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Children's Oncology Group Hospital Membership and Survival of Pediatric Lymphoblastic Leukemia

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This is to certify that the doctoral dissertation by

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Walden University
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Abstract

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MS, Texas State University, 2002

BS, Stephen F. Austin State University, 1986

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

Doctor of Philosophy

Public Health

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Abstract

Acute lymphoblastic leukemia (ALL) predominates in children ages 0-14 years and has an excellent prognosis for cure with 5-year survival exceeding 90% in the United States. However, not all children experience such positive outcomes. The purpose of this quantitative, retrospective cohort study was to evaluate differences in survival of ALL among children who reside in the 32-county Texas-Mexico border region. While factors such as poverty and health insurance have been strongly associated with poorer cancer outcomes, additional factors such as geographic isolation and treatment disparities are not as well-documented in children. This study examined the association between use of Texas Children's Oncology Group (COG) pediatric research facilities and survival among children in Texas diagnosed with ALL. This study used cancer incidence data 1995-2009 from the Texas Cancer Registry. Differences in survival and use of COG facilities were investigated between children who reside within the 32-county Texas-Mexico border region and the combined remaining 222 Texas counties. Chi-square was used to analyze area of residence, gender, race/ethnicity, and poverty status between COG and non-COG reported cases. Logistic regression was used to examine ALL survival differences between COG and non-COG facilities controlling for multiple variables. COG affiliation alone was not a significant predictor of survival. An interaction between race/ethnicity, region, poverty status, and COG facility affiliation was observed as a significant predictor of poorer survival. The results of this study have the potential to promote positive social change by implementing interventions addressing access to equivalent pediatric cancer care in the 32-county Texas-Mexico border area.

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Dedication

This work is dedicated to my late father and mother, Mr. and Mrs. Charles Donald Betts, who taught me the most important things no book or classroom could.

Acknowledgments

I would like to express my sincere thanks to my entire family over this long and challenging process. I could have never reached this point without you.

I would also like to think my Dissertation Chair, Dr. Talmage Holmes for his help and patience though this entire project. Dr. Richard Palmer was also a source of outstanding guidance and support.

Additionally, warm and heartfelt thanks to Drs. Michael O'Brien and the late Sidney Stewart. It was an honor, pleasure, and an incredible learning experience working with such skilled and caring physicians.

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Chapter 1: Introduction to the Study

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer in the United States, accounting for about one-quarter of all malignancies diagnosed in children 0-14 years of age (Hunger et al., 2012). Using the latest statistics from the American Cancer Society (2016), approximately 3,000 children between the ages 0-14 years will be diagnosed with ALL in the United States in 2016. Most of those children will be between the ages of 2 and 5 years at the time of diagnosis (Robison, 2011).

The successful treatment of children diagnosed with ALL is considered one of modern medicine's greatest success stories against cancer, with current overall 5-year survival rates of over 85% in developed countries (Pui, Mullighan, Evans, & Relling, 2012). Why 15% percent of children with ALL have poorer outcomes remains under robust investigation. Such studies have revealed both clinical and demographic factors to be involved in both short and long-term survival of the disease (Bhatia, 2011).

Acute leukemia is thus named as the disease progresses rapidly. The best outcomes are marked by not only initial expedient intervention, but treatment targeted to the patient's specific disease metrics. The most advanced therapies for ALL are based on several personal and biological metrics to assess the disease in a particular individual and determine the best course of proven treatment. This risk-based treatment strategy requires advanced technology testing, complex chemotherapy treatment, expert specialty care, multiple visits, and long-term followup care. Specialized pediatric oncology research centers that offer such protocols are members of the Children's Oncology Group (COG).

Children diagnosed with ALL treated at these facilities experience survival approaching 95% (Pui, Pei, et al., 2012). In this study I examined the extent of COG facility participation of children diagnosed with ALL in Texas. The purpose of this study was to determine if facilities in Texas that have achieved COG membership offer prognostic significance in pediatric ALL survival, and identify possible underserved areas for positive interventions. This chapter describes key factors and issues related to the study.

Background of the Study

Texas is currently home to 15 pediatric oncology research centers that have been designated COG institutions (COG, 2015). This organization is the world's largest pediatric cancer research cooperative, with over 200 facilities and 5,000 specialist physicians (O'Leary, Krailo, Anderson, & Reaman, 2008). In a meta-analysis of pediatric ALL survival, children treated at COG institutions were consistently found to have significant survival advantage compared to children treated at facilities that are not associated with COG membership (Bhatia, 2011).

During the time period examined in this study for ALL diagnosis (1995-2009), COG facilities were located within eight major metropolitan areas covering east, west, north, and central Texas, including the Panhandle area. The metropolitan areas of Dallas/Fort Worth, San Antonio and Houston were all home to two COG facilities. No COG facilities were located within the entire 32-county Texas-Mexico border area in southern Texas (Cure Search, 2009). Travel of hundreds of miles would be required by south Texas residents to reach any Texas COG facility. This is also true of any COG facilities located in adjoining states of New Mexico, Oklahoma, Arkansas, and Louisiana.

Figure 1 illustrates the 32-county Texas-Mexico border region and the locations of COG facilities within the state of Texas.

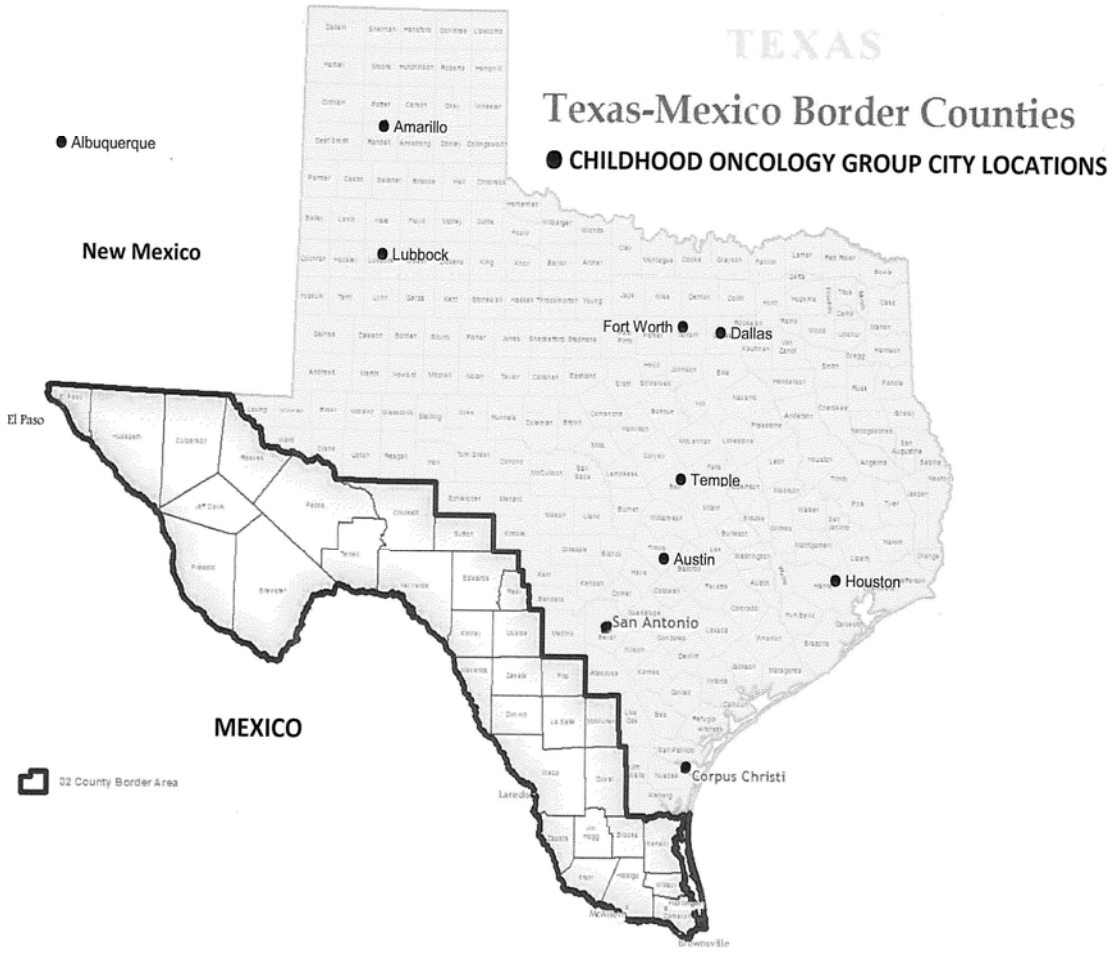

Figure 1. The Texas-Mexico border area and COG facility locations.

Problem Statement

Despite continued advances in diagnostics and treatment protocols which have resulted in increased survival, cancer remains the leading cause of disease-related mortality in children and the second leading cause of death overall (American Cancer

Society, 2016). A large area of the Texas population does not have access to COG facilities. The Texas-Mexico border region of the state is particularly isolated from the advanced care provided by pediatric oncology research centers. As discussed in Chapter 2, a lack of literature exists on access to care disparities in children. This population may be medically underserved resulting in tragic and needless loss of life from a curable disease.

Researchers have consistently shown that the type of facility administering care to children diagnosed with ALL to be associated with survival (Bhatia, 2011; Hunger et al., 2012). During the study period (1995-2009) the Texas-Mexico border area was void of COG institutions that offer the best treatment regimens available for ALL.

The population of this area is primarily Hispanic and poor (U.S. Census Bureau, 2013). Researchers have repeatedly shown that both opportunity and cultural factors result in the underrepresentation of minorities in clinical trials, the gold standard for improved cancer treatments and survival (Ford et al., 2008). The multiple factors of geographic isolation, poverty, and ethnicity pose a high risk in seeking treatment at more local non-COG affiliated facilities, and thus poorer survival in the Texas-Mexico border area.

Purpose of the Study

The purpose of this quantitative study was to examine the survival of children in Texas diagnosed with ALL in regards to the facility of treatment, poverty status, gender, race/ethnicity, and geographic location. Of additional interest was to document survival of those children residing in the Texas-Mexico border region. There are no current

published statistics for ALL specific to the Texas-Mexico border area. These data were compared to the nonborder area of the state to identify possible disparities in survival of the disease. A more thorough discussion of the variables examined and analyses is covered in Chapter 3.

Research Questions and Hypotheses

The research questions reflect the need to examine survival of ALL in Texas in more detail. The study seeks to examine several important questions:

1. What are the descriptive epidemiology statistics of childhood ALL in Texas? These statistics will include ALL incidence, mortality, and survival rates for children 0-14 years of age residing in Texas diagnosed 1995-2009.
2. Is there an association between COG facility affiliation and 5-year survival of ALL?

   H_o2: COG facility affiliation has no effect on 5-year survival of ALL.

