between SOS and Relapse Risk

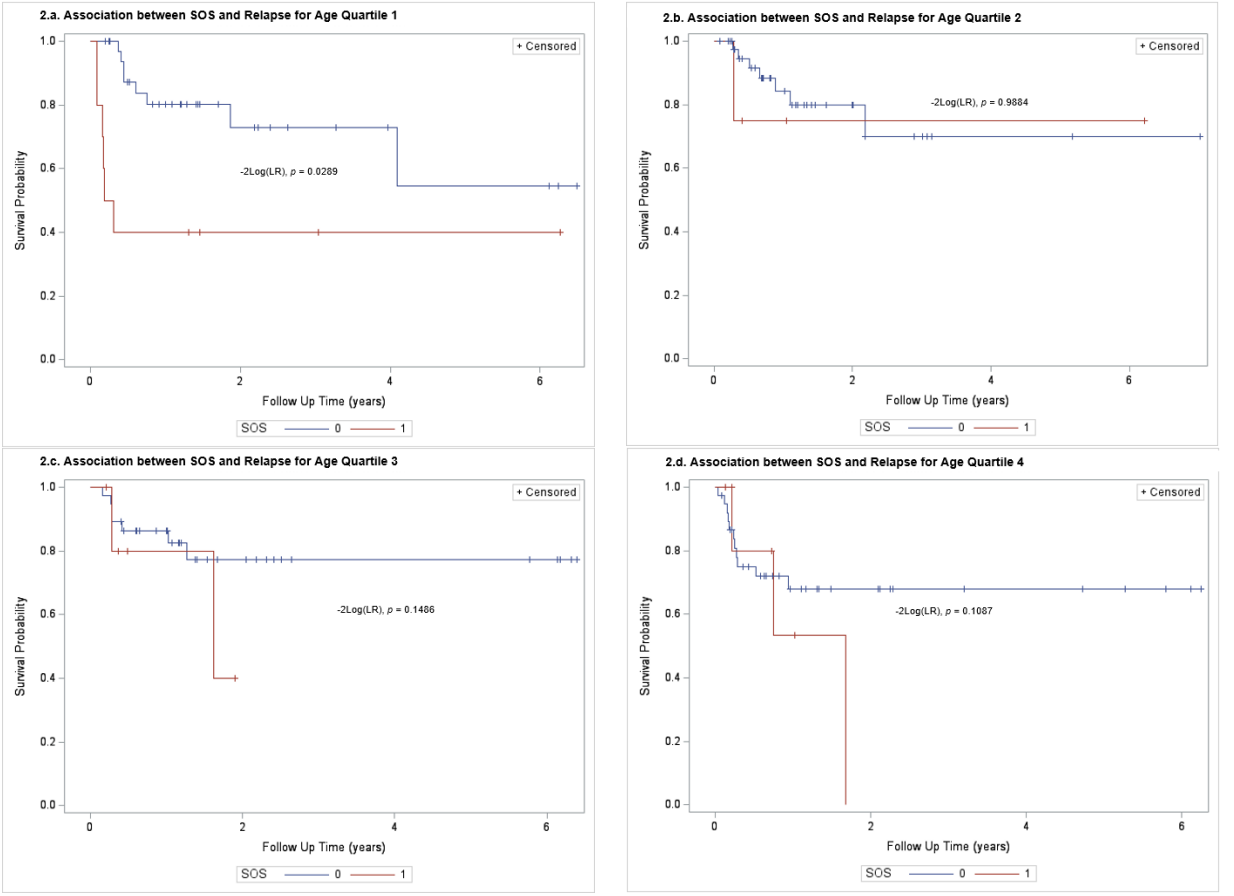


Figure 3. Contrast of the Effect of Alkylating Agents on the Association Between SOS and Relapse Risk

