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# Minding the Gap: Exploring the Impact of Structural Inequity and Adverse Social Determinants of Health on Hematopoietic Cell Transplant Access and Outcomes

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# Minding the Gap: Exploring the Impact of Structural Inequity and Adverse Social Determinants of Health on Hematopoietic Cell Transplant Access and Outcomes

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An abstract of a thesis submitted to the faculty of the Rollins School of Public Health of Emory University in partial fulfillment of the requirement for the degree of Master of Public Health in Behavioral, Social, and Health Education Sciences for the year 2025

**Abstract**

Minding the Gap: Exploring the Impact of Structural Inequity and Adverse Social Determinants of Health on Hematopoietic Cell Transplant Access and Outcomes

By: Erin L. Frost, MD

*Introduction:* While social determinants of health (SDoH) impact hematopoietic cell transplant (HCT) access in adult populations, there are limited data on this phenomenon in children. Using Fundamental Causes Theory, we hypothesized that children facing higher rates of structural inequity and adverse SDOH would receive HCT at lower rates than their peers facing less structural inequity.

*Methods:* This IRB-approved retrospective cohort study included children aged 0-21 with a hematologic malignancy or myelodysplastic syndrome (MDS) referred for first allogeneic HCT between January 1, 2015 and June 31, 2023. Data were abstracted from the electronic health record and address at referral was linked to the Social Vulnerability Index (SVI), Area Deprivation Index (ADI), and Childhood Opportunity Index (COI). Cox proportional hazard models were used to determine the association between SDoH and transplant receipt.

*Results:* Of 230 patients referred for HCT, 100 (43.5%) had acute lymphoblastic leukemia (ALL), 78 (33.9%) had acute myeloid leukemia (AML), and 29 (12.6%) had MDS. Sixty-three (27.5%) self-identified as Black, 60 (26.4%) self-identified as Hispanic, and 124 (54.2%) were insured through Medicaid. One hundred thirteen (49.1%) resided in low/very low COI areas and 62 (27.0%) resided in areas with a high/very high SVI. Seventy patients (30.4%) did not proceed to HCT. Of these individuals, 26 with ALL (68.4%) received alternative therapies including CAR-T, while 15 (83.3%) with AML died from disease progression or complications prior to HCT. There were no significant differences in HCT receipt based on age, sex, insurance, COI, or ADI. After adjusting for all significant variables found through univariable modeling, a high SVI at the national (HR 1.60, CI 1.06-2.41) and state level (HR 1.59, CI 1.06-2.38) remained factors associated with HCT receipt.

*Conclusions:* Contrary to our hypothesis, higher vulnerability, as proxied by the SVI, was associated with increased HCT receipt in children with hematologic malignancies and MDS. Pediatric patients may receive more comprehensive supports accounting for successful HCT in at-risk populations. Alternatively, patients from more vulnerable cohorts may be referred at lower rates or present with higher risk features that necessitate HCT over alternative therapies. To better understand these associations, prospective studies are warranted.

# Exploring the Impact of Structural Inequity and Adverse Social Determinants of Health on Hematopoietic Cell Transplant Access and Outcomes

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**Chapter 1: Introduction**

***Introduction and Rationale:*** In the United States, nearly 10,000 children under the age of 14 are diagnosed with cancer each year, a number that has steadily increased over the past 50 years. Amongst the most common of these malignancies is acute leukemia, which accounts for 25.4% of all new diagnoses and effects 4.8 per 100,000 children. While advances in therapy have resulted in survival rates exceeding 90%, relapsed, refractory, and high-risk disease remain significant clinical challenges. [1,2] Additionally, certain pre-leukemic states including myelodysplastic syndrome require transplantation to ensure remission, as chemotherapy alone has proven inadequate for disease control.[3] In these situations, physicians often turn toward alternative definitive treatments in the hopes of reaching a durable cure.[4,5]

Hematopoietic cell transplantation (HCT) is a well-established, curative treatment for a myriad of pediatric malignant and non-malignant diseases, with over 1,000 allogeneic transplants occurring annually within the United States.[6–9] Prompt referral and completion of HCT in eligible patients results in superior outcomes, including improved disease-free and overall survival.[8,10–12] Despite this, many studies, primarily conducted among adult populations, have shown significant disparities in access to HCT based on sociodemographic factors including race, gender, and insurance status.[7,8,13–17] In fact, many adult providers recognize a lack of equity in referral to HCT, citing barriers including insurance coverage, unclear referral guidelines, barriers in support, and resource limitations.[18] Disparities continue even amongst patients who are ultimately able to undergo transplantation, with additional research revealing an increased risk of transplant related morbidity and mortality based on neighborhood poverty and insurance status.[19,20]

These data demonstrating inferior access and outcomes amongst HCT patients based on sociodemographic factors are consistent with general trends seen in the general pediatric oncology cohort. Specifically, non-Hispanic White children, those from families with higher socioeconomic status

(SES), and those from families with higher educational levels have superior outcomes, including 5 year event free survival and overall survival, compared to non-Hispanic Black or Hispanic children, children from families with lower SES, and children from families with less educational attainment.[21–23] With 1 in 5 children living below the Federal Poverty Level and 2 in 5 living in low income homes, large numbers of children are therefore left at undue risk.[24]

Social determinants of health (SDoH) represent a number of both proximal and distal non-medical aspects of an individual's environment which influence health outcomes over the lifespan.[25] These determinants, including educational attainment, household and individual income, robustness of neighborhood-based resources, employment status and associated benefits, stress, and structural racism represent an elaborate network of resources and constraints that interact with each other, and with features unique to each individual over space and time, to impact health status and outcomes. [25,26] The relationships between various factors, as well as those between each individual factor and any given health outcome, are non-linear, complex, and evolve over time. Given this complex and often intertwined nature, singular measures are often unable to provide a comprehensive understanding of an individual's risk. Metrics have therefore been created to more comprehensively estimate SDoH and provide a holistic understanding of the myriad factors that may be contributing to health. The Area Deprivation Index (ADI) quantifies socio-economic variations in health outcomes; the Social Vulnerability Index (SVI) quantifies 16 census variables to identify communities at excess risk from external stressors; and the Childhood Opportunity Index (COI) measures neighborhood resources and conditions that impact the healthy development of children.[27–29] Together, these indices account for a broader spectrum of structural inequities across different geographical locales while capturing a more comprehensive understanding of the lived experiences of individual patients.

While studies have looked at the impact of SDoH on outcomes in general oncology and following HCT, studies evaluating SDoH and larger structural inequities that impact *receipt* of HCT following referral

are lacking. This time is of upmost importance, as delays in transplant receipt can be met with disease progression or relapse, making the patient ineligible for transplant. Further, minimal to no data exists on this phenomenon in children, for whom HCT is often the only curative option.[13,30–33] While understanding barriers to referral is also key, issues cited by adult providers are less prevalent amongst the pediatric population given clear treatment algorithms set forth by the Children's Oncology Group, universal health insurance access for children, and the built in support that comes with children living at home and having legal guardians responsible for their care. This makes the focus on the post-referral process more critical, as understanding the ongoing gaps within the HCT-process can provide key insights that will inform future interventions and help ensure equitable care for all patients.

***Theoretical Framework:*** Several existing theoretic frameworks consider the impact of SDoH on access to care and overall health status. These theories focus on how material and social capital can be utilized in times of need to achieve desired health outcomes.[34–39] One, the Fundamental Causes Theory, proves critical to our understanding of the ways that social disadvantage and vulnerability may result in inequities in HCT related care. Fundamental Causes Theory posits that individuals with higher social standing, often due to socioeconomic status, have access to more goods or services that can be leveraged in times of medical need. [37,38] Additionally, these individuals often have more extensive social networks and connections to other individuals who can help ensure the desired outcome. This occurs through several avenues including established relationships with providers who can offer quality care and their ability to personally provide layers of added support both physically and financially.[35,39]

With this theoretical framework in mind, we conducted a preliminary analysis which revealed that nearly one third of patients cared for at Children's Healthcare of Atlanta and eligible for transplant did not ultimately receive this treatment following referral. Given our established criteria, existing protocols, standardized operating procedures, and knowledge of access limitations based on sociodemographic factors in adults, we began to consider factors beyond clinical and disease status that

could explain this discrepancy. We considered the ways that social standing, social determinants of health, and social vulnerability, may be able to predict which children receive HCT following referral, and which do not. Our preliminary analysis reinforced the need to understand the ways that material goods, community resources, and interpersonal connections have impacted access in other clinical settings and across numerous patient populations; thus, we decided to explore this hypothesis within the patient population at Children's Healthcare of Atlanta.

***Purpose Statement and Specific Aims:*** The purpose of this study is to determine if social determinants of health, after controlling for clinical features, impact receipt of first allogeneic transplantation in pediatric patients with hematologic malignancies and myelodysplastic syndromes .

*Central Hypothesis:* Children facing higher rates of structural inequity and adverse social determinants of health will receive HCT at lower rates than their peers who face less structural inequity after controlling for disease subtype and related clinical features.

*Specific Aim 1:* To describe the social determinants of health and clinical features of pediatric patients with hematologic malignancies and myelodysplastic syndromes referred to the Aflac Blood and Marrow Transplant Program at Children's Healthcare of Atlanta for first allogeneic transplant.

*Specific Aim 2:* To determine both singular and comprehensive social determinants of health metrics and clinical features associated with receipt of first allogeneic transplant in pediatric patients with hematologic malignancies and myelodysplastic syndromes following initial referral to the Aflac Blood and Marrow Transplant Program at Children's Healthcare of Atlanta.

***Significance:*** To date, there is a paucity of literature exploring the impact of SDoH on access to and outcomes following HCT. Existing data are primarily centered around the experiences of adults, which are inherently different than those of children and adolescents. Given that HCT is often the only curative option available to children with several malignant and non-malignant conditions,

understanding barriers to access is critical to provide comprehensive, equitable care to all eligible patients.

To that end, our study will leverage a large, diverse, single institution database in addition to several validated indices of SDoH to determine the associations with receipt of first intended HCT in patients referred to our center. This will impact childhood health as we expect the results to enable physicians to more systematically identify and coordinate services earlier in the treatment process for patients facing excess barriers to care.

***Definitions of Terms:*** *Pediatric patient:* Any individual aged 0-21 referred to Children's Healthcare of Atlanta for consideration of HCT. While individuals over the age of 18 are eligible to and often receive care in adult settings, they are also able to receive care within dedicated children's hospitals until the age of 21, leading to our current inclusion criteria.

*Social Vulnerability Index (SVI):* A database and associated geographical map that uses 16 census level variables obtained from the American Community Survey to identify communities at excess risk from disasters. It includes four main categories, socioeconomic status, household characteristics, racial and ethnic minority status, and housing type and transportation. Within these are more granular metrics including unemployment rates, housing costs, number of single-parent households, residential crowding, and racial/ethnic composition.[28]

*Area Deprivation Index (ADI):* A geographical map that that quantifies the socioeconomic status of census blocks through the incorporation of publicly available income, education, employment, and housing data.[29]

*Childhood Opportunity Index (COI):* A database that measures and compares, at the census tract level, the educational, environmental, social, and economic resources of communities. More specifically, metrics including early childhood educational resources, pollution, household income, and concentrated inequities are used to understand the environment in which children are living and growing for the

current study with a goal of identifying at risk communities and promoting the healthy development of children. [27]

## Chapter 2: Literature Review

***Introduction:*** HCT is a well-established and curative therapy that is offered to patients with malignant, pre-malignant, and non-malignant hematologic conditions. Prompt completion of transplantation in eligible patients is crucial while they are in remission. Delays can result in disease progression or relapse, which would then make patients ineligible for transplantation and reduce the chance of cure. With delays in referral or receipt of HCT following referral, studies have consistently shown reduced overall survival and event free survival.[8,10–12] It is therefore important to understand the barriers to transplant receipt to best optimize this process and maximize cure across the board.

