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2014

Evaluation of Racial Disparities in United States Veterans with Diffuse Large B-Cell Lymphoma

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THESIS

Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Public Health Sciences
in the Graduate College of the University of Illinois at Chicago, 2014

Chicago, Illinois

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This thesis is dedicated to my wife, Emily Jungheim, and our daughters Caroline and Katherine, all of whom endured my absence on numerous late nights and weekends while this dissertation was being finished. Without their love and support, it would have never been completed.

PREFACE

Despite all of the advances in medical technology over the past several decades, racial disparities in cancer outcomes remain a vexing problem in medicine. The purpose of this dissertation was to examine if there are modifiable causes of race-based outcome disparities in the most common form of non-Hodgkin lymphoma, diffuse large B-cell lymphoma. Identification of the causes of outcome disparities could potentially then be a first step toward intervention and ultimately their elimination. As a clinical oncologist with an academic practice focusing on the treatment of the lymphomas, this work leveraged my strengths and experience in clinical medicine with the analytic skills imparted upon me during my graduate school training.

ACKNOWLEDGEMENTS

I would like to thank my thesis committee—(Elizabeth Calhoun, Graham Colditz, Stephanie Crawford, Peter Gann, and Surrey Walton)—for their considerable patience, support, and assistance. They provided guidance in all areas that helped me accomplish my research goals. I would also like to specifically acknowledge Graham A. Colditz, MD, DrPh, who encouraged me to pursue research work at the St. Louis Veterans Affairs health care system, when my other mentors and peers believed doing so was a waste of time.

A number of individuals in the data collection site were also helpful to me during data collection, and I would like to thank them as well—Washington University research staff Katiuscia O'Brian, MA; Jason Gumbel, BS; and Suhong Luo, MPH; Washington University School of Medicine oncology fellows Ryan Roop, MD and Kristen M. Sanfilippo, MD MPHS; Washington University School of Medicine internal medicine residents Peter Riedell, MD and Ryan Lynch, MD; and Washington University School of Medicine medical student Arun Ganti.

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LIST OF ABBREVIATIONS

ABVD	Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine
AIDS	Acquired Immune Deficiency Syndrome
AITC	Austin Information Technology Center
ARDI	Average Relative Dose Intensity
BMI	Body Mass Index
BSA	Body Surface Area
CAPRI	Compensation and Pension Records Interchange
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
CI	Confidence Interval
DLBCL	Diffuse Large B-cell Lymphoma
EMR	Electronic Medical Record
FL	Follicular Lymphoma
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
HR	Hazard ratio
ICD-9	*International Classification of Diseases*, 9th Edition
ICD-O3	*International Classification of Diseases—Oncology*, 3rd edition
IPI	International Prognostic Index
LDH	Lactate Dehydrogenase
MGF	Myeloid Growth Factor
MM	Multiple Myeloma
NHL	Non-Hodgkin Lymphoma
OR	Odds Ratio

LIST OF ABBREVIATIONS (continued)

OS	Overall Survival
PBM	Pharmacy Benefits Management
PFS	Progression-Free Survival
PTCL	Peripheral T-cell Lymphoma
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
SEER	Surveillance Epidemiology and End Results
SES	Socioeconomic Status
VACCR	Veterans Administration Central Cancer Registry
VHA	Veterans Health Administration

SUMMARY

There is a well-described, race-based outcome disparity in patients diagnosed with the most common form of non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL). Despite significant speculation regarding the source of this disparity, few conclusions have been made. Using data from the United States Veterans Health Administration (VHA), this dissertation evaluated the sources of outcome disparities in that patient population. Patients diagnosed with DLBCL at any VHA facility between October 1, 1998 and September 30, 2008 were identified and included in the initial cohort (n=3,227). Consistent with previous studies, black patients had poorer overall survival (OS) compared to white patients in age-adjusted analyses. Black patients were also younger, and more likely to have advanced stage disease. In addition, a new finding from this study was a higher prevalence of Human Immunodeficiency Virus (HIV) in black patients versus white patients (21% versus 4%, p <.0001), and higher frequency elevated lactate dehydrogenase (64% versus 54%, p=.003), a serum tumor marker. Cox analysis controlling for differences in baseline characteristics noted between the black and white patients demonstrated that patients who were HIV positive had a markedly increased risk of death (hazard ratio [HR]=1.67, 95% confidence interval [CI] 1.27–2.2). Treatment variables associated with a reduced risk of death included: doxorubicin (HR=.57, 95% CI 0.49–0.67), rituximab (HR=.6, 95% CI 0.52–0.69), and myeloid growth factors (HR=.74, 95% CI 0.56–0.98). Logistic regression analyses demonstrated no race-based differences in the use of doxorubicin, rituximab, or myeloid growth factors. While univariate analyses suggested decreased rituximab use in black patients, multivariate analysis demonstrated that this was driven by the differences in HIV prevalence. Patients who were HIV positive were less likely to receive

rituximab (odds ratio [OR]=.1, 95% CI 0.06–0.18). Taken together, these results suggest that a higher prevalence of HIV in black patients is a factor in the apparent racial outcome disparity. There was no evidence of systematic bias in the application of curative intent therapy in this population. Measures to prevent or control HIV may be the best way to reduce racial disparities in DLBCL.

1. INTRODUCTION

1.1 The Problem of Racial Disparities in Non-Hodgkin Lymphoma

In 2014, there will be an estimated 70,800 new diagnoses of Non-Hodgkin lymphoma (NHL) in the United States, associated with 18,990 deaths. Based on these estimates, it is the seventh most common malignancy in men and women behind lung, breast, prostate, colon, bladder, and melanoma skin cancers (National Cancer Institute, 2014). When viewed from a population perspective, NHL is frequently classified as a single disease entity. However, NHL actually represents a heterogeneous group of many discrete diseases with differing treatment paradigms and prognoses (Armitage, 1993; Campo et al., 2011). The most common form of NHL is diffuse large B-cell lymphoma (DLBCL), a subtype which is treated with curative intent in a majority of newly diagnosed patients (Armitage, 2007).

While the incidence of NHL is lower in the black population compared to the white population (Groves et al., 2000), black patients diagnosed with NHL have poorer OS compared to their white counterparts (Ghafoor et al., 2002; Shenoy et al., 2011a). Elimination of health disparities remains an unmet goal of the Healthy People 2010 initiative and it remains as an important part of the Healthy People 2020 initiative, which aims "to achieve health equity, eliminate disparities, and improve the health of all groups" (United States Department of Health and Human Services, 2014). This dissertation will investigate the factors associated with race-based differences in OS observed in US veterans diagnosed with DLBCL between 1998 and 2008 within the Veterans Health Administration (VHA) hospital system. While the primary objective is to identify factors that may be associated with race-based differences in survival, this dissertation will perform additional analyses to evaluate possible differences in treatment patterns, as this is a potentially modifiable source of outcome disparity and is thus clinically relevant.