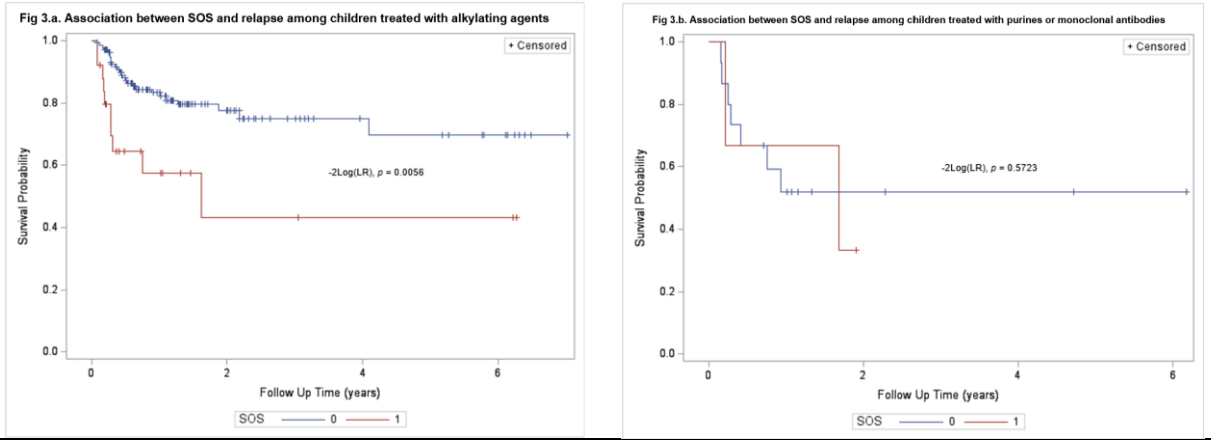


Figure 4. Association Between Alkylating Agents and Time to Relapse

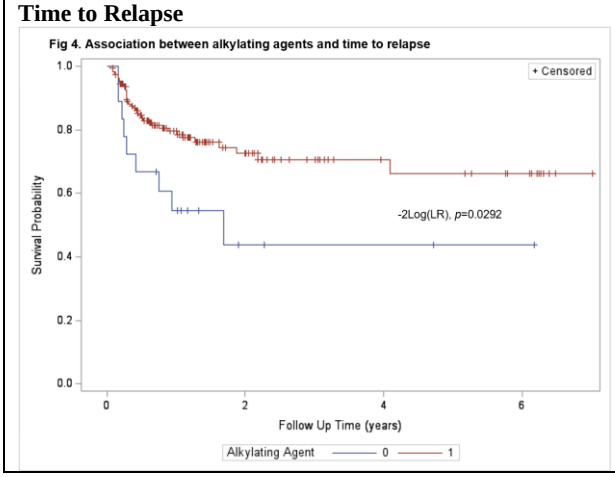


Table 2 Bivariate and Multivariable Models

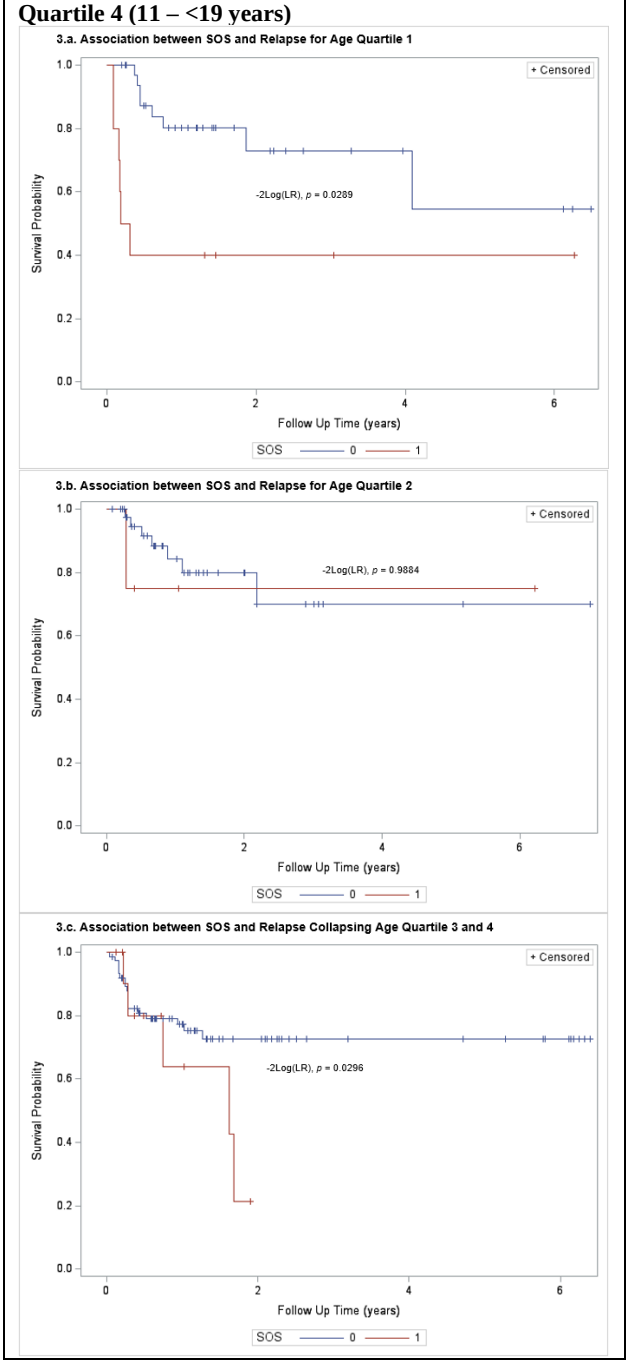
	Bivariate OR (95% CI)	Odds Ratio (95% Confidence Interval)								
Covariate		**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**	**Model 8**	**FINAL MODEL**
SOS										
Affected (vs. unaffected)	2.705 (1.165, 6.277) $p = 0.0206$*	2.710 (1.166, 6.298) $p = 0.0206$*	2.781 (1.177, 6.572) $p = 0.0197$*	2.201 (0.883, 5.489) $p = 0.0907$	1.963 (0.785, 4.908) $p = 0.1489$	2.720 (1.169, 6.329) $p = 0.0202$*	2.855 (1.215, 6.708) $p = 0.0161$*	2.641 (1.131, 6.164) $p = 0.0248$*	3.074 (1.290, 7.329) $p = 0.0113$*	3.203 (1.292, 7.938) $p = 0.0119$*
Age Difference from Mean (centered)	1.021 (0.959, 1.087) $p = 0.5196$	1.021 (0.958, 1.088)	1.002 (0.936, 1.072) $p = 0.9533$	1.008 (0.942, 1.078) $p = 0.8281$	1.008 (0.944, 1.077) $p = 0.8052$	1.022 (0.959, 1.088) $p = 0.5102$	1.015 (0.952, 1.083) $p = 0.6413$	1.019 (0.956, 1.085) $p = 0.5703$	1.022 (0.958, 1.090) $p = 0.5075$	0.996 (0.928, 1.068) $p = 0.9099$
Chemotherapy Class										
