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Influence of Socioeconomic Status on Event-Free Survival in Children Diagnosed with Acute Lymphoblastic Leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) is the most common type of cancer diagnosed in children. However, little is known about how socioeconomic status (SES) influences the outcomes of children diagnosed with ALL. The goal of the research study was to understand how SES impacted the outcomes of children diagnosed with ALL, with a particular interest in children living in West Michigan. Children ages 0-14 years who received treatment for ALL at Spectrum Health's Helen DeVos Children's Hospital's Pediatric Hematology and Oncology program between the years 2002-2011 were considered for this study. Eligible participant's zip codes and dates of relapse/death were obtained through retrospective chart reviews to investigate the association of interest. Zip codes were utilized to create neighborhood SES scores based on census data related to education, occupation, and household income. Time to relapse/death was determined to calculate five-year event-free survival. Differences in survival across socioeconomic tertiles were evaluated using Kaplan-Meier survival analysis, with Cox-proportional hazard regression conducted to describe the association between all collected variables. Statistical analyses revealed that children of higher socioeconomic standing were shown to have an increased risk of relapse or death compared to children of lower socioeconomic standing, however these findings did not show a statistically significant difference between the neighborhood socioeconomic tertiles. Although previous research has shown that those of higher SES tend to have better overall health and better health outcomes, compared to those of lower SES, this research study suggests that these differences may not always occur as expected. Decreased exposure to early childhood infectious agents by way of improved hygiene and changes in childcare may explain why children of higher socioeconomic may be at greater risk of poor health outcomes compared to those of lower socioeconomic standing. These findings may also indicate that differences in outcomes between various

socioeconomic groups may have diminished over the period of interest through the use of better health communication and health services.

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Key to Symbols

Symbol	Meaning
↓	Worse outcome compared to reference population
↑	Better outcome compared to reference population
=	Similar outcome compared to reference population
‡	$p<0.05$
*	Adjusted for neighborhood socioeconomic status scores (based on tertiles created), age, race, and sex
†	Adjusted for neighborhood socioeconomic status scores (based on tertiles created), age, race, sex, immunophenotype, and white blood cell count at diagnosis

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Abbreviations

Abbreviation	Meaning
AHRQ	Agency for Healthcare Research and Quality
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myelogenous Leukemia
B-ALL	B-Cell Acute Lymphoblastic Leukemia
CCR	California Cancer Registry
CD	Cluster of Differentiation
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
EMR	Electronic Medical Record
HR	Hazard Ratio
MRN	Medical Record Number
SEER	Surveillance, Epidemiology, and End Results
SES	Socioeconomic Status
SD	Standard Deviation
T-ALL	T-Cell Acute Lymphoblastic Leukemia

I. Introduction

Leukemia is a form of blood/bone marrow cancer that affects people of all ages. While many types of leukemia exist within nature, children under the age of 15 years are more notably diagnosed with acute lymphoblastic leukemia (ALL), the most common type of cancer for this age group (United States Cancer Statistics Working Group, 2016). Between the years 2009-2013, the incidence rate for all leukemias in children ages 0-14 was 5.23 cases per 100,000 children (United States Cancer Statistics Working Group, 2016). Leukemias of lymphoid origin accounted for 4.00 of those cases (United States Cancer Statistics Working Group, 2016). A variety of risk factors for this disease exist, including genetic mutations and environmental exposures, however most patients do not have any of the known risk factors for leukemia (Hunger & Mullighan, 2015). Similarly, little is known about how some factors, such as socioeconomic status and race/ethnicity, influence patient outcomes among those that have been diagnosed with ALL. Lower socioeconomic status has been associated with worse outcomes for many health problems across the world, however its influence on the outcomes of those diagnosed with ALL is not well understood (Demakakos, Nazroo, Breeze, & Marmot, 2008). And although the association between socioeconomic status and ALL outcomes has been studied by other researchers, few studies have been conducted within the United States, with none looking specifically at a West Michigan population (Bona, Blonquist, Neuberg, Silverman, & Wolfe, 2016; Charalampopoulou et al., 2004; Erdmann et al., 2014; Gupta, Sutradhar, Guttmann, Sung, & Pole, 2014; Gupta, Wilejto, Pole, Guttmann, & Sung, 2014; Kent, Sender, Largent, & Anton-Culver, 2009; Lightfoot et al., 2012; Metzger et al., 2003; Njoku, Basta, Mann, McNally, & Pearce, 2013; Petridou et al., 2015; Sergentanis et al., 2013; Son, Kim, Oh, & Kawachi, 2011; Viana, Fernandes, de Carvalho, & Murao, 1998).

Purpose

The purpose of this research study is to determine if there is a difference in five-year event-free survival among West Michigan children diagnosed with ALL living in various socioeconomic standings.

Scope

This study will be used to determine if there is a difference in event-free survival for children diagnosed with ALL among different socioeconomic groups studied. The study population will be defined as children receiving pediatric cancer care for ALL from Spectrum Health's Helen DeVos Children's Hospital's Pediatric Hematology and Oncology program who live within a specific set of counties in West Michigan. For children diagnosed with ALL between January 1, 2002 and December 31, 2011 who meet the inclusion criteria stated above, demographic information, as well as leukocyte count at diagnosis, age at diagnosis, immunophenotype of the child's cancer, and zip code will be collected via electronic medical record (EMR) review to assess for potential differences in survival based on neighborhood socioeconomic scores.

Hypothesis

Null Hypothesis (H_0): there is no difference in survival between those with lower socioeconomic status and those with higher socioeconomic status

Alternative Hypothesis (H_a): there is a difference in survival between those with lower socioeconomic status and those with higher socioeconomic status

Although the formal hypotheses are stated as being two-sided to allow for a difference in either direction, the researcher hypothesizes that there will be difference in survival by the level of socioeconomic status, with children of lower socioeconomic standing having worse outcomes compared to children of higher socioeconomic standing. People of higher socioeconomic

standing tend to have better overall health and better health outcomes, compared to those of lower socioeconomic standing (Demakakos et al., 2008). Among studies that looked at socioeconomic status' influence on ALL outcomes within the United States, most of the studies found differences in survival between different socioeconomic groups, with those being of lower socioeconomic standing having worse ALL outcomes, further supporting the researcher's hypothesis (Abrahão et al., 2015; Acharya et al., 2016; Kent et al., 2009).

Significance

Due to the previous establishment of socioeconomic status' influence on health outcomes for a variety of health problems, it is imperative that individuals understand its impact on those diagnosed with ALL. As of 2016, Michigan ranked seventh within the United States for estimated new cases of leukemia with 1,890 possible new cases (Siegel, Miller, & Jemal, 2016). Michigan also ranked eighth within the United States for estimated deaths from leukemia, with 850 possible deaths likely to have occurred in 2016 (Siegel et al., 2016). While this study will only look at those diagnosed with ALL within West Michigan, the understanding of this possible difference in survival among various socioeconomic groups can allow doctors and communities to tailor their accommodations for these cancer patients on a one-to-one basis. While treatment protocols typically remain the same for all pediatric patients diagnosed with ALL, physicians may be able to modify the types of conversations they are having with their various patients based on their socioeconomic status.

II. Literature Review

Acute lymphoblastic leukemia is known to have a variety of factors that can affect overall survival and event-free survival. Each case of ALL is unique due to a combination of these factors, which include leukocyte count at diagnosis, age at diagnosis, the patient and his or her family's socioeconomic status, the patient's primary form of medical insurance, the patient's race and ethnicity, the immunophenotype and cytogenetics of the leukemic cells, and the sex of the patient (Alperstein, Boren, & McNeer, 2015; Lustosa de Sousa, de Almeida Ferreira, Cavalcante Félix, & de Oliveira Lopes, 2015; Teachey & Hunger, 2013). Many studies have been designed to understand how these various factors influence outcomes in children with ALL, however additional studies continue to be published due to the differences seen among different places within the United States and the world. Other potential predictive factors of outcome in ALL, such as the level of adherence to treatment therapy, the existence of a mediastinal mass, and central nervous system involvement, have also been studied but have limited research to confirm their predictive nature (Bhatia et al., 2012, 2014; Teachey & Hunger, 2013). Nevertheless, it is important that all factors are discussed in order to understand how each influence the outcome of the research question that will be studied.

Purpose

While many factors for ALL have been identified, some factors have various effects in different parts of the world, namely socioeconomic status and form of health insurance. Socioeconomic status is a complex entity that can be influenced by a variety of factors, such as income, education, and occupation (Diez Roux et al., 2001). Socioeconomic status can also impact health insurance opportunities, potentially limiting treatment options for children with ALL. Thus, it is important that the effect of socioeconomic status is studied in various population

settings to determine how it affects children who are diagnosed with ALL. However, other factors also play an important role in the survival of children with ALL, therefore these predictive factors will also be included within the study's analyses. All factors will be discussed to provide baseline knowledge of its known effects on children diagnosed with ALL.

Literature Synthesis

Leukocyte count at diagnosis. One of the primary prognostic factors used by the National Cancer Institute to determine a child's prognosis when first diagnosed with ALL is their leukocyte, or white blood cell, count at diagnosis (n.d.). Hyperleukocytosis, or a leukocyte count above the normal range of 3,500-10,500 cells/µL, has been described as an emergency situation within the hematological oncology field, as it has been linked to early morbidity and mortality in children (Mayo Foundation for Medical Education and Research, n.d.; Vaitkeviciene et al., 2013). Children who are diagnosed with ALL and have a leukocyte count equal to or less than 50,000 cells/µL at diagnosis are considered to be standard risk patients, while those who have a count of more than 50,000 cells/µL leukocytes are considered high risk patients (National Cancer Institute, n.d.). These interpretations were consistent with Hunger and Mulligan's (2015) and Alperstein et al.'s (2015) research. Lustosa de Sousa et al. (2015) noted that patients who present with hyperleukocytosis when first diagnosed with ALL may also arrive with other complications, such as tumor masses, enlargement of the spleen and liver, and lymphadenopathy, further impacting the patient's prognosis. While hyperleukocytosis at diagnosis typically indicates advanced disease state and a worse prognosis, strategies have been put in place to limit the strength of treatment, as aggressive treatment plans can cause tumor lysis syndrome and be lethal (Kong, Seo, Jun, Lee, & Lim, 2014). Although leukocyte count at diagnosis is one of the most important prognostic factors for children diagnosed with ALL, age has also been shown to have a strong impact on the outcomes of children with ALL.