1.2 Clinical Background Information on Lymphoid Malignancies

A review of the existing literature investigating associations between race and survival disparities in the lymphoid malignancies will be presented later in this introduction. In order to fully understand how the study variables might influence race-based survival disparities in DLBCL, additional clinical background information on the lymphoid malignancies is required. There is a relative paucity of data in the area of racial disparities in DLBCL specifically, so an expanded literature search of the lymphoid malignancies was performed.

1.2.1 Hematologic Malignancies

As a group, the hematologic malignancies all arise from descendants of the multipotent hematopoietic stem cell (Vardiman et al., 2002). Within the hematopoietic malignancies, specific disease subtypes are related to where the malignant cells arise within the stem cell differentiation pathway, and each subtype demonstrates different clinical behavior (Jaffe et al., 2008; Vardiman et al., 2002). The first differentiation event in hematopoietic stem cell biology is separation into myeloid and lymphoid cell lines (Orkin and Zon, 2008). Myeloid progenitor cells give rise to all red blood cells, platelets, and granulocytes. There are a relatively small number of myeloid malignancies, such as acute myeloid leukemia and chronic myeloid leukemia (Vardiman et al., 2002). Within the lymphoid cell line, another major differentiation occurs early on in cell development, dividing lymphoid cells into T-lymphocytes, B-lymphocytes, and natural killer cell subsets (Orkin and Zon, 2008). Lymphoid cells give rise to a large number of discrete malignancies, though these are generally classified into four categories: lymphoblastic leukemia/lymphoma, Hodgkin lymphoma (HL), NHL, and multiple myeloma (MM) (Jaffe et al., 2008). Non-Hodgkin lymphoma is the most diverse group of diseases with nearly 60 subtypes (Armitage and Weisenburger, 1998; Jaffe et al., 2008). Within the literature review, evidence of racial disparities will be examined in five distinct lymphoid malignancy subtypes. The diseases

that will be examined include: DLBCL, follicular lymphoma (FL), HL, MM, and peripheral T-cell lymphoma (PTCL). These diseases were selected largely based upon population burden as measured through annual disease incidence, allowing for a more robust associated literature.

Common attributes of the hematologic malignancies should be highlighted beyond their derivation from the hematopoietic progenitor cell. With the exception of HL, incidence of the lymphoid malignancies is positively correlated with age (Rodriguez-Abreu et al., 2007). Next, treatments used for the hematologic malignancies are associated with a higher frequency of treatment-related toxicities and death, compared to those used for solid tumor malignancies (Lyman et al., 2005). As a result, a significant number of patients, due to age or infirmity, do not receive any treatment even when potentially curative therapy is available (Link et al., 2011). Another factor common to many of the lymphoid malignancies is that they are now treated with molecularly targeted therapies that block the growth or spread of cancer by interfering with specific molecules involved in tumor growth or progression. Most of these drugs are associated with significant acquisition expense (Armand et al., 2007; Hamilton et al.; Schrag, 2004). While the required co-payments for veterans served by the VHA vary based on income level and other factors, the VHA has a long-standing policy to provide no-cost care to veterans who are indigent or have catastrophic conditions (United States Deparment of Veterans Affiars, 2014). Thus, patient concerns about drug cost, which could result in treatment differences in patients without health insurance, may be less prominent within this cohort. A final factor common to these diseases is use of autologous stem cell transplantation as a treatment modality, depending upon the clinical scenario (Archuleta et al., 2004). Stem cell transplant is also associated with significant costs, potentially resulting in treatment disparities based on insurance status outside of the VHA.

1.2.2 **Diffuse Large B-cell Lymphoma**

Approximately 25% of all NHL is DLBCL (Morton et al., 2006), corresponding to roughly 17,500 new diagnoses in the United States in 2014. Incidence is age-related, with a median age at diagnosis of 64 years (Shenoy et al., 2011a). Individuals with a family history of NHL are at higher risk for development of DLBCL (Chatterjee et al., 2004). Patients who are seropositive for HIV have a 60- to 200-fold increased risk for the development of NHL compared to the non-HIV infected population, and the majority of those cases are DLBCL (Dunleavy and Wilson, 2012). This is important when considering racial disparities in DLBCL because the prevalence of HIV is eight times higher in the blacks compared to whites in the US population (Moore, 2011). Another major risk factor for the development of DLBCL is obesity, which is associated with a relative risk of 1.4 compared to the non-obese (Larsson et al., 2007). This too is important when considering racial disparities because of the higher prevalence of obesity in the black population (Flegal et al., 2010). For reasons that are not well understood, the incidence of DLBCL is lower in blacks compared to whites with an incidence rate ratio of 0.7 (Shenoy et al., 2011a).

The prognosis associated with DLBCL is generally good, with a five-year survival rate of more than 50% (Armitage, 2007). Prognosis can be further stratified into good, intermediate, and poor prognostic categories using a combination of clinical and laboratory factors: age, performance status, serum lactate dehydrogenase level (LDH), more than one extranodal site of disease, and stage (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993). While DLBCL is considered a single clinical entity, microarray technology has allowed further subclassification into three molecular phenotypes associated with different prognoses (Rosenwald et al., 2002). Microarray data are not currently used in routine clinical practice.

Currently, clinical studies are underway to determine if disease phenotype should influence treatment selection, but this approach is not yet proven (Friedberg, 2011).

Like other aggressive lymphomas, under most circumstances DLBCL is treated with a curative intent. Current standard of care treatment of DLBCL uses a combination of the following drugs: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (National Comprehensive Cancer Network, 2012). The R-CHOP regimen is administered for three to six cycles, depending upon the stage of the disease at the time of treatment initiation. Since the introduction of the CHOP (same drugs as R-CHOP but without the rituximab) regimen as a treatment for NHL in the 1970s (McKelvey et al., 1976), the only major change to the treatment standard of care has been in the addition of rituximab, which was supported by the pivotal study by Coiffier et al. (2002). Treatment related mortality in trials of DLBCL treatment with R-CHOP ranges from 6% to 8% (Coiffier et al., 2002; Habermann et al., 2006; Pfreundschuh et al., 2008). Younger patients who experience disease relapse are treated with curative intent using salvage chemotherapy and autologous stem cell transplantation, while older patients with relapsed disease are sometimes treated with palliative intent (Philip et al., 1995).