Alkylating (vs. purines/monoclonal antibodies)	0.286 (0.106, 0.773) $p = 0.0136$*		0.279 (0.098, 0.796) $p = 0.0170$*							0.235 (0.078, 0.710) $p = 0.0103$*
Malignancy Type										
Hematologic (vs. solid tumors)	2.011 (1.001, 4.040) $p = 0.0497$			1.573 (0.705, 3.505) $p = 0.2678$						
HSCT Type										
Allogenic (vs. autologous)	2.406 (1.196, 4.841) $p = 0.0138$*				1.937 (0.891, 4.212) $p = 0.0953$					
Sex										
Male (vs. female)	0.971 (0.494, 1.906) $p = 0.9314$					0.929 (0.467, 1.849) $p = 0.8338$				0.942 (0.456, 1.946) $p = 0.8709$
Race										
Non-white (vs. White)	1.358 (0.680, 2.711) $p = 0.3860$						1.447 (0.704, 2.975) $p = 0.3151$			1.224 (0.574, 2.609) $p = 0.6002$
Ethnicity										
Non-Hispanic (vs. Hispanic)	0.638 (0.324, 1.257) $p = 0.1936$							0.671 (0.336, 1.340) $p = 0.2582$		0.721 (0.345, 1.507) $p = 0.3850$
Poverty										
LAC low SES SPAs (vs. LAC high SES SPAs)	1.936 (0.827, 4.531) $p = 0.1278$								2.254 (0.932, 5.453) $p = 0.0713$	2.417 (0.955, 6.118) $p = 0.0626$
Zip codes outside LAC (vs. LAC high SES SPAs)	1.395 (0.552, 3.528) $p = 0.4818$								1.469 (0.567, 3.809) $p = 0.4288$	1.739 (0.646, 4.679) $p = 0.2733$
Deviance Statistic Model comparison			5.51, $p = 0.01891$	NS	NS	NS	NS	NS	NS	NS