Age at diagnosis. Few studies have openly discussed the significance that a child's age at the time of their ALL diagnosis has on their prognosis, however, the National Cancer Institute (n.d.) recognizes this as one of its two primary prognostic factors. Teachey and Hunger (2013) described age as a strong predictor of relapse, stating that children who are diagnosed with ALL under the age of one year or above the age of nine years tend to have worse prognoses than children ages 1-9 years. Wang, Bhatia, Gomez, and Yasui (2015) later determined that children aged 0-1 year and 10 years and above had a much greater risk of death compared to children ages 1-9 years. Within their study, children less than one year of age were 7.57 times more likely to die from ALL compared to children ages 1-9 years (Wang et al., 2015). Children 10 years and above did not have as great of a risk of death, but were still 4.01 times more likely to die from ALL compared to those ages 1-9 years (Wang et al., 2015) . Lustosa de Sousa et al.'s (2015) study also showed a correlation between age at diagnosis and the prognosis of that child, as children under the age of nine years had a five-year survival probability of 80%, compared to 55% for children over the age of nine years (Lustosa de Sousa et al., 2015). An earlier study by Khalid, Moiz, Adil, and Khurshid (2010) showed that only age and immunophenotype had a significant influence on a child's outcome status, although only 46 patients were included in their studied. They found that 78% of the children diagnosed between ages 1-9 years (n=27) had survived ALL for the 17-year duration of the study, compared to 0% of children under the age of one year (n=2) and 53% over the age of nine years (n=17) (Khalid et al., 2010). Reasons for the differences in survival rates based on age have been hypothesized, but few studies have confirmed why these differences occur. Alperstein et al. (2015) mentioned that children younger than one year of age typically have a very aggressive form on the disease compared to children above the age of one year, possibly due to the rearrangement of the *MLL* gene, which is

commonly found within these children (Wang et al., 2015). Similarly, children 10 years and above are also likely to have gene rearrangements associated with poor prognoses, along with having other unfavorable factors such as high leukocyte counts (Lustosa de Sousa et al., 2015). Wang et al. (2015) discussed the limited access to pediatric clinical trials seen by children over the age of nine years which may potentially impact the survival of this age group as well (Wang et al., 2015). Unfortunately, many of these hypotheses remain unstudied, leaving doctors unsure of why these differences occur, however it has been well documented that age at diagnosis is a strong predictor of outcome in ALL.

Socioeconomic status. Although the National Cancer Institute (n.d.) only recognizes leukocyte count at diagnosis and age as primary prognostic factors for children with ALL, socioeconomic status has also been shown to be an important factor in the outcomes of these children. Most studies discussed socioeconomic status by means of parental education levels, monthly income, number of people living within one house, marital status, healthcare access, area remoteness, along with a few other factors that were not frequently mentioned (Charalampopoulou et al., 2004; Gupta, Sutradhar, et al., 2014; Petridou et al., 2015; Viana, et al., 1998). While it has been shown that socioeconomic status has had an impact on other disease outcomes, few studies have been conducted within the United States to understand the impact of socioeconomic status on children with ALL and their event-free survival. However, worldwide studies appeared to be more common, especially within developing countries. Differences in study outcomes were noted between the United States and other countries across the world, possibly due to variations in the structure of healthcare systems within these countries. Particular attention should be given to studies conducted within the United States as it pertains to the area of interest for this study.

United States studies. Without having a national health care system, yet being economically developed, the United States provides a unique perspective for the association between socioeconomic status and ALL outcomes. Families who are considered economically advantaged within the United States may not have issues getting access to treatment for their child with ALL, yet those who are economically disadvantaged typically do not have the same fate. And although treatment techniques for ALL have improved over the past few decades, a global meta-analysis completed by Petridou et al. (2015) found that children who were considered to have lower socioeconomic standing tended to be impacted by these changes in treatment the least. Twenty-three studies specific to ALL were included within the meta-analysis that assessed a variety of outcomes, such as overall survival, event-free survival, and post-relapse survival (Petridou et al., 2015). Researchers found that specific indicators of socioeconomic status, such as education, level of poverty, employment status, and household income, had a significant impact on overall survival (Petridou et al., 2015). Differences were noted between the countries included within the analysis, as studies done within the United States often saw discrepancies in childhood ALL outcomes between different socioeconomic groups, while other countries did not see these differences (Petridou et al., 2015). The following studies are the most recent reports that look at the association between socioeconomic status and ALL outcomes in children in the United States. Other studies have been conducted in previous decades, however changes in treatment throughout the past few decades were thought to compromise the external validity of those studies in comparison to today's population.

In a study conducted across seven different tertiary care centers within the United States, researchers reported an association between time to relapse and the calculated socioeconomic status of the patient (Bona et al., 2016). Zip codes and United States Census Bureau data were

utilized to create a measurement system of the socioeconomic status of a specific area, while information on ALL diagnosis was extrapolated from the tertiary care centers (Bona et al., 2016). The overall survival of children living with ALL was only 85% within high-poverty areas, compared to 92% for those that lived in low-poverty areas, however no difference was observed in event-free survival (Bona et al., 2016). However, among the studies completed within the United States, this study was the only one to collect data via another source besides a state cancer registry, possibly adding bias to the findings of this study. Those who had the means to seek treatment from one of the Dana-Farber Cancer Institute Consortium centers may have been more advantaged compared to those who did not, thus it is best to consider additional findings when reviewing the significance of socioeconomic status' impact on ALL outcomes in children.

By using the California Cancer Registry (CCR), Kent, Sender, Largent, and Anton-Culver (2009) also completed a study on socioeconomic status' influence on ALL outcomes. The study was open to those aged 0-39 years and not specified by leukemia type, different from most of the studies analyzed within this review. To understand the importance of socioeconomic status on leukemia outcomes, Kent et al. (2009) utilized the CCR's neighborhood socioeconomic status variable, which was calculated using, "median educational attainment, median household income, proportion below 200% of the federal poverty level, median house value, median rent, percent employed, and proportion of the population with blue-collar employment (p. 1410)." Results showed that among all types of leukemia, with the exception of chronic lymphocytic leukemia, those living within the lowest socioeconomic quintile were shown to have a 31% increased risk of death compared to those living within the highest socioeconomic quintile (Kent et al., 2009). A similar study completed by Abrahão et al. (2015) found that children and young adults with ALL, aged 0-19 years, who lived within the lowest socioeconomic quintile were seen

to have a 39% increase in the risk of death compared to those that lived in the highest socioeconomic quintile. Following the conclusion of their study, Abrahão et al. (2015) hypothesized that these results could be due to the migrant population seen in California, as undocumented workers may not wish to seek medical attention for their child until they see it as an absolute necessity, which could lead the child to becoming much sicker in a short period of time. A study that looked at other high migration states found comparable results, supporting this hypothesis. Acharya et al. (2016) used a study population composed of children, ages 0-18 years, which resided in Florida or Texas. They found that those living in areas where 20-100% of the people lived in poverty were at 2.16 times greater risk of death compared to those living in areas where less than 5% of the people live in poverty, with areas having 5-20% of the population living in poverty having 1.36 times the risk of death compared to that same group (Acharya et al., 2016). As with Abrahão et al. (2015), Acharya et al. (2016) reported that more studies need to be conducted within the United States to support this association. Although many other studies have been conducted worldwide, few countries are structurally similar to the United States, contributing to the possibility of differences occurring among the findings of each respective study.

Worldwide studies. A vast assortment of studies have been conducted worldwide to determine the effects of socioeconomic status upon children diagnosed with ALL. Studies reviewed spanned across four out of the seven continents around the world, and included countries such as Brazil, Canada, England/United Kingdom, Germany, Greece, Honduras, Scotland, South Korea, and Wales (Charalampopoulou et al., 2004; Erdmann et al., 2014; Gupta, Sutradhar, Guttman, Sung, & Pole, 2014; Lightfoot et al., 2012; Metzger et al., 2003; Njoku, Basta, Mann, McNally, & Pearce, 2013; Sergentanis et al., 2013; Son, Kim, Oh, & Kawachi,

2011; Viana, et al., 1998). The influence of socioeconomic status varies in each country due to the unique social and governmental structure found in each, providing the importance of studying each country individually.

Low to middle-income countries have continued to see inferior cure rates for ALL compared to developed countries, as cure rates within these countries have remained near 35% while developed countries often see cure rates of 80% or more (Metzger et al., 2003). With only one treatment hospital available for all patients, Honduras often sees these reduced cure rates (Metzger et al., 2003). Metzger et al. (2003) tried to identify the specific reasons for these poor outcomes by studying children ages 0-18 years that were receiving treatment for ALL in Honduras. Although socioeconomic variables were not available for their study, it was discussed that these factors more than likely pertained to the worse outcomes seen within low- to middle-income countries. Metzger et al. (2003) identified that the most common reason for treatment failure was due to treatment abandonment, possibly influenced by lack of transportation to the hospital, lack of parental education, or general non-compliance. A study from El Salvador found that maternal illiteracy, presence of a central line, and the belief that weather caused fever were all associated with sepsis in children diagnosed with either ALL or acute myelogenous leukemia (AML), further relating poor outcomes in children with leukemia to lack of parental education, a factor of socioeconomic status (Gavidia et al., 2012). Within Brazil, children with ALL that had lower socioeconomic standing had 2.51 times the risk of relapse compared to children with higher socioeconomic standing (Viana, et al., 1998). Viana et al. (1998) evaluated socioeconomic status using a questionnaire that assessed various socioeconomic factors for each child's family. These factors included number of individuals living under one roof, monthly income for each individual in the family, general electric consumption, physical characteristics

of each family's house, feeding habits of the family, sources of entertainment for the family, mechanisms used by the family to cope, and the family's level of perception of leukemia (Viana, et al., 1998). This thorough assessment added strength to the association found between socioeconomic status and risk of relapse. Among the studies reviewed, Central and South American countries continued to struggle to have higher cure rates for leukemia compared to other parts of the world, more than likely due to lower socioeconomic standings among their citizens. However, low- and middle-income countries were not the only ones that faced these issues, as some developed countries have also experienced these associations as well.