   H_a2: COG facility affiliation has an effect on 5-year survival of ALL.
3. Is there an association between COG facility affiliation and 5-year survival of ALL controlling for race, place of residence, and poverty?

   H_o3: There is no association between facility affiliation and 5-year survival of ALL when controlling for race, place of residence, and poverty.

   H_a3: There is an association between facility affiliation and 5-year survival of ALL when controlling for race, place of residence, and poverty.

Results will increase understanding of the burden of ALL in Texas, including the expansive Texas-Mexico border area and identify specific target areas for further study and public health interventions.

Theoretical Foundation

This study will use Krieger's model of ecosocial theory, which poses as its main question "who and what is responsible for population patterns of health, disease, and wellbeing" and addresses social inequalities in health (Krieger, 2001; Krieger, 2002). The researcher theorizes that geographical isolation as a barrier to the best risk-based treatment is more a factor in pediatric ALL survival than poverty or Hispanic ethnicity.

This ecosocial theory of health encompasses more than the traditional theories in epidemiology and disease, many of which focus primarily on the occurrence of disease and causation. Krieger (2013) combines the social and ecological aspects of population health, including physical environment, with more traditional epidemiologic theory. Ecosocial theory examines the relationships between biological, social, political, and economic aspects of population patterns of not only disease, but well-being (Krieger, 2001). One of the theory constructs stresses the role of discrimination and health inequalities created by social systems that contribute to both disease and outcomes. The result is a more complete epidemiological approach that may also be used to examine and explain disease survival.

Further, Krieger (2013) argues that it is the also the obligation of epidemiologists and researchers to become activists against injustice when such health disparities due to social constructs are identified. Social change is a key construct to healthier populations.

Rationale for the Research

Studies addressing racial/ethnic health disparities in children are few compared to their adult counterparts (Flores, 2010). Limited data also exists on Hispanic children diagnosed with ALL. The large Hispanic population of Texas including the predominantly Hispanic population of the expansive Texas-Mexico border area presents an opportunity to contribute to these areas of study and expand the literature available.

Pediatric cancers are much less common than the disease in adults. In addition, pediatric cancers are unique in outcomes research in that the behaviors and actions of others (parents) instead of the individual are a predominant factor in treatment and survival. As a result pediatric studies are greatly lacking in the literature.

Using 1988-2008 SEER data, Goggins and Lo (2012) found poorer survival for Black, Hispanic, Asian, and American Indian/Alaskan Native (AIAN) children diagnosed with ALL when compared to non-Hispanic Whites. In an analysis of both SEER data and cooperative group clinical trials, Bhatia (2011) reported higher mortality in both Hispanics and Blacks, even when controlling for biological factors associated with poorer outcomes.

In contrast, studies by Pui et al. (2003, 2012) at St. Jude Children's Research Hospital consistently found that with equal therapy, outcomes were the same for all children, regardless of race. The authors suggested reported race/ethnicity health disparities in the treatment of ALL are due to unequal healthcare access and differences in treatment protocols. It is of note that the St. Jude studies only used White and Black race categories, without regards to Hispanic ethnicity.

For children who do not have access to these specialty facilities, advanced treatment protocols, and quality followup care, the question of equal treatment/outcomes is a moot point. O'Leary et al. (2008) reported that 90-95% of children in the United States aged 0-14 years diagnosed with cancer are seen at a COG facility. To date, only one state-based study assessing overall COG facility affiliation has been completed, with 87% participation reported in Georgia (Howell, Ward, Austin, Young, & Woods, 2007).

Nature of the Study

This population-based quantitative study used a retrospective cohort design utilizing secondary data. This type of study is well-suited for population-based cancer epidemiological studies, especially for rarer neoplasms. State cancer registries and/or Surveillance, Epidemiology, and End Results (SEER) data are sources of secondary data for many such population studies. This study compared groups of children in Texas diagnosed with ALL in terms of survival and the association with the type of facility administering care, geographic area of residence, race/ethnicity, gender, and poverty status. All data are secondary, having been previously collected by the Texas Department of State Health Services through the Texas Cancer Registry (TCR), who mandated by state law maintain a registry of all incidence cases. Appropriate rates, chi-square, and logistic regression analyses were conducted. More detailed discussions of study methodology specifics are discussed in Chapter 3.

Definitions

Acute lymphoblastic leukemia (ALL): The most common cancer in children characterized by the abnormal production of immature lymphocytes, a specific type of white blood cell, in the bone marrow and blood stream (Pui, 2012).

Children's Oncology Group (COG) facility: One of 12 member-affiliated pediatric oncology specialty centers located within the state of Texas. The defining factor of these facilities is pediatric cancer research including clinical trials (COG, 2016).

Risk-based treatment: Treatment based on a comprehensive diagnostic profile that considers several clinical and biological factors, including advanced morphology, immunology, genetics, and molecular laboratory analyses. This difficult process requires the most advanced technology and trained personnel, and thus is very expensive (Carroll et al., 2003).

Texas Cancer Registry (TCR): A statewide population-based registry in Texas that collects cancer incidence and mortality data per state mandated law (TCR, 2014). The registry meets all standards set forth by the National Program of Central Cancer Registries of the Centers for Disease Control. Data from the TCR have the highest quality certification from the North American Association of Central Cancer Registries (TCR, 2014).

Abstract report: The original document submitted to the Texas Department of State Health Services/TCR from a healthcare facility reporting a case of ALL or other cancer. Per state law, a facility is required to file a report for any patient seen with cancer, even if the patient was diagnosed/treated prior at another facility (TCR, 2014). As a

result, a report should be received from every facility each cancer patient visits, regardless of the reason/condition for admission.

Assumptions

While the incidence data required for this study from TCR were subjected to rigorous quality assurance protocols and have achieved high national standards, the chance for miscoding and other inaccuracies exists. Data are assumed to reflect actual ALL cases and other coding as to age and address at time of diagnosis correct. Facility identification and address from the reports is assumed accurate and was used only to indicate that the patient was seen at that facility. No followup was made to confirm or refute any data element.

Scope and Delimitations

Cancer data collection at TCR is passive, relying on reports from healthcare facilities throughout the state, including hospitals, cancer treatment centers, and pathology laboratories. Cancer is a reportable condition to the state health department per Texas state law, with reports required to be sent to TCR within 6 months of initial diagnosis or admission (TCR, 2014). Vital status and date of death are contained in these reports and included in the incidence database. The scope of this study was limited to ALL diagnosed among children residing in the state of Texas. Further comparisons between state and national populations are common in cancer epidemiology studies.

Cancer incidence reports in this study were limited to the following:

1. Reports must have a diagnosis date falling between January 1, 1995 and December 31, 2009.

2. Patient must be recorded as a resident of the state of Texas at the time of diagnosis.
3. Patient must be less than 15 years of age at the time of diagnosis.

Limitations

The exact reasons as to why an individual did not visit a COG facility cannot be determined from this study. Given all COG facilities provide care regardless of inability to pay along with multiple financial and transport support resources (Cure Search, 2009) physical access to such facilities must be considered. Support services are also provided in Spanish and include local providers. Given the citizenship status of many residents along the Texas-Mexico border, this must also be considered in seeking care from institutions located long distances from resident communities.

The possibility exists that facilities did not file cancer reports with the TCR. This could result in an incomplete assessment of patient care. However, COG facilities not only maintain a cancer registry for reporting per state law but also to meet criteria for membership in the COG research collaborative. COG facilities not reporting should be minimal and possibly even nonexistent.

The possibility exists that cancer patients may obtain care at a COG facility in another state. However, given the location of the Texas border area and the highly-rated and professionally respected facilities within the state, this would probably be a rare occurrence. When considering COG facilities, the locations in neighboring states are even further from in-state locations. This further illustrates the geographic isolation of

this area from pediatric oncology research facilities. Visits to out-of-state facilities were noted in the analyses.

Most Hispanic children in Texas reside in the border area, and populations of non-Hispanic Whites and other races are extremely low. As childhood cancer is an uncommon condition compared to adult cancers, many other areas of the state will not have the population size to produce the case counts needed to calculate stable incidence and mortality rates. Only the Dallas/Fort Worth and Houston metropolitan areas contain a Hispanic population large enough for comparison to areas located within the border area. As a result this study was limited to comparing Hispanic children in the Texas border area to Hispanics and non-Hispanic Whites residing in the collective nonborder counties of Texas. It is of note there were four COG facilities in the Dallas/Fort Worth and Houston metropolitan areas during the study period.

Life tables representing the survival of the general United States population are used in calculation of relative survival. The life tables are used in substitution of a cancer-free cohort for comparison to observed survival of cohorts of individuals diagnosed with cancer. This methodology provides measures for comparing survival between groups defined by variables such as race/ethnicity, and is currently used in NCI/SEER statistical publications (Howlader et al., 2016). However, at the time of this research specific life tables for Hispanics were not available. As a result, relative 5-year survival was only calculated for all races combined.

The question of actual treatment, if any and the extent of any treatment protocols were not assessed and out of the scope of this study. Howell et al. (2007) and O'Leary et al. (2008) only examined documented facility visits and not actual treatment.

Significance of the Study

Not all children in the United States have benefited from the advances in treatment and increased survival of ALL. This has proven especially true for minority children and children from low SES families. However, many of those cancer studies used data provided by the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI). This program consists of 18 state and city cancer registries, representing 26% of the United States population (SEER, 2009). Jamal, Siegel, Xu, and Ward (2010) published United States childhood cancer survival statistics using only SEER data. Siegel et al. (2012) reported 91% survival for ALL cases diagnosed 2001-2007 using only a SEER dataset.

The state of Texas is not currently included in the SEER program. This study offers a unique opportunity to examine ALL among a large and unique population of Hispanic children and identify potential health disparities. The large geographic layout of the state, larger than many European countries, provides the opportunity for unique geospacial comparisons. This study utilizing 15 years of data created a substantial pediatric cancer dataset for epidemiological analyses that has previously not been examined.

Significance to Social Change

It was estimated that in 2016 over 1.6 million new cases of invasive cancer would be diagnosed in the United States with over 595,000 deaths from the disease, an average of almost 1,600 per day (ACS, 2016). Cancer is only surpassed by heart disease in the United States as the overall leading cause of death (Jemal, Siegel, Xu, & Ward, 2010). This gap has narrowed substantially over recent years, and since 1999 cancer has become and remains the leading cause of death for people younger than age 85 years (Jemal et al., 2010).

Children also die of cancer, and some of treatable and survivable malignancies such as ALL. When examined in further detail, many of these children are found to have similar demographic characteristics associated with mortality. The goal of this study was to further identify such health disparities, and reveal the needless suffering and death of children living in the United States.