*$p \leq 0.05$ LAC=Los Angeles County, SES=socioeconomic status, SPA=Service Planning Areas

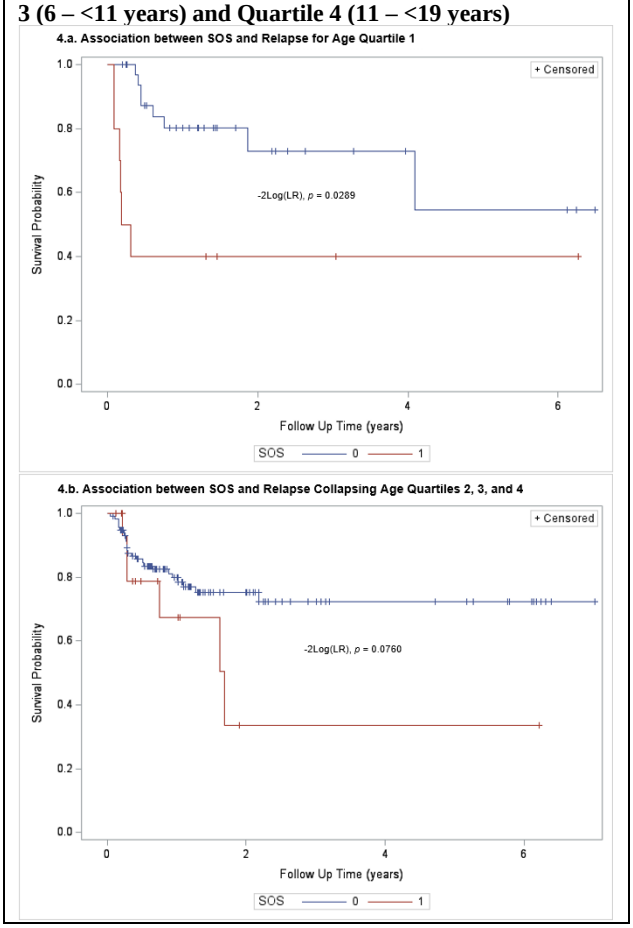
Supplemental Table 1. ICD 9 & 10 Codes

Code Type	ICD 9		ICD 10	
	Code	Description	Code	Description
Malignant Neoplasms	176-189	Malignant neoplasms of genitourinary organs	C51-68	Malignant neoplasms of genitourinary organs
	190-199	Malignant neoplasm of other and unspecified sites	C69-72	Malignant neoplasms of eye, brain, and other parts of central nervous system
	200-209	Malignant neoplasm of lymphatic and hematopoietic tissue	C81-96	Malignant neoplasms of lymphoid, hematopoietic, and related tissue
	235-239	Neoplasms of uncertain behavior or nature	D37-48	Neoplasms of uncertain behavior, polycythemia vera, and myelodysplastic syndromes
SOS	573	Other disorders of the liver	K71-77	Diseases of liver
HSCT	v42.8-42.9	Organ and tissue replaced by transplant	Z94	Bone marrow and stem cell transplant status
			PCS 3023X0 30240X0, 0250X0, 30260X0, 0233X0, 30243X0, 0253X0, 30260X0, 30263X0	Autologous cord blood stem cells
			PCS 30250G1, X1, Y1 30253G1, X1, Y1 30260G1, X1, Y1 30263G1, X1, Y1	Non-autologous bone marrow, cord blood, stem cells, hematopoietic stem cells
			PCS 30230G2, X2, Y2 30233G2, X2, Y2 30240G2, X2, Y2 30243G2, X2, Y2	Allogeneic related bone marrow, cord blood stem cells, hematopoietic stem cells
			PCS 30230G3, X3, Y3 30233G3, X3, Y3 30240G3, X3, Y3 30243G3, X3, Y3	Allogeneic unrelated bone marrow, cord blood stem cells, hematopoietic stem cells
			PCS 30230G4, X4, Y4 30233G4, X4, Y4 30240G4, X4, Y4 30243G4, X4, Y4	Allogeneic unspecified bone marrow, cord blood stem cells, hematopoietic stem cells