Developed countries such as England/United Kingdom, Scotland, Wales, and Greece have also seen associations between socioeconomic status and various ALL outcomes among their children (Charalampopoulou et al., 2004; Lightfoot et al., 2012; Njoku et al., 2013; Sergentanis et al., 2013). Furthermore, a study including all childhood cancers in South Korea had similar findings (Son et al., 2011). Within this study, a birth cohort was established and followed for 10 years, or until death occurred (Son et al., 2011). Death from cancer was analyzed based on parental education and occupation found on birth certificates within the area studied (Son et al., 2011). After stratifying specifically for children with leukemia, parental occupation was the only socioeconomic variable seen to impact the mortality of the child (Son et al., 2011). Similar findings occurred within a study conducted within England/United Kingdom (Njoku et al., 2013). Njoku et al. (2013) studied socioeconomic status based upon the parental education reported on the birth certificates of participating individuals. After collecting data on leukemia (both ALL and AML) from the Northern Region Young Persons Malignant Disease Registry, Njoku et al. (2013) found significantly decreased rates of survival at one-year, five-years, and ten-years post-leukemia diagnosis. Researchers were somewhat surprised by these findings since

England/United Kingdom has a national healthcare system where all treatments are free for children diagnosed with leukemia (Njoku et al., 2013). It was hypothesized that these differences could be due to the challenges in gaining access to the health care provided to the country's citizens (Njoku et al., 2013). Nonetheless, comparable results were also seen in a different study done within England/United Kingdom, which also included Scotland and Wales into its analysis (Lightfoot et al., 2012). Lightfoot et al. (2012) found that there was a greater risk of death at five years post-diagnosis for those in the lower socioeconomic quintiles compared to individuals in the higher socioeconomic quintiles. Although Njoku et al. (2013) and Lightfoot et al. (2012) had similar findings, not all studies conducted within the same country showed similar findings at the conclusion of their study.

Two studies in Greece investigated the effect of socioeconomic status on ALL outcomes in children. Of the two studies carried out in Greece, one study used a nationwide registry (Nationwide Registry for Childhood Hematological Malignancies) for their study population while the other study used cases occurring within four Grecian hospitals across the country (Charalampopoulou et al., 2004; Sergentanis et al., 2013). Within the study using the nationwide registry, personal interviews were conducted to obtain information relating to a variety of sociodemographic variables (Sergentanis et al., 2013). Parental job status significantly impacted the outcomes of children with leukemia (either ALL or AML), as children who had parents with lower professional statuses were seen to have a 40% decrease in survival compared to children whose parents were in higher professions. Charalampopoulou et al. (2004) obtained data relating to socioeconomic status at the time of diagnosis, but did not find any socioeconomic status factors that statistically impacted survival in children with ALL. Both distance from treatment facility and maternal schooling were shown to be suggestive of poor survival in the children

studied, however were not found to be statistically significant (p = 0.08 and 0.14, respectively). Although the studies were completed during two different time periods (1996-2010 and 1996-2002) and used different methods of assessing socioeconomic status, it was expected that similar results would be found (Charalampopoulou et al., 2004; Sergentanis et al., 2013). Nevertheless, the differences in association found within Greece show the importance of studying different areas within a country, as contrasting results can be found even in similar populations.

Although most of the studies reviewed found an association between socioeconomic status and poor outcomes for children with ALL, two studies, along with Charalampopoulou et al. (2014), did not observe an association. Gupta et al. (2014) studied children ages 0-18 years living in Ontario, Canada who were diagnosed with ALL during the years 1995-2011. Socioeconomic status was evaluated by using the patient's zip code address and relating it to median income quintiles for that particular neighborhood (Gupta et al., 2014). No association between five-year event-free survival and socioeconomic status was seen after univariable and multivariable analysis (Gupta et al., 2014). Similarly in West Germany, family income, maternal education, and residential area had no influence on overall survival or event-free survival (Erdmann et al., 2014). Cases of ALL were established through the German Childhood Cancer Registry and were only included within the study if the child had been diagnosed between October 1992 and September 1994 and was under the age of 15 at the time of diagnosis (Erdmann et al., 2014). Socioeconomic status was evaluated via questionnaire or telephone interview (Erdmann et al., 2014). Both studies postulated that the null association they concluded was possibly due to the universal healthcare insurance provided to the citizens of each of the countries studied, as it can help to prevent the cost of treatment from interfering with adequate access to treatment for children with ALL (Erdmann et al., 2014; Gupta et al., 2014).

Unfortunately, the lack of access to treatment continues to impact the outcomes of the child with ALL in many other countries due to a variety of factors, including lack of health insurance and the location of treatment centers.

As shown, differences in ALL outcomes based on socioeconomic status occur all over the world and even differ among various areas of the United States. Different areas across the United States and the world need to be further examined to better understand this association. It is important to remember that ALL is the most common type of leukemia in children, accounting for nearly 75-80% of all childhood leukemias, and accounts for nearly 25% of all childhood cancers (Lustosa de Sousa et al., 2015; National Cancer Institute, n.d.). Nevertheless, socioeconomic status has been shown to be influential among the outcomes of children diagnosed with ALL. However, health insurance, an entity relating to one's socioeconomic status, may also impact ALL outcomes in children independently.

Studies involving health insurance. A limited number of studies have examined the association between health insurance and leukemia outcomes. Of the studies reviewed, none looked exclusively at leukemia outcomes in children, and only one studied the influence of health insurance on patients with ALL. In the study that looked at outcomes among those with ALL, only young adults 18-30 years of age were assessed to understand the influence of insurance on overall survival (Fintel, Jamy, & Martin, 2015). Data was collected using the Surveillance, Epidemiology, and End Results (SEER) database between the years 2007-2010, and it was concluded that there was no statistical difference in the overall survival of the patients studied based on health insurance (Fintel et al., 2015). However, in a study looking at patients with AML, type of insurance was found to have an effect on overall survival (Master, Munker, Shi, Mills, & Shi, 2016). Within this study, the National Cancer Database was used to study

patients of all ages diagnosed with AML between the years 1998 and 2011 (Master et al., 2016). Among the 67,443 patients included in the study, those that were uninsured had a 20% increased risk of death from AML, while patients with Medicare or Medicaid had a 19% and 16% increased risk of death from AML compared to those with private insurance (Master et al., 2016). A study completed in Puerto Rico showed similar results, as those covered by the government healthcare plan were at 1.6 times greater risk of death from leukemia compared to those covered by a non-government healthcare plan (Ortiz-Ortiz et al., 2014). However, these results were only seen among patients 65 years of age or older, meaning that these results do not necessarily apply to children (Ortiz-Ortiz et al., 2014). Nonetheless, knowledge in this area of study is limited, and further research in this field is needed.

Race and ethnicity. In children with ALL, race and ethnicity have commonly been identified as possible prognostic factors. Numerous studies have shown that blacks, Hispanics, and Native Americans have worse survival rates compared to non-Hispanic white children, while Asian children have been shown to have differing survival rates compared to non-Hispanic white children (Abrahão et al., 2015; Acharya et al., 2016; Bhatia et al., 2002; Goggins & Lo, 2012; Hunger & Mullighan, 2015; Kadan-Lottick et al., 2003). Hunger and Mullighan (2015) stated within their review that these differences in survival rates might be due to the difference in the incidence of various genetic mutations among these races and ethnicities. For example, *TCF-3PBX1* ALL is more common in blacks, while the *CRLF-2* ALL is more commonly found in Hispanics (Hunger & Mullighan, 2015). Thus, genetic differences may confound the impact that race and ethnicity have been shown to have.

Differences in survival between non-Hispanic white children and black, Hispanic, and Native American children were reported within two of the studies reviewed (Bhatia et al., 2002;

Kadan-Lottick et al., 2003). In these same studies, Asian children were not found to have significantly different survival rates compared to non-Hispanic white children (Bhatia et al., 2002; Kadan-Lottick et al., 2003). Although non-Hispanic white children were more commonly represented within each of these studies, this skewed population distribution was expected, as non-Hispanic white children tend to have higher rates of leukemia compared to other races and ethnicities (McCance, Huether, Brashers, & Rote, 2010). Only Kadan-Lottick et al. (2003) were able to capture a Native American population within their study, however the proportion of the sample size represented by this population was minute. Nevertheless, black and Hispanic children were found to be at significantly higher risk of poor outcomes in ALL compared to non-Hispanic children within both studies, with Native American children having worse ALL outcomes compared to non-Hispanic white children within Kadan-Lottick et al.'s (2003) study (Bhatia et al., 2002). In contrast, Bhatia et al. (2002) found that Asian children were at decreased risk of poor outcomes compared to non-Hispanic white children, however Kadan-Lottick et al. (2003) reported that neither group experienced superior outcomes compared to the other. This difference may have been due to a larger population size utilized by Kadan-Lottick et al. (2003), but no other explanations for these differences could hypothesized by the researcher. Although both studies had relatively large sample sizes (N=4,952 in Kadan-Lottick et al. [2003] and N=8,447 in Bhatia et al. [2002]), the sample size for a specific race or ethnicity may have been small, impacting the external validity of these results. This can be seen in Kadan-Lottick et al.'s (2003) studying involving Native Americans, in which only 1.2% of the study population identified as Native Americans.

Among the studies that did not find similar outcomes between Asian children and non-Hispanic children, differences were still found between non-Hispanic white and black, Hispanic,

and where applicable, Native American children (Abrahão et al., 2015; Acharya et al., 2016; Goggins & Lo, 2012). Archarya et al. (2016) did not find similar outcomes between non-Hispanic white children and Asian children since their study only compared the outcomes between non-Hispanic white, Hispanic, and black children. Asian and Native American children were excluded from their study due to low population sizes among all patients identified for their study (Archarya et al. (2016). Similarly, Goggins and Lo (2012) further stratified Asian children into the categories of East Asian (Chinese, Filipino, Korean, Japanese, Vietnamese, and other Southeast Asian), Other Asian, and South Asian. Therefore, each of these subpopulations had different findings with varying levels of significance. East Asian children were found to have an increased risk of poor outcomes in ALL, as were black, Native American, and Hispanic children when compared to non-Hispanic white children, however other Asian populations did not have these same findings, possibly due to the small sample population seen within these racial groups (Goggins & Lo, 2012). Abrahão et al. (2015) also found worse outcomes among Asian, black, and Hispanic children when comapred to non-Hispanic children. Black children were seen to have the worst outcomes of all races, having 1.78 times the risk of death compared to non-Hispanic white children while Hispanic children were at 1.33 times greater risk and Asian children at 1.33 times greater risk (Abrahão et al., 2015). Even so, it can be difficult to study the association of ALL outcomes in children based upon race and ethinicity due to differences in the distribution of ALL cases among all races and ethinicities, especially when studying different areas across the world, thus all results should be reviewed with caution. A brief summary of all the racial and ethnic studies reviewed can be found in Table 1.