The debate exists whether healthcare is a privilege or a right. Opinions have changed over the years, and the Patient Protection and Affordable Care Act of 2010 allowed many access to healthcare that previously were without health coverage. However, many states including Texas refused to implement the policy. Due to politics, many Texas families still do not have health insurance coverage. The health of the population should be a priority issue, especially for children. This study seeks to further illustrate the urgent need for policy and social change at all levels for equality in health care.

Summary

Acute lymphoblastic leukemia (ALL) is the most common cancer in children, and one of the most treatable malignancies with some facilities reporting overall 5-year survival rates of 95% (Pui, Pei, et al., 2012). Successful outcomes are influenced by several factors, including timely diagnosis, administration of proven effective risk-based treatment protocols, adherence to treatment, and continued followup. Access to such care can be limited by geographic location and SES. Researchers have had mixed results when examining race, ethnicity, and survival, and studies focusing on Hispanic children have been limited. In this study I seek to provide data from a unique population that has not been previously examined to contribute to this important area of study.

This study examines the survival of children residing in Texas diagnosed with ALL 1995-2009. The purpose was to examine if COG membership holds prognostic significance on ALL survival. Large areas of Texas are isolated from COG facilities and residents must travel hundreds of miles to obtain expert pediatric oncology care. Such barriers have been associated with poorer cancer outcomes, including survival.

Chapter 2 focuses on the complete background of ALL, a condition that physicians and researchers alive today remember was 100% fatal during their early careers. While great advances have been made in ALL survival, a significant number of children still die from the disease. Chapter 3 focuses on the data used in this study, study design, and the data analyses conducted. Chapter 4 reveals the results of the data analyses and Chapter 5 provides a discussion and interpretation of these results, as well as future implications.

Chapter 2: Literature Review

Introduction

The purpose of this study was to examine if affiliation with Children's Oncology Group (COG) facilities for treatment of childhood acute lymphoblastic leukemia (ALL) was associated with improved 5-year survival. These facilities offer the most comprehensive and effective treatments available administered by expert specialty physicians. Large areas of Texas are isolated from such facilities. It is the hypothesis of the author that this isolation creates an access to care barrier resulting in significant poorer survival.

Several variables have been documented as having an association with poor ALL survival in children. These established predictors of ALL 5-year survival among children include facility-type associated with treatment, geographic area of residence, and residence-area poverty. State cancer registry data is commonly used in such studies. Kent et al. (2009) conducted a retrospective design study of childhood leukemia survival using cancer incidence data 1996-2005 from the California Cancer Registry. Howell et al. (2007) used data from the Georgia Cancer Registry 1998-2002 to examine COG participation among pediatric cancer patients residing in Georgia. Goggins and Lo (2012) used SEER data 1988-2008 to examine disparities among children diagnosed with ALL. Gutierrez, Cheung, Zhuge, Koniaris, and Sola (2010) used Florida cancer registry data to study COG efficacy in treating childhood malignancies. This quantitative retrospective cohort study used incidence data from the Texas Cancer Registry (TCR) for diagnosis years 1995-2009.

Literature Search Strategy

The primary search engine used in the literature review was PubMed, accessing primarily the MEDLINE database. Key search terms were *"acute lymphocytic leukemia" and "Children's Oncology Group."* Additional terms used were *"survival," "childhood," "pediatric," "access to care," "treatment," and "health disparities."* In addition several authors names were used who are considered experts in the field, such as Ching-Hon Pui, MD, and Smita Bhatia, MD, PhD.

Several textbooks from the author's private collection were also used from both public health and clinical education and training. Additional texts and peer-reviewed journals from the Texas State Department of Health Services library were also used.

Children's Oncology Group Facilities

The specialty of pediatric oncology is a relative new area of medical expertise. The American Board of Pediatrics did not offer an examination for a subspecialty in hematology/oncology until 1974 (Wolff, 1991). According to Health Grades (2009), the nation’s leading independent health care rating organization, fewer than 2,000 pediatric oncologists/hematologists combined practice in the United States, with only 169 in the entire state of Texas. Beginning in the 1950s, several groups were organized in the United States to focus on childhood cancer research. Over the next three decades these included the Cooperative Acute Leukemia Group A (CALGA) which soon became the Children’s Cancer Study Group (CCSG), the Southwest Oncology Group (SWOG), the Cooperative Acute Leukemia Group B (CALGB), the National Wilms Tumor Study Group (NWTSG), and others (Wolff, 1991). In 1986 several merged to form the Pediatric

Oncology Group (POG) eventually representing over 40 institutions. In 2000 all pediatric groups were merged into the Children's Oncology Group (COG), currently the world's largest pediatric cancer research organization with over 200 member institutions conducting clinical trials (American Academy of Pediatrics, 2009). During the time period studied, 12 COG institutions were located within the state of Texas (Cure Search, 2009).

Nationally it is estimated that 90-95% of childhood cancer patients aged 0-14 years are treated at COG facilities (O'Leary et al., 2008). However, analyzing Surveillance, Epidemiology, and End Results (SEER) data for pediatric cancer cases diagnosed 1992-1997 (N = 10,108) from 11 SEER registries, Liu, Krailo, Reaman, and Berstein (2003) found only 71% had been registered at a COG facility. As the TCR is not a SEER registry, Texas data were not included in the Liu et al. study. Carrol (2003) had reported previously over 80% of children will ALL in the United States would be treated at a COG facility.

Researchers have repeatedly shown children with ALL treated at COG facilities had significant improved survival (Bhatia, 2011). St. Jude Children's Research Center (2010) reported 94% 5-year survival for ALL and 77% for AML, well above published national survival rates. Texas Children's Hospital (2010) reported increasing ALL 5-year survival in infants from 20% to 50% through clinical trials, with their developed therapy protocol becoming the national standard. The improved survival of ALL through clinical trial participation at pediatric oncology research centers has been documented as far back as 1983 (Meadows et al., 1983).

In a study of COG facility access in the state of Georgia, Howell et al. (2007) found 87% participation for children aged 0-14 years, with no disparity between Black and White children. For children diagnosed with ALL, 5-year survival was 86.3% for COG institutions and 53.3% for other facilities. No regional differences within the state were examined. This was in part due to the multiple COG facilities located in several states bordering Georgia. There were no areas within Georgia fully isolated from a COG pediatric oncology facility.

This study used Texas population-based cancer data, collected directly by the state of Texas, and not a national database.

Health Disparities

Health disparities refer to differences in health, healthcare, and health outcomes based on personal demographic and socioeconomic factors (Bhatia, 2011). The U.S. Department of Health and Human Services (2000) targeted the elimination of health disparities as the second major public health objective to be achieved by the year 2010. These population-specific factors include race, ethnicity, socioeconomic status (SES), and geographic location. Health disparities are uniquely involved in childhood cancer in that these factors can apply to both the child diagnosed with cancer and parents seeking to provide care. Unfortunately, little improvement has been made in overall cancer health disparities despite decades of studies and public health interventions (Kagawa-Singer, Dadia, Yu, & Surbone, 2010).

In a self-assessment of the goal of eliminating health disparities by 2010, the U.S. Department of Health and Human Services (2012) found that no state had achieved the

set goal of health insurance coverage, with Texas having the highest percentage of uninsured residents. More of the stated health objectives actually worsened (24%) than were achieved (23%), and was even more pronounced among Hispanics. In specific regards to health disparities, 80% of the targeted objectives remained unchanged. As a result, health disparities and basic healthcare access remained target goals for improvement by 2020. Even with these national targeted interventions, the literature for health disparity interventions addressing mortality and chronic disease in non-infant children remains severely limited (Flores, 2010).

Race/Ethnicity

Hispanic children in the United States experience the highest incidence rate of ALL (ACS, 2012). Racial/ethnic minorities experience poorer cancer outcomes when compared to their White counterparts (Kagawa-Singer et al., 2010). Black, Hispanic, and American Indian/Alaskan Native (AIAN) children diagnosed with ALL have also been shown to have overall worse survival when compared to non-Hispanic Whites (Bhatia, 2011).

The mechanisms behind race/ethnicity and effect on ALL survival remain under investigation. Using population-based studies, Bhatia (2011) and Liu et al. (2003) reported that even with equal treatment Black, Hispanic, and AIAN children still experienced worse survival. In a followup examination, Goggins and Lo (2012) also reported poorer ALL survival for minorities when compared to non-Hispanic Whites using SEER data.

Examining cooperative group trial data 1990-2005, Hunger et al. (2012) found poorer survival in Black and Hispanic children treated for ALL. Trend analyses conducted revealed that survival had increased for Black children 1990-2005, but decreased for Hispanics. The authors cite higher-risk biological factors (T-cell vs. B-cell origin) and genomic mutations at possible explanations.

However, in institutional studies, Pui et al. (2003, 2012) found that with equal treatment, children of all races/ethnicities experienced the same outcomes, regardless of disease metrics at diagnosis. This would indicate that race/ethic differences are more associated with variances in complete administered treatment protocols.

Socioeconomic Status

Socioeconomic status (SES) plays a major role as a determinant in healthcare and health. The social stratification of individuals based on education, occupation, income, and residence in turn influences health status, access to care, and decisions about healthcare (Kagawa-Singer, Dadia, Yu, & Surbone, 2010). Later stage at diagnosis and less aggressive treatment have been identified as key risk factors in low SES groups (Byers et al., 2008). For many conditions, when SES factors are controlled disparities are greatly reduced or even eliminated. Social factors play a larger role than biologic factors in explaining racial/ethnic disparities (Byers et al., 2008).

Characteristics associated with SES have a substantial impact on both cancer incidence and mortality. For adult cancers, SES and poor outcomes can be in part attributed to lifestyle choices (tobacco use, diet, exercise, other behaviors, etc.) and nonuse of cancer screening. These factors are not as closely related to ALL and other

cancers in children. There are few identified lifestyle risk factors (parent or offspring) for childhood ALL and no screening protocols exist.

Where prevention and early detection are mortality hallmarks of such adult neoplasms as prostate, cervical, colorectal, and breast cancer, ALL survival relies solely on precise timely diagnosis and treatment. The costs, time investment, and required resources between screening/prevention and treatment strategies are substantial. Even with comprehensive health insurance, associated out-of-pocket expenses such as copayments, travel, missed working hours or even employment termination resulting in lost income, and homecare expenses can be substantial (Bona et al., 2014). The poor suffer disproportionate financial losses, and costs associated with childhood cancer can cause families not in poverty to fall below the federal poverty level (Bona et al., 2014).

Comprehensive, optimal treatment for ALL involves repeated visits for two and often three years (Diller, 2011). Even under the most favorable financial conditions such a treatment protocol presents many challenges. Parsons (2006) reported that even with health insurance families with a child receiving treatment for ALL spent up to one-third of their after-tax income on related expenses. In 2007, 62% of all bankruptcies in the United States were caused by medical expenses, with 75% of those claims affirming having health insurance (Himmelstein, Thome, Warren, & Woolhandler, 2009).