***Pediatric Hematologic Malignancies and Myelodysplastic Syndromes:*** Hematopoietic stem cells are a pool of self-regenerative, un-specialized cells that differentiate over several steps into the red blood cells, white blood cells, and platelets that circulate in our peripheral blood. These cells in turn carry oxygen, fight infection, and maintain a delicate balance between clotting and bleeding respectively.[40] In the case of leukemogenesis, or the development of leukemia, the normal differentiation of hematopoietic stem cells to multipotential progenitor cells, then to committed progenitor cells, and ultimately to the unique cells in peripheral circulation is thwarted. Instead, mutations occur during hematopoietic stem cells self-renewal, resulting in aberrant stem cells which drive the development of clones of abnormal, leukemic cells which result in systemic disease.[40,41]

Leukemia is amongst the most common malignancies of childhood, accounting for 25.4% of all new diagnoses and effecting 4.8 per 100,000 children. Rates have steadily increased since the 1970s, with an approximately 0.7% annual increase over the past decade. Children aged 1-4 are most likely to be diagnosed with leukemia with a median age of 6 years at diagnosis, and rates are slightly higher in males compared to females. When considering racial and ethnic variability in leukemia diagnosis, Hispanic patients having the highest relative incidence, with 6.8 new diagnosis per 100,000 children compared to 4.7 in 100,000 non-Hispanic White patients.[1]

Within the realm of leukemia there are several distinct subtypes. Most notable are acute lymphoblastic leukemia, in which abnormal cells are of the lymphoid (T and B cell) lineage, and acute myelogenous leukemia, in which abnormal cells are of the myeloid (red blood cell, platelet, neutrophil, basophil, eosinophil, monocyte) lineage.

Acute lymphoblastic leukemia is the most common subtype of pediatric leukemia and with advances in therapy survival exceeds 90% in contemporary cohorts. The backbone of therapy remains chemotherapy, with the choice of regimen based largely on age and total white blood cell count at presentation, with special considerations given for rare subsets of patients found to have specific, high risk disease features (Philadelphia-positive, Philadelphia-like, hypodiploid, 11q23 rearranged, and Down Syndrome). Given that chemotherapy alone is often successful, alternative definitive therapies are not needed by most patients. Relapse, however, remains a major concern and portends a poor prognosis. Conventional chemotherapy alone is often insufficient to induce and maintain remission in these children, and cellular therapies or HCT are required to achieve durable cure.[4,5]

While the management of acute lymphoblastic leukemia is primarily centered around chemotherapy with modifications to the regimen based on age, number of white blood cells, and response to therapy, this is not the case in acute myelogenous leukemia. Following a diagnosis of acute myelogenous leukemia, cytogenetics become crucial for determining the best treatment modality. There are a myriad of genetic mutations that occur within acute myelogenous leukemia blasts. Some of these genetic mutations are considered favorable, in that they alone do not portend a worse prognosis. These children can often be treated with conventional chemotherapy alone followed by prolonged monitoring for relapse. On the other hand, there are currently 19 genetic mutations that are considered unfavorable given that they are associated with an overall poorer prognosis including higher risk of relapse. Given the overall poor prognosis and higher risk of relapse and treatment failure associated with these mutations, children in this cohort often require not only chemotherapy but also HCT to achieve cure.[42] Additionally,

similar to acute lymphoblastic leukemia, outcomes amongst patients with relapse remain poor, with HCT offering the best chance of remission.

Myelodysplastic syndrome  while not itself a true malignancy, poses significant risk for the development of acute myelogenous leukemia and is treated aggressively in the pediatric population. A rare condition, effecting only 1-4/1,000,000 patients, myelodysplastic syndrome encompasses a spectrum of abnormalities in hematopoiesis and often first presents with decreases in peripheral cell lines, namely platelets and neutrophils. While earlier stages of disease, including refractory cytopenia of childhood in which the patient is not transfusion dependent, can be managed with watchful waiting, more progressive states of disease rely on HCT for definitive treatment. Unlike leukemia, myelodysplastic syndrome treated with chemotherapy alone has not been shown to provide acceptable cure rates, and therefore HCT is required to achieve the lowest risk of disease recurrence. [3]

***Pediatric Hematopoietic Cell Transplantation:*** While conventional chemotherapy can treat leukemic cells in the bone marrow and circulation by targeting rapidly dividing cells through several cellular level mechanisms, hematopoietic stem cells, both healthy and leukemic, can prove resistant to their effects. It is often, therefore, necessary to administer what would be lethal doses of chemotherapy and radiation in combination, followed by “rescuing” the patient with donor stem cells. These stem cells not only repopulate the now empty marrow space but also eliminate any residual cancer cells that may have evaded even the strongest therapeutic modalities through a process known as graft-versus leukemia.[40]

Allogeneic HCT is the process in which a patient is given a preparatory regimen, consisting of a combination of chemotherapy and radiation, prior to receiving an infusion of harvested stem cells from either a related or unrelated donor (**Figure 1)**. After a patient is identified as meeting criteria for transplantation based in part on disease subtype and status, a search is started to identify a donor. Donor selection considers several demographic factors including sex and age, but most importantly

focuses on HLA compatibility, or the similarity in protein markers on antigen presenting cells of the immune system between the patient and the potential donor. If poorly matched, the cells derived from the donor can attack the patient's healthy tissue and result in a condition known as graft-versus-host disease, which carries with it high rates of morbidity and mortality. Therefore, the goal is to find as close of a match as possible, with potential sources including siblings who have a one in four chance of having the same exact HLA type, unrelated donors who may coincidentally have the same type, unrelated donors who are similar but not exactly matched, and parents who are half matched.[40]

Once the donor is selected, the patient receives a preparatory regimen of chemotherapy and radiation, with a combined goal of eliminating any residual leukemia, suppressing the immune system to allow the donor cells to take up residence in the marrow, and decreasing the burden of cells in the bone marrow to allow room for the transplanted cells. Once this has been completed, the donor's cells are collected from either their peripheral blood or from their bone marrow, and then promptly administered through a central line to the patient. Over the course of two to three weeks, these cells migrate from the peripheral blood to the bone marrow where they start the process of differentiating and replenishing the patient's supply of health blood and immune cells, a process known as engrafting.[40] The initial post-transplant period is marked by a profound risk for infection, graft-versus host-disease, and a number of other complications related to the pre-transplant treatment received, the intensity of the preparative regimen, and the process of cell engraftment itself. Despite this, many patients go on to achieve cure, with 74% survival 3 years post-HCT.[40,43]

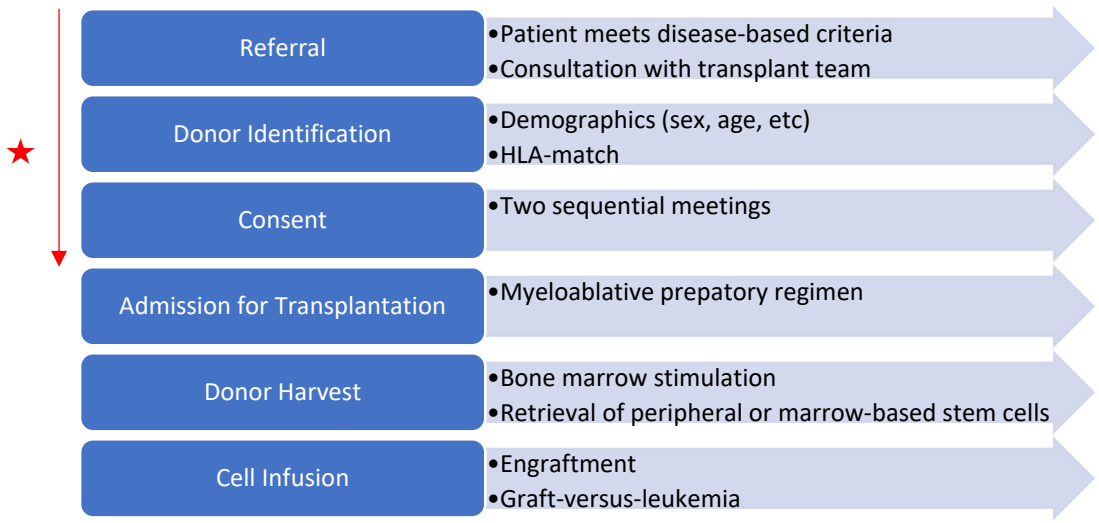



**Figure 1: Overview of HCT Highlighting Area of Interest**

***Trends in Pediatric Hematopoietic Cell Transplantation:*** In the United States, more than twenty thousand HCTs are performed annually of which approximately 8,500 are allogeneic. Pediatric patients account for nearly 1,300 (15%) of these allogeneic HCTs with the predominant malignant indications being acute lymphoblastic leukemia and acute myelogenous leukemia and the predominant non-malignant indications including aplastic anemia and sickle cell disease.[44,45] Overall, amongst children receiving allogeneic HCT, nearly 40% carry a diagnosis of acute leukemia.[6]

To streamline and standardized HCT related care, a Task Force was created in 2015 by the American Society for Blood and Marrow Transplantation to provide consensus guidelines and recommendations on which conditions should be treated with HCT based on available evidence at the time. This resulted in five separate categories of recommendation: standard of care, standard of care-clinical evidence available, standard of care-rare indication, developmental, and not generally recommended. In conditions where HCT is designated as standard of care, the use of transplant has been shown effective and of greater benefit than risk based on clinical trials or large observational trials. For conditions where HCT is designated as standard of care – clinical evidence available, there are no

clinical trials or large observational studies available to support the recommendation for HCT, though existing evidence from single or multi-center studies supports it's with acceptable rates of morbidity and mortality.

Amongst pediatric hematologic malignancies, a standard of care designation has been given to high risk acute myelogenous leukemia in first complete remission, acute myelogenous leukemia in second complete remission, high risk acute lymphoblastic leukemia in first complete remission, any acute lymphoblastic leukemia in second complete remission, high risk myelodysplastic syndrome, and therapy related myelodysplastic syndrome. A standard of care – clinical evidence available designation has been given to low risk acute myelogenous leukemia in first complete remission, acute myelogenous leukemia not in remission, acute lymphoblastic leukemia in third or higher complete remission, acute lymphoblastic leukemia not in remission, chronic myeloid leukemia, and low risk myelodysplastic syndrome. Additional ratings of standard of care and standard of care – clinical evidence available have been given to conditions including high risk lymphomas and severe aplastic anemias, however this is beyond the scope of the current study.[44]

In addition to having a transplantable condition, receipt of HCT depends on donor availability. Historically, patients of racial and ethnic minorities had lower rates of transplantation due to the poor availability of well-matched donors. Of late, however, advances in field have resulted in expanded donor options including the successful use of haplo-identical, or half-matched donors. Additionally, newer means of preventing graft versus host disease through the incorporation of agents including Abatacept and post-transplant cyclophosphamide have allowed for an increased number of partially matched unrelated donors to occur without the significant morbidity and mortality associated with older cohorts.[46]

***Social Determinants of Health and Pediatric Oncology:*** As previously outlined, continuous advances in the treatment of pediatric cancer have resulted in cure rates exceeding 90% for some

diagnoses. This progress, however, is not equally distributed across all children, and significant disparities remain. Therefore, many multi-institutional studies have been conducted to investigate the impact of social determinants of health on oncology outcomes within this cohort.