Supplemental Figure 1: Contrast of the Effect of Age (in quartiles) on the Association Between SOS and Relapse Risk, Collapsing Age Quartile 3 (6 – <11 years) and Quartile 4 (11 – <19 years)



Supplemental Figure 2: Contrast of the Effect of Age (in quartiles) on the Association Between SOS and Relapse Risk, Collapsing Age Quartile 2 (2.5 – <6 years), Quartile 3 (6 – <11 years) and Quartile 4 (11 – <19 years)



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CHAPTER 5: DISSERTATION SUMMARY

The historical literature review highlighted five main areas of study in pediatric SOS research: diagnostic and severity guidelines, pharmaceutical research into prophylactic use and varying doses of defibrotide, genetic markers as indicators for disease, the use of advancements in ultrasound technologies for earlier diagnosis, and clinical practice approach differences. Despite the breadth of aspects represented in the literature, there is a lack of research exploring nurses' sensitive contributions to diagnostic conversations through the use of routinely collected clinical data. Additional studies in this area may promote earlier identification of SOS and allow for an improved multidisciplinary approach to care for affected children.

In the second manuscript, heart rate pattern changes were noted to differ during the days directly following HSCT between youth who developed SOS and those who did not. Analyses for both time periods showed children who developed SOS showed a positive association between heart rate and time (following HSCT). Heart rate increased approximately 1.2- to 1.4-fold over the period between HSCT and days 14 and 28 for youth that developed SOS compared to a 1.15-fold increase observed among unaffected youth across all age groups. Moreover, SOS-affected youth were shown to have lower heart rates at the time of transplant than unaffected children and adolescents. Other data routinely collected throughout the transplant process, beginning with admission for preconditioning therapies, may be useful in identifying new risk factors for SOS. Identification of nurse-sensitive aspects of routine care may be significant in improving care and the outcomes of HSCT-treated SOS-affected patients.

The third manuscript explored the relationship between SOS and the risk of malignancy relapse among HSCT-treated children and adolescents. Specifically, SOS-affected youth showed a shorter median time to relapse (p=0.005) and logistic regression analyses suggested youth with

SOS showed a 3.2-fold higher odds of relapse (95% CI:1.292, 7.938) compared to unaffected youth. The multivariable logistic regression analyses also showed that alkylating medications administered during preconditioning independently lowered a child's risk of relapse (OR=0.235, 95% CI: 0.078, 0.710). Increasing knowledge about factors that impact the risk of malignancy relapse will help decrease premature mortality in HSCT children (Kreidieh et al., 2022).

In summary, heart rate pattern changes show potential as a biomarker of disease that may be detected in the clinical setting and promote earlier supportive care initiation. An improved understanding of the effect of SOS on malignancy relapse may assist in decreasing morbidity and mortality. Together, applying these findings to practice may improve care by enabling earlier disease recognition and decreasing premature mortality.

Implications for Future Research

Collectively, these findings highlight the need for additional research using routinely collected physiologic measures as predictors for patient health outcomes. EMRs catalog large troves of unexplored physiologic and observational data that, when analyzed, may inform safe care. Immediately, these analyses could be expanded to examine associations between SOS and repeated heart rate measurements following HSCT for youth treated with non-malignant conditions. Additionally, examining factors that precede HSCT as a predictor for heart rate changes may be informative. These studies suggest a causal relationship between SOS and malignancy relapse, however future research is needed to better understand the impact of life-saving SOS treatments on factors that may alter the success of engraftment.

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