For poor families without health insurance the situation can be especially devastating both financially and psychologically. Even such basic needs as lack of nutritious food can have serious effects. Margolin et al. (2011) reported undernourished children diagnosed with ALL suffer 2.5 times the mortality from the disease.

The SES gradient, however, in childhood cancer is not always as linear as in adult cancers. In a study of California children diagnosed with ALL Kent et al. (2009) found that survival did not differ among SES levels for Hispanic children. The authors theorized that geographic location and access to the best care was a survival factor among Hispanic children in California.

Geographic Location

The U.S. Department of Health and Human Services (2010) defined attaining adequate access to health care as being received timely, achieving the best results possible, and having three defined components:

1. Gaining entry into the health care system.
2. Getting access to sites of care where patients can receive needed services.
3. Finding providers who meet the needs of individual patients and with whom patients can develop a relationship based on mutual communication and trust. (p.141)

Children and their parents who live in geographically isolated areas are challenged to meet any or all of those criteria, especially those who are poor with language barriers and are in need of advanced specialty oncology care.

Youlden et al. (2011) found that children diagnosed with cancer residing in remote areas of Australia had significantly lower survival compared to children living in cities. This was especially true for children diagnosed with ALL. Schillinger et al. (2011) found place of residence, and not poverty, was more significant in survival among children diagnosed with ALL in England.

Goodwin, Freeman, Mahnken, Freeman, and Nattinger (2002) used incidence, mortality, and survival to reveal geographic variations in breast cancer survival in the United States. Geographic variations in cancer survival have been identified in Europe, particularly when examining breast cancer (Sant et al., 2009). In both the American and European studies, variations in access to care, treatment protocols, adherence, and followup are viewed as likely reasons for these differences. In examining European Cancer Registry childhood cancer data, Gatta et al. (2005) found higher survival for lymphoid leukemia in Western Europe compared to Eastern Europe. Access to higher quality treatment was considered the reason for this discrepancy.

One geographically isolated area of the United States that has been studied is Appalachia, a mountainous region that stretches from New York down to the costal southern states. Characteristics of this area include poor health, poverty, and low education levels (Behringer et al., 2007). This region suffers from higher and premature mortality from many conditions including cancer (Wingo et al., 2008). The size and geographic isolation of many parts of the Appalachia area creates a distance to care barrier. High poverty and the unique cultural characteristics of the area create additional barriers to health care.

The Texas-Mexico border represents a very similar geographically isolated and culturally diverse region. In addition, over 5 million children in the United States have undocumented parents with over half living at twice below the federal poverty level (Urban Institute, 2010). This environment not only restricts access to quality care in the

United States, but forces many Texas residents to cross the Rio Grande and seek care and medications in the border towns of Mexico (Rivera, Ortiz, & Cardenas, 2009).

At over 268,000 square miles Texas is physically the second largest state in the Union with 254 counties and a population of over 26 million, 27% of which are under the age of 18 years (U.S. Census Bureau, 2013). Texas is home to a large Hispanic population (38.2%), with the border area population 74.1% Hispanic (U.S. Census Bureau, 2013).

The border counties of El Paso, Hidalgo, Cameron, and Webb are among Texas's most populated, ranked 6th, 7th, 11th, and 21st respectively (U.S. Census Bureau, 2013). The border cities of El Paso, Brownsville, Laredo, and McAllen account for almost half the border area population, and are among the areas located furthest from COG facilities. Over 705,000 children below the age of 18 years reside in the Texas-Mexico border area (U.S. Census Bureau, 2013).

In 2004, Texas Children's Hospital, a COG facility in Houston, opened a satellite clinic in McAllen to provide some oncology services to children in south Texas. Clinical trials, the defining characteristic of COG membership, were not conducted during the study period. Clinical trials offer the latest innovative and most effective therapies available, and as a result children treated at these facilities have a significant survival advantage (Bhatia, 2011). Substantial progress and continued advances in childhood cancer treatment are the result of high-participation clinical trials at COG facilities (Siegel, Naishadham, & Jemal, 2012). Survival for ALL based on clinical trial strategies administered in COG facilities has collectively exceeded 90% (Robison, 2011).

As with much of Texas, a large portion of the border area is also rural. Rural areas have been identified as having higher poverty rates and increased health disparities (Eberhardt et al., 2001). Access to physicians in general can be a barrier to persons living in rural areas. Van Dis (2002) reported that while 20% of persons in the United States lived in rural areas, only 9% of the country's physicians practiced in rural areas. The distribution of specialist physicians poses an even larger challenge.

The predominantly Hispanic Texas border area is not only the poorest area of Texas, but one of the highest poverty areas of the United States (U.S. Census Bureau, 2010). This is especially true for persons under 18 years of age. Over 37% of children residing in the 32-county border area were living in poverty in 2008 compared to 22.5% for the state and 18.2% for the United States (U.S. Census Bureau, 2010).

McCarthy et al. (2009) reported that Texas ranks last in the nation for the number of children with health insurance. The largest concentration of these uninsured children occurs along the Texas-Mexico border (U.S. Census Bureau, 2010). The U.S. Census Bureau (2010) reported that for 2008 the population of the 32-county Texas-Mexico border area was 80% Hispanic, with some counties reporting over 95% persons of Hispanic origin. Researchers have shown that Hispanics are much more likely to be employed in occupations without employer-based benefits (Escarce & Kapur, 2006).

The small communities in the border area known as "colonias" suffer from extreme poverty and poor health (Texas Secretary of State, 2014). These migrant neighborhoods are home to over 400,000 people and often lack the most basic of services and infrastructure including electricity, water, sewage, decent housing, and paved roads

(Texas Secretary of State, 2014). These areas are isolated from even the most basic medical and dental care.

Literature Review of Pediatric ALL Epidemiology/Survival

For the years 2007-2011, the overall incidence rate for ALL among children aged 0-14 years in the United States was 4.2 per 100,000 population, with a mortality rate of 0.3 per 100,000 (Howlader et al., 2014). While males experienced a slightly higher incidence rate than females, mortality rates were the same for both genders (Howlader et al., 2014). Males have been shown to have poorer outcomes (Kaden-Lottick et al., 2003; Hossain, Xie, & McCahan, 2014).

Hispanic children experienced the highest incidence, and Blacks the highest mortality. Barrington-Trimis et al. (2015) reported that ALL incidence in Hispanic children was increasing at a statistically significant higher rate non-Hispanic children. Kaden-Lottick et al. (2003) reported poorer survival in Hispanic children when compared to non-Hispanics. However, as described earlier, all of SEER-based studies and many nationally published statistics do not include states/areas such as Texas with large Hispanic populations.

Age at Diagnosis

Age at diagnosis is a key prognostic factor in risk classification of ALL. Ages 1-4 years of age experience the highest incidence and have the most favorable outcomes, with survival over 90% in the United States (Siegel, Naishadham, & Jemal, 2012). Infants younger than one year of age experience poor outcomes with 46% survival (Hossain et al., 2014). Survival of childhood ALL decreases with each additional year of age

beginning with diagnosis at 5 years of age, with survival decreasing to 57% for ages 15-19 years (Hossain et. al., 2014).

Importance of Risk-Based Treatment

Four major types of leukemia are identified (Lichtman, 2008):

1. Acute Lymphoblastic Leukemia (ALL)
2. Acute Myeloid Leukemia (AML)
3. Chronic Lymphoblastic Leukemia (CLL)
4. Chronic Myeloid Leukemia (CML)

The terms “acute” and “chronic” refer respectively to whether the progression of the disease is rapid or slow. The leukemia type is then designated by the blood cell type affected. Lymphoblastic leukemia refers to the uncontrolled proliferation of lymphoblasts, an immature type of white blood cell (Torpy, Lynm, & Glass, 2009). Myeloid leukemia is defined by the proliferation of cells other than lymphoblasts, such as other white blood cells, red blood cells, and platelets in the bone marrow (Altman & Fu, 2011). Myeloid leukemia is rare in children and has a much poorer prognosis. The vast majority of childhood leukemia cases are acute - ALL and AML account for approximately 95% of all childhood leukemia cases (Onciu & Pui, 2012). Chronic leukemia in children is rare.

ALL is further classified into subgroups based on the pathobiology of the leukemic lymphoblasts. The identification of the type of lymphoid cell from which the disease originates is of great importance and determined at diagnosis. Approximately 85% of childhood ALL is of B-cell origin (Margolin, Rabin, Steuber, & Poplack, 2011).

Further classification based on cell morphology, immunology, cytogenetics, and molecular structure define the disease into even smaller sub-types. Detailed classification systems include the French-American-British (FAB) scheme and the World Health Organization (WHO) criteria (Onciu & Pui, 2012). With improved genetic analyses, these classifications continue to be expanded.

Based on the multiple criteria of these systems, approximately 85% of children diagnosed with ALL are classified into the low risk category associated with the most favorable outcomes (Onciu & Pui, 2012). Basic criteria of this category include B-cell type disease diagnosed at 1-9 years of age, low leukocyte counts, and no testicular or CNS lesions (Pui, 2012). The detailed stratification of children into these risk groups has greatly improved the selection, administration, and effectiveness of treatment and subsequent survival (Seibel, 2008). Recent advances in molecular medicine, in particular pharmacogenomics which examines both patient and malignant leukemia cell genetic features, has shown great promise (Pui et al., 2008). Researchers continue to develop the most accurate risk categorization of ALL to administer the most effective treatments at the appropriate levels (Siebel, 2008).

Treatment of ALL Protocols

Unlike solid tumors where surgery or radiation can be specifically directed to a particular location, hematologic malignancies require a systemic approach. Solid tumors can often be detected and removed surgically at the early stages before the malignancy spreads which greatly improves the odds of successful treatment. Prior to the 1950s a

diagnosis of leukemia in a child was virtually a death sentence with zero treatment options available (Margolin et al., 2011).

The selection of St. Jude, the patron saint of lost causes, in naming the now famous pediatric cancer research center in Memphis, Tennessee, directly reflected the general outlook in the early 1960s towards treating children with cancer. At that time a child diagnosed with ALL had less than 10% chance of survival (Hunger et al., 2012). As late as 1965 many medical experts were still publishing articles harshly criticizing research in childhood leukemia (Lichtman, 2008).

With continued drug developments, improved multi-treatment components, and more focused risk-based treatment including cytogenetics, 10-year survival for ALL in children improved from 20% in the early 1970s to over 80% by 1995 (Margolin et al., 2011). This is an important statistic as once 10-year survival is achieved the chance of relapse is very low. For low-risk categories of ALL treated with optimal protocols, 5-year survival progressed to exceed 90% (Pui et al., 2009). Many of the therapeutic agents initially identified and administered remain in present-day treatment protocols for ALL in children.