Over time, race has repeatedly been shown to impact both incidence of, and survival following, a diagnosis of cancer. While leukemia rates have slowly though consistently increased across the board, this is most profound amongst Hispanic children. This has been theoretically attributed to several environmental factors including tobacco use and pesticide exposure, though no causative factors have been definitively identified.[47] Once diagnosed, these children often face more difficult treatment courses with lower rates of cure. In fact, studies have consistently shown that white patients have improved outcomes compared to their non-Hispanic Black and Hispanic counterparts, with minority racial and ethnic groups experiencing both lower disease free and overall survival across most cancer subtypes.[15,21–23]

While socioeconomic status is a critical component of the relationship between race/ethnicity and outcomes given its concurrent correlation with access to care, correcting for SES does not itself fully account for the race-based trends that are seen.[15,22,23] It is instead, likely a multifactorial process including the impact of SES, delays in diagnosis, and decreased enrollment on active clinical trials, all of which come together to increase the risk assigned to Black and Hispanic children.[22]

While SES does not wholly account for racial and ethnic disparities in pediatric oncology outcomes, it is itself associated with worse outcomes during leukemia treatment. In a large secondary analysis conducted through the Children's Oncology Group, researchers found that more than ten percent of children enrolled on an active acute lymphoblastic leukemia trial were living in extreme poverty. These children had significantly higher rates of relapse than their counterparts who were not living in extreme poverty.[48] This finding was supported by additional studies including a large multi-center study of pediatric patients with neuroblastoma, in which children experiencing household poverty

had inferior event free survival and overall survival.[49] These findings become increasingly alarming when considered in the context of the current economic climate. In the United States, 1 in 5 children are living below the Federal Poverty Level, with 2 in 5 living in low-income homes. This potentially places many children diagnosed with cancer at significantly higher risk based solely on their SES.[24] Important to note, while differences in compliance have been cited as potential contributors to the differences in outcomes, they alone do not account for the entire association.[48] This again highlights the complex, interconnectedness of social determinants of health as they interplay and together impact health outcomes.

***Social Determinants of Health and Hematopoietic Cell Transplantation:*** While the majority of allogeneic HCT continue to occur in non-Hispanic white patients, an increasing number of HCT have occurred in minority populations over the recent years. In fact, while the overall number of annual allogeneic HCTs has steadily increased over time, between 2010 and 2019 there was a 51% increase for Black patients and a 53% increase for Hispanic patients compared with only 19% for non-Hispanic Whites.[43] With these recent changes, patients of minority race/ethnicity now represent 34% of the overall allogeneic HCT patient population compared to 26% a decade ago.[6,45] As mentioned earlier, this trend of increasing HCT rates amongst minority patients be explained in part by the increasing use of alternative donor sources and the advent of new means of preventing graft versus host disease, which together increase the number of available options for patients who historically were not candidates given lack of well-matched or matched unrelated donors.[6,46]

Despite the gains made in access, significant sociodemographic disparities remain. A large Center for International Bone and Marrow Transplant Research study amongst patients with acute myelogenous leukemia, acute lymphoblastic leukemia, and myelodysplastic syndrome found that individuals living in areas of higher poverty, defined as the percentage of residents living below the poverty line, were less likely to receive a transplant than those living in areas with less poverty.[13] This

finding was supported by another multi-center, registry based study that revealed adults with acute myelogenous leukemia or acute lymphoblastic leukemia living in areas of lower ecological SES at the time of diagnosis had lower rates of both chemotherapy use as well as transplantation. This metric of SES considered not only poverty rates, but also educational attainment, average rent, unemployment rates, and home values in its scoring highlighting the multifactorial nature of vulnerability.[14] Important to note, while regional SES was a key predictor of access, race, ethnicity, rurality, and family size were not associated with HCT rates in either cohort.[13,14]

The impact of neighborhood poverty on the HCT process extends beyond access. In fact, in another large Center for International Bone and Marrow Transplant Research study focusing on the pediatric cohort, children and adolescents with malignant conditions who lived in areas of higher neighborhood poverty, defined by the percentage of residents living below the federal poverty level, had higher transplant related mortality than their counterparts living in areas with lower neighborhood poverty.[19] Patients from disadvantaged areas therefore face not only disparities in access to care but also in outcomes following care as well.

Beyond neighborhood poverty, several additional factors have been shown to impact the HCT process. The most prevalent of these is the patient's insurance carrier. Large multi-center studies in both pediatric and adult patient have shown disparities in HCT-related care for those with government sponsored insurance plans. Adult oncology patients with Medicaid are less likely to receive HCT than those with private insurance.[17] Further, in adults that do access HCT, primary Medicaid is associated with lower event free survival and higher rates of graft failure.[20] These poorer outcomes are also seen in pediatric HCT patients, where those insured through Medicaid have inferior overall survival and higher transplant related mortality than their counterparts who are insured through the private sector.[19] While no differences in overall survival have been shown based on insurance carrier, access to and outcomes following HCT remain disparate.[17,19,20]

***Gaps in Existing Literature*:** While studies have examined the impact of SDoH on referral for transplantation in adults and on outcomes following HCT in adult and pediatric populations alike, studies evaluating SDoH and larger structural inequities that impact *receipt* of HCT following referral are lacking. As previously mentioned, this time is of upmost importance, as delays in transplant receipt can be met with disease progression or relapse, making the patient ineligible for transplant. Further, minimal to no data exists on the impact of social variables on the pre-transplantation process in pediatric patients for whom HCT, once deemed necessary, is often the only curative option.[13,30–33] This is a critical gap in our current understanding of the HCT-process and further research is crucial to begin dismantling barriers and maximizing the equitable access to life saving therapies for all children.

***Theoretical Framework:*** While several theories were considered during the conception and conduct of this study, an understanding of Fundamental Causes Theory was instrumental in the study design and hypothesis generation. It also provided a deeper understanding of the results that were obtained during analysis and helped to make sense of disparate findings from what was anticipated.

The Fundamental Causes Theory put forward by Link and Phelan, posits that individuals of higher socioeconomic standing have access to, and the ability to utilize, resources that minimize the risk and consequences of disease. Resources, in this theory, range from money to social connections to knowledge and can be leveraged to ensure better access to and outcomes within the health sector.[37,38] Knowledge, for example, can result in improved advocacy while connections can help ensure individuals are referred to and, receive care from, high-quality, skilled physicians.[37] Through access and the purposeful utilization of resources, individuals of higher socioeconomic standing attain health outcomes superior to their counterparts of lower standing.[37,38]

The Fundamental Causes Theory shines light on the dynamic and inter-related nature of social conditions as they impact individual health and well-being while also highlighting the importance of contextualizing risk factors. Without viewing a person's risks through the lens of social conditions and

lived experiences, undue pressure and ultimately blame is placed on the individual for negative outcomes rather than focusing on the systemic issues they face.[38] To combat this, physicians have a responsibility to understand and practice structural competency, or the ways that myriad social and economic factors impact health outcomes. They have a responsibility to not only understand these underlying factors, but to recognize and mitigate the larger SDoH at play for the welfare of their patients.[50] By making fundamental interventions, including efforts to improve universal access to the resources that dismantle inequity, such as education, gaps in outcomes can begin to close and discrepancies in care based on socioeconomic status narrowed.[37]

Fundamental Causes Theory was used to inform our study questions and hypothesis generation. With the understanding that individuals with better social conditions have more access to quality care, knowledge about new and existing technologies, resources that allow for better self-advocacy, and improved overall health outcomes as result of their ability to leverage any number of resources, we hypothesized that individuals with less conditions, as proxied by higher vulnerability and lower opportunity, would have the opposite.[36] In the scope of HCT, we predict that they will have decreased access and increased barriers to HCT, resulting in reduced numbers of HCT receipt in those at highest risk. We also propose that this knowledge, if supported by our findings, can be used to promote fundamental interventions targeting the larger causes of health inequities. This may come in the way of fiscal supports for families, additional time spent in patient and family education, and the institution of universal SDoH screening to expedite identification of high-risk patients and receipt of social services that can help mitigate disparities.[37]

***Conclusions:*** Leukemia is amongst the most common malignancies of childhood, accounting for 25.4% of all new diagnoses and effecting 4.8 per 100,000 children.[1] While many children with acute lymphoblastic leukemia and acute myelogenous leukemia are treated with chemotherapy alone, many with high-risk features or relapse require HCT to have the best chance of a durable cure.[4,5,42] Each year,

over 1,000 of these allogeneic transplants occur in pediatric patients. [44,45] While strides have been made towards more equitable transplantation, primary based on race and insurance status, significant sociodemographic disparities remain.[6,17,43,45] This has predominantly been demonstrated in large studies that have shown that higher poverty is associated with lower HCT rates in adult populations.[13,14] Poverty has also been studied in pediatric patients, but has centered around post-transplantation outcomes rather than transplant access itself.[19]

With this knowledge in mind, and based on existing theoretical frameworks, we are investigating the impact that comprehensive social determinants of health measures may have on access during the pre-transplant process for pediatric patients. This knowledge will be used to inform care, create interventions, and work towards equitable care practices for all children.

**Chapter 3: Study Design, Recruitment, and Data Analysis**

***Study Design:*** To determine the impact of both singular social determinants of health and more comprehensive social determinants of health indices on transplant access, we conducted an IRB approved retrospective cohort study. This study included all children aged 0-21 with a hematologic malignancy or myelodysplastic syndrome referred to the Aflac Cancer and Blood Disorder Center at Children's Healthcare of Atlanta for first allogeneic transplant between January 1, 2015 and June 31, 2023.

***Sampling/Recruitment:*** Patients were identified through an internally maintained excel database of all referred patients using the following disease identifiers: Acute lymphoblastic leukemia (B-cell, T-cell), acute myelogenous leukemia (including transplant-associated acute myelogenous leukemia), infant leukemia, bi-phenotypic leukemia, mixed-phenotype acute leukemia, undifferentiated leukemia, acute megakaryocytic leukemia, acute pro-myelocytic leukemia, and myelodysplastic syndrome. This revealed a total of 230 unique patients within the timeframe of interest. Preliminary power analysis revealed that to identify between group differences while maintaining 80% statistical power and an alpha of 0.05, 170 total patients would be required.

***Data Collection:*** Following patient identification, data were manually abstracted from the electronic health record into a secure excel file housed on Emory OneDrive. The investigative team including Drs. Frost, Schoettler, and Arnold worked together to develop a list of key data points to be abstracted for the purposes of the study. Demographic data consisted of name, medical record number, date of birth, age, sex (male, female), race (Black, White, Asian, other, Declined), ethnicity (Hispanic, Non-Hispanic, other, declined), primary language (English, Spanish, other), primary insurance (Medicaid, Private, Charity Care, Uninsured, TriCare), and address at time of referral. Disease related data consisted of primary diagnosis, date of initial diagnosis for patients in first remission or date of most recent relapse in patients in greater than first remission, remission status (complete remission, active disease, not

applicable), and minimal residual disease status (positive, negative, not applicable). Data regarding key points in the HCT process including referral date, date of initial consult, date of consents one and two, date of transplant, and date of death or last known alive were collected. Time between referral and consult and consult and transplant were then calculated in days.

Following initial data abstraction, address at time of referral was linked to three existing national datasets of social determinants of health, the SVI, ADI, and COI. The Social Vulnerability Index quantifies 16 census variables to identify communities at excess risk from external stressors. It provides vulnerability data at both the national and state level and for both counties as well as census tracts, further defined by seven unique data years (2000, 2010, 2012, 2014, 2016, 2018, 2020). To capture the SVIs of the patients within our cohort, each individual's address was linked to both the state and national level using census tracts as the geographical unit. Data year was chosen as the year of referral, or for odd numbered years, the even year prior to the year of referral (example: referral in 2019 coded using 2018 data). This resulted in 4 unique potential categories of vulnerability (high, medium-high, low-medium, and low) which were then recoded into three categorical variables - high, medium, and low.

The Childhood Opportunity Index measures neighborhood resources and conditions that impact the healthy development of children focusing on three domains – education, health/environment, and social/economic. Zip Code Tabulation Areas are used to define census blocks and weighted averages of various domains as well as overall opportunity are calculated using z-scores. For the COI, zip code tabulation areas were used to determine census block level data for each year of referral based on 2015 zip codes (for example, 2019 COI based on 2015 zip codes). This resulted in five levels of opportunity (very low, low, moderate, high, and very high) which were then recoded into three categorical variables - low/very low, moderate, and high/very high.