1.2.3 **Follicular Lymphoma**

Follicular lymphoma is the second-most common subtype of NHL, representing approximately 20% of new NHL diagnoses (Morton et al., 2006) and roughly 14,000 new diagnoses in the United States in 2014. Like DLBCL, FL is a malignant proliferation of B-lymphocytes. Incidence is age-related, with a median age at diagnosis of 60 years (Non-Hodgkin's Lymphoma Classification Project, 1997). While there is some evidence associating FL incidence with aspects of the Western lifestyle such as diet and obesity (Ambinder et al., 2012), many of the associations are weak, or disputed by other studies (Ma, 2012). In addition, there is

no clear association between HIV and FL incidence (Vajdic et al., 2010). Like DLBCL, the incidence of FL is lower in black patients than in white patients with an incidence ratio of 0.5 (Groves et al., 2000).

The prognosis associated with FL is good, with a five-year survival rate of approximately 70% (Solal-Celigny et al., 2004). Prognosis is stratified based upon: Number of nodal groups involved, LDH, age, stage, and hemoglobin level (Solal-Celigny et al., 2004). While there is some evidence that molecular markers may predict survival in FL, as in DLBCL these markers are not used in routine clinical practice (Dave et al., 2004).

As an indolent NHL, treatment of FL is administered with the intent of palliating symptoms and prolonging life as opposed to treatment with curative intent. If patients are asymptomatic and do not have a compelling reason to initiate therapy, then observation is a reasonable initial management strategy (Friedberg et al., 2009). Previous studies examining outcomes associated with early versus delayed chemotherapy demonstrated increased toxicity without survival benefit in those receiving early treatment (Ardeshna et al., 2003).

Historically, treatment has been similar to that used for DLBCL, using combination regimens such as R-CHOP with or without doxorubicin. Unlike DLBCL, there is no clear standard of care treatment for FL, resulting in significant regional variations in front-line therapy for this disease (Friedberg et al., 2009). Even treatment guidelines do not prioritize front-line or salvage therapies (National Comprehensive Cancer Network, 2012). With the exception of allogeneic stem cell transplantation, the treatment of advanced stage FL is not curative (Khouri, 2011). However, due to the significant toxicities associated with allogeneic transplantation, only select patients are offered this treatment. Once remission is obtained in FL, additional strategies such as maintenance rituximab therapy or consolidation with radioimmunotherapy can be

pursued to maintain that remission and lengthen the interval between therapies (Marcus et al., 2005; Morschhauser et al., 2008).

1.2.4 **Hodgkin Lymphoma**

Hodgkin lymphoma is an aggressive lymphoma of B-cell lineage associated with approximately 9,000 new diagnoses and 1,200 deaths annually in the United States (Siegel et al., 2012). There is a bi-modal age distribution in incidence with an incidence peak noted in the third decade of life, followed by a gradual rise that is age-dependent, peaking again in the seventh decade of life. Evidence from population-based tumor registries suggests that there may be differences in this pattern based on race (Evens et al., 2012). Like the aggressive B-cell NHLs, a major risk factor for the development of HL is HIV seropositivity (Clifford et al., 2005). In HIV-negative patients there is evidence that higher socioeconomic status (SES) in early childhood may correlate with development of the nodular sclerosis subtype of HL (Cozen et al., 1992).

The prognosis associated with HL is excellent, with five-year OS of nearly 85% (Surveillance, Epidemiology and End Results Program, 2013). There is no consensus regarding the best approach to prognostication in patients with early-stage disease; however, the most commonly used systems are based upon variables including: tumor size >10 cm, erythrocyte sedimentation rate, age >50, presence of B-symptoms (fevers, night sweats, or unintentional weight loss), involvement of four or more nodal regions (Cosset et al., 1992; Engert et al., 2010). Prognosis in patients with advanced-stage disease is stratified based upon: male sex, age >45 years, stage IV disease, serum albumin <4g/dL, hemoglobin <10.5 g/dL, total white blood cell count ≥15,000/μL, and absolute lymphocyte count <600/μL (Hasenclever and Diehl, 1998). At this time there are no widely accepted molecular markers associated with prognosis in HL.

Treatment is usually initiated with curative intent. Standard chemotherapy treatment utilizes four drugs: doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) (Canellos et

al., 1992). Patients with early stage HL are often treated with two to four cycles of ABVD chemotherapy followed by involved field radiotherapy (Engert et al., 2010). Due to longer-term side effects associated with radiotherapy and excellent response rates associated with chemotherapy alone, some are beginning to question the risk-benefit of radiotherapy in patients with early-stage HL (Meyer et al., 2012), though it is still considered standard of care. Treatment of patients with advanced-stage HL typically involves six cycles of ABVD chemotherapy (Canellos et al., 1992). In Germany, more aggressive regimens are frequently used in patients with stage III and IV disease, though this has not yet been accepted as standard of care in the United States (Diehl et al., 2003; Viviani et al., 2011). Standard treatment for patients with relapsed disease is combination salvage chemotherapy followed by autologous stem cell transplantation (Josting et al., 2000). More recently, brentuximab vedotin, an anti-CD30 monoclonal antibody, has become available for the treatment of patients with relapsed or refractory HL (Younes et al., 2010). Given the high response rates associated with its use, it may ultimately change the standard of care for patients with HL, but due to its recent approval, it will not influence observed disparities.

1.2.5 **Peripheral T-cell Lymphoma**

Peripheral T-cell lymphoma is a rare and heterogeneous group of lymphomas representing 5% to 10% of all NHLs in Western countries, or roughly 5,000 new diagnoses in the United States each year. While there are some prognostic distinctions between PTCL subtypes, in general the prognosis associated with PTCL is worse than that seen with the B-cell lymphomas (Vose et al., 2008). There is an association between PTCL and some inflammatory conditions (Catassi et al., 2002). There is also some suggestion that the incidence of PTCL is higher in blacks compared to whites (Abouyabis et al., 2008).

Generally, patients diagnosed with PTCL have a poor prognosis, with approximately 40% of newly diagnosed patients living five years or more after diagnosis. Some PTCL subtypes such as anaplastic large-cell lymphoma have a better prognosis with 55% alive at five years, while others such as hepatosplenic T-cell lymphoma have a poorer prognosis with only 16% alive at five years (Abouyabis et al., 2008). Like other lymphomas, prognostic categories are defined based on a combination of clinical and laboratory factors (Gallamini et al., 2004; Vose et al., 2008). There are no molecular markers available to predict prognosis.

Due to the rarity of these diseases, the most commonly used treatments are regimens developed in patients with B-cell lymphomas, such as CHOP. Attempts have been made to intensify therapy in light of the poor prognosis, though these efforts have been associated with only limited success (Escalon et al., 2005). Treatment intensification with autologous stem cell transplantation in first remission is employed at some centers, though this practice remains controversial (Reimer et al., 2009).