Preventing Disease Relapse

Pui et al. (2008) reported that initial clinical remission, in which there is no physical or microscopic evidence of leukemia, could be achieved in 99% of children diagnosed with ALL. This first step in the treatment of ALL is known as the induction phase where the selected chemotherapy drugs and dose levels are administered over a period of several weeks (Margolin et al., 2011).

Leukemic cells can often reside in the central nervous system (CNS) where some antileukemic drugs are not effective. It is imperative that during the induction phase no residual leukemic cells remain in the blood, bone marrow, or CNS. Physicians began using radiotherapy in the 1960s and 1970s to prevent CNS relapse in ALL cases, but this was later questioned due to the dangers of exposing a child's brain and/or spinal cord to radiation (Margolin et al., 2011). Based on continued studies today most COG pediatric oncologists only advocate cranial radiation at diagnosis for the most high-risk ALL groups. With the improved success of risk-based chemotherapy, Pui et al. (2009) recommended eliminating radiotherapy completely in ALL treatment. Sophisticated and complex testing only available at pediatric oncology specialty facilities is needed to determine the risk/benefit ratio of various ALL treatments (Margolin et al., 2011)

Late Effects of Treatment

The successful treatment of ALL with toxic anticancer agents created additional problems for researchers and clinicians to address, noted from the first clinical trials. The synthesis of less-toxic compounds improved side effects, but adverse conditions remained a problem. Immunosupression was eventually successfully treated with antibiotics. Radiotherapy, used in the 1960s and 1970s to prevent CNS relapse in ALL cases, was later reserved for only the most high-risk categories due to the dangers of exposing a young child's brain to radiation (Margolin et al., 2011).

Oeffinger et al. (2006) found that childhood cancer survivors in general were more likely to have later diminished health status and die prematurely when compared to adults who were not diagnosed with cancer as a child. Two out of three childhood cancer

survivors developed complications due to therapy, with 25% of childhood cancer survivors developing a severe condition (Oeffinger et al., 2006) Survivors of ALL in particular are at risk for second neoplasms, neurological problems, cardiac dysfunction, infertility, and growth failure (Mody et al., 2008). Psychological and psychosocial problems, especially in individuals who received cranial radiation, are also of major concern in the ALL survivor (Zeltzer et al., 2009). Mertens (2007) reported significant mortality risk from treatment-related complications for up to 25 years after initial childhood diagnosis.

Given the chance of relapse and the high incidence of associated late effects from ALL treatment, routine followup care is essential (Robison, 2011). The specific treatment-related risk factors of ALL must be continuously monitored for the earliest possible detection. As with initial evaluation and subsequent treatment, comprehensive risk-based care from the most skilled professionals in continued followup care is vital to long-term survival. Margolin et al. (2011) stressed that in addition to blood therapy and infection control, addressing nutritional needs and providing psychosocial support for the patient and family must also be included in any treatment protocol. Cultural issues must also be addressed (American Academy of Pediatrics, 2009). This comprehensive care must also be accessible. The American Academy of Pediatrics reported that many children diagnosed with cancer experience barriers, including having to travel long distances to facilities that deliver such care.

Summary

This chapter reviewed the treatment of pediatric ALL, and key factors associated with that treatment and survival. The successful treatment of ALL is one of the few major victories in treating children with cancer. Once 100% fatal, through research and technology survival in the United States has now exceeded 90%. Some COG facilities have even pushed survival of pediatric ALL to 95%.

However, not all children in the United States have access to such expert care, and survival can vary due to several factors. Physicians and researchers at COG facilities have revealed that when treating the disease there are no clinical or biological factors that reduce survival with equal treatment. Even demographic factors such as gender, race, and ethnicity have no effect when the best risk-based treatments are applied. Thus, the reasons for poorer survival must be explained outside of the clinical environment. In order for children to experience the same level of survival, each child much be treated with the same level of care throughout their disease process available only at COG facilities.

This study further examines the effectiveness of COG facility-affiliation in the treatment of pediatric ALL, and in a population previously not studied. Additional covariate variables were also examined. Chapter 3 describes the variables used in this research and the analyses conducted.

Chapter 3: Methodology

Introduction

The purpose of this study was to determine if facilities in Texas with COG membership offer prognostic significance in pediatric ALL survival. This chapter will discuss this study's design, study population, data collection, variables of interest, and data analyses. Quality assurance, confidentiality, and protection of human subjects are also addressed.

Research Design and Rationale

The design used for this study was a retrospective cohort design. This type of study is well-suited for population-based cancer epidemiological studies, especially for rarer neoplasms. State cancer registries and/or Surveillance, Epidemiology, and End Results (SEER) data are sources of secondary data for many such population studies. Data for this study was obtained from the Texas Cancer Registry (TCR).

This study was approved by the Walden University Institutional Review Board (IRB), approval number 11-04-16-0101571. As no confidential data elements were used in the analyses, no approval from the Texas Department of State Health Services (DSHS) IRB was needed. DSHS provides requested datasets for research from their available public-use list at no charge, requiring only a signed data use agreement.

The study population for this study was all individuals residing in the state of Texas diagnosed with ALL 1995-2009 at age 14 years or younger. All incidence data used in this study was previously collected by TCR via passive surveillance through abstract reports, primarily from Texas hospitals and cancer treatment facilities. The

reports then must complete a series of quality assurance protocols to ensure high data quality before being accepted as a legitimate incidence case of cancer in Texas. By state law, TCR maintains a statewide cancer incidence database from these reports.

In addition to specific cancer information, these reports include key fields for epidemiological study such as reporting facility, race/ethnicity, the address of residence at diagnosis, date of birth, date of diagnosis, vital status, and date of death (Table 1). TCR meets all standards of the Centers for Disease Control (CDC) National Program of Cancer Registries (NPCR) program, and is certified by the North American Association of Central Cancer Registries (NAACCR) for consistently achieving high data quality standards (TCR, 2010).

The dependent variable in this study was 5-year survival. The independent variables were COG facility status (yes/no), geographic region of residence (border/nonborder), and poverty status (>= 20% for residents of county based on census tract data from U.S. Census Bureau). Galster (2012) found that most negative effects associated with poverty begin to manifest and progress rapidly once a neighborhood exceeds an overall 20% poverty rate.

Table 1

Study Variables

Variable	Type	Coding	Source
Date of Birth	Date	MM/YYYY	TCR
Date of Death	Date	MM/YYYY	TCR
Gender	Binomial	Male/Female	TCR
Race/Ethnicity	Categorical	NHW,H,B,O*	TCR
Date of Diagnosis	Date	MM/YYYY	TCR
Age at Diagnosis	Continuous	0-14 Years	TCR
Residence County	Binomial	Border/Nonborder	TCR
Vital Status	Binomial	Alive/Dead	TCR
COG Facility	Binomial	Yes/No	TCR
Poverty Status	Binomial	>=20% = Poverty	U.S. Census

*NHW=Non-Hispanic White, H=Hispanic, B=Black, O=Other

To be included in the study, each reported incidence record must meet the following criteria:

1. A diagnosis of ALL per the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3).
2. Diagnosed between the years 1995-2009.
3. Diagnosed at age 14 years or younger.
4. Resident of Texas at the time of diagnosis.
5. No previously diagnosed malignant neoplasm.

No personal identifying information was requested or collected or used in any way in this study. No contact was or was made with any individual or medical personnel. All dates only include month and year for additional confidentiality. No individual case was identified with a specific facility, or any specific individual facility total case counts given.

Wright (1995) recommended 50 cases per predictor variable to achieve appropriate statistical power in a logistic regression. Currently, there are 3,266 cases of ALL in the TCR database that meet the study inclusion criteria. This cohort size greatly exceeds the minimum required sample size to obtain accurate parameter estimates. In addition, to detect a small effect size (r^2=.01) given the three independent variables at a statistical significance value of $p < .01$, Cohen (1992) calculated that 698 participants would provide 80% power in a multiple logistic regression.

Research Methodology

Research Questions

1. What are the descriptive epidemiology statistics for childhood ALL in Texas? These statistics included ALL incidence, mortality, and relative 5-year survival rates for children 0-14 years of age residing in Texas diagnosed 1995-2009. As of this writing there are no published epidemiological statistics of pediatric ALL specific to the Texas-Mexico border region.
2. Is there an association between COG facility affiliation and 5-year survival of ALL?

   H_o2: COG facility affiliation has no effect on 5-year survival of ALL.

H_a2: COG facility affiliation has an effect on 5-year survival of ALL.

3. Is there an association between COG facility affiliation and 5-year survival of ALL controlling for race, place of residence (border/nonborder), and poverty?

   H_o3: There is no association between COG facility affiliation and 5-year survival of ALL when controlling for race, place of residence, and poverty.

   H_a3: There is an association between COG facility affiliation and 5-year survival of ALL when controlling for race, place of residence and poverty.

Data Analysis

After application and approval from the Texas Department of State Health Services, Texas Cancer Registry, ALL incidence data was provided in text file format for convenient import into multiple software packages. Descriptive statistics were calculated using SEER*Stat software from the National Cancer Institute (Table 2). Further analyses were performed using Statistical Analysis System (SAS), version 9.4. Correlations between binomial/categorical variables and COG affiliation were made using the chi-square test (Table 3). These variables included gender, race/ethnicity, geographic region, and poverty status. Given at least three predictor variables of interest (facility affiliation, area of residence, poverty status) pending the chi-square tests, logistic regression was used to examine these variables in reference to the dependent variable of 5-year survival (Tables 4 and 5). Odds ratios with 95% confidence intervals were calculated to assess the strongest predictor(s) of survival. No censoring, loss to followup, or time to event sequences were used or analyzed.

Table 2

Childhood Acute Lymphocytic Leukemia, Texas, 1995-2009

Residence	Incidence	Mortality	5-Year Survival
Texas			
Border			
Nonborder			

Note: All rates are age-adjusted to the 2000 US Census Standard.

Table 3

Association of Type of Facility with Demographic Variables

Variable	COG, *N* =	Non-COG, *N* =	X^2	*P**
Gender				
Male				
Female				
Race/Ethnicity				
White				
Black				
Hispanic				
Other				
Residence				
Border				
Nonborder				
Poverty				
>= 20%				
< 20%				

*P-value by chi-square for association between variables.