The Area Deprivation Index measures area level deprivation across four key domains – income, education, employment, and housing quality. It is used to identify communities in need of investment

and quantifies socio-economic variations in health outcomes. For the ADI, again address was linked to both the state and national level using census tract as the geographic unit of interest. This resulted in a continuous variable for both national and state deprivation, with national being a continuous percentile from 1-100, and state being a continuous decile from 1-10.

Once all key data were abstracted, any areas of uncertainty were verified by Dr. Michelle Schoettler or Dr. Staci Arnold to ensure data accuracy. Data were then cleaned with several categorical variables recoded numerically for ease of analysis. First, disease subtype was recoded as follows: 1=B-cell acute lymphoblastic leukemia, 2=T-cell acute lymphoblastic leukemia, 3=acute myelogenous leukemia, 4=treatment-associated acute myelogenous leukemia, 5=Infant leukemia, 6=acute megakaryocytic leukemia, 7=mixed-phenotype acute leukemia, 8=bi-phenotypic leukemia, 9=undifferentiated leukemia, 10=acute promyelocytic leukemia, 11=myelodysplastic syndrome. Next, remission status was recoded so that a number was assigned consistent with number of complete remission, aside from 10 which was used to code for active disease. For example, if remission status was 1, then the patient was in their first complete remission, whereas a remission status of 4 meant the patient was in their fourth complete remission. Lastly, insurance was recoded so that 1=Medicaid, 2=Private, 3=Uninsured/Charity Care, and 4= TriCare.

***Data Analysis:*** Following data abstraction and cleaning, analysis was performed using SAS 9.4 (Cary, NC). First, descriptive statistics were used to describe the demographics of the entire cohort, as well as to compare the differences in sociodemographic and disease factors between those who received HCT and those that did not. Univariable cox proportional hazard models were then used to determine the association between social determinants of health (race, ethnicity, primary language, insurance), social determinant of health indices (SVI, ADI, and COI) and transplant receipt while controlling for disease sub-type and status. Multivariable analysis was subsequently performed, adjusting for all variables that were significant in the univariable model. A sub-analysis of the acute myelogenous leukemia/myelodysplastic

syndrome cohort was also completed with both univariable and multivariable cox proportional hazard models being created.

Once data were analyzed, geographical maps were created to visually represent SVI, the significant variable in our analysis. First, Georgia (2020) Shapefiles from the US Census Bureau and the Social Vulnerability Index (2020) from Centers for Disease Control and Prevention were downloaded. Data joins and cleaning between the Georgia Shapefile Census Tracts and CDC SVI were completed in RStudio version 2023.12/1+402 and R version 4.3.3 using tidyverse, rio, readxl, writexl, and readr. Patient-specific census tracts were extracted from the United States Census Bureau Geocoder and cross-referenced with the SVI Interactive Map. Each census tract was added to the existing excel file for tracking purposes. Using QGIS version 3.34.10-Prizren, each census tract was entered and colored according to the degree of vulnerability with low SVI tracts having RPL_themes >=25 being green, medium SVI tracts having RPL_themes 25-75 being yellow, and high SVI tracts having RPL_themes >75 being red. This resulted in two maps, one for transplant recipients and one for non-recipients, containing census tracts corresponding to unique patients, each color-coded by vulnerability.

***Data Management:*** All data was abstracted on an Emory laptop by an Emory physician with access to the Electronic Health Record. Abstracted data were maintained in a secure Excel File on Emory OneDrive. This file was accessible only to investigators and statisticians.

***Positionality***: As a white, cisgender, female oncologist from a middle-class background, mentored primarily by female academic oncologists, my experiences and professional position inherently shape my approach to not only the practice of medicine but the conduct of research as well. These factors also impact my understanding and interpretation of the impact of health disparities and structural inequities on patient care. While I am the beneficiary of social privileges based on factors including race and educational attainment, I am sensitive to the ways that systemic biases impact access to care and outcomes for patients of marginalized and minority status. I therefore attempt to prioritize research that

aims to understand the ways that structural inequities further the gaps in care experienced by so many patients. I also strive to involve the voices of diverse individuals through my work, so that the most impactful questions are asked, and acceptable solutions put forward.

## Chapter 4: Manuscript

**Abstract:**

**Background:** Prompt receipt of hematopoietic cell transplantation (HCT) in eligible patients with hematologic malignancy results in superior outcomes, though significant disease-related and sociodemographic barriers exist. While these factors have been investigated in the adult HCT population, exploration has been largely limited to singular sociodemographic variables such as race and insurance status rather than more comprehensive indices aimed at capturing a comprehensive view of vulnerability. Further, little is known about the role of either singular or comprehensive social determinants of health (SDoH) on receipt of HCT following initial referral in eligible pediatric patients. We therefore investigated the impact of three comprehensive SDoH metrics – the Social Vulnerability Index (SVI), Childhood Opportunity Index (COI), and Area Deprivation Index (ADI) – on transplant receipt following initial referral in pediatric patients with hematologic malignancies and myelodysplastic syndromes.

**Methods:** In this retrospective single-center study, we identified all patients aged 0-21 years with a hematologic malignancy or MDS referred to our institution for first allogeneic transplant between January 1, 2015 and June 31, 2023. Demographic data was abstracted from the medical records and linked to publicly available datasets for the SVI, COI, and ADI. Descriptive statistics were used to summarize the cohort and univariable cox proportional hazard models were used to determine the association between social determinants of health, social determinant of health indices, and transplant receipt.

**Results:** 230 pediatric patients with hematologic malignancies and myelodysplastic syndromes referred for first allogeneic transplant and explore the impact of both singular and comprehensive SDoH on ultimate receipt of HCT. Of the total cohort, 70 patients (30.4%) did not receive a transplant of whom 38 (54.3%) had ALL, 18 (25.7%) had AML, and 9 (12.9%) had MDS. Indications for failure to proceed to

transplant varied by disease subtype, with pursuit of alternative therapy predominating in the ALL cohort and death secondary to disease progression predominating in the AML cohort. AML and high social vulnerability at the national and state level, as proxied by the Social Vulnerability Index, were factors associated with HCT receipt in both univariate and multivariable models. There was no significant association between HCT receipt and age, sex, insurance status, childhood opportunity, or area deprivation. Given the unexpected association between higher vulnerability and increased HCT receipt in children with hematologic malignancies and MDS, further prospective studies are warranted.

**Background:**

In the United States, nearly 10,000 children under the age of 14 are diagnosed with cancer each year, with nearly 5 in 100,000 children being diagnosed with acute leukemia and 1-4 in 100,000 being diagnosed with myelodysplastic syndrome.[1,2] While advances in therapy have resulted in survival rates exceeding 90%, relapsed, refractory, and high-risk disease remain significant clinical challenges, and certain pre-leukemic states including myelodysplastic syndrome require transplantation to ensure remission, as chemotherapy alone has proven inadequate for disease control.[3,5] In these situations, physicians often turn toward alternative definitive treatments in the hopes of reaching a durable cure.[4,5]

Hematopoietic cell transplantation (HCT) is a well-established, curative treatment for a myriad of pediatric malignant diseases. Over 1,000 children receive an allogeneic transplant annually within the United States.[6–9] Prompt referral and receipt of HCT in eligible patients with malignancy results in superior outcomes, including improved disease-free (DFS) and overall survival (OS).[8,10–12] Despite this, many studies, primarily conducted among adult populations, have shown significant disparities in access to HCT based on sociodemographic factors including race, gender, and insurance status.[7,8,13–17] Additional research has revealed an increased risk of transplant related morbidity and mortality based on neighborhood poverty and insurance status amongst pediatric and adult patients.[19,20] In line with the Fundamental Causes Theory,

Data demonstrating inferior access and outcomes within HCT patients based on sociodemographic factors are consistent with general trends seen in the pediatric oncology cohort [21–23]. Specifically, outcomes including 5 year event free survival (EFS) and OS are superior in families with higher socio-economic status (SES) and higher educational levels compared to children from families of lower SES and with less educational attainment.[21–23] With 1 in 5 children living below the Federal Poverty Level and 2 in 5 living in low income homes, large numbers of children are therefore left at an increased risk.[24]

Social determinants of health (SDoH) represent a number of both proximal and distal non-medical aspects of an individual's environment which influence health outcomes over the lifespan.[25] These determinants are often complex and intertwined, and singular measures fall short in providing a comprehensive understanding of an individual's risk. Metrics have therefore been created to more comprehensively estimate SDoH and provide a holistic understanding of the myriad factors that may be contributing to health. The Area Deprivation Index (ADI) quantifies socio-economic variations in health outcomes; the Social Vulnerability Index (SVI) quantifies 16 census variables to identify communities at excess risk from external stressors; and the Childhood Opportunity Index (COI) measures neighborhood resources and conditions that impact the healthy development of children.[27–29] Together, these indices can capture a broader spectrum of structural inequities across different geographical locales while capturing a more comprehensive understanding of the lived experiences of individual patients.

While studies have looked at the impact of SDoH on outcomes in general oncology and following HCT, studies evaluating SDoH and larger structural inequities that impact *receipt* of HCT following referral are lacking. There are minimal to no data in children, for whom HCT is often the only curative option.[13,30–33] If SDoH are impacting receipt of transplant, it's possible that a chiasm exists to having an opportunity for curative therapy that is currently unrecognized. This is a critical gap in our current understanding of the HCT process and further research can provide key insights that will inform future interventions and help ensure equitable care for all patients.

In this study, we describe the SDoH and clinical features of pediatric patients with hematologic malignancies and myelodysplastic syndromes (MDS) referred for first allogeneic transplant and determine the impact of both singular and comprehensive SDoH metrics on progression through the pre-transplant process and ultimate receipt of HCT.

*Theoretical Framework*

Existing literature within the world of oncology, and HCT in particular, have lent support for the role of Fundamental Causes Theory as put forward by Link and Phelan, in which individuals of higher socioeconomic standing have access to, and the ability to utilize, resources that minimize the risk and consequences of disease. These resources, ranging from money to social connections to knowledge, can be leveraged to ensure better access to and outcomes within the health sector.[37,38] Through access and the purposeful utilization of resources, individuals of higher socioeconomic standing attain health outcomes superior to their counterparts of lower standing.[37,38]

With this understanding that individuals with better social conditions have more access to quality care, knowledge about new and existing technologies, resources that allow for better self-advocacy, and improved overall health outcomes as a result of their ability to leverage any number of resources, we hypothesized that individuals with worse social conditions, as proxied by higher vulnerability and lower opportunity, would have the opposite.[36] In the scope of HCT, we predict that they will have decreased access and increased barriers to HCT, resulting in reduced numbers of HCT receipt in those at highest risk. We also propose that this knowledge, if supported by our findings, can be used to promote fundamental interventions targeting the larger causes of health inequities. This may come in the way of fiscal supports for families, additional time spent in patient and family education, and the institution of universal SDoH screening to expedite identification of high-risk patients and receipt of social services that can help mitigate disparities.[37]

**Methods:**

*Study Design and Data Collection*

In this single center, IRB approved, retrospective study, all children aged 0-21 years with a hematologic malignancy or MDS referred to our institution for first allogeneic transplant between

January 1, 2015 and June 31, 2023 were included. Patients were identified through an internally maintained database using the following disease identifiers: Acute Lymphoblastic Leukemia (ALL), Acute Myelogenous Leukemia (AML), Infant Leukemia, Bi-Phenotypic Leukemia, Mixed-Phenotype Leukemia (MPAL), Undifferentiated Leukemia, Acute Megakaryocytic Leukemia (AMKL), Acute Pro-Myelocytic Leukemia (APML), and MDS.