Brentuximab vedotin has been used in patients with relapsed or refractory anaplastic large-cell lymphoma (a subtype of PTCL) and is associated with exceptional response rates of 80% or higher; as mentioned above, this disease demonstrates good response rates to front-line therapy (Pro et al., 2012; Vose et al., 2008). Romidepsin and pralatrexate are approved for the treatment of all forms of PTCL in the relapsed setting (Coiffier et al., 2012; O'Connor et al., 2011). Neither is associated with overall response rates greater than 40%, and most responses are short-lived.

1.2.6 **Multiple Myeloma**

Multiple myeloma is the second most common hematologic malignancy in the United States, with 20,000 new diagnoses annually (National Cancer Institute, 2014). Incidence is age-related, and patients under age 40 represent only 2% of cases (Kyle et al., 2003). Obesity is

associated with increased MM incidence and represents the only known modifiable risk factor for this disease (Birmann et al., 2012). By a factor of two, the incidence of MM is higher in blacks than whites, making it the most common hematologic malignancy among blacks. While some of this may be due to higher rates of obesity in the black population, genetic factors may also be responsible (Benjamin et al., 2003).

Multiple myeloma is associated with a five-year survival of 45% (Surveillance, Epidemiology and End Results Program, 2013). As a disease that is incurable with standard therapies, the two-fold increase in MM incidence seen in black patients translates into a two-fold increase in overall MM-related mortality. Staging in MM is performed with the Durie-Salmon staging system or the International MM Prognostic score, though neither has demonstrated superiority (Greipp et al., 2005; Hari et al., 2009). Greater attention is paid to cytogenetic profiles in patients with MM, which are strongly associated with prognosis (Fonseca et al., 2003). Furthermore, there is evidence that treatment responses are largely dictated by MM cytogenetics (Reece et al., 2009; San Miguel et al., 2008).

Historically, treatment of MM consisted largely of oral melphalan and prednisone as other regimens were no better, and often more toxic (Cavo et al., 2002). Since the 1990s, high dose melphalan with autologous stem cell rescue has been considered a standard of care treatment for younger patients due to proven survival benefit from this approach (Moreau et al., 2002). More recently, the novel agents: thalidomide, lenalidomide, and bortezomib have become available (Richardson et al., 2005; Singhal et al., 1999; Weber et al., 2007). Autologous transplant and the novel agents are thought to be responsible for recent improvements in MM survival seen across the population of MM patients (Palumbo and Anderson, 2011).

1.3 Focused Literature Review

1.3.1 Data Sources and Searches

A literature search was performed using systematic methods to identify studies that examined disparities in survival outcomes or treatment patterns in patients with lymphoid malignancies (Counsell, 1997). Studies published from 1974 to 2012 were identified in electronic databases (Medline, Embase, Scopus, and Cochrane). The search utilized the Medical Subject Heading search terms: healthcare disparities, or health status disparities, or health services accessibility, or prejudice, or insurance selection bias, or vulnerable populations, and lymphoma and all related search terms for lymphoma. The related search terms in lymphoma included search the names of all subtypes of Hodgkin and NHL. This strategy identified a total of 101 citations in PubMed, 396 in Embase, 131 in Scopus, and 160 duplicates leaving a total of 470 studies of disparity in lymphoma. A similar search for articles using the same Medical Subject Heading search terms related to disparities listed above for MM resulted in a total of 96 additional articles, of which 42 had not been obtained on the previous search. This resulted in a total of 512 articles that were reviewed.

1.3.2 Study Selection

Since the purpose of this dissertation is to examine the factors associated with differences in survival after diagnosis and treatment patterns noted between black and white patients with a diagnosis of DLBCL, studies that only evaluated differences in disease incidence were excluded. Similarly, studies focusing on the potential mechanisms (e.g., molecular pathways) of racial disparity without supporting clinical data were excluded. Finally, due to variances previously noted between abstract presentations and final publications, studies that were presented only as meeting abstracts were excluded (Tam and Hotte, 2008). This resulted in a final group of 24

studies that were included in this literature review. Studies were grouped according to disease state.

1.3.3 **Diffuse Large B-cell lymphoma**

There are two published studies specifically evaluating race-based differences in outcomes in white and black patients with DLBCL. The first study by Komrokji et al. (2011) was an analysis of 55,528 DLBCL patients (51,795 white, 3,733 black) diagnosed from 1973 to 2004 obtained from the Surveillance Epidemiology and End Results (SEER) registry. This study found a significant difference in median OS between white (47 months) and black (29 months) patients (log-rank p<.001). On subset analysis, the significant survival difference was observed only in patients with advanced-stage, but not early-stage disease. Another SEER analysis by Shenoy et al. (2011a) of 38,522 patients (32,121 white, 2,512 black) diagnosed 1992 to 2007 found a two-year OS of 60% in white DLBCL patients and 50% in black DLBCL patients (p<.001). While the Shenoy et al. (2011a) authors speculated about a number of potential mechanisms, there was prominent mention of previous studies that showed no survival difference in black and white patients receiving standard of care therapy, suggesting differences in treatment patterns may be responsible for the observed difference. These studies highlight the existence of a survival disparity in patients with a diagnosis of DLBCL.

Since a survival disparity has been observed, another four studies then evaluated treatment patterns in DLBCL and NHL. A study by Flowers et al. (2012) using data for 38,002 patients diagnosed with DLBCL from 2001 to 2004 in the National Cancer Database demonstrated odds of immunotherapy administration of 0.83 (95% CI 0.78–0.89) for black DLBCL patients compared to white DLBCL patients. Another interesting finding from this study was the observation that high-volume teaching centers were associated with increased odds of immunotherapy administration (OR=1.69, 95% CI 1.52–1.89) compared to nonteaching centers.

These results were similar to a previous study of 207,581 patients diagnosed with all forms of NHL from 1998 to 2004 using the National Cancer Database that showed an OR for rituximab use in black patients to be 0.71 (95% CI 0.63–0.79) and 0.66 (95% CI 0.61–0.71) for patients over and under age 65, respectively, compared to white NHL patients (Shih, 2009). Using SEER-Medicare linked data of 7,048 patients with DLBCL over age 65, Griffiths et al. (2010) showed that black patients had a lower treatment rate overall (HR=.77, p<.001), as did patients over age 80 and those in lower socioeconomic strata. Finally, Mitchell et al. (1997) used inpatient hospital discharge data to show that in 1988 and 1991, black NHL patients had reduced odds of receiving stem cell transplantation for lymphoma (OR=.34 to 0.45, p<.01).