The variables for the logistic regression analysis were:

- Dependent Variable: 5-year survival, yes/no
- Independent Variable: COG Facility, yes/no
- Independent Variable: Residence, border/nonborder
- Independent Variable: Poverty Status >= 20%

Table 4

Logistic Regression with COG Facility

Source	*B*	*SE*	χ^2	*p*	*OR*	95% CI for OR
COG Facility						

B: slope
SE: standard error
χ^2: test statistic
p: p-value
OR: Odds ratio
95% CI for OR: 95 percent confidence interval for odds ratio

Table 5

Logistic Regression with COG Facility, Residence, and Poverty

Source	*B*	*SE*	χ^2	*p*	*OR*	95% CI for OR
COG Facility						
Residence						
Poverty						

B: slope
SE: standard error
χ^2: test statistic
p: p-value
OR: Odds ratio
95% CI for OR: 95 percent confidence interval for odds ratio

Summary

This chapter described the research methods to examine the survival of acute lymphoblastic leukemia (ALL) among children living in Texas. The author wishes to investigate the poorer survival of the disease among some children and if the type of

treatment facility is associated with 5-year survival. ALL is a very treatable condition in children and one of medicine's few major success stories against cancer. However, some children in Texas may not be receiving the best care available. No child should be at a disadvantage from such care. Chapter 4 presents the results to the specific research questions.

Chapter 4: Results

Introduction

The purpose of this quantitative retrospective epidemiologic study was to determine if facilities in Texas with Children's Oncology Group (COG) affiliation offer prognostic significance in pediatric acute lymphoblastic leukemia (ALL) survival. All data used is the study were previously collected by the Texas Cancer Registry (TCR). Texas law mandates that the state maintain a cancer registry. By Texas law cancer is a reportable condition to the state cancer registry. All hospitals and treatment centers are required to report each case diagnosed and/or treated. TCR is a member of the Centers for Disease Control (CDC) National Program of Cancer Registries and the North American Association of Central Cancer Registries (NAACR).

Datasets with no personal health information are available from TCR to the public upon request. No personal health information was requested or used in this study. All counts, rates, and analyses were calculated at aggregate levels. The TCR data-use agreement requires that no aggregate data rates below the count of 16 individuals be presented.

The initial selection criteria for the dataset was incident cases off ALL diagnosed during the years 1995-2009 among children less than 15 years of age residing in the state of Texas. This chapter first presents the descriptive epidemiological statistics of the study population, and then examines variables associated with ALL survival.

Variables

The variables used in this study were gender, race, ethnicity, diagnosis date, county of residence, reporting facility, vital status, date of death, poverty status, and five-year survival. Poverty status was recorded from the United States Census Bureau based on the geocoded census tract of resident address. Poverty was defined as census tracts with ≥ 20% poverty among residents. Five-year survival was defined as living at least five years from the date of diagnosis. Date of death indicates the date the individual died, or the date of last contact depending of the vital status being "alive" or "dead." The examined dataset had complete vital status followup through 2014, thus allowing for complete 5-year survival status of all included incident cases.

Reporting facilities were dichotomized into two groups based on affiliation with the COG program. During the time of the study, COG member facilities were located in the metropolitan areas of Amarillo, Lubbock, Dallas/Fort Worth, Temple, Austin, San Antonio, Corpus Christi, and Houston. No COG facilities were located within the 32-county border area. Border or nonborder county residence was based on the reported county of residence at the time of diagnosis. Race/ethnicity were combined into four groups of Non-Hispanic White, Black, Hispanic, and Other/Unknown.

Based on the study selection criteria, 3,266 records of ALL were received from TCR. Incident counts for the variables of interest are given in Table 6. Of particular note was of the 482 cases of ALL from the 32-county border area, 417 (86.5%) cases were from just four counties: Hidalgo, El Paso, Cameron, and Webb.

Table 6

Variable Counts, Childhood ALL, Ages 0-14 Years, Texas, 1995-2009

Variable	*n*	%
Sex		
Male	1,795	55.0
Female	1,471	45.0
Race		
Hispanic	1,699	52.0
Non-Hispanic Black	204	6.2
Non-Hispanic White	1,225	37.5
Other or Unknown	138	4.2
Residence		
Nonborder	2,784	85.2
Border	482	14.8
Poverty status		
< 20%	2,125	65.1
≥20%	1,141	34.9
Facility affiliation (COG)		
No	259	7.9
Yes	3,007	92.1
5-Year Survival of ALL		
No	453	13.9
Yes	2,813	86.1

Note. All percentages may not sum to 100 due to rounding error.

Research Question 1

What are the descriptive epidemiology statistics of childhood ALL in Texas? Using SEER*Stat software from the National Cancer Institute, the rates for incidence, mortality, and 5-year survival were calculated (Table 7).

Table 7

Childhood Acute Lymphocytic Leukemia Rates, Texas, 1995-2009

Residence	Incidence	Mortality	5-Year Survival
Texas	4.2	0.4	86.3%
Nonborder	4.1	0.3	87.8%
Border	5.1	0.9	77.5%

Note. All rates are per 100,000 and age-adjusted to the 2000 US Census Standard.

The overall ALL incidence rate was 4.2 per 100,000 population for children ages 0-14 years. The corresponding mortality rate for childhood ALL was 0.4 per 100,000 population. The incidence rate of childhood ALL in the 32-county border region was 5.1 per 100,000 population compared to 4.1 per 100,000 for the nonborder area of Texas. Border area Hispanics had an incidence rate of 5.4 compared to 5.2 for nonborder Hispanics. Childhood ALL mortality in the border area was 0.9 per 100,000 population compared to 0.3 per 100,000 for the nonborder area of the state. The mortality rate for border Hispanics was 0.9 compared to 0.5 for nonborder Hispanics.

While five-year survival in Texas was consistent with national statistics at 86.3%, the 32-county border area was significantly lower for 5-year survival at 77.5%, and the nonborder area slightly higher at 87.8%. A 2x2 chi-square analysis revealed this difference was statistically significant, $\chi^2(1) = 32.023$, $p < .001$. In addition, the COG participation rate for the border area was 56.2% compared to 98.3% for the nonborder region of Texas.

Research Question 2

Is there an association between facility affiliation and 5-year survival of ALL?

H_o2: Facility affiliation has no effect on 5-year survival of ALL.

H_a2: Facility affiliation has an effect on 5-year survival of ALL.

A series of chi-square tests of independence were conducted to examine the relationships between sex, race, residence, poverty, and COG facility affiliation. The results are presented in Table 8.

Table 8

Association of Type of Facility with Demographic Variables

Variable	COG, *N* = 3,007	Non-COG, *N* = 259	χ^2	*p**
Gender			0.05	.830
Male	1,651 (50.6%)	144 (4.4%)		
Female	1,356 (41.5%)	115 (3.5%)		
Race/Ethnicity			120.18	<.001
White	1,190 (36.4%)	35 (1.1%)		
Black	202 (6.2%)	2 (0.1%)		
Hispanic	1,480 (45.3%)	219 (6.7%)		
Other	135 (4.1%)	3 (0.1%)		
Residence			995.10	<.001
Border	271 (8.3%)	211 (6.5%)		
Nonborder	2,736 (83.8%)	48 (1.4%)		
Poverty			144.55	<.001
>= 20%	962 (29.5%)	179 (5.4%)		
< 20%	2,045 (62.6%)	80 (2.4%)		

*P-value by chi-square for association between variables. *Note.* All percentages may not sum to 100 due to rounding error.

Of all variables examined, only sex was not statistically significant, suggesting sex and COG facility affiliation were not significantly associated with one another. Race, residence, and poverty were all statistically significant, indicating a significant association with COG facility participation.

To address whether COG facility affiliation had an effect on 5-year survival of ALL, logistic regression was conducted. Logistic regression is an appropriate statistical analysis when assessing the predictive relationship between an independent variable and a dichotomous outcome variable. Facility affiliation was entered into the model as the predictor variable (1 = COG and 0 = Not COG). The outcome variable corresponded to 5-year survival of ALL (1 = Yes and 0 = No Survival). The results of the logistic regression are presented in Table 9.

Table 9

Logistic Regression with COG Facility Affiliation Predicting Survival of ALL

Source	*B*	*SE*	Wald	*p*	*OR*	95% CI for OR
COG Facility	0.07	0.18	0.15	.699	1.07	[0.75. 1.54]

Note. Overall model fit: $\chi^2(1) = 0.15$, $p = .699$, Nagelkerke $R^2 < .001$

The results of the logistic regression were not statistically significant, $\chi^2(1) = 0.15$, $p = .699$, suggesting that COG facility affiliation alone was not significantly associated with 5-year survival of ALL. As such, the null hypothesis cannot be rejected. Facility affiliation alone does not have an effect on 5-year survival. Statewide, there was not a statistically significant difference between patients being seen at COG-affiliated facilities compared to facilities that were not COG affiliated.

Research Question 3

Is there an association between COG facility affiliation and 5-year survival of ALL controlling for race, place of residence, and poverty?

H_o3: There is no association between COG facility affiliation and 5-year survival of ALL when controlling for race, place of residence, and poverty.

H_a3: There is an association between COG facility affiliation and 5-year survival of ALL when controlling for race, place of residence, and poverty.

To address research question three, a logistic regression was conducted. Residence, poverty status, race, and COG facility affiliation were entered into the model as predictor variables. Residence was treated as a dichotomous response, with 1 = border and 0 = nonborder. Poverty status was treated as a dichotomous response, with 1 = poverty rate $\geq$ 20% and 0 = poverty rate < 20%. Facility affiliation was treated as a dichotomous response, with 1 = Yes (COG) and 0 = No (Non-COG). Due to race being a categorical variable with four levels, the variable was dummy coded into three separate dichotomous variables for comparison. During the dummy coding process, non-Hispanic White was treated as the reference group. The outcome variable corresponded to 5-year survival (1 = Yes and 0 = No). The results are presented in Table 10.

Table 10

Logistic Regression with COG Facility, Residence, Poverty, and Race

Source	*B*	*SE*	Wald	*p*	*OR*	95% CI for OR
Residence	-0.71	0.16	19.32	<.001	0.49	[0.36, 0.68]
Poverty status	-0.26	0.12	4.67	.031	0.77	[0.61, 0.98]
Race (reference: White)						
Hispanic	-0.18	0.13	2.00	.157	0.84	[0.65, 1.07]
Black	-0.36	0.21	2.91	.088	0.70	[0.46, 1.06]
Other	0.57	0.36	2.56	.110	1.77	[0.88, 3.56]
Facility affiliation	-0.60	0.21	7.95	.005	0.55	[0.36, 0.83]

Note. Overall model fit: $\chi^2(6) = 55.17$, $p < .001$, Nagelkerke $R^2 = .030$

The overall regression model was statistically significant, $\chi^2(6) = 55.17$, $p < .001$, suggesting that residence, poverty status, race, and facility affiliation have a significant collective effect on survival of ALL. The regression coefficient for residence was significant, $B = -0.71$, $p < .001$, $OR = 0.49$, indicating that for individuals on the border, the odds of observing survival of ALL would decrease by approximately 49%. The regression coefficient for poverty status was also significant, $B = -0.26$, $p = .031$, $OR = 0.77$, indicating that for individuals in poverty areas, the odds of observing survival of ALL would decrease by approximately 77%. None of the race coefficients were significant in the regression model. The regression coefficient for facility affiliation was significant, $B = -0.60$, $p = .005$, $OR = 0.55$, suggesting that for participants with a COG facility affiliation, the odds of observing survival of ALL would decrease by approximately 55%. Due to significance of the overall model and the individual predictor variables, the null hypothesis for research question three can be rejected. There

was an association between COG facility affiliation and 5-year survival of childhood ALL when controlling for race, place of residence, and poverty.