Following cohort identification, medical records were reviewed and demographic, disease-related, and data regarding completion of steps in the pre-transplant process including occurrence of and timing to consultation, consents, and receipt of cells were abstracted manually. Address at the time of referral was linked to three national datasets of social determinants of health: the SVI, ADI, and COI.

To capture the SVIs of the patients within our cohort, individual patient addresses were linked to both the state and national level using census tracts as the geographical unit. Data year was chosen as the year of referral, or for odd numbered years, the even year prior to the year of referral given that the database includes only even number years (example: referral in 2019 coded using 2018 data). This resulted in 4 unique potential categories of vulnerability (high, medium-high, low-medium, and low) which were then recoded into three categorical variables - high, medium, and low.

For the COI, zip code tabulation areas were used to determine census block level data for each patient. patients COI was abstracted from the dataset that matched their referral year, with all referrals from 2020 onward being abstracted from the 2020 file. Of note, the COI 2.0 incorporates neighborhood level metrics from 2015 into data files for each year from 2015 through 2020 with each file incorporating changes in individual zip code definitions for that year. This process resulted in five levels of opportunity (very low, low, moderate, high, and very high) which were then recoded into three categorical variables - low/very low, moderate, and high/very high.

Lastly, for the ADI, again address was linked to both the state and national level using census tract as the geographic unit of interest. This resulted in a continuous variable for both national and state deprivation, with national being a continuous percentile from 1-100, and state being a continuous decile from 1-10.

*Data Analysis*

Descriptive statistics were used to summarize the cohort. Univariable cox proportional hazard models were used to determine the association between social determinants of health (race, ethnicity, primary language, insurance), social determinant of health indices (SVI, ADI, and COI) and transplant receipt. Multivariable analyses were subsequently performed, adjusting for all variables that were significant in the univariable model. Multivariable model 1 included age, sex, diagnosis, and national SVI, while multivariable model 2 included age, sex, diagnosis, and state SVI. A sub-analysis of the AML/MDS cohort was completed with both univariable and multivariable cox proportional hazard models being created. Data analysis was performed using SAS 9.4 (Cary, NC).

Once data were analyzed, geographical maps were created to visually represent SVI. Georgia (2020) Shapefiles from the US Census Bureau and the Social Vulnerability Index (2020) from Centers for Disease Control and Prevention were downloaded, joined, and cleaned. Patient-specific census tracts were abstracted from the United States Census Bureau Geocoder and cross-referenced with the SVI Interactive Map. Using QGIS version 3.34.10-Prizren, each census tract was entered and colored according to the degree of vulnerability. This resulted in two maps, one for transplant recipients and one for non-recipients, containing census tracts corresponding to unique patients, each color-coded by vulnerability.

*Definitions*

The SVI quantifies 16 census variables to identify communities at excess risk from external stressors. It provides vulnerability data at both the national and state level and for both counties as well as census tracts, further defined by seven unique data years (2000, 2010, 2012, 2014, 2016, 2018, 2020).[28] The higher the SVI for any given census tract, the higher the vulnerability and associated risk.

The Childhood Opportunity Index measures neighborhood resources and conditions that impact the healthy development of children focusing on three domains – education, health/environment, and social/economic. Zip Code Tabulation Areas are used to define census blocks and weighted averages of various domains as well as overall opportunity are calculated using z-scores.[27] Lower COI scores are associated with less opportunity and therefore higher risk.

The Area Deprivation Index measures area level deprivation across four key domains – income, education, employment, and housing quality. It is used to identify communities in need of investment and quantifies socio-economic variations in health outcomes.[29] Similar to the SVI, higher ADI scores are reflect higher degrees of deprivation and associated risk.

**Results**

A total of 230 patients with a hematologic malignancy or MDS were referred for consideration of first allogeneic HCT during the study period. One hundred (43.5%) patients were referred for B-ALL?, 78 (33.9%) for AML, and 29 (12.6%) for MDS. The median patient age at first referral was 9.5 years (IQR 3.6, 15.2). Sixty-three patients (27.5%) self-identified as Black, 78 (33.9%) self-identified as Hispanic, and 38 (16.6%) had a primary language other than English. Medicaid was the primary insurance for 124 (54.2%). There was significant social diversity amongst the cohort, with 113 (49.1%) residing in low/very-low COI areas and 62 (27.0%) living in areas with a high/very-high SVI (**Table 1**).

*Transplant Receipt by Disease Subtype*

Seventy patients (30.4%) never received a transplant -- 38 (54.3%) had ALL, 18 (25.7%) AML, 9 (12.9%) MDS, and 5 (7.1%) had an alternative leukemia subtype. The reasons for not proceeding to transplant were variable depending on underlying disease phenotype. Among patients with ALL, the most common reason for not receiving an HCT was pursuit of alternative therapy including traditional chemotherapy or CAR-T (n=26 ,68.4%, **Figure 2)**. Among patients with AML, disease progression or complications related to the underlying malignancy accounted for most patients who did not receive an HCT (n=15, 83.3%, **Figure 2).**

*Demographic and Disease-Related Factors Associated with Transplant Receipt*

In a univariable analysis including all referred patients, factors associated with HCT receipt included female sex (HR 1.35, CI 1.12-2.08), a diagnosis of AML (Ref: B-ALL, HR 2.10, CI 1.43-3.07) or infant leukemia (HR 2.44, CI 1.23-4.84), and a high SVI (indicative of high SDoH burden) at the national (Ref: low, HR 1.57, 95% CI 1.04-2.37) and state level (HR 1.66, 95% CI 1.11-2.48) (**Figure 3)**. There were no significant differences in HCT receipt based on age, sex, insurance, COI, or ADI. Additionally, there was no difference in HCT receipt based on duration of time between initial referral and consultation and no difference in time to death or last known alive between those who received transplant and those that did not (**Table 2**).

Among all referred patients, in a model adjusting for disease subtype, sex, national SVI and state SVI, high SVI at the national (HR 1.60, CI 1.06-2.43) and state level (HR 1.68, CI 1.12-2.52) remained statistically significantly associated with receipt of HCT (**Table 3**). Additional features associated with receipt of HCT included AML (HR 2.16, 95% CI 1.45-3.22) or infant leukemia (HR 2.27, 95% CI 1.06-4.85) as indication for HCT and female sex (HR 1.45, 95% CI 1.05-2.04).

*Sub-Analysis of Factors Associated with Transplant Receipt in Patients with AML and MDS*

To ensure that availability of alternative definitive therapies including CAR-T did not significantly impact the relationships between vulnerability and HCT receipt seen in the cohort, a sub-analysis of the AML/MDS cohort was conducted. A diagnosis of AML (ref: MDS, HR 2.48, CI 1.40-4.40) and a high SVI at the national (ref: low SVI, HR 1.96, CI 1.10-3.51) and state level (ref: low SVI, HR 1.81, CI 1.02-3.21) remained factors associated with HCT receipt (**Table 4**).

*Outcomes*

Among all referred patients there was a total of 88 deaths, 34 amongst those who did not undergo transplant (49%) and 54 amongst those who received HCT (34%). There was no significant difference in long term OS based on transplant status (HR 0.92, CI 0.66, 1.28) (**Figure 4**).

**Discussion:**

HCT for pediatric patients with hematologic malignancies and myelodysplastic syndromes is a critical and often life-saving intervention. Despite this, there are barriers to transplant receipt including disease control, availability of a suitable donor, and comorbidities. Social determinants of health may prove additional barriers, given the impact of factors such as poverty, insurance status, and marginalization on health status, access to care, and ability to comply with the rigorous requirements of the HCT process.

In this single institution cohort of 230 patients, 70 (30.4%) did not go on to receive HCT, a substantially lower percentage than the 55-65% failure rate reported in the adult literature for similar disease states.[51,52] Patients with a diagnosis of ALL most often received an alternative curative therapy, including CAR-T, while those with AML did not proceed to HCT largely secondary to disease progression. There was no association with transplant receipt and area deprivation (as proxied by the ADI), childhood opportunity (as proxied by the COI), race, ethnicity, primary language, or insurance status. Contrary to our hypothesis, higher social vulnerability at the national level, as proxied by the SVI, was associated

with a higher rate of HCT receipt (HR 1.63, p=0.02). This same association was seen at the state level (HR 1.62, p=0.02) amongst the whole cohort.

Given the discrepancies in reasons for failure to proceed to HCT, we sought to explore the potential impact of CAR-T availability on the study findings. Despite ongoing advances in cellular therapy, there is no consensus within the field on whether CAR-T or HCT is the preferred treatment modality for certain high risk patients with B-ALL.[53–55] The decision to proceed with HCT, CAR-T, or CAR-T as a bridge to HCT is often individual, based on the patient's clinical features, the providers experience, and the overarching institutional protocols.[53–56] In addition to the known variations in treatment patterns, our center was involved in early phase studies of cellular therapy for pediatric B-ALL, which was offered to eligible patients both on study prior to its FDA approval and following its approval in 2017. Prior work has shown sociodemographic variability amongst patients who go on study and those who elect for standard of care approaches, with underrepresentation of minority and marginalized populations.[57,58] This inclusion of study-eligible patients and of those with B-ALL who were eligible for CAR-T following its approval in a center that had the capacity to perform this procedure may have proven confounders, as more non-Hispanic White patients and those from higher socioeconomic backgrounds may have elected to pursue CAR-T, while patients from racial and ethnic minorities as well as those from communities with higher social disadvantage may have opted for HCT during these earlier years. Despite this concern, a sub-analysis of AML and MDS patients again revealed higher SVI at the national (HR 1.96, p=0.02) and state level (HR 1.81, p=0.04) was associated with higher rates of HCT receipt. These findings confirmed those seen in the total cohort and lent further support for the relationship between higher vulnerability and increased transplantation amongst pediatric patients.

In this analysis, only the SVI, not the ADI or COI, was associated with transplant receipt. This is likely in part due to the variability between the indices with regards to geographical unit of interest and original intended use of each metric. The ADI was specifically designed and validated for health

outcomes research while the SVI was meant to identify communities most vulnerable to natural disasters. [28,29,59] Given the variations in intended use, individual index components vary at both subtle and larger levels and may account for differences in associations with various health outcomes.[28,29,60] For example, while the SVI contains race, ethnicity, and language variables, these were not significantly associated with transplant receipt in the univariable analysis. Therefore, the relationship is likely being driven by more subtle variations in measures including housing and household composition that vary between the indices included. [61,62]

While the use of several indices allows for the capture of a wide array of patient experiences, it can complicate the analysis and interpretation of at times contradictory results. In fact, many studies conducted using various combinations of vulnerability indices have had mixed findings. While some have shown a strong association between all three of our included indices, others have shown strong correlation between only two of the three indices with any given outcome of interest.[59,63] It is therefore critical to keep in mind the population being studied and the exposure and outcomes of interest when conducting such research.