Table 1.

Differences in ALL outcomes in children based upon race and ethnicity by research study

	Races and Ethnicities Studied				
Authors	African American/Black	Asian	Non-Hispanic White/Caucasian	Hispanic	Native American
Abrahão et al. (2015)	↓ ‡	↓ ‡	reference	↓ ‡	n/a
Acharya et al. (2016)	↓ ‡	n/a	reference	↓ ‡	n/a
Bhatia et al. (2002)	↓ ‡	↑ ‡	reference	↓ ‡	n/a
Goggins & Lo (2012)	↓ ‡	↑/↓	reference	↓ ‡	↓ ‡
Kadan-Lottick et al. (2003)	↓ ‡	(=)	reference	↓ ‡	↓ ‡

Note. ↓ indicates worse outcome compared to reference population; ↑ indicates better outcome compared to reference population; and (=) indicates similar outcome compared to reference population

‡ $p<0.05$

While a variety of studies have examined the correlation of race and ethnicity and ALL outcomes in children, a lack of standardization and a large variance in the number of cases among all races and ethnicities often makes it hard to compare these studies. A majority of the studies assessed showed that black and Hispanic children often had the worst outcomes among all races and ethnicities evaluated, with two studies finding the highest levels of risk in Native American children (Abrahão et al., 2015; Acharya et al., 2016; Bhatia et al., 2002; Goggins & Lo, 2012; Kadan-Lottick et al., 2003). It is evident that although non-Hispanic white children have higher rates of incidence for ALL, they often experience the best outcomes in relation to the disease. Numerous reasons, ranging from genetic to socioeconomic, could explain for these results, however limited studies have been conducted to assess these speculations.

Sex. Many studies describe sex as having prognostic importance for childhood ALL, yet it remains relatively unknown to what extent. In all cancer sites, males have had higher death rates per 100,000 compared to females since the early 1900s (Siegel et al., 2016). And while sex appears to have some prognostic importance, Khalid et al. (2010) did not find a difference in

survival rates between males and females, ages 0-16 years, within their study. However, a limitation of this study was the limited amount of females (*n*=11) included in the study compared to males (*n*=35) (Khalid et al., 2010). Conversely, Teachey and Hunger (2013) stated within their review of predictors of leukemia relapse that sex does have some level of prognostic importance, but the extent of this importance remains undetermined. While some of this significance lies in the fact that the incidence rate for all types of leukemia is higher in males than females, young males may have worse outcomes in ALL specifically due to worse DNA indices, higher T-ALL incidence rates, along with other biological differences compared to females (McCance et al., 2010; Teachey & Hunger, 2013; Wang et al., 2015). Regardless of these differences, sex is currently only seen to have limited prognostic value, and is generally not used to stratify the risk of children with ALL (Teachey & Hunger, 2013).

Immunophenotype. Another important prognostic factor for children diagnosed with ALL is immunophenotype. Immunophenotype is used to describe the presence of specific cell molecules found on the surface of leukocytes, specifically lymphocytes in the case of ALL, in order to direct treatment therapies for a child or adult with ALL (Hunger & Mullighan, 2015). These surface molecules, otherwise known as cluster of differentiation (CD) markers, are used to differentiate T-cells from B-cells, and ultimately guide treatment therapy in ALL patients (Shu & Chen, 2005). Within children who have ALL, roughly 85% of cases are found to be of B-cell origin, with the other 15% having T-cell origins (Hunger & Mullighan, 2015). For a variety of reasons, T-cell ALL (T-ALL) has often been noted to be the least favorable type of childhood ALL in terms of outcome status (Alperstein et al., 2015; Hunger & Mullighan, 2015; Lustosa de Sousa et al., 2015; Teachey & Hunger, 2013). Hunger and Mullighan (2015) noted within their study that this could be because those with T-ALL tend to also be males, black, and also present

with higher leukocyte counts at diagnosis, along with having central nervous system involvement or mediastinal masses, thus already having an unfavorable prognosis. Nevertheless, patients diagnosed with T-ALL are subjected to more intense treatments due to its extremely aggressive nature (Alperstein et al., 2015). Fortunately, the differences in survival outcome between children who have B-cell ALL (B-ALL) and T-ALL have slowly decreased as treatments have improved (Teachey & Hunger, 2013). However, in children that end up relapsing, those with B-ALL can still typically be cured, whereas relapsed T-ALL children have a very poor rates of three-year event-free survival, with rates typically below 15% (Teachey & Hunger, 2013). Thus, it is important that the diagnosis is accurate from the beginning and that treatment is adequate.

Cytogenetics. The understanding and relative importance of the cytogenetics of a patient's leukemic cells has vastly increased over the past several decades. Cytogenetic analysis first began back in 1956 when it was discovered that a normal human cell housed 46 chromosomes (Harrison, 2009). As described by Harrison in 2009, the two primary informational pieces that physicians look at following chromosomal analysis are if there is a change in the number of chromosomes found within the leukemic cells or if there are changes in the genetic make-up of the chromosomes within these cells. Cells that contain less than 44 chromosomes are often referred to as being "hypoploidy," while cells containing more than 50 chromosomes are referred to as being "hyperploidy," (Alperstein et al., 2015). Although the National Cancer Institute does not currently recognize any cytogenetic abnormalities as being prognostic factors for relapse in those diagnosed with ALL, various authors have noted that some cytogenetic abnormalities have been associated with favorable or unfavorable prognosis (Alperstein et al., 2015; Harrison, 2009; Hunger & Mullighan, 2015; National Cancer Institute, n.d.; Pui, Mullighan, Evans, & Relling, 2012; Teachey & Hunger, 2013). Differences in the

importance in various cytogenetic abnormalities were noted within each article, however it is likely that new mutations were discovered throughout the years, creating these differences. Nonetheless, children containing hyperploidy leukemic cells, as well as cells containing a translocation between chromosomes 12 and 21 (creating a fusion protein known as *ETV6-RUNX1*) were commonly associated with having a favorable prognosis (Alperstein et al., 2015; Harrison, 2009; Hunger & Mullighan, 2015; Pui et al., 2012; Teachey & Hunger, 2013). Children that had leukemic cells that were hypoploidy, or contained either a translocation between chromosomes 9 and 22 (creating the *BCR-ABL1* fusion protein), an *MLL* rearrangement, or had an intrachromosomal amplification of chromosome 21 (iAMP21), were all identified as having unfavorable chromosomal abnormalities (Alperstein et al., 2015; Hunger & Mullighan, 2015; Pui et al., 2012; Teachey & Hunger, 2013). Additional chromosomal abnormalities are currently being evaluated for their prognostic value, with current estimations of their frequencies and prognostic value being shown in Figure 1 (Pui et al., 2012; Teachey & Hunger, 2013).

Treatment adherence. Although many people tend to study the overall impact of the factors that cannot be controlled, one factor that can often be controlled and has been shown to impact overall survival and event-free survival is adherence to prescribed treatment therapies. Treatment adherence can be influenced by socioeconomic status factors such as education and income, however race and ethnicity can also play contribute to the effectiveness of a treatment (Bhatia et al., 2012, 2014). For those diagnosed with ALL, treatment typically follows a similar path as depicted in Figure 2, but can differ depending on the factors discussed previously (Alperstein et al., 2015). Patient adherence becomes important during the maintenance phase of treatment, which lasts between two and three years depending on the sex of the child with ALL (Alperstein et al., 2015; Bhatia et al., 2012). In a study conducted by Bhatia et al. (2012),

adherence rates to oral mercaptopurine, a drug commonly used within the maintenance phase of ALL treatment, were studied in children under the age of 21 who were either of Caucasian or Hispanic descent. At the end of the six month study, statistical analysis was completed to see if there was an association between adherence rates and the risk of relapse (Bhatia et al., 2012). Compared to children who adhered to the medication 95% or more of the time, children adhering to the oral treatment only 90-94.9% of the time had four times greater risk of relapse, with those adhering 85-89.9% and less than 85% of the time having 3.6-5 times greater risk of relapse (Bhatia et al., 2012). Bhatia et al. (2014) found similar findings within a later study conducted, however it was also discovered that African-American and Asian-American children had more trouble adhering to treatment compared to Caucasian children, along with children living in low-income households (<$50,000) compared to children living in higher-income households (≥$50,000). African Americans had adherence rates of 87.1% ± 2.2% and Asian Americans had adherence rates of 90.0% ± 2.5%, decreased from the 95.2% ± 0.6% adherence rates found in non-Hispanic white children (Bhatia et al., 2014). Similarly, children living in low-income households only had adherence rates of 89.7% ± 1.8% compared to the 95.3% ± 0.8% adherence rates observed in higher income households. Thus, the importance of treatment adherence should not be disregarded in studies that cannot obtain long-term follow-up information on treatment adherence within their study population.

Summary

While a variety of factors have been explored within this literature review, others may exist in addition to those already discussed. At the present, researchers have found that socioeconomic status, race and ethnicity, leukocyte count at diagnosis, immunophenotype, age at diagnosis, and sex have shown to have an impact on the survival of children with ALL, yet differences in these influences have been seen among different populations. It is difficult to say

which factor has the largest impact on ALL survival in children, as each factor can possibly intertwine within another factor and increase the risk of poor outcomes in these children. In general, the National Cancer Institute (n.d.) stratifies children into risk groups based only upon leukocyte count at diagnosis and age, however as we have seen within the literature, other factors also play an important role in the survival of children diagnosed with ALL.

Conclusion

A variety of factors affecting the survival of children diagnosed with ALL have been introduced and examined within this literature review. Some of these variables have been well-established as prognostic factors, however others have rarely been studied or have shown various levels of importance based upon the study population. For that reason, it is important to study specific factors, such as socioeconomic status and race and ethnicity within the West Michigan population of children diagnosed with ALL to establish the level of importance of these factors for this particular population. Other factors are important to assess for within the study, as their effects have shown value within other studies and should not be excluded. In the following chapter, the methodology of this study will be discussed in further detail, and will relate back to a majority of the variables discussed within this literature review.