Multicollinearity can pose problems in regression models when intercorrelation among multiple predictor variables is moderate or high (Stevens, 2009). Highly correlated variables can result in inflated variances and unstable coefficient estimates. To further explore these results, Variance Inflation Factors (VIFs) were calculated to detect the presence of multicollinearity between the predictor variables. Variance Inflation Factors greater than 5 are cause for concern, whereas VIFs of 10 should be considered the maximum upper limit (Stevens, 2009). A score below 5 indicates little collinearity with the other variables (Stevens, 2009). The VIF values for each dependent variable are presented in Table 11.

Table 11

VIF Values for Predictor Variables

Source	*VIF*
Residence	1.72
Poverty Status	1.33
Race (reference: non-Hispanic White)	
Hispanic	1.43
Non-Hispanic Black	1.12
Other	1.07
Facility Affiliation	1.44

All predictors in the regression model had VIFs less than 5, and thus there in no cause for concern of multicollinearity in the model.

To further assess the significant predictor variables, chi-square analyses were conducted between residence and 5-year survival, and poverty and 5-year survival. The results are presented in Table 12.

Table 12

Association of Residence and Poverty with ALL 5-Year Survival

Variable	No Survival $N = 453$	Survived $N = 2{,}813$	χ^2	p*
Residence			32.84	<.001
Border	346 (10.6%)	2,438 (74.6%)		
Nonborder	107 (3.3%)	375 (11.5%)		
Poverty			25.70	<.001
< 20%	247 (7.6%)	1,878 (57.5%)		
>= 20%	206 (6.3%)	935 (28.6%)		

*P-value by chi-square for association between variables. *Note.* All percentages may not sum to 100 due to rounding error.

Residence and poverty were both statistically significant, indicating a significant association independently with childhood ALL 5-year survival. In addition, 2x2 chi-square analysis between residence and poverty revealed a statistically significant association between the variables, $\chi^2(1) = 535.39$, $p < .001$.

To further examine the issue of COG facility participation given the extreme rate difference between border (56.2%) and nonborder (98.3%) counties, a chi-square analysis was conducted using only border data. This analysis revealed a statistically significant

association between COG facility participation and childhood ALL 5-year survival, $\chi^2(1) = 9.35$, $p = .002$. This calculation also produced a statistically significant odds ratio of 2.0, 95% CI [1.3, 3.2]. While COG facility participation was not prognostic for 5-year survival statewide, COG facility participation was associated with increased survival for the 32-county border area.

Summary

The purpose of this study was to determine if facilities in Texas with COG facility membership affiliation offer prognostic significance in pediatric ALL survival. Incidence rates were consistent for Texas and the 32-county border and nonborder areas, and consistent with national statistics. Mortality was higher in the predominantly Hispanic border area while Hispanics in the nonborder area did not experience a significant mortality difference from Texas or national ALL mortality rates.

Calculated 5-year survival rates revealed a statistically significant difference between survival in the 32-county border area and the collective nonborder region of Texas. In addition, the COG participation rate in the border area was 56%, far below the nonborder area rate of 98% and the national SEER rate of 95%.

Descriptive statistics and chi-square tests of independence were used to examine trends in the nominal level variables. The chi-square tests of independence determined that there was a significant relationship between race, residence, poverty status, and facility affiliation. The results of the logistic regression analysis for research question two indicated that there was not a significant predictive relationship between COG facility affiliation alone and survival of ALL statewide. The null hypothesis for research

question two cannot be rejected. The results of the logistic regression for research question three indicated that there was a collective predictive relationship between residence, poverty status, race, COG facility affiliation, and survival of pediatric ALL. In addition, three of the predictor variables, residence, poverty, and COG facility affiliation were individually statistically significant in the regression model. The null hypothesis for research question three can be rejected.

To further assess the stability of the regression model, Variance Indicator Factors were calculated indicating no multicollinerarity between the predictor variables. Additional chi-square tests were conducted to further investigate the relationship between the significant predictor variables and childhood 5-year survival. An additional chi-square test was conducted to examine the association of COG facility participation and 5-year survival in the 32-county border area. While COG facility participation was not statistically significantly associated with 5-year survival statewide, the association was statistically significant for the border area alone.

Chapter 5 will continue to discuss and interpret the findings of the data collection and analyses. Connections will be made to the existing literature and theoretical framework. Suggestions will also be provided for continued future research.

Chapter 5: Discussion, Conclusions, and Recommendations

Overview

The purpose of this study was to determine if facilities in Texas with Children's Oncology Group (COG) affiliation offer prognostic significance in pediatric acute lymphoblastic leukemia (ALL) survival. Among children ages 0-14 years, leukemia is the most common malignancy with ALL accounting for 75% of those cases. While this disease predominates in children, it is also one of the most curable malignancies with expedient and proper diagnosis, treatment, and followup care. Pediatric oncology research centers are the hallmark of such care, especially those that have achieved COG membership.

During the time period of this study, 1995-2009, Texas was home to 12 COG facilities located within eight metropolitan areas of the state. Those areas included the cities of Dallas, Fort Worth, Houston, San Antonio, Austin, Lubbock, Amarillo, Temple, and Corpus Christi. One area lacking a COG facility was the 32-county area of the Texas-Mexico border. The Texas-Mexico border area is home to over 2.5 million people, with over 700,000 children and adolescents. Along with the extreme poverty of the area, this geographic isolation poses a significant barrier to the comprehensive and complex treatment needed to cure pediatric ALL. Health disparity studies among children are much fewer compared to adults, and geospatial studies extremely lacking.

Race/ethnicity disparity studies among children diagnosed with ALL have been conflicting in regards to survival. Population-based studies using Surveillance, Epidemiology, and End Results (SEER) data from the National Cancer Institute have

revealed poorer survival for minorities. However, several facility-based studies have shown no differences in survival with equal treatment. Texas data is not included in the SEER dataset, and many studies examining racial disparities do not include Hispanics as a separate group. This study of children in Texas was unique in that 52% of the cases were recorded as Hispanic ethnicity. This was not surprising given Hispanics are the fastest growing population in Texas and ALL incidence is slightly higher in Hispanic children. A large Hispanic cohort along with the geospatial component and facility affiliation allowed for the examination of variables lacking in the literature.

Summary of Findings

Incidence and mortality rates and 5-year survival were calculated for Texas, the 32-county border area, and the nonborder area of the state. Childhood ALL incidence was consistent across Texas and both the border and nonborder areas, and consistent with national statistics. The overall statewide mortality rate of 0.4 per 100,000 population for childhood ALL in Texas was consistent with the United States rate of 0.3 per 100,000 population (ACS, 2013) for the same time period. Hispanics in the border and nonborder area had similar incidence rates which were also consistent with national statistics. However, the mortality rate in in the predominantly Hispanic 32-county border area of 0.9 per 100,000 population was three-times that of the mortality rate for the United States. Nonborder area Hispanics did not experience significant increased mortality. While 86.3% 5-year survival for childhood ALL in Texas was also consistent national statistics of 85% (Pui, Pei, et al., 2012), survival in the border area (77.5%) was statistically significantly lower when compared with the nonborder area ($p < .001$).

The overall Texas COG participation rate for childhood ALL was 92.0%, consistent with published studies using SEER data where over 90% of children under the age of 15 years with cancer were seen at a COG facility (Hunger et al., 2013). However, when examining the 32-county Texas-Mexico border area the COG participation rate for children diagnosed with ALL was 56.2% compared to 98.3% for the nonborder area of the state. The extremely low nonborder area COG participation rate surpasses any current published studies.

Chi-square analyses were conducted comparing COG facility affiliation with the other independent variables of gender, race/ethnicity, area of residence, and poverty status. There was a statistically significant association ($p < .001$) between COG facility affiliation and race/ethnicity, area of residence, and poverty status. There was no association identified between COG facility affiliation and gender.

While the COG participation rate for the border area was far below the rate for the nonborder area, COG facility affiliation alone was not a statistically significant predictor of 5-year survival. Logistic regression was performed using only COG facility affiliation as a dependent variable and 5-year survival as the outcome. As a result the null hypothesis of research question two cannot be rejected. There was no evidence that COG facility affiliation alone was associated with 5-year survival of childhood ALL statewide.

Logistic regression was then conducted adding race, residence, and poverty status to the model. The overall regression model was statistically significant ($p < .001$) suggesting that residence, poverty status, race, and COG facility affiliation had a significant collective effect on 5-year survival of childhood ALL. The coefficients for

residence, poverty status, and COG facility affiliation were all individually significant, while the coefficient for race/ethnicity was not. Race and Hispanic ethnicity were not statistically significant factors in ALL survival.

Due to significance of the overall model and three individual predictor variables, the null hypothesis for research question was rejected. There was an association between COG facility affiliation and 5-year survival of childhood ALL when controlling for race, place of residence, and poverty.

It was surprising to find that overall in Texas, COG affiliation actually decreased the chance of 5-year survival. When examining the data, this result was due to the overwhelming 98.3% COG participation rate in the nonborder area of the state. In the United States, about 15% of children do not survive ALL (Pui, Pei, et al., 2012). Texas fared slightly better during the 1995-2009 time period at 86.3% 5-year survival. Most of those deaths occurred in the nonborder area of the state, and among individuals who had been seen at a COG facility. This paradox is discussed more thoroughly in the next section.

To further assess the predictor variables in the regression model, chi-square was conducted between residence and survival, poverty status and survival, and residence and poverty status. All three associations were statistically significant ($p < .001$).

Interpretation of Findings

This study set out to investigate COG facility affiliation and 5-year survival of childhood ALL in Texas. Of particular interest was survival and COG utilization in the 32-country Texas-Mexico border area, a known region of poverty and limited medical

resources. During the time of the study (1995-2009), no COG membership facilities were located within the 32-county border area, while the nonborder area of the state was home to 12 COG facilities.