While the lack of consistency across SDoH metrics is well established in the literature, what contrasts with many previous studies, and with our theoretical framework more broadly, is the seemingly protective impact of higher social vulnerability and receipt of HCT. Prior studies of adult HCT and solid organ transplant recipients have noted lower incidence of both waitlist placement and organ receipt in patients with higher social vulnerability.[64–67] These findings are particularly striking amongst individuals with hematologic malignancies. A large Center for International Blood and Marrow Transplant Research study of patients with ALL, AML and MDS found that adults living in the counties with the highest poverty rates were the least likely to receive unrelated allogeneic HCT, though this relationship was not significant amongst the pediatric cohort.[13] Two additional large retrospective studies, one of patients referred to the Cleveland Clinic and one using the California Cancer Registry, had similar findings

amongst adult patients with acute leukemia, namely that individuals living in the lowest neighborhood socioeconomic status quintiles, those with public insurance, and those of Hispanic and non-Hispanic black race and ethnicity had the lowest rate of transplant receipt.[14,68] In these previous studies, vulnerability was thought to be a surrogate for potential barriers to the transplantation process including delayed listing for transplantation, financial barriers, limitations in insurance coverage, poor health literacy, and lack of financially and medically suitable donors.[51,66,69–71]

There are several potential explanations for the seemingly contradictory findings of our study. First, it is possible that pediatric patients from areas of higher vulnerability were not referred for consideration of transplantation and thus excluded from the study population. Referring centers may have deemed patients unsuitable for HCT based on disease or sociodemographic variables, or they may have had higher risk features that ultimately precluded the disease control necessary to move forward with the HCT process, a likely possibility given multiple previous studies that have shown racial and ethnic disparities in acuity and severity of disease at time of diagnosis with reduced EFS in minority populations.[72,73] Alternatively, it could be that pediatric comprehensive cancer centers such as ours, are better equipped to identify families at excess risk from social disadvantage and provide resources to help mitigate the negative impact of these risk factors on care access and outcomes. Reassuringly, all children referred did meet eligibility criteria and had a viable donor, negating the potential impact of referrals for diseases in which transplant is not indicated or for patients without a HCT option. While the exploration of these potential explanations is beyond the scope of the current report, it does provide rich prospective hypotheses to expand on in the future. Overall, these findings suggest that the most vulnerable patients in our center are receiving definitive therapy at rates not only equal to but exceeding those of less vulnerable populations.

This study has several strengths and limitations. It is a single center retrospective study, which may limit generalizability. However, based in part on our location within the greater Atlanta area, our

center cares for a large, diverse population with nearly two thirds of all patients identifying as a racial or ethnic minority and nearly 60% having Medicaid or no insurance coverage. Being the only pediatric HCT center in the state, we also cover a large catchment area, further increasing the geographic and sociodemographic diversity of the children cared for at our center. This provides a rich environment in which to study the impact of vulnerability and deprivation on healthcare access and outcomes. Additionally, the high-volume nature of our center allowed for the inclusion of over 200 unique patients within a relatively short period of time.

Due to the retrospective nature of this study, individual and finite measures of social vulnerability at the patient level were not captured, which may help to explain some of the variations seen. Additionally, it is important to note that within any given index, the individual variables may have varying relationships with the outcome of interest. The combination of variables into one overarching index may mask underlying differences between each exposure and outcome resulting in insignificant associations on the larger scale despite potential associations at more finite levels. Despite this, we leveraged widely recognized and validated indices that allowed us to capture several unique aspects of vulnerability while increasing the generalizability of findings to other populations of patients. This enhances the usefulness of our findings for public health researchers, clinicians, and policymakers alike.

Lastly, our team was unable to assess potential barriers to referral itself. Previous studies have suggested that biased referral processes may be an additional barrier to receipt of HCT/organ transplantation. If providers deem families unsuitable to move forward with the transplant process, a decision that is often based on multiple factors including race, insurance status, socioeconomic status, and underlying comorbidities, then they would not be referred or captured in this study[18,66] An advantage of focusing on the pediatric population, however, is that all pediatric oncology practices within the state and in surrounding areas follow Children's Oncology Group protocols which outline who and when to refer for HCT. By following established protocol, providers in these institutions would

presumably refer when indicated. While we are unable to confirm that all patients in need were sent for consultation, the protocols set forward by this larger governing body help mediate the potential for unreferred patients.

In conclusion, we found that nearly one third of eligible pediatric patients with hematologic malignancies and MDS who were referred for consideration of first allogeneic HCT did not ultimately go on to receive this definitive therapy. High social vulnerability, as proxied by the SVI, was associated with increased receipt of HCT across both the entire cohort as well as the AML/MDS sub-cohort. While there is no evidence from our study that children with higher social vulnerability are receiving HCT at lower rates, and in fact may be more likely to proceed to an HCT, further prospective studies are warranted to better understand this association.

**Table 1. Demographic and Disease Characteristics by Transplant Receipt Status**

| Characteristic | Total n (%), n = 230 | Transplant Yes, n = 160 | Transplant No, n = 70 |
|---|---|---|---|
| **Age at referral (mean, SD)** | 9.4 (5.8) | 9.1 (5.8) | 9.9 (6.0) |
| **Diagnosis** | | | |
| B-ALL | 85 (37.0%) | 51 (31.9%) | 34 (48.6%) |
| T-ALL | 15 (6.5%) | 11 (6.9%) | 4 (5.7%) |
| AML/T-AML | 78 (33.9%) | 60 (37.5%) | 18 (25.7%) |
| Infant Leukemia | 14 (6.1%) | 10 (6.3%) | 4 (5.7%) |
| Other Leukemia | 9 (3.9%) | 8 (5.0%) | 1 (1.4%) |
| MDS | 29 (12.6%) | 20 (12.5%) | 9 (12.9%) |
| **Remission Status*** | | | |
| CR1 | 72 (51.8%) | 72 (51.8%) | - |
| CR2 | 57 (41.0%) | 57 (41.0%) | - |
| >/CR3 | 6 (4.3%) | 6 (4.3%) | - |
| Active Disease | 4 (2.9%) | 4 (2.9%) | - |
| (Missing) | 21 | 21 | - |
| **MRD status*** | | | |
| Positive | 20 (14.8%) | 20 (14.8%) | - |
| Negative | 115 (85.2%) | 115 (85.2%) | - |
| (Missing) | 25 | 25 | - |
| **Sex** | | | |
| Male | 129 (56.1%) | 82 (51.3%) | 47 (67.1%) |
| Female | 101 (43.9%) | 78 (48.8%) | 23 (32.9%) |
| **Race** | | | |
| White | 130 (56.8%) | 87 (54.4%) | 43 (62.3%) |
| Black | 63 (27.5%) | 48 (30.0%) | 15 (21.7%) |
| Asian/Pacific Islander | 15 (6.6%) | 11 (6.9%) | 4 (5.8%) |
| Alaskan Native/ American Indian | 1 (0.4%) | 1 (0.6%) | 0 (0.0%) |
| Declined | 17 (7.4%) | 10 (6.3%) | 7 (10.1%) |
| Other | 3 (1.3%) | 3 (1.9%) | 0 (0.0%) |
| (Missing) | 1 | 0 | 1 |
| **Ethnicity** | | | |
| Hispanic | 60 (26.4%) | 42 (26.3%) | 18 (26.9%) |
| Non-Hispanic | 166 (73.1%) | 117 (73.1%) | 49 (73.1%) |
| Declined | 1 (0.4%) | 1 (0.6%) | 0 (0.0%) |
| (Missing) | 3 | 0 | 3 |
| **Primary Language** | | | |
| English | 191 (83.4%) | 133 (83.1%) | 58 (84.1%) |
| Spanish | 35 (15.3%) | 24 (15.0%) | 11 (15.9%) |
| Other | 3 (1.3%) | 3 (1.9%) | 0 (0.0%) |
| (Missing) | 1 | 0 | 1 |
| **If above not English, interpreter used?** | | | |
| Yes | 37 (97.4%) | 26 (96.3%) | 11 (100%) |

| | | | |
|---|---|---|---|
| No | 1 (2.6%) | 1 (3.7%) | 0 (0.0%) |
| **Primary Insurance type** | | | |
| Medicaid | 124 (54.2%) | 86 (53.8%) | 38 (55.1%) |
| Private | 88 (38.4%) | 63 (39.4%) | 25 (36.2%) |
| Charity Care/Uninsured | 7 (3.1%) | 4 (2.5%) | 3 (4.4%) |
| Tricare | 10 (4.4%) | 7 (4.4%) | 3 (4.4%) |
| (Missing) | 1 | 0 | 1 |
| **National COI at referral (mean, SD)** | 44.4 (27.3) | 43.0 (27.3) | 47.7 (27.0) |
| **National COI at Referral** | | | |
| Low | 113 (49.1%) | 82 (51.3%) | 31 (44.3%) |
| Moderate | 46 (20.0%) | 30 (18.8%) | 16 (22.9%) |
| High | 71 (30.9%) | 48 (30.0%) | 23 (32.9%) |
| **State COI at Referral** | | | |
| Low | 77 (33.5%) | 55 (34.4%) | 22 (31.4%) |
| Moderate | 50 (21.7%) | 37 (23.1%) | 13 (18.6%) |
| High | 103 (44.8%) | 68 (42.5%) | 35 (50.0%) |
| (Missing) | | | |
| **ADI National** | 55.9 (25.8) | 56.6 (26.0) | 54.1 (25.5) |
| (Missing) | 1[+] | 0 | 1[+] |
| **ADI State** | 5.1 (2.9) | 5.2 (2.9) | 4.9 (2.9) |
| (Missing) | 1 | 0 | 1 |
| **SVI National** | | | |
| Low | 62 (27.0%) | 41 (25.6%) | 21 (30.0%) |
| Medium | 99 (43.0%) | 65 (40.6%) | 34 (48.6%) |
| High | 69 (30.0%) | 54 (33.8%) | 15 (21.4%) |
| **SVI State** | | | |
| Low | 69 (30.0%) | 47 (29.4%) | 22 (31.4%) |
| Medium | 99 (43.0%) | 64 (40.0%) | 35 (50.0%) |
| High | 62 (27.0%) | 49 (30.6%) | 13 (18.6%) |

*At time of transplant, included patients who received HCT only

[+]Data unavailable in existing dataset

Definitions: ALL (acute lymphoblastic leukemia), AML (acute myelogenous leukemia), MDS (myelodysplastic syndrome), CR (complete remission), MRD (minimal residual disease), COI (childhood opportunity index), ADI (area deprivation index), SVI (social vulnerability index)

**Table 2: Univariable and Multivariable Analysis of Factors Associated with HCT Receipt Amongst Pediatric Patients with Hematologic Malignancies or MDS Referred for First Allogeneic HCT**

| | **Univariable** | | **Multivariable, Model 1‡** | | **Multivariable, Model 2‡** | |
|---|---|---|---|---|---|---|
| Characteristic | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | |
| **Age at referral** | 0.98 (0.96, 1.01) | 0.20 | 1.00 (0.97, 1.03) | 0.86 | 1.00 (0.97, 1.03) | 1.00 |
| **Diagnosis** | | | | | | |
| B-ALL | Ref. | | Ref. | | Ref. | |
| T-ALL | 1.68 (0.87, 3.23) | 0.12 | 1.84 (0.94, 3.59) | 0.07 | 1.99 (1.01, 3.93) | 0.05 |
| AML/T-AML | 2.21 (1.51, 3.24) | **<0.001** | 2.16 (1.45, 3.22) | **<0.001** | 2.07 (1.39, 3.09) | **<0.001** |
| Infant Leukemia | 2.47 (1.25, 4.89) | **0.01** | 2.27 (1.06, 4.85) | **0.04** | 2.15 (1.01, 4.56) | 0.05 |
| Other Leukemia | 1.96 (0.92, 4.16) | 0.08 | 1.84 (0.85, 3.97) | 0.12 | 1.78 (0.83, 3.82) | 0.14 |
| MDS | 1.02 (0.61, 1.71) | 0.95 | 1.00 (0.59, 1.69) | 1.00 | 1.02 (0.61, 1.73) | 0.93 |
| **Sex** | | | | | | |
| Female | Ref. | | Ref. | | Ref. | |
| Male | 0.64 (0.47, 0.87) | **0.004** | 0.69 (0.49, 0.95) | **0.02** | 0.70 (0.50, 0.97) | **0.03** |
| **Race** | | | | | | |
| White | Ref. | | | | | |
| Black | 1.36 (0.96, 1.94) | 0.09 | | | | |
| Other | 1.13 (0.72, 1.78) | 0.59 | | | | |
| **Ethnicity** | | | | | | |
| Non-Hispanic | Ref. | | | | | |
| Hispanic | 0.79 (0.55, 1.12) | 0.19 | | | | |
| **Primary Language** | | | | | | |
| English | Ref. | | | | | |
| Spanish | 0.84 (0.54, 1.29) | 0.42 | | | | |
| Other | 2.18 (0.69, 6.89) | 0.19 | | | | |
| **National COI at referral** | 1.00 (0.99, 1.00) | 0.10 | | | | |
| **National COI at Referral** | | | | | | |
| Low | Ref. | | | | | |
| Moderate | 0.76 (0.50, 1.16) | 0.20 | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| High | 0.81 (0.57, 1.16) | 0.25 | | | | |
| **ADI National, Continuous** | 1.00 (1.00, 1.01) | 0.19 | | | | |
| **ADI State, Continuous** | 1.05 (0.99, 1.11) | 0.10 | | | | |
| **SVI National** | | | | | | |
| Low | Ref. | | Ref. | | | |
| Medium | 1.12 (0.76, 1.65) | 0.58 | 1.37 (0.91, 2.08) | 0.14 | | |
| High | 1.54 (1.02, 2.31) | **0.04** | 1.63 (1.08, 2.46) | **0.02** | | |
| **SVI State** | | | | | | |
| Low | Ref. | | | | Ref. | |
| Medium | 1.01 (0.70, 1.48) | 0.94 | | | 1.15 (0.77, 1.72) | 0.50 |
| High | 1.58 (1.06, 2.36) | **0.03** | | | 1.62 (1.08, 2.43) | **0.02** |
| **Time from referral to consult in days, continuous** | 1.00 (0.99, 1.01) | 0.60 | | | | |
| **Time from consult to transplant in days, continuous** | 0.96 (0.95, 0.96) | **<0.001** | | | | |
| **Survival status** | | | | | | |
| Yes | Ref. | | | | | |
| No | 0.92 (0.66, 1.28) | 0.62 | | | | |
| **Time to death/LKA** | 1.00 (1.00, 1.00) | 0.09 | | | | |