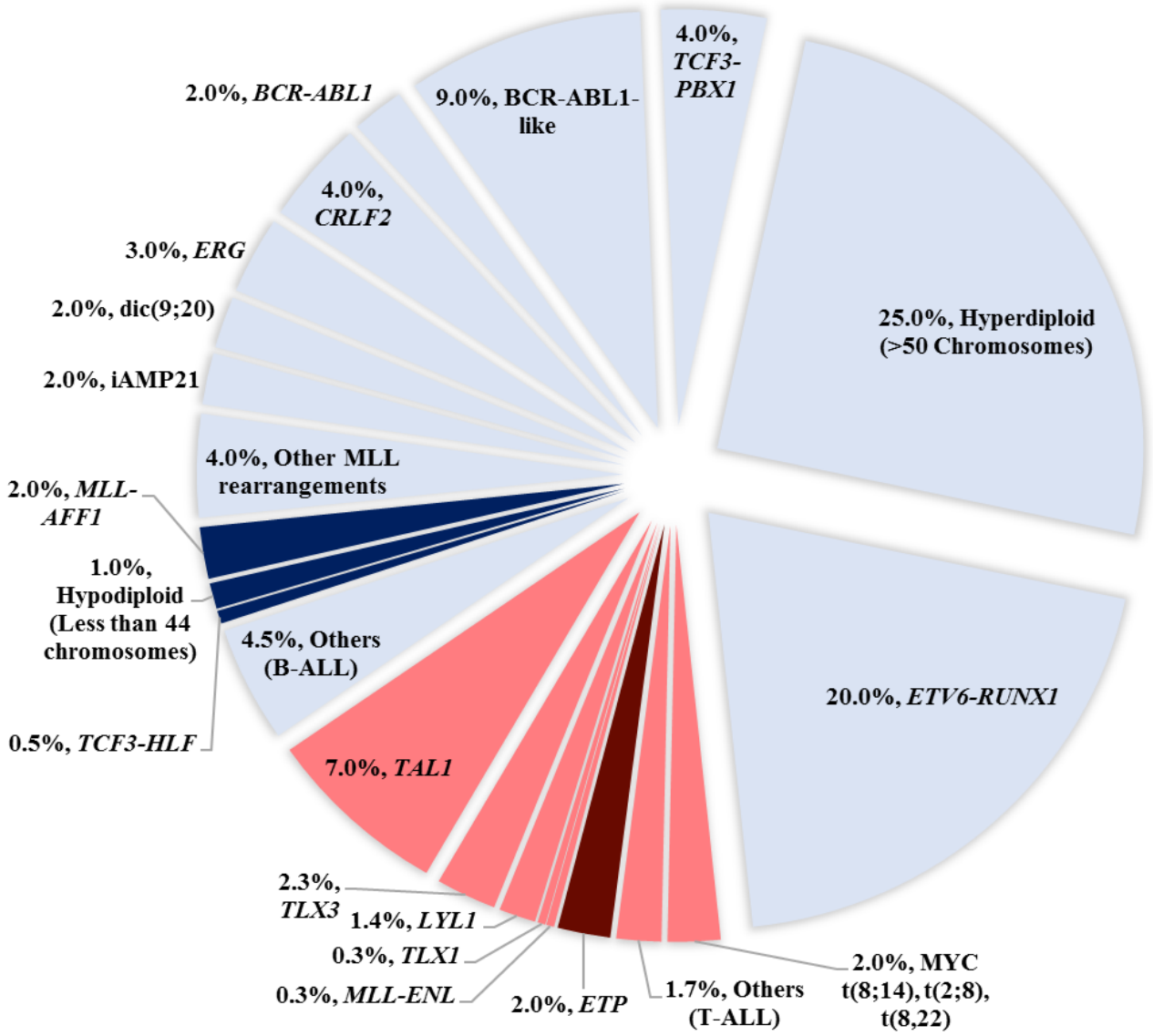

Figure 1. Approximate frequency of genetic subtypes found in leukemic cells among children diagnosed with ALL. Blue colors indicate subtypes commonly found in children diagnosed with B-ALL, while red colors indicate subtypes commonly found in children diagnosed with T-ALL. Darker colors indicate subtypes that have been correlated with poor prognosis. Data for chart retrieved from Pui, Mullighan, Evans, & Relling (2012).

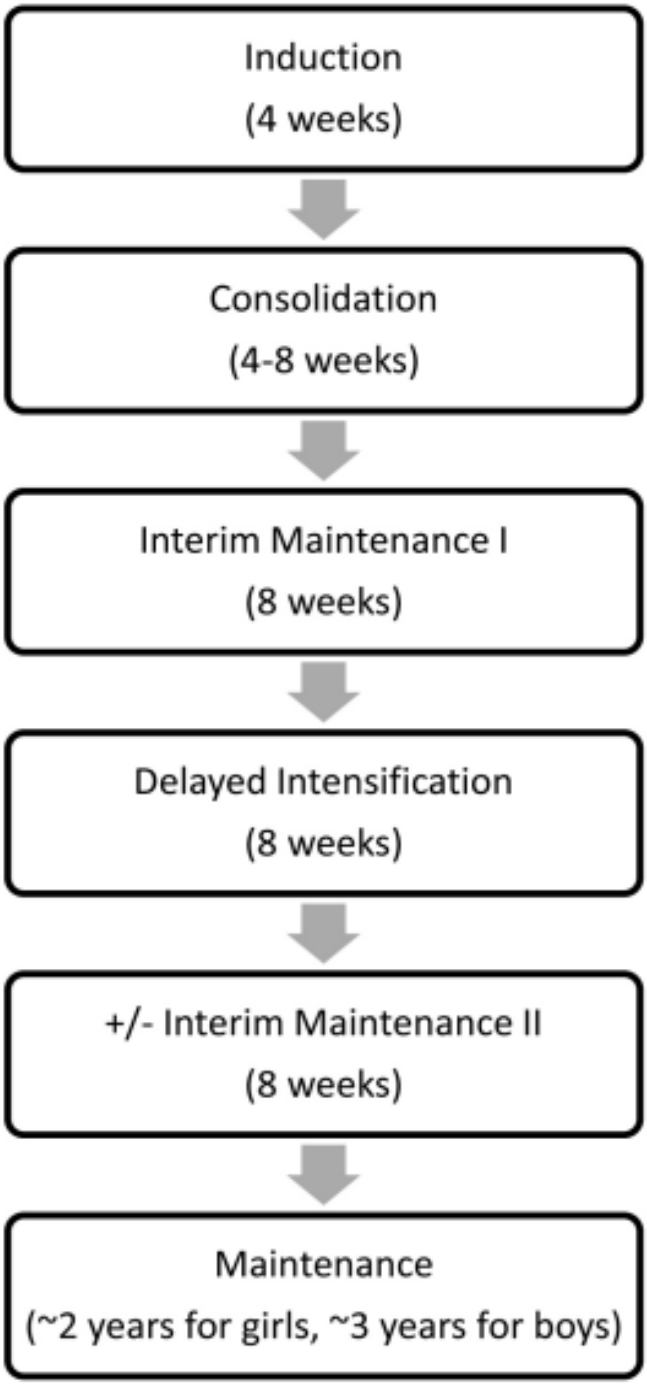

Figure 2. Standard treatment therapy progression for children with ALL.

Image from Alperstein et al. (2015).

III. Methodology

Socioeconomic status has negatively influenced the outcomes of many diseases around the world, however its association with five-year event-free survival in children with ALL has not been frequently assessed within the United States. Furthermore, the association between socioeconomic status in the population of West Michigan children diagnosed with ALL and event-free survival has yet to be examined. Determining what risk factors influence five-year event-free survival in West Michigan children ages 0-14 years is important to add to the limited literature on this topic. Within this section, the overall study design for this research question, including study participants, data collection methods, and data analysis methods, will be discussed.

Participants/subjects

ALL accounts for roughly 26% of all cancers in children ages 0-14 years (American Cancer Society, n.d.). In 2013, the United States Cancer Statistics Working Group (2016) calculated the age-adjusted incidence rate for ALL in children ages 0-14 years to be 3.72 per 100,000 people, the highest incidence rate among all cancers. Thus, children ages 0-14 years who were diagnosed with ALL between the years 2002-2011 were considered for this study. To restrict the chance of differences in treatment affecting any associations found, the study population was limited to children receiving treatment from the Helen DeVos Children's Hospital's Pediatric Hematology and Oncology program. Then, only those residing within one of the following Michigan counties (Allegan, Barry, Eaton, Ionia, Isabella, Kent, Lake, Mason, Mecosta, Montcalm, Muskegon, Newaygo, Oceana, Osceola, or Ottawa) were included in the study population. These counties are all supported by a nearby Spectrum Health hospital, which provided treatment plans set-up in coordination with the Helen DeVos Children's Hospital

Pediatric Hematology and Oncology program (D. Dickens, personal communication, July 21, 2017). Children living outside of these counties were excluded from the study population due to possible differences in treatment regimens.

The choice in the years that were retrospectively analyzed was done to allow for the access of electronic medical records within the Spectrum Health system and a complete five-year analysis of those diagnosed in 2011. No data has currently been presented on the association of socioeconomic status and five-year event-free survival within this population, which provided interest for the completion of this study.

Data Collection

Data access to the medical records at Helen DeVos Children's Hospital required approval through the Spectrum Health Institutional Review Board, Grand Valley State University's Human Research Review Committee, and the permission of the Helen DeVos Children's Hospital's Pediatric Hematology and Oncology program. After approval by the above institutions, a list of previously identified patients diagnosed with ALL was obtained from the Helen DeVos Children's Hospital's Pediatric Hematology and Oncology program containing the medical record numbers (MRNs) for these patients. The list of these MRNs was created on a Microsoft Word file that was password protected on a password protected computer at Spectrum Health's Grand Rapids location. The file was transported as a paper file within a manila envelope directly to the lead investigator which was then directly input into a correlation tool file within Microsoft Excel. The paper file was shredded immediately upon transfer of the MRNs into the correlation tool file. The computer file containing only the MRNs was destroyed upon transfer of the file to the lead investigator.

Once the initial record of patient MRNs was input into the correlation tool file, Cerner Millennium (Cerner Corporation, North Kansas City, MO) electronic medical record (EMR)

system was utilized to complete chart reviews. Information received from the chart reviews included date of diagnosis, leukocyte count at diagnosis, age at diagnosis via date of birth, race, sex, immunophenotype, and the patient's zip code at the present time. Date of relapse or date of death, whichever occurred first, was also obtained for outcome measures if applicable. Data viewed in Cerner Millennium was then recorded within the correlation tool file, a file that contained all identifiable information that remained at the hospital for security purposes, with the researcher being the only one able to access it if needed. Once all data had been entered into the correlation tool file, a new data file, or final data set, was created so that it contained no identifiable information. Identification numbers were used in place of identifiable MRNs, with zip codes and dates of birth also being deidentified and removed from the new data file. The correlation tool file was destroyed following the completion of the research study. The final data set file to be stored following the completion of the study contained only de-identified information. All files utilized for data collection purposes were password protected along with being secured through a password protected computer. In addition to this, the correlation tool file and final data set file were saved onto separate computers as well.