The relationships between SES, racial disparities, and outcomes in NHL have been previously investigated and are worth discussion. A study from 2008 using a SEER-Medicare linked database of 13,321 patients (11,868 white, 533 black) with incident NHL (of all subtypes) diagnosed 1992 to 1999 found that a larger proportion of black patients were in the poorest quartile of SES, and fewer black patients received chemotherapy (Wang, M. et al., 2008). After controlling for SES, comorbidity, and treatment differences, there was no significant difference in all-cause mortality between black and white patients. Similarly, a study of 6,324 NHL patients diagnosed between 2000 and 2008 in Denmark demonstrated an inverse association between education and survival in both the 2000–2004 and 2005–2008 time periods (HR=1.4; 95% CI 1.27–1.54 and HR=1.63; 95% CI 1.4–1.9, respectively) (Frederiksen et al., 2012).

1.3.4 **Follicular Lymphoma**

Only one published study evaluating racial disparities in FL was found. Using data from the National Lymphocare study, a prospective registry study for patients with FL, Nabhan et al. (2012) compared treatment patterns in between 2,476 white and 95 black patients. Significant differences were noted in the use of anthracycline chemotherapy, which was used in 49% of

black FL patients and 64% of white FL patients (p=.03). Due to the indolent nature of FL, additional follow-up will be required in order to determine if the observed difference in treatment will result in a survival difference.

Since FL is an indolent lymphoma, relevant lessons may be drawn from findings in other indolent lymphoproliferative disorders. The literature search identified a single publication of a SEER analysis of outcomes in 27,703 white and 2,059 black patients with B-cell chronic lymphocytic leukemia and the related disorder, small lymphocytic lymphoma, diagnosed from 1992 to 2007 (Shenoy et al., 2011b). That study identified a significant difference in five-year survival (77% and 64% for white and black patients, respectively, P<.01) and increase risk of death on univariate Cox modeling (HR=1.48, 95% CI 1.37–1.60).

1.3.5 **Hodgkin Lymphoma**

Three studies examined race-based differences in HL outcomes. The first study by Evens et al. (2012) examined 15,662 HL cases from the SEER registry diagnosed 1992–2007, of which 11,211 were white and 1,662 were black. Five-year OS was 82% for whites and 76% for blacks. After adjusting for age, sex, and stage, blacks had a higher risk of death on Cox analysis (HR=1.23; 95% CI 1.02–1.43). A similar survival disparity was noted by Keegan et al. (2009) in an analysis of 12,492 HL patients diagnosed in California from 1988 to 2006. In that study, black HL patients had a 40% to 74% increased risk of death from HL depending upon age at diagnosis. Also, patients from neighborhoods in the lowest quintile of SES had an increased risk of death from both HL and other causes. To further explore the relationship between SES and HL outcomes, Yung et al. (2011) used Medicaid enrollment as a proxy for lower SES in an analysis comparing outcomes between Medicaid enrolled and not enrolled in California and New York Medicaid enrollment was associated with increased risk of death in patients diagnosed with HL in California (HR=1.9; 95% CI 1.47–2.68) and New York (HR=1.89; 95% CI 1.43–2.49).

1.3.6 **Peripheral T-cell lymphoma**

There are two studies examining racial disparities in the PTCLs. An analysis of SEER data on 3,287 cases of PTCL (2,519 white, 372 black) diagnosed from 1992 to 2005 demonstrated no significant difference in survival by race (Abouyabis et al., 2008). Similarly, SEER analysis of 4,208 white and 745 black patients with mycosis fungoides (an indolent form of PTCL) identified no significant difference in survival between white and black patients (Wilson et al., 2011). Both studies pointed out that the relative rarity of the T-cell lymphoproliferative disorders complicates efforts to draw firm conclusions about survival, due to smaller numbers.

1.3.7 **Multiple Myeloma**

Four studies evaluated the influence of race on OS in black and white patients with MM. In the first study from 1984, Savage et al. found no significant difference in OS based upon race in a cohort of 92 MM patients 46 black, 46 white) drawn from one hospital in New York City (Savage et al., 1984). This study did, however, find a highly significant difference in survival when these patients were compared with a second group of black patients from poorer socioeconomic strata, finding an association between poorer SES and higher mortality, described only with a p-value of <.001. A few years later, Lenhard et al. (1987) evaluated race and survival in a cohort of 1,479 patients (1,141 white, 324 black) drawn from 21 comprehensive cancer centers. Those authors found that black race was significantly associated with decreased risk of mortality in a multivariate Cox analysis (HR=.8, p=.03), while SES was not significant. In 2006, Abou-Jawde et al. (2006) found no significant difference in survival based on race or distance from treatment center in a cohort of 292 patients (254 white, 38 black), though this study may have lacked the power to detect a significant difference. Finally, in a 2010 analysis of SEER data Waxman et al. (2010) found that black MM patients had better OS than white patients. At the

same time, survival gains in recent years were more pronounced in white MM patients, suggesting either issues of access to newer MM therapies or differential response rates between races.

Since autologous stem cell transplantation has been a major therapeutic tool in MM for the past two decades, three additional studies evaluated survival outcomes following autologous transplantation in black and white patients to evaluate if differential response rates might influence race-based survival comparisons. All three demonstrated no significant difference in progression free survival (PFS) or OS following autologous transplant, though one found evidence of decreased utilization of transplantation in black patients (Auner et al., 2012; Hari et al., 2010; Verma et al., 2008).

1.3.8 **Conclusions from Literature Review**

Across the lymphoproliferative disease types, certain patterns emerged that will be further explored in the data analysis. First, in patients with DLBCL and HL, two aggressive forms of lymphoma, more than one source has provided clear evidence of a survival disparity. Second, lower SES was associated with a worse prognosis in DLBCL, HL, and MM. Third, there is evidence of race-based differences in the use of treatments in patients with DLBCL, FL, and MM. Unfortunately, none of the studies were able to directly tie together these variables, since the survival studies tended to be from large databases that do not have complete treatment information. Meanwhile, studies that did have treatment information were often too small or still did not have enough information on potential confounding variables in order to link treatment differences to survival differences, which is the purpose of this dissertation.

1.4 **Study Setting**

The VHA was chosen as the primary data source for the analytic portions of this dissertation for a number of reasons, the most important being that the VHA provides access to care regardless of ability to pay (Page, 1982). Thus, issues of insurance coverage will not be a major driver of healthcare access disparity. This is a critical advantage of this dataset, as it may provide insights into factors associated with outcome disparity that will be relevant in the era of healthcare reform and expanded insurance access (Eibner et al., 2010). Like health reform, the VHA covers patients who do not have insurance, but VHA coverage still does not fully address all of the access issues associated with lower SES (e.g., transportation issues). Next, detailed treatment information is available through the common format Electronic Medical Record (EMR) system that has been in place at the VHA for more than a decade (Jha et al., 2009). This allows capture of detailed, patient-level treatment data that are not readily available in administrative datasets. In addition, information on comorbid conditions is available in the VHA dataset, allowing for control of these competing risk factors for death when examining OS outcomes. Finally, previous research has demonstrated that cancer patient outcomes among elderly VHA patients are equal or superior to those observed in the Medicare population (Landrum et al., 2012), suggesting the VHA may be a model for evidence based cancer care.