‡Empty cells in multivariable models represent non-significant variables from univariable model. Multivariable model 1 incorporates all significant variables from the univariable model except stat SVI. Multivariable model 2 incorporates all significant variables from the univariable model except national SVI.

Definitions: ALL (acute lymphoblastic leukemia), AML (acute myelogenous leukemia), MDS (myelodysplastic syndrome), CR (complete remission), MRD (minimal residual disease), COI (childhood opportunity index), ADI (area deprivation index), SVI (social vulnerability index)

**Table 4. Multivariable Sub-Analysis of Factors Associated with HCT Receipt Amongst Pediatric Patients with AML or MDS Referred for First Allogeneic HCT**

| | **Multivariable, Model 1** | | **Multivariable, Model 2** | |
|---|---|---|---|---|
| Characteristic | HR (95% CI) | p | HR (95% CI) | p |
| **Age at Referral** | 1.01 (0.98, 1.05) | 0.50 | 1.01 (0.98, 1.05) | 0.52 |
| **Diagnosis** | | | | |
| MDS | Ref. | | Ref. | |
| AML/T-AML | 2.48 (1.40, 4.40) | **0.002** | 2.45 (1.37, 4.38) | **0.003** |
| **Sex** | | | | |
| Female | Ref. | | Ref. | |
| Male | 0.83 (0.53, 1.30) | 0.42 | 0.85 (0.54, 1.33) | 0.46 |
| **SVI National** | | | | |
| Low | Ref. | | | |
| Medium | 1.43 (0.79, 2.59) | 0.23 | | |
| High | 1.96 (1.10, 3.51) | **0.02** | | |
| **SVI State** | | | | |
| Low | | | Ref. | |
| Medium | | | 1.36 (0.76, 2.44) | 0.30 |
| High | | | 1.81 (1.02, 3.21) | **0.04** |

**Figure 2. Indications for Failure to Proceed to Transplant by Disease Subtype**

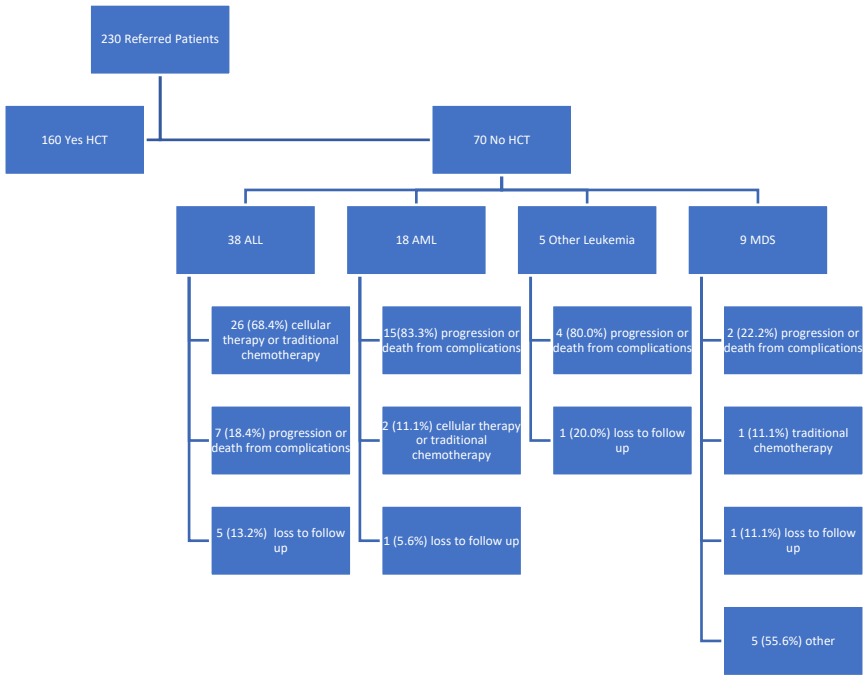


**Figure 3: State-Level SVI by Census Tract for Georgia Patients with Hematologic Malignancies or MDS Referred for First Allogeneic HCT**

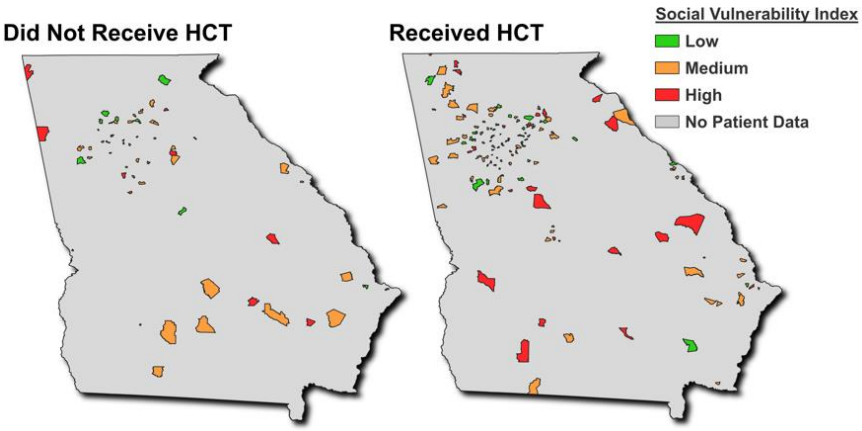
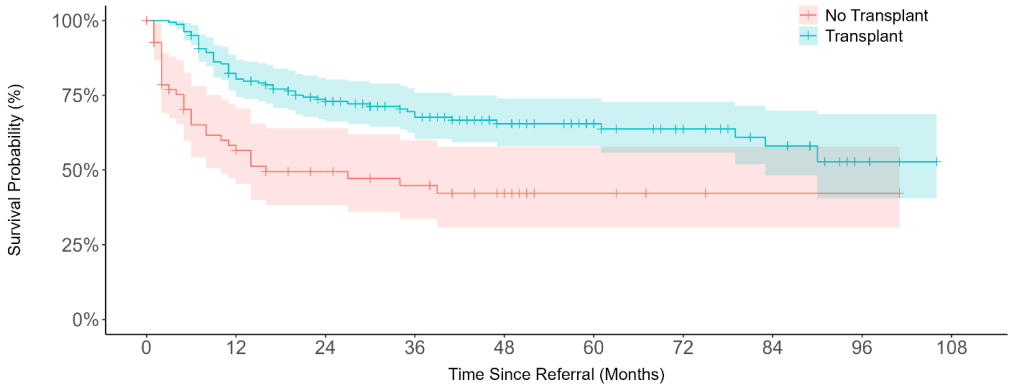



**Figure 4. Long-Term Overall Survival Based on Transplant Status**



## Chapter 5: Discussion, Public Health Implications, and Conclusions:

### *Study Findings and Discussion*

In the United States, nearly 5 in 100,000 children are diagnosed with leukemia each year. While many with acute lymphoblastic leukemia are cured with chemotherapy alone, relapsed and refractory disease remain a challenge.[1] Further, many children with acute myelogenous leukemia and myelodysplastic syndrome present with high-risk cytogenetics that necessitate the incorporation of additional therapeutic modalities. In these challenging cases, physicians often refer for HCT with the goal of achieving a durable remission.

HCT for pediatric patients with hematologic malignancies and myelodysplastic syndromes is a well-established, critical, and often life-saving intervention. While over 1,000 pediatric patients undergo this procedure annually in the United States, significant barriers to transplant receipt remain in place. [6–9] Some of these barriers are related to the underlying malignancy and the transplant process itself, including need for disease control, issues with donor availability, and prohibitory comorbidities. However, social determinants of health may prove additional barriers, given the impact of factors such as poverty, insurance status, and marginalization on health status, access to care, and ability to comply with the rigorous requirements of the HCT process. [7,8,13–17]

In this single institution, retrospective cohort study of 230 pediatric patients with hematologic malignancies or MDS who were referred for consideration of first allogeneic HCT, 70 (30.4%) did not go on to receive HCT. While this is a substantially lower percentage than the 55-65% failure rate reported in the adult literature for similar disease states, nearly one in three children did not receive the definitive therapy that was deemed critical to their care, highlighting an important gap in the system.[51,52] Interestingly, reasons for failure to proceed to HCT were variable depending on the primary diagnosis. Patients with a diagnosis of ALL most often received an alternative curative therapy, including CAR-T, while those with AML did not proceed to HCT largely secondary to disease progression.

When considering factors associated with transplant receipt, no singular sociodemographic feature was significant including race, ethnicity, primary language, or insurance status. Similarly, there was no association with transplant receipt and area deprivation (as proxied by the ADI) or childhood opportunity (as proxied by the COI). Contrary to our hypothesis, however, higher social vulnerability at the national level, as proxied by the SVI, was associated with a higher rate of HCT receipt (HR 1.63, p=0.02). This same association was seen at the state level (HR 1.62, p=0.02) amongst the whole cohort.

It is important to recognize the potential impact of acceptable variations in treatment patterns for certain disease subtypes on the outcomes of this study. There is currently no consensus within the field of pediatric oncology as to whether CAR-T or HCT is the preferred treatment modality for patients with B-cell acute lymphoblastic leukemia who require definitive therapy beyond standard chemotherapy.[53–55] CAR-T is a cellular therapy in which a patient's own T cells are removed from their circulating blood and then engineered in the lab to express receptors specific to antigens found on the circulating tumor cells. These T cells can recognize and remove cancer cells from circulation as an extension of the individual's immune system. They can also proliferate in the patient, thereby providing long term surveillance and cancer control. Unlike with HCT, there is no myeloablative chemotherapy requirement, no risk for graft-versus-host disease, and no prolonged period of immune compromise making it an enticing alternative to children with comorbidities that may make transplantation especially high risk.[56,74]

While an exciting potential alternative to HCT, CAR-T only received FDA approval for children with B-cell acute lymphoblastic leukemia in 2017. There is currently no FDA approved product for T-cell acute lymphoblastic leukemia, acute myelogenous leukemia, or any other hematologic malignancy. Given the relative novelty of this technology, there is a lack of standardization on CAR-T implementation. While some centers offer it as a standalone procedure, many others view it as a bridge to definitive transplantation. The decision to proceed with HCT, CAR-T or CAR-T as a bridge to HCT is often individual,

based on the patient's clinical features, the providers experience, and the overarching institutional protocols.[53–56] Given this variability, it is plausible that there are cases in which the treatment of choice for B-cell acute lymphoblastic leukemia would vary based on the center. Additionally, it is important to note that Children's Healthcare of Atlanta was involved in early phase studies of cellular therapy for pediatric acute lymphoblastic leukemia. CAR-T was offered to eligible patients both on study prior to the FDA approval and following its approval for certain high risk leukemias. Prior studies have consistently shown that the demographics of patients who go onto active studies are different than those that opt for current standard of care, with underrepresentation of minority and marginalized populations.[57,58] This inclusion of study-eligible patients may have therefore influenced the results seen, as more non-Hispanic White patients and those from higher socioeconomic backgrounds may have elected to pursue CAR-T, while patients from racial and ethnic minorities as well as those from communities with higher social disadvantage may have opted for HCT during these earlier years.