Data Analysis

Prior to starting statistical analysis, data obtained during data collection were deidentified and recoded into categorical variables. The MRN for each patient was recoded starting from a value of 0001 for the first patient, followed by subsequent numbers until all MRNs had been recoded. Date of birth was used to identify what age the child was when they were diagnosed with ALL, but then further recoded into age categories. Age at diagnosis was categorized into the following categories: 1-4 years, 5-9 years, and ≥10 years of age. The categorization of race was dependent on the distribution of the sample collected, thus categorization of the data fell into just two groups: Caucasian and Other.

United States Census information from 2000 was used to create a neighborhood socioeconomic score for each child's particular zip code based on the calculation utilized by Diez Roux et al. (2001). The score encompassed three main areas connected with socioeconomic status: education, income, and occupation. Data from the 2000 United States Census used for the calculation of each neighborhood socioeconomic score based on each individual's zip code included median household income (log value), median value of housing units (log value), percentage of households receiving interest, dividend, or net rental income, percentage of adults 25 years of age or older who had completed high school, percentage of adults 25 years of age or older who had completed a college (bachelor's) degree, and the percentage of employed persons 16 years of age or older in executive, managerial, or professional specialty occupations (Diez Roux et al., 2001). Once all areas were assessed for each individual, z-scores for each variable used within the neighborhood socioeconomic score were calculated by subtracting the mean from the value of the variable and then dividing by the standard deviation. The z-score represented the amount of deviations from the mean. For example, a calculated z-score value of 3.0 for the variable "percentage of households receiving interest, dividend, or net rental income means" for that specific zip code shows that the Census value is three standard deviations above the mean for all values obtained for that variable. Similarly, a z-score of -3.0 means the value is three standard deviations below the mean value. Once all z-scores were calculated, individual neighborhood socioeconomic scores were created by adding all z-scores from each variable specific to that child's zip code. For instance, if a child had z-scores of 1.9, 2.3, -1.2, 1.0, and 3.2, the neighborhood socioeconomic score for that child was equal to 7.2. Increasing scores signified increased advantage among the neighborhood. Scores were stratified into three socioeconomic groups (lowest, middle, and highest) based upon their standing among the other

values, with the lowest third of scores being coded as the lowest socioeconomic group, and so on. These scores were linked to the initial zip code recorded for each patient prior to the zip code being removed.

Descriptive statistics were utilized to reflect the distribution of the predictive factors collected based upon the socioeconomic tertiles created. Frequency and percent were reported for categorical variables and mean (SD) for continuous variables. Five-year event-free survival was assessed based on either relapse to any type of cancer or death for each child included in the study. Differences in survival for each socioeconomic tertile were evaluated via Kaplan-Meier survival analysis, generating Kaplan-Meier survival plots. Cox proportional hazard models were conducted to explore the association between all factors studied. The initial unadjusted model assessed the risk of relapse or death between the neighborhood socioeconomic tertiles created, which was then adjusted for age, race, and sex. A final model included the additional adjustment of leukocyte count at diagnosis and immunophenotype. Hazard ratios were calculated to understand the risk of relapse or death between the various neighborhood socioeconomic tertiles. The assumptions for proportional hazards were tested and were met. SAS 9.4 (SAS Institute, Inc., Cary, NC) was used for all statistical analysis.

IV. Results

During the investigation period between the years 2002-2011, 133 patients sought care for ALL at the institution of interest. Twenty-one subjects did not meet inclusion criteria due to residing outside of the selected study area. Among the 112 eligible subjects, eight were excluded due to having missing information for age at diagnosis, leukocyte count at diagnosis, event status, or a combination of these three variables. One additional individual was excluded from the study population due to a lack of available information of their socioeconomic status, leaving a total of 103 subjects to be utilized for data analysis. Figure 3 displays a flow diagram of the exclusionary process among study subjects from the beginning of data collection for the time period of interest to the time of data analysis.

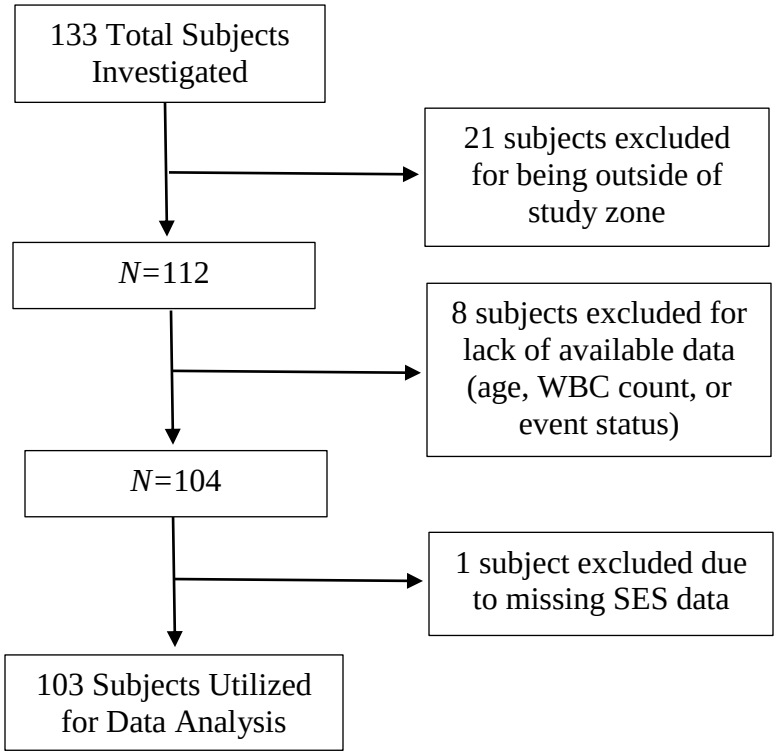

Figure 3. Flow diagram of subject inclusion during the study period of interest from the beginning of data collection to the time of data analysis.

Descriptive Statistics

Among the 103 study participants that were included within the data analyses, 61.2% were male. Mean age at diagnosis was almost six years (*M* = 5.91, *SD* = 3.71) with a median of five years (*IQR=6.00*). Age was later categorized into three different categories, ages 1-4 years, 5-9 years, and ≥10 years, with most of the population falling into the age range of 1-4 years (46.6%). The study population primarily identified as being Caucasian (80.6%) and was most commonly diagnosed with B-ALL (84.5%). A full summary of the descriptive characteristics of the study population can be found in Table 2. Following the calculation of the neighborhood socioeconomic scores, the mean score of the population was 0.18 (*M* = 0.18, *SD* = 4.75), with a median score of -0.11 (*IQR* = 8.02). Neighborhood socioeconomic scores ranged from -8.61 to 15.9.

Table 2.
Descriptive statistics for the 103 eligible ALL cases from 2002-2011

Demographic Variable	*N (%)*	*M (SD)*
Age at diagnosis (years)		5.91 (3.71)
1-4	48 (46.7%)	
5-9	32 (31.1%)	
10+	23 (22.3%)	
Sex		
Male	63 (61.2%)	
Female	40 (38.8%)	
Race		
White	83 (80.6%)	
Hispanic	12 (11.7%)	
Other	8 (7.8%)	
Immunophenotype		
B-ALL	87 (84.5%)	
T-ALL	15 (14.6%)	
Missing	1 (1.0%)	
Leukocyte count at diagnosis ($x10^9$/L)		36.8 (39.2)

Note. Based on 103 study subjects utilized for data analysis. B-ALL= B-cell acute lymphoblastic leukemia; T-ALL = T-cell acute lymphoblastic leukemia

Survival Analyses

During the five-year follow-up period in which subjects were assessed, a total of eleven participants (10.7%) experienced an event, defined as either relapsing into any form of cancer or death. All events that were recorded were relapses, with one death occurring after an initial relapse. Among the subjects that experienced an event, two subjects were from the lowest neighborhood socioeconomic tertile, with the middle tertile having three children experience an event, and the highest tertile having six children that experienced an event. Kaplan-Meier survival analysis did not show a difference in survival between the different socioeconomic tertiles assessed, χ^2 (2, N = 103) = 2.70, p = 0.26, as demonstrated by Figure 4.

Three sequential Cox Proportional Hazards models were conducted for this study. The proportional hazards assumption was checked and met for the initial unadjusted model. The results for this assumption can be found in the Appendix. In the initial unadjusted Cox Proportional Hazards model, the risk of relapsing or dying within five years varied across the tertiles of socioeconomic scores, however these differences did not prove to be statistically significant. Children who were categorized as being within the middle tertile saw a 1.48 times greater risk of relapsing or dying within five years of their diagnosis compared to children of the lowest tertile (HR = 1.48, p = 0.67, 95% CI [0.25, 8.86]), while children who were categorized as being within the highest, or most affluent, tertile had a 3.17 times greater risk of relapse or death within five years compared to children who were categorized as being within the lowest socioeconomic tertile (HR = 3.17, p = 0.16, 95% CI [0.64, 15.7]).

When adjusting for the demographic variables age, race, and sex, the association between neighborhood socioeconomic score and relapse or death attenuated. Children that were in the middle tertile of the calculated neighborhood socioeconomic scores had a 1.26 times greater risk

of relapsing or dying within five years after adjusting for age, race, and sex (HR = 1.26, $p = 0.81$, 95% CI [0.19, 8.33]) compared to children in the lowest tertile. Children categorized into the highest tertile were at 3.02 times greater risk of having an event within five years after adjusting for age, race, and sex as well (HR = 3.02, $p = 0.19$, 95% CI [0.59, 15.5]) compared to children in the lowest tertile. However, neither of these associations reached the threshold for statistical significance. Among the demographic variables analyzed and adjusted within the model, children above the age of four-years, non-whites, and males were all at greater risk of experiencing an event within five years of their diagnosis compared to their counterparts, however none of these results were statistically significant (Table 3).