2. METHODS

2.1 **Design**

This is a population-based observational study using a retrospectively assembled cohort of patients with DLBCL. Prior to cohort assembly and analysis, approval was obtained from the Institutional Review Boards at the St. Louis VHA medical center, Washington University in St. Louis, and University of Illinois at Chicago. An expedited review was permitted since this project was classified as, "research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis)."

Numerous safeguards were put in place to reduce the risk of inadvertent release of protected health information. First, all study files were stored electronically on the St. Louis VHA research server, which is located in a secure facility with key card access, motion and heat sensing alarm equipment, 24-hour video monitoring, and patrols by the VHA police department. Second, the research server can only be accessed from behind the VHA firewall and all analyses were performed in locked research facilities located on VHA property. Third, all electronic communications and data transfers relevant to the study were made using public key infrastructure encryption software, consistent with VHA regulations. Fourth, at no time were paper records utilized. Finally, prior to any study activity all study personnel were required to obtain without compensation appointments at the St. Louis VA medical center, undergo fingerprinting and background checks, and complete Collaborative Institutional Training Initiative modules on human-subject protection.

2.2 **Study Population**

All patients with a new diagnosis of DLBCL made in the inpatient or outpatient setting between October 1, 1998 and September 30, 2008 at any VHA medical facility nationwide were included in the initial study cohort. The earlier date corresponds to the universal implementation of the VHA Computerized Patient Records System, thereby ensuring that detailed patient records could be obtained on nearly all patients in the cohort. The latter date was chosen to allow for adequate follow-up time to detect disease relapse and death, as a significant majority of DLBCL relapses occur within two years of treatment (Larouche et al., 2010).

The initial cohort was identified in the VACCR using *International Classification of Diseases—Oncology*, 3rd edition (ICD-O3) codes for DLBCL. The ICD-O3 codes have been used to classify NHL into histologic subtypes using methods previously described by the InterLymph consortium, specifically using ICD-O3 codes 9680 and 9684 to identify DLBCL (Turner et al., 2010). Patients who could not be linked to the vital status files were excluded, since outcome could not be reliably determined for these patients. Next, patients with primary cutaneous DLBCL or with central nervous system involvement at the time of diagnosis were excluded due to a different prognosis associated with those disease variants (Ferreri, 2011; Rijlaarsdam et al., 1996). Since fine needle aspiration biopsy is generally considered inadequate pathologic confirmation of DLBCL diagnosis, patients without a core needle or excisional biopsy specimen were excluded, as were patients found to have an alternate NHL histology during chart abstraction (Hehn et al., 2004). A small number of patients had progress notes from oncology providers indicating treatment at a facility outside the VHA system without a clear description of the treatment drugs and doses, making it impossible to analyze patients along these variables. Thus these patients were also excluded. Patients with race that was either not ascertained or coded as other than black or white were excluded, as the small number of patients

made drawing conclusions about other races impossible. Finally, patients who did not receive chemotherapy treatment were excluded since the primary goal of this dissertation is to investigate any race-based differences in treatment patterns. An initial cohort of 3,227 DLBCL patients was obtained from the VACCR (see CONSORT diagram, Figure 1). After application of the exclusion criteria, an analytic cohort of 2,163 patients remained, of whom 1906 (88%) were white and 257 (12%) were black. Baseline characteristics of the excluded patients were compared to the patients in the analytic cohort of 2,163 with the only notable difference being that 95% of the 188 patients with documentation of treatment outside the VHA were white. There were no other racial differences in patients excluded from analysis.

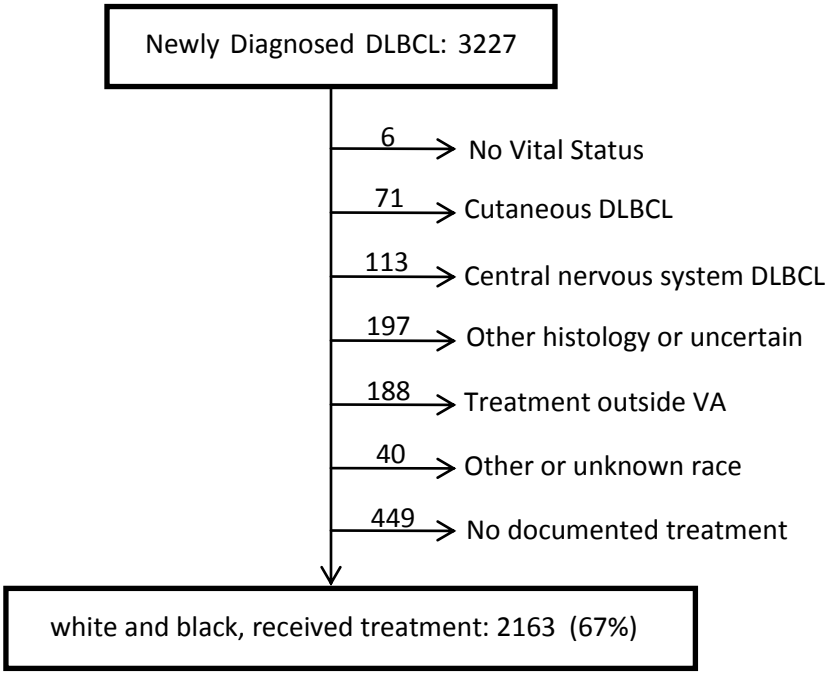

Figure 1. CONSORT diagram.

2.3 **Data Sources**

The VACCR provided the following information for all patients in the initial cohort: race, date of birth, date of diagnosis, Ann-Arbor stage, anatomic locations of disease, method of biopsy used to determine diagnosis, presence of B-symptoms, use of radiation therapy, sex, zip code of residence, scrambled social security number, and real social security number. The procedure to scramble social security numbers was performed prior to data download by staff of the VACCR, using a formula not made available to investigators.

Scrambled social security numbers obtained from the VACCR were used to electronically link DLBCL cases to patient information housed at the VHA Austin Information Technology Center (AITC). This provided additional data on *International Classification of Diseases*, 9th edition (ICD-9) codes for comorbid conditions, date of death (when available), vital signs at the time of diagnosis (including height and weight), presence of HIV infection, and hospital within the VHA system where treatment was administered.