The 56.2% COG participation rate for the border area was far below the 98.3% participation rate for the nonborder area and 90-95% published participation rates for the United States. Chi-square revealed a statistically significant association between area of residence and COG facility affiliation ($p < .001$). In addition, childhood ALL mortality in the border area was three times that of the nonborder area of the state. Five-year survival was statistically significantly lower in the border area when compared the nonborder area of the state. The 77.5% 5-year survival rate in the border area would be comparable to United States figures from the 1970s. There was clearly a disparity in Texas for childhood ALL 5-year survival in the 32-county Texas-Mexico border area with just over half of children diagnosed being seen at a COG affiliated facility.

However, COG facility membership alone did not explain the survival disparity. When examined individually, COG facility membership alone was not statistically significantly associated with 5-year survival of childhood ALL in Texas. Upon examining the data, the reason for this becomes clear.

While the nonborder area of the state recorded 98.3% COG participation, 5-year survival was only 87.8%. Children diagnosed will ALL in this part of the state were visiting COG facilities but many did not achieve 5-year survival. The reasons for this cannot be determined from this study. But possible explanations are adherence to treatment regimens and following a complete treatment protocol with followup. This

study only examined if the child was at least seen at a COG facility. Others factors could include distance to care from rural areas, timely diagnosis, and unfavorable biological disease characteristics at time of diagnosis, such as T-cell ALL which has a poorer prognosis (Dores, Devesa, Curtis, Linet, & Morton, 2012). The vast majority of children diagnosed will ALL in the nonborder area were seen at a COG facility and thus the non-COG comparison group was very small.

In addition, while the 32-county border area only experienced 56.2% COG participation, many children did survive 5 years, although overall 5-year survival for the population was poor at 77.5%. While general ALL treatment protocols have been shown to be not as effective as individual risk-based designed protocols, standardized treatments can produce positive results. In 2004 Children's Hospital in Houston opened a satellite treatment clinic in the city of McAllen, located in Hidalgo County where 165 of the border area cases in this study were diagnosed. Adjacent Cameron County accounted for another 82 cases. This clinic may have proved beneficial for children diagnosed with ALL in that area. These types of clinics and "treatment sharing" have proved effective even in developing countries (Aristizabal et al., 2015). Such treatments may have also been used in the major hospitals in El Paso, where 131 of the cases were located. In 2015, facilities in both El Paso and McAllen received full COG membership affiliation. However, when border-only data were examined, COG facility participation not only becomes a statistically significant variable, but with a positive association towards survival. Children diagnosed with ALL residing in the 32-county border area seen at a COG facility were two-times more likely to survive than those not seen at a COG facility.

Overall, of the 453 cases of childhood ALL in Texas that did not achieve 5-year survival, only 38 were not seen at a COG facility. However, 33 of those non-COG affiliated deaths were cases from the 32-county border area. A much higher percentage (98.6%) of cases seen at a COG facility that did not achieve 5-year survival occurred in the nonborder area of the state. In the border area COG-affiliated cases only accounted for 69.2% of the cases that did not survive 5 years. While COG affiliation alone was not significant statewide when associated with childhood ALL 5-year survival, 30.8% of the cases that did not survive in the border area were not seen at a COG facility compared to 1.4% for the nonborder area.

In the final regression model, COG facility affiliation actually had a statistically significant but negative association with childhood ALL 5-year survival. Many children, even though seen at a COG facility, did not survive. In the United States 10-15% of children diagnosed with ALL do not survive (Pui, Pei, et al., 2012). In Texas for the years 1995-2009, 13.7% of children diagnosed with ALL did not survive five years, yet 91.6% of those cases were seen at a COG facility. This high participation rate actually skews the association in a negative direction. The fact that poverty was a significant factor statewide in 5-year survival must be considered with this observation. One can only hypothesize what the survival rate would be without such high COG participation.

Both region of residence (border, nonborder) and poverty status were statistically significantly associated with childhood ALL survival. Living in the border area and in poverty both decrease chances for survival. And unlike COG facility participation, these variables were both independently statistically significantly associated with childhood

ALL survival in chi-square analyses. Poverty and region of residence are stronger predictors of childhood ALL 5-year survival than COG facility affiliation statewide. The significant association between all three of those variables when combined sets the stage for a perfect storm. For children in Texas diagnosed with ALL residing in the 32-county Texas-Mexico border area, living in a neighborhood with high poverty, and not being seen at a COG facility, survival can be predicted to be much poorer.

The major limitation of this study is there was no documentation of full treatment and followup. Full treatment of ALL can last up to three years. This study only documented children residing in Texas diagnosed with ALL being seen at least one time at a COG facility. Another limitation was that even with 15 years of data, only 3,266 cases were collected. Pediatric ALL is a rare condition and multiple years of data are require to assemble even a small dataset. These data did reveal a major health disparity in the 32-county Texas-Mexico border area. The 77.5% ALL survival for the 32-county border area is consistent with national rates 40 years ago.

Theoretical Basis of the Study

Krieger's model of ecosocial theory (Krieger, 2001) was the theoretical basis of this study. The driving hypothesis behind this research was that geographical isolation as a barrier to the best risk-based treatment is more a factor in pediatric ALL survival than poverty or Hispanic ethnicity. Ecosocial theory examines the relationships between biological, social, political, and economic aspects of population patterns of not only disease, but well-being.

Analyses of Texas childhood ALL data 1995-2009 revealed no statistically significant association between gender or race/ethnicity and 5-year survival. Statewide poverty and area of residence were associated with poorer survival. Residing in the border area and living in a poor neighborhood were both predictors of poor survival. In addition, while not significant statewide, COG facility participation was significant in the border area and was associated with increased survival. These results describe an area of great health disparity due to social and economic factors. The poverty of the Texas-Mexico border area and lack of access to the best and equal care were associated with poorer survival.

Future Recommendations

This study examined ALL diagnosed among children ages 0-14 years residing in the state of Texas 1995-2009. A large health disparity was identified among children residing in the 32-county Texas-Mexico border region. These children experience poorer outcomes when compare to those who reside in the nonborder area of the state, resulting in mortality from a curable disease.

This study was limited in using population-based data previously collected from the Texas Cancer Registry. Further studies are needed to examine why so many children in the Texas-Mexico border region diagnosed with ALL are not receiving the best care possible. The vast distance distances to these facilities and available resources are no doubt factors. But other social factors such as trust and lack of education could also be involved in not seeking expert treatment. The thought of traveling with a very sick child to some of the largest cities in the country hundreds of miles from home is obviously an

extremely frightening situation. Even when these expert care facilities fully treat children with cancer regardless of a family's ability to pay, also including ancillary expenses such as lodging, travel, and food, many children do not get the best care available.

A more detailed geospatial study is needed to assess rural/urban differences and actual distances between residence and treatment facilities. Even in the nonborder region of the state, many rural counties are far away from major metropolitan areas. This could be achieved using geocoded data of residence and treatment facility.

In 2015 two facilities in the 32-county Texas-Mexico border region received COG membership. El Paso and McAllen, two of the largest populated areas of the region, now are home to a COG facility. Future studies are needed to examine the effect of these facilities on the poorer ALL survival of the region, and further interventions applied if necessary. Even with these two new COG designations, complete treatment and followup must occur for the best outcomes. As the data become available, 10-year survival studies need to be conducted to assess that a full cure was achieved. Not only is initial and expedient diagnosis critical and the best precise risk-based treatment applied, but that the full treatment protocol is diligently followed, including annual followup for 10 years.

Implications for Social Change

Acute lymphoblastic leukemia (ALL) is the most common cancer among children ages 0-14 years in the United States (Hunger et al., 2012). Fortunately it is also one of science's greatest triumphs against cancer, with 5-year survival exceeding 95% with the best treatments available (Pui, Pei, et al., 2012). Some facilities have even achieved the

cure standard of 10 years at 90% (Pui & Evans, 2013). Still, ALL remains the leading cause of cancer mortality in children less than 15 years of age. (Hunger et al., 2013).

Unfortunately some children in the United States do not access and experience the care needed for such great achievements. This study has identified such a population. Children residing in the Texas-Mexico border area diagnosed 1995-2009 with ALL only achieved 77.5% 5-year survival. This study has the potential to promote positive social change in revealing such disparities, and hopefully increasing the understanding of childhood ALL and the need for expert, individual-based treatment. These data revealed that the reasons for poorer survival are associated with the social factors of poverty and access to care. Such social and cultural factors must be considered along with the latest evidence-based medicine for the best outcomes.

Conclusion

Prior to the 1960s a diagnosis of acute lymphoblastic leukemia (ALL) in a child was a literal death sentence. While men were walking on the moon, physicians and scientists were diligently trying to achieve a cure for the most common childhood cancer. Now in the United States 85.5% of children diagnosed with the horrible disease can be cured (Ma, Sun, & Sun, 2014). For the most advanced pediatric oncology research centers, 95% of children who receive full treatment and followup care are cured. Over 200 of these facilities in the United States form the Children's Oncology Group (COG).

Yet for many children in the United States, obtaining care at one of these facilities remains very difficult. This study has revealed such a population, and poorer survival of pediatric ALL among children 0-14 years of age. Almost half the children diagnosed with

ALL 1995-2009 who resided in the 32-county area along the Texas-Mexico border were not seen at pediatric oncology research center. This area is also plagued by high poverty rates, creating additional barriers to care. And while poverty occurs statewide in Texas, over 98% of children diagnosed with ALL in the nonborder region of the state were seen at a COG facility. Being predominantly Hispanic and a border area, cultural and social factors are involved, as well. For some children today, even with the advanced treatments available a diagnosis of ALL can still be a death sentence. Unlike many adult cancers where lifestyle changes and screening are associated with improved survival, accurate diagnosis and expedient treatment are the main factors involved with pediatric ALL survival. Inherited genetics, a hallmark risk factor in adult cancers, has only been associated with about 5% of pediatric ALL cases (Spector, Charbonneau, & Robison, 2012). The best care available after diagnosis is the only plan for a child to survive the disease. This must be considered as the United States struggles with how to deliver the best healthcare to its population, and who should or should not be a part of that population.

In 1971 President Richard M. Nixon issued the ambitious challenge to cure a group of diseases that had longed plagued mankind. Just as President John F. Kennedy had declared to make travel to the moon a reality just 10 years prior, Nixon called on the best scientists and researchers in the country to conquer cancer (DeVita, 2002). Nixon later signed the National Cancer Act of 1971 which mandated eliminating the disease an issue of national importance (DeVita, 2002). The “War on Cancer” as it would be later known, had officially begun, and almost 50 years later continues.

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Appendix A: List of the 32 Texas-Mexico Border Counties

Brewster
Brooks
Cameron
Crockett
Culberson
Dimmit
Duval
Edwards
El Paso
Frio
Hidalgo
Hudspeth
Jeff Davis
Jim Hogg
Kenedy
Kinney
La Salle
McMullen
Maverick
Pecos
Presidio
Real
Reeves
Starr
Sutton
Terrell
Uvalde
Val Verde
Webb
Willacy
Zapata
Zavala