The final, full model contained all the variables collected for the study: neighborhood socioeconomic scores, age, race, sex, leukocyte count at diagnosis, and immunophenotype. After adjusting for these variables, the association between neighborhood socioeconomic status and relapse or death further attenuated. Similar to the previous models explored, when compared to the lowest socioeconomic tertile, both the middle tertile, and the highest tertile had a greater risk of relapsing or dying within five years of the initial diagnosis. The middle tertile saw a 1.27 times greater risk of having an event within five years of diagnosis (HR = 1.27, $p = 0.80$, 95% CI [0.19, 8.48]), while the highest tertile saw a 2.95 times greater risk within five years (HR = 2.95, $p = 0.20$, 95% CI [0.57, 15.3]), when adjusting for all the variables included within the full model. In addition to these findings, children over the age of four-years, non-whites, males, and those diagnosed with B-ALL were all found to have a greater risk of relapsing or dying within five years compared to their counterparts. None of these findings proved to be statistically significant, however. Table 3 contains the full results from each of the respective Cox Proportional Hazards models discussed above.

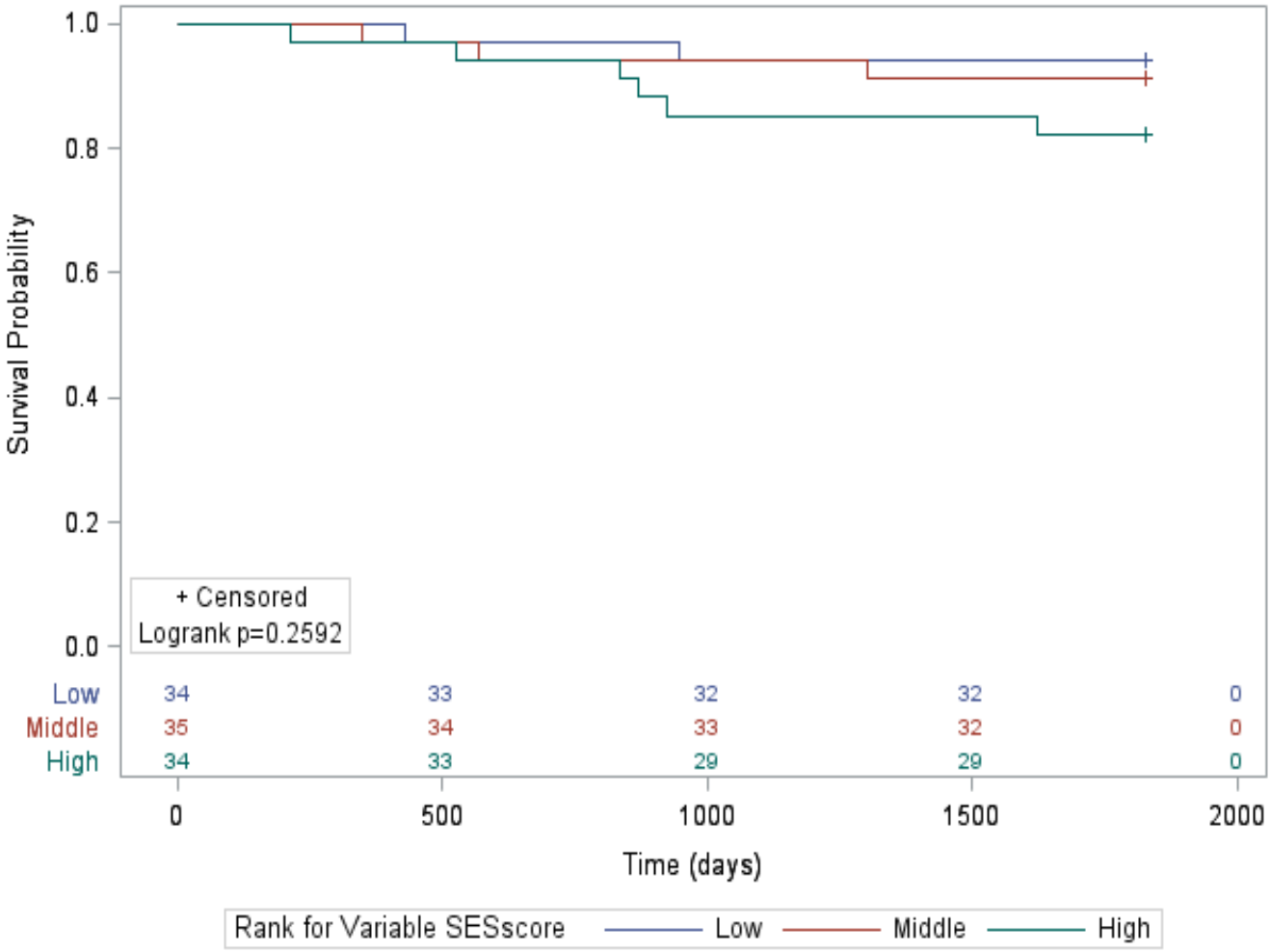

Figure 4. Kaplan-Meier estimates of five-year event-free survival for children diagnosed with ALL by calculated neighborhood socioeconomic score tertiles. Log-rank test of homogeneity: $\chi^2 = 2.70$, $p = 0.26$. Blue numbers indicate the number of children within the lowest socioeconomic tertile who did not have an event (event-free survival) at each point in time, with red numbers being indicative of event-free survival within the middle socioeconomic tertile and green numbers being indicative of event-free survival in the highest socioeconomic tertile.

Table 3.

Cox Proportional Hazards model results related to five year event-free survival in children ages 0-14 years with ALL

	Model 1			Model 2*			Model 3†		
Variables	HR	[95% CI]	*p*	HR	[95% CI]	*p*	HR	[95% CI]	*p*
Neighborhood Socioeconomic Score Tertile									
Lowest		Reference			Reference			Reference	
Middle	1.48	[0.25, 8.86]	0.67	1.26	[0.19, 8.33]	0.81	1.27	[0.19, 8.48]	0.80
Highest	3.17	[0.64, 15.7]	0.16	3.02	[0.59, 15.5]	0.19	2.95	[0.57, 15.3]	0.20
Age (years)									
1-4					Reference			Reference	
5-9				2.44	[0.53, 11.2]	0.25	2.92	[0.63, 13.5]	0.17
10+				2.99	[0.64, 13.9]	0.16	3.48	[0.73, 16.5]	0.12
Race									
Caucausian					Reference			Reference	
Other				1.46	[0.36, 5.94]	0.60	1.48	[0.36, 6.05]	0.58
Sex									
Female					Reference			Reference	
Male				1.51	[0.46, 5.01]	0.50	1.54	[0.46, 5.19]	0.49
Immunophenotype									
T-ALL								Reference	
B-ALL							3.58	[0.23, 56.7]	0.36
Leukocyte Count at Diagnosis ($x10^9$/L)							1.00	[1.00, 1.01]	0.46

Note . ALL = acute lymphoblastic leukemia; HR = hazard ratio; CI = confidence interval

*Adjusted for neighborhood socioeconomic status scores (based on tertiles created), age, race, and sex

†Adjusted for neighborhood socioeconomic status scores (based on tertiles created), age, race, sex, immunophenotype, and leukocyte count at diagnosis.

V. Discussion

A difference in five-year event-free survival was not detected between those of lower socioeconomic standing and those of higher socioeconomic standing when studying children, ages 0-14 years, who were diagnosed with ALL within West Michigan. While many studies have previously shown that those of lower socioeconomic standing are more likely to have worse health outcomes for a variety of health issues, little research has been done to describe this association among those diagnosed with ALL, especially within children (Demakakos et al., 2008). This study was one of the few to look at this association among children diagnosed with ALL in the United States, and the first to try and understand the association within the West Michigan area. Those of higher socioeconomic standing within the population under investigation were found to have a greater risk of relapsing or dying within five years of their initial ALL diagnosis, but not statistically. These results differ from previous studies conducted in the United States, which found protective effects of the higher socioeconomic class (Abrahão et al., 2015; Bona et al., 2016; Kent et al., 2009; Petridou et al., 2015). The differences in these findings suggest that more research within this field should continue to be conducted to better understand the association of interest.

Finding that patients from higher socioeconomic neighborhoods were more likely to experience relapse or death compared to those of living within lower socioeconomic neighborhoods was contrary to the original hypothesis. Although unanticipated, the results of this study add to the limited current literature, especially within the United States. The study was able to assess for a multitude of possible confounding variables, increasing the ability to understand the true association between socioeconomic status and five-year event-free survival among the population of interest. And while the small sample size (N=103) likely contributed to an

underpowered study, the results can further the discussion between the association of socioeconomic status and health-related outcomes, especially among those diagnosed with ALL. Prior to the start of data analysis, it was initially hypothesized that those of lower socioeconomic standing would be more likely to experience relapse or death, as those of higher socioeconomic status tend to have better overall health and health outcomes, compared to those of lower socioeconomic standing (Lynch et al., 2004). However, in 1997, Greaves described that advances in hygiene and changes to the typical contact children had with one another via day-care, particularly among those of higher socioeconomic status, may contribute to decreased exposure to early childhood infectious agents. This decreased exposure to infectious agents may leave children to be more at risk for diseases such as ALL due to the lack of immune system regulation during the child's early childhood years. In addition to this, it was hypothesized that mothers living in developed areas may be less likely to pass on immunity to their newborn child if they were not exposed to various infectious agents prior to, or during the pregnancy (Greaves, 1997). A case-control study utilizing data from the CCR, along with another case-control study using data collected around the world, were able to support the hypothesis that early childhood infections may be able to protect individuals from developing ALL (Marcotte, Ritz, Cockburn, Yu, & Heck, 2014; Rudant et al., 2015). These studies were able to look at a variety of variables related to early childhood exposure to infections, further helping to support the hypothesis discussed by Greaves (1997) and the findings of our study.