In addition, scrambled social security numbers were used to obtain additional data on inpatient and outpatient medications from the VHA Pharmacy Benefits Management (PBM) service housed in Hines, Illinois. These data included chemotherapy drugs, doses, and dates of administration through a query of antineoplastic agents used in the identified cohort. Records on the use of myeloid growth factors (MGF) were also obtained in this manner.

After linking the above data sources, real social security numbers were used to query individual patient records using the VHA Compensation and Pension Records Interchange (CAPRI) software system. This allowed verification of all drugs, doses, and dates of administration based on the chemotherapy nursing notes contained in the EMR. This also permitted abstraction of laboratory data such as serum LDH level, which are not available in the administrative records. Data abstraction was performed by a team of medical students, internal

medicine residents, oncology fellows, and paid research staff under the direction of Dr. Carson, who identified the variables of interest for abstraction and trained the team in the use of CAPRI. Data abstraction was recorded in a Microsoft Access file allowing easy importation into statistical software.

Income quartile estimates were made based on median household income by zip code-tabulated area data obtained from the United States Census Bureau (United States Census Bureau, 2007). Finally, academic affiliation or "teaching intensity" at each VHA medical center was determined based upon data from the department of Veterans Affairs on the number of residency positions and the number of actively used hospital beds for each facility where chemotherapy treatment was administered. The ratio of residency positions to active inpatient hospital beds provided the teaching intensity measurement.

2.4 **Study Measures**

2.4.1 **Outcome Variables**

The primary outcome of interest was OS, which was calculated in months from the date of DLBCL diagnosis to the date of death. Death information was last accessed July 10, 2013, allowing nearly five years of follow-up for all patients. Patients who did not have date of death information were assumed to be alive but were censored at the time of the last recorded death within the cohort, April 23, 2013. Right censoring in this situation allows use of survival data up to a uniform time of final follow-up across the entire cohort (Prinja et al., 2010). The assumption that patients were still alive within two or three months of the time of last reported death within the cohort is supported by previous literature demonstrating that more than 97% of death events are captured by VHA vital status files (Savas et al., 2009; Sohn et al., 2006).

A secondary outcome of interest was progression-free survival (PFS). While there is considerable controversy in the oncology community regarding the validity of PFS as a clinical endpoint, it is still routinely measured in prospective randomized studies of both indolent and aggressive NHL (Booth and Eisenhauer, 2012; Salles et al., 2011; Stiff et al., 2013). In an effort to understand its utility in this observational study, an a priori decision was made to evaluate PFS. Progression-free survival was measured from the date of NHL diagnosis to the date of: death, documentation of disease progression, or start of the next treatment regimen.

2.4.2 **Independent Variables**

A summary of independent variables is provided in Table I.

TABLE I

SUMMARY OF PREDICTOR VARIABLES

Independent variables	Variable type	Measurement	Value	Source
Non-modifiable				
Race	Dichotomous	White—referent	0	VACCR
		Black	1	
Age	Continuous	Years		VACCR
Stage	Categorical	I–II - referent	0,0	VACCR
		III–IV	1,0	
		Unknown	0,1	
Serum LDH	Categorical	Normal—referent	0,0	CAPRI
		Elevated	1,0	
		Unknown	0,1	
Sex	Dichotomous	Male	1	AITC
		Female	0	
B-symptoms	Categorical	Absent	0,0	VACCR
		Present	1,0	
		Unknown	0,1	
Treatment-related				
ARDI	Dichotomous	≥80%,≥85%,≥90%	1	CAPRI
		<80%,<85%,<90%	0	
	Continuous	Percentage		
Rituximab	Dichotomous	Yes	1	PBM
		No	0	
Doxorubicin	Dichotomous	Yes	1	PBM
		No	0	
MGF	Dichotomous	Yes	1	PBM
		No	0	
Nontreatment related				
HIV status	Dichotomous	Negative	0	AITC
		Positive	1	
Comorbidity score	Continuous	1–12		AITC
SES	Ordinal	Quartile I	0,0,0	AITC
		Quartile II	1,0,0	
		Quartile III	0,1,0	
		Quartile IV	0,0,1	
		Unknown	0,0,0,1	

SUMMARY OF PREDICTOR VARIABLES

Independent variables	**Variable type**	**Measurement**	**Value**	**Source**
Teaching Intensity	Categorical	Very Major	1,0,0	AITC
		Major	0,1,0,0	
		Minor	0,0,1,0	
		None- referent	0,0,0,0	
		Unknown	0,0,0,1	
BMI	Categorical	Underweight	1,0,0,0	AITC
		Normal- referent	0,0,0,0	
		Overweight	0,1,0,0	
		Obese	0,0,1,0	
		Unknown	0,0,0,1	

2.4.3 **Selection of Independent Variables**

An a priori selection of clinically relevant independent variables was performed to avoid the potential problems of spurious statistically significant correlation due to data mining (Wu and Yang, 2006). The independent variables of greatest interest for this study are those that are directly modifiable by physicians, namely the treatment variables, since race-based differences in treatment patterns might be amenable to corrective intervention. The first treatment variable of interest is average relative dose intensity (ARDI), which measures the actual amount of drug delivered per unit of time, divided by the expected dose per unit of time (Green et al., 1980). Previous studies have suggested better outcomes in DLBCL are associated with ARDI≥85% to 90% (Bosly et al., 2008; Lyman et al., 2004). Race-based differences in ARDI might contribute to outcome differences. The second treatment variable considered was doxorubicin use. Previous literature has suggested higher rates of doxorubicin-related cardiac toxicity in black patients (Hasan et al., 2004). This might discourage use in black patients, systematically altering clinical outcomes. Furthermore, Nabhan et al. (2012) found that black patients being treated for FL were less likely to receive doxorubicin. The third variable considered was rituximab use. Rituximab is a biologic agent that has provided the only improvement in OS for patients with DLBCL over the past 30 years (Coiffier et al., 2002). Race-based differences in rituximab use could also potentially explain the observed outcome disparity, and there is previous evidence of a race-based difference in rituximab use that was identified during the literature review (Flowers, 2012; Shih, 2009). The fourth treatment variable considered was MGF use. The MGFs reduce the incidence of febrile neutropenia (fever>100.4^0 Fahrenheit and absolute neutrophil count less than 500), a major complication of chemotherapy, and provide a subtle improvement in OS (Lyman et al., 2013; Scott et al., 2003).