With the recognition that variations in both practice patterns and trial enrollment were potential confounders in the study, we performed a sub-analysis of the acute myelogenous leukemia and myelodysplastic syndrome cohort in which no alternative definitive therapy existed during the study period. Again, higher SVI at the national (HR 1.96, p=0.02) and state level (HR 1.81, p=0.04) was associated with higher rates of HCT receipt. This sub-analysis confirmed the findings seen in the total cohort and lent further support for the relationship between higher vulnerability and increased transplantation amongst pediatric patients.

In this analysis, only the SVI, not the ADI or COI, was associated with transplant receipt. To best understand the discrepancies seen, it is critical to understand the differences between the metrics used. First, the geographical unit of measurement and therefore the granularity of vulnerability ascertained by each metric is variable. The SVI and COI measure variables at the census tract level while the ADI measures variables at the census block group level. Census tracts are larger conglomerates and therefore

may provide less specific data on any given neighborhood in which a child is residing. [19–21] Secondly, the metrics were created for different indications. The ADI was specifically designed and validated for health outcomes research and the COI was intended to understand the impact of neighborhood level social and environmental features on childhood development. The SVI on the other hand was meant to identify communities most vulnerable to natural disasters and was not initially intended to study individual health outcomes. [27–29,59] Given the variations in intended use, individual index components vary at both subtle and larger levels and may account for differences in associations with various health outcomes.[28,29,60] For example, while the SVI contains race, ethnicity, and language variables, these were not significantly associated with transplant receipt in the univariable analysis. Therefore, the relationship is likely being driven by more subtle variations in measures including housing and household composition that vary between the indices included. [61,62]

While the use of several indices allows for the capture of a wide array of patient experiences, the variability between metrics can complicate the analysis and interpretation of at times contradictory results. In fact, many studies conducted using various combinations of vulnerability indices have had mixed findings. While some have shown a strong association between all three of our included indices, others have shown strong correlation between only two of the three indices with any given outcome of interest.[59,63] It is therefore critical to keep in mind the population being studied and the exposure and outcomes of interest when conducting such research.

While the lack of consistency across SDoH metrics is established in the literature, what contrasts with many previous studies, and to the underlying framework of Fundamental Causes Theory as a whole, is the seemingly protective impact of higher social vulnerability on receipt of HCT. Prior studies of adult hematopoietic cell and solid organ transplant recipients have noted lower incidence of both waitlist placement and organ receipt in patients from areas of higher vulnerability.[64–67] More specifically amongst patients with acute leukemia and myelodysplastic syndromes, a large Center for International Blood and

Marrow Transplant Research study found that individuals living in the counties with the highest poverty rates were the least likely to receive unrelated allogeneic HCT.[13] This relationship was interestingly seen amongst adult populations alone, with no significant correlation amongst pediatric patients. Two additional large retrospective studies, one of patients referred to the Cleveland Clinic and one using the California Cancer Registry, had similar findings amongst adult patients with acute leukemia, namely that individuals living in the lowest neighborhood socioeconomic status quintiles, those with public insurance, and those of Hispanic and non-Hispanic Black race and ethnicity had the lowest rate of transplant receipt.[14,68] In these studies, vulnerability was thought to be a surrogate for potential barriers to the transplantation process including delayed listing for transplantation, financial barriers, limitations in insurance coverage, poor health literacy, and lack of financially and medically suitable donors.[51,66,69–71]

There are several possible explanations as to why a relationship between higher vulnerability and increased transplantation receipt was seen amongst our cohort. It is possible that pediatric patients from areas of higher vulnerability were not referred for consideration of transplantation and thus were excluded from the study population. Referring centers may have deemed patients unsuitable for transplantation based on disease or sociodemographic variables. Reassuringly, all children referred for transplantation did meet eligibility criteria and had a viable donor, negating the potential impact of referrals for diseases in which transplant is not indicated or for those without a HCT option. Alternatively, patients may have had higher burdens of disease or adverse cytogenetics that precluded the disease control necessary to move forward with the HCT process, a plausible explanation given that prior studies have shown racial and ethnic disparities in acuity and severity of disease at time of diagnosis with reduced event free survival in minority populations.[43,44]

Beyond potential referral bias, it could be that pediatric comprehensive cancer centers such as ours, are better equipped to identify families at excess risk from social disadvantage and provide resources to help mitigate the negative impact of these risk factors on care access and outcomes. In

providing supports including rent assistance, transportation assistance, and meal vouchers the effects of resource-limitations on families may be lessened. Lastly, in considering Fundamental Causes, there could be an aspect of social capital that is at play and providing a protective factor for more objectively vulnerable patients. For example, the children from areas of higher vulnerability may have had larger or more intricate social support networks that provided a buffer against the detrimental effects of economic disadvantage. While the exploration of these potential explanations is beyond the scope of the current report, it does provide rich prospective hypotheses to expand on in the future. What is perhaps most important at this juncture is the fact that these findings are reassuring and indicate that the most vulnerable patients in our center are receiving definitive therapy at rates not only equal to but exceeding those of less vulnerable populations.

This study has several strengths and limitations. It is a single center retrospective study utilizing convenience sampling, which may limit generalizability both to other disease states and other institutions. However, based in part on our location within the greater Atlanta area, our center cares for a large, diverse population. Nearly two thirds of all patients seen at Children's Healthcare of Atlanta identify as a racial or ethnic minority and nearly 60% having Medicaid or no insurance coverage.[75] This is consistent with the larger metropolitan area in which nearly 50% of residents are Black, 6% are Hispanic, and 18% are living in poverty.[76] The catchment area of the pediatric HCT center is even larger, given that it is the only one in the state, further increasing the geographic and sociodemographic diversity of the children served. This provides a rich environment in which to study the impact of vulnerability and deprivation on healthcare access and outcomes. Additionally, the high-volume nature of our center allowed for the inclusion of over 200 unique patients within a relatively short period of time, allowing for a robust understanding of the impacts of social determinants on a contemporary cohort.

Due to the retrospective nature of this study, individual and finite measures of social vulnerability at the patient level were not captured. For example, we were not able to ascertain

individual family composition, income, or resource insecurity, all of which are known to be significant factors for families pursuing HCT and which may have contributed to the variations seen.[77] We were also not able to determine the extent of each individual's social support and connectedness, which may have illuminated a potential protective factor in terms of social capital within the overarching framework of Fundamental Causes. Despite this, we leveraged widely recognized and validated indices that allowed us to capture several unique aspects of vulnerability while increasing the generalizability of findings to other populations of patients. This enhances the usefulness of our findings for public health researchers, clinicians, and policymakers alike.

Lastly, our team was unable to assess potential barriers to referral itself, given that we focused on patients who had already been referred for transplantation. Previous studies have suggested that biased referral processes may be an additional barrier to receipt of both hematopoietic and solid organ transplantation. If providers deem families unsuitable to move forward with the transplant process, a decision that is often based on multiple factors including race, insurance status, socioeconomic status, and underlying comorbidities, then they would not be referred or captured in this study[18,66] Unfortunately, this often results in underinsured individuals, Black individuals, and those with limited social supports being disproportionately left without access to this potentially life-saving intervention.[18] An advantage of focusing on the pediatric population, however, is that all pediatric oncology practices within the state and in surrounding areas follow Children's Oncology Group protocols which outline who and when to refer for HCT. By following established protocols, there is no subjectivity in the decision of who is eligible for transplantation, and providers would presumably refer when indicated. While we are unable to confirm that all patients in need were sent for consultation, the protocols set forward by this larger governing body help mediate the potential for unreferred patients.

*Public Health Implications*

The findings of this study have important implications for both public health research and practice. First, the striking difference in findings between adult and pediatric populations raises an interesting question about what variations exist between these cohorts that can explain the discrepancy and that can be mitigated to provide equitable care to all patients. It is reasonable to hypothesize that vulnerable pediatric patients may be given more resources within the health system, including the default availability of Medicaid, a luxury not afforded to all adults. This, and the availability of charity care, financial assistance programs, grant funding and the like may provide a more equitable milieu in which care is delivered. Further, sociodemographic barriers including degree of available social support and socioeconomic standing are not seen as deterrents to providing high risk and intensive interventions to children the same way they are in adults. It is rare within pediatrics to deny a child certain treatments based solely on their station in life, a reality that is seen across adult centers in which poor, socially isolated individuals are often faced with less options in their care.[13] While this may in part be a commentary on our societies view of social worth, the importance of prioritizing care for those who have lived only a small fraction of life, and the inherent desire to protect vulnerable children and adolescents, it may also provide insight into the ways that pediatric and adult hospitals function differently.[78] For example, while adult transplant centers on average have much higher patient volumes than pediatric hospitals, there are a greater number of psychosocial clinicians for any given number of patients within pediatric centers compared to adult centers.[79] These individuals may be able to provide support and resources while advocating for patients, and their paucity on the adult side may be part of the reason for the disparities seen.

Based on the results of our study, much can be learned from the care delivery models of pediatric comprehensive cancer centers, and this knowledge can be applied to both adult oncology patients as well as patients with other disease states. By performing prospective studies to understand

the variations in care, we can better understand where providers and systems may be falling short in the care of adult patients. This will allow us to integrate beneficial pediatric models into the adults care system, improving access to high quality, equitable care for all patients.

In addition to the potential differences between adult and pediatric care, the findings of this study raise interesting questions about the potentially disparate impact of tangible resources on health outcomes. In line with Fundamental Causes Theory, children from more disadvantaged backgrounds would be posited to have worse access and outcomes. In fact, across a large body of literature social disadvantage in childhood is linked to worse health outcomes across a wide spectrum of physical and mental conditions.[25] Therefore, the conclusion that vulnerability was associated with increased receipt of definitive therapy in our cohort is contradictory to what is not only expected but what has been recapitulated over years and across subspecialties. To better understand this relationship, prospective studies are again critical. They could home in on individual level factors of the patients within this population, focusing on aspects such as social support, social networks, and the degree and nature of fiscal support provided by the treating institution, as this may prove a fundamental difference in the realm of pediatric oncology compared to other chronic disease states. Building these studies with Social Capital Theory in mind in addition to Fundamental Causes Theory, and an understanding that bonding capital can result in a dismantling of care seeking barriers, may help to shine additional light on this phenomenon.[34,35]

*Conclusion*

In conclusion, we found that nearly one third of eligible pediatric patients with hematologic malignancies and MDS who were referred for consideration of first allogeneic HCT did not ultimately go on to receive this definitive therapy. While a number of those who failed to proceed died from complications related to their underlying malignancy, a problem that is well known and a driver of

ongoing research into novel treatment approaches, a significant number also went on to receive alternative definitive therapies or were lost to follow up. In contrast to our proposed hypothesis, high social vulnerability, as proxied by the SVI, was associated with increased receipt of HCT across both the entire cohort as well as the AML/MDS sub-cohort. While we are reassured that in this study children with social vulnerability are not receiving HCT at lower rates, and in fact may be more likely to proceed to an HCT, further prospective studies are warranted to better understand this association.

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