In the study completed by Rudant et al. (2015), researchers tried to gain an understanding of the effects of breastfeeding, day care attendance, and birth order on the risk of a child developing ALL (Rudant et al., 2015). It was found that breastfeeding for six months or longer, higher birth order, and day-care attendance within the first year of life all had a protective effect

against the development of ALL in children, likely due to the increased immunity provided by the mother during breastfeeding and due to the increased exposure to infectious agents via siblings and other children (Rudant et al., 2015). Marcotte et al. (2014) also looked at various markers related to the possibility of exposure to infections and risk of ALL later in life. Variables analyzed within Marcotte et al.'s (2014) large case-control study included birth month, birth order, and the time of birth in comparison to influenza and common respiratory virus cycles. It was determined that those born during the spring and summer months, and those exposed to the common childhood viruses later in life, were at increased risk of developing ALL (Marcotte et al., 2014). Birth order also appeared to be a protective factor when looking at the risk of the development of ALL, as there was a decreased risk of ALL among those higher within their family's birth order (Marcotte et al., 2014). This is likely due to the fact that as a child is born higher into the birth order, a child is exposed to more infectious agents from his or her siblings born before him or her. Nonetheless, the findings seen within the studies completed by Marcotte et al. (2014) and Rudant et al. (2015) support the early hypothesis created by Greaves (1997) that early childhood exposures to infectious agents may reduce the risk of a child getting ALL. These studies, along with future research within this area, may help to explain why children of higher socioeconomic status may be at greater risk of relapsing or dying compared to children with lower socioeconomic backgrounds.

Strengths

The overall design of the study helped to create several strengths. By identifying the location of all the hospitals within the Spectrum Health organization, it was possible to limit the study population to only counties located near a Spectrum Health facility, limiting the chance that an individual may seek treatment at a facility other than Spectrum Health during the study period. This also led to better retention and tracking of the patients included within the study and

helped to limit travel distance to treatment facility as a potential confounder. Furthermore, the sampling method utilized within the study allowed for a population that was distributed similar to previous studies that had been completed. Hunger and Mullighan (2015) noted that more males tended to be diagnosed with ALL compared to females (male to female ratio of 55% to 45%), similar to the ratio found within the study (61% males, 39% females). The distribution of the various races observed within the study was similar to the much larger study (N=14,192) completed by Hossain, Xie, and Mccahan (2014), as 83% of children within their study were Caucasian, compared to the 81% of children identified as being Caucasian within this study. After further discussion of the population utilized for the study, it was determined that the study was also distributed as expected by the doctors within the Helen DeVos Children's Hospital's Pediatric Hematology and Oncology program (D. Dickens, personal communication, July 21, 2017). Along with the strengths listed above, the short time period of interest allowed for fewer changes in the treatment protocol to occur over the study period, further limiting the chance that changes in treatment could have been a confounder within the study.

Limitations

With fewer subjects eligible for the study than previously expected, the limited sample size (N = 103) available for statistical analysis largely impacted the power to detect statistically significant findings. The lack of events that occurred within the population, although showing positive outcomes for those diagnosed with ALL, may have also contributed to the lack of an observed association between neighborhood socioeconomic scores and event-free survival in children diagnosed with ALL. The small sample size also limited the power available to be able to explore possible interactions between various variables collected during the data collection process. As discussed by Vanderweele and Knol (2014), in order to look into the interaction between various variables included within the study, a larger sample size would be necessary.

Individual-level socioeconomic status information was not obtained from each child included within the study, however the neighborhood socioeconomic score used to look at the association of interest has been shown to be predictive of various health-related outcomes, even after controlling for individual and family-level socioeconomic status (Chen & Paterson, 2006). Individual-level insurance status was also not able to be obtained during the final data analysis due to inconsistent reporting within the medical record. Individual treatment plans were also unable to be viewed, leaving the possibility for selection bias in who sought care at Spectrum Health, to influence the results. Lastly, the impact of genetic mutations within the leukemic cells found in each patient could not be assessed for, as information regarding the genetic analysis of the leukemic cells could not be uniformly obtained for all individuals included within the study. In addition to this, cytogenetic analysis has improved and changed throughout the years under investigation within this study, thus comparing each patient's cytogenetics using the same threshold would be unclear, as there were changes in the testing and reporting of these genetic factors during the study period.

Recommendations for Practice

As the survival rate for those diagnosed with ALL has risen from below 10% during the 1960s, to roughly 90% over the past several decades, changes in the relative treatment of the disease are not a necessity, however it is important to continue to address the impacts of treatment inequalities (Lustosa de Sousa et al., 2015; Nguyen et al., 2008; Wang et al., 2015). Petridou et al. (2015) found within their meta-analysis that although improvements have been made in the treatment of ALL, those within lower socioeconomic settings are less likely to be able to take advantage of these improvements. However, improvements in caring for those of lower socioeconomic status continue to be made in the healthcare setting, as various hospitals are incorporating the use of social workers and other faculty members to better facilitate an open line

of communication between physicians and families, along with addressing additional needs certain families might have. Currently, Spectrum Health's Helen DeVos Children's Hospital's Pediatric Hematology and Oncology programs is able to help provide transportation and support the payment of co-pays for various individuals who seek treatment within their clinic, helping to decrease the chance that socioeconomic status may lead to different ALL outcomes (personal communication, D. Dickens, July 21, 2017). Additional improvements within the practice, such as strictly enforcing medication adherence, ensuring that follow-up care is completed, and the quick identification of new possible ALL cases, have also helped to limit and potentially overcome differences between the various socioeconomic groups that exist (personal communication, D. Dickens, July 21, 2017). The further development of such practices may lead to hospital systems being able to overcome socioeconomic status disparities seen in many health outcomes.

In addition to the improvements described above, the state of Michigan continues to fund the "Children's Special Health Care Services" program, as those diagnosed with roughly 2,700 severe diseases, such as ALL, are eligible to receive financial assistance regardless of socioeconomic status as long as the child is a resident of the state of Michigan and under the age of 21 (Michigan Department of Health and Human Services, 2017). Nonetheless, while improvements in the care of all socioeconomic backgrounds have been made via policies and healthcare practices, it is imperative that continual research be conducted to better understand the association between socioeconomic status and relapse and/or death in children diagnosed with ALL. Limited research still exists across the United States for public health officials to be able to understand the true impact of socioeconomic status on ALL outcomes. It may also be of interest to further investigate the impacts that improved hygiene and changes to childcare have had on

various immune-mediated diseases, such as ALL, as this field of research may explain why those of higher socioeconomic standing were at greater risk of relapse within our study. With many major healthcare services already in place for those of all socioeconomic backgrounds, the continuation and adaptation of these services to better meet the needs of all levels of wealth is important to improve the health of children diagnosed with ALL.

Future Directions

While the association of interest did not prove to be statistically significant, changes within the methodology of this study can be made to improve the statistical power of a future study. It is proposed that by gaining a larger population to study, possibly by sampling all children within the state of Michigan, ages 0-14 years, who were diagnosed with ALL, a better understanding of the research question under investigation can be gained. This can be completed by working with other hospital systems across the state, or by utilizing data collected by the Michigan Cancer Surveillance Program. However, differences in treatment may occur across the state, potentially confounding the association of interest. It may also be difficult to accurately assess for socioeconomic status depending on the method chosen from those described above, thus it is important to explore both avenues of study adequately. Nevertheless, the research question of interest for this study has been understudied within the United States, thus the completion of a larger study would greatly benefit those researching, treating, or undergoing treatment within the pediatric ALL community.

It would also be advantageous for future research to look further into the differences in event-free survival based on socioeconomic status in other areas of the United States, as each area has different racial compositions and hospital system availability compared to West Michigan. Currently, one of the Office of Disease Prevention and Health Promotion's (2014) Healthy People 2020 goals is to achieve equality in its medical care for all people, as the Agency

for Healthcare Research and Quality (AHRQ) (2014) still reports differences in the quality of healthcare received by different racial groups. Additionally, Horwitz (2005) discussed how different types of hospitals, specifically for-profit compared to non-profit, often have differences in the services and quality of services they provide. With many areas across the United States having different racial compositions and hospital systems compared to that of West Michigan, it is important to understand how these differences may affect ALL outcomes. The AHRQ reported in 2014 that although improvements in treating disparities among minority populations has improved, access and quality of care remain issues for many minorities. Language barriers and healthcare insurance status were reported as major barriers for many minorities in gaining access to care, however the predominately non-Hispanic white population seen within West Michigan may not see these barriers compared to other areas around the United States that are composed primarily of minority races (AHRQ, 2014). Similarly, for-profit hospitals have been shown to be less likely to provide services that are not profitable compared to their counterparts, even if the need for that service is evident within the community (Horwitz, 2005). Private hospitals also tended to serve higher-income individuals compared to those that have lower socioeconomic standing, possibly suggesting that there may be a difference in who is more likely to seek treatment at a specific health institution (Basu, Andrews, Kishore, Panjabi, & Stuckler, 2012). Thus, future research should further investigate other areas of interest across the United States, especially ones that are composed of different racial groups and hospital systems compared to those seen here in West Michigan.

In addition to the suggestions given above, following the discussion of the study's findings, it would be beneficial to continue the investigation on the impact of early infectious disease exposures on the risk of developing ALL and/or relapsing or dying from the disease once

diagnosed. The studies that have been completed within this context of study have shown promising results, similar to those investigating the importance of socioeconomic status in identifying those who may relapse or die from ALL, however a limited number of studies have been completed within this field of research. Looking further into the association between early childhood infectious exposures and the development of ALL may help to identify new risk factors for the development of this disease or risk factors for possible relapse or death among those already diagnosed. As improvements in hygiene and changes to childcare continue to occur, the need for ongoing research in this field is important for those who are diagnosed with ALL, may become diagnosed with ALL, along with others who may suffer from other immune-mediated diseases.

Conclusions

The results of this study show that there is a need to continue the research efforts being put forth to look at the association of socioeconomic status and event-free survival in children diagnosed with ALL, particularly within the United States. Our study showed that children living in areas of greater socioeconomic status may be more likely to experience either a relapse or death from their ALL compared to children of lower socioeconomic status, differing from the results observed within other studies completed within the United States (Abrahão et al., 2015; Bona et al., 2016; Kent et al., 2009; Petridou et al., 2015). These differences may be able to be explained by decreases in early childhood exposure to infectious agents caused by improvements in hygiene and changes in childcare over the years. Further research should be conducted in looking at the association between socioeconomic status and event-free survival in children diagnosed with ALL, along with exploring other relevant areas mentioned previously. It is important to continue research in this field, as well as in other areas of healthcare research, in

order to decrease the differences observed between the health outcomes of the various socioeconomic backgrounds that exist.

Appendix

Cox Proportional Hazard Model Assumption Testing

Analysis of Maximum Likelihood Estimates									
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
SEStert	1	1	0.00720	1.13382	0.0000	0.9949	1.007	0.109	9.295
SEStert	2	1	0.34524	1.70538	0.0410	0.8396	1.412	0.050	39.954
ses_time		1	0.0005378	0.00104	0.2695	0.6037	1.001	0.999	1.003

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