Another important group of independent variables are those that are generally not considered modifiable. However, to control for individual-level and race-based differences in patient characteristics that influence prognosis, these variables were also evaluated in the multivariate modeling. Age, LDH, and stage are all measured at the time of diagnosis and are not modifiable, since there is no accepted mechanism to screen for and diagnose DLBCL earlier in the natural history of the disease. These variables are also components of the International Prognostic Index (IPI) in aggressive lymphoma, a previously validated score used to stratify prognosis in patients with DLBCL (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993). Systemic B-symptoms at the time of diagnosis—fevers greater than 100.4^0 Fahrenheit, drenching night sweats, and unintentional weight loss greater than 10% of baseline weight—are also not modifiable and have prognostic significance, so the presence of B-symptoms was considered in the analyses (Sharma et al., 2009). Patient sex is known to have prognostic significance in other forms of lymphoma, so this non-modifiable variable was also considered. Finally, race was considered as one of the primary variables of interest in this study. Thus, the final list of non-modifiable prognostic variables was race, sex, age, disease stage, serum LDH level, and presence of B-symptoms.

The final group of independent variables may be partially modifiable through improved medical management of nonmalignant conditions and/or better support services. These variables were designated as “nontreatment related” and include comorbid medical conditions, presence of HIV infection, body mass index (BMI) at the time of diagnosis, SES, and teaching intensity of the treating VHA medical center. In previous work with this cohort, I have demonstrated an inverse association between Charlson comorbidity score and OS as well as a surprising positive association between BMI and OS (Carson et al., 2012). Presence of HIV infection causes a considerable increase in DLBCL incidence and reduces OS, so this variable was considered

(Dunleavy and Wilson, 2012). In other diseases, treatment at academic medical centers has been associated with better outcomes and there was a suggestion in the literature review that use of rituximab was greater at high-volume teaching centers (Flowers, 2012; Gillum and Johnston, 2001). Finally, SES differences are thought to explain some of the race-based outcome differences in several of the disease states evaluated in the literature review, necessitating inclusion of this variable. Ultimately, all of these variables are chronic problems that will not completely resolve with intervention, but their influence on OS may be mitigated with medical and/or social work interventions during or after DLBCL treatment. Thus, significance of any of these variables might represent an alternate mechanism to reduce outcome disparities.

2.4.4 **Measurement of Independent Variables**

2.4.4.1 **Treatment Variables**

The ARDI was calculated for the use of cyclophosphamide and doxorubicin using the methods of Hryniuk et al., in the patients who received the standard of care CHOP chemotherapy regimen with or without rituximab (Hryniuk and Goodyear, 1990). The expected dose for the purposes of ARDI calculations was based upon the following assumptions: (1) Chemotherapy treatments would be administered every 21 days for all patients, consistent with treatment guidelines in the United States; (2) Patients with advanced-stage (III and IV) disease were expected to receive at least six total cycles of chemotherapy with or without rituximab; (3) Patients with early-stage disease could receive three cycles of systemic treatment followed by external beam radiation therapy, or six cycles of therapy without radiation (National Comprehensive Cancer Network, 2012); (4) Treatment cycles beyond six were not counted in dose intensity calculations; (5) The expected dose of doxorubicin was 50mg/m^2 and the expected dose of cyclophosphamide was 750mg/m^2. Overall, these assumptions resulted in an expected doxorubicin dose of 16.7mg/m^2/week and an expected cyclophosphamide dose of

250mg/m^2/week. Initial analyses dichotomized ARDI at <or≥85%, consistent with previous literature.

Since ARDI is a variable that is derived from several others, in an effort to reduce the impact of missing variables on results, a strategy was developed to determine the number of expected cycles of therapy in the absence of information on disease stage. In patients who received no radiation therapy, six cycles of chemotherapy was expected. In patients who received radiation therapy, only three cycles was expected.

Most chemotherapeutic agents are dosed based upon body surface area (BSA), a practice related to historical experiments that demonstrated the metabolic rate (and by extension, rate of drug metabolism) is proportional to BSA (Hoppeler and Weibel, 2005). The BSA was calculated using the Dubois formula [BSA=.007184 x height(cm)$^{0.725}$ x weight(kg)$^{0.425}$] (DuBois and DuBois, 1916). Height and weight data were recorded in VHA vital sign files in inches and pounds, respectively. Pounds were converted to kilograms by dividing by 2.2 and inches were converted to centimeters by multiplying by 2.54. Weight measurements within one month of the time of treatment initiation were used for BSA calculations. Weight measurements were screened for extreme values using the Rosner outlier detection algorithm (Rosner, 1975). Since height is reasonably conserved over the course of a lifetime, the modal observation of height rounded to the nearest inch was used in all calculations. Patients with height below 58 inches or above 80 inches underwent additional scrutiny since current and historic military standards prohibited enlistment of those with height outside of this range (Karpinos, 1958; Powers, 2014). One height outlier was detected, and the observed height of 84 inches was corrected to 73 inches, based on heights recorded elsewhere in the EMR.

The first clinical trial demonstrating improved OS with rituximab use in DLBCL was published in early 2002, though publication was preceded by the presentation of preliminary

results in several venues (Coiffier et al., 2002). Considerable time may be required before new clinical developments are widely adopted in routine clinical practice (Morris et al., 2011). Furthermore, the VHA often requires cost-effectiveness analyses before a drug is widely adopted on the formulary (Aspinall et al., 2005). For these reasons, analysis of race-based differences in rituximab use was performed on the entire cohort and those diagnosed in 2002 or later. Any exposure to rituximab in conjunction with induction/front-line chemotherapy was considered positive for receipt of rituximab, consistent with an intention to treat analysis.

Similarly, doxorubicin use was considered as a dichotomous variable classified as positive if patients received at least one dose of doxorubicin at any time during induction/front-line therapy. Because ARDI measures the intensity of both doxorubicin and cyclophosphamide use, analyses of ARDI did not include the dichotomous doxorubicin variable due to concerns about collinearity. The ARDI analyses were confined to patients who received both doxorubicin and cyclophosphamide.

Myeloid growth factor use was classified as a dichotomous variable coded as "yes" if used at any time within 14 days of any chemotherapy cycle during initial chemotherapy. Use outside of this time frame would not be expected to greatly influence outcome, and was not considered.

2.4.4.2 **Non-Modifiable Variables**

Race was recorded in VACCR files as white, black, other or unknown. A previous study found poor agreement between self-identified and recorded race/ethnicity for groups other than Caucasians and African Americans within the VHA system (Boehmer et al., 2002; Stroupe et al., 2010). Based on this knowledge and because race ascertainment is a critical dimension of this study, race codes obtained from the VACCR for a random sample of 50 white and 50 black patients were compared to race designations contained within the text of the medical records.

This validation sub-study demonstrated 98% concordance (Cohen's kappa statistic 0.96, standard error 0.03, 95% CI 0.9–1) (McHugh, 2012).

Age at diagnosis was measured in years between birth and date of diagnosis and was considered as a continuous variable in all analyses.

Stage at the time of diagnosis was measured according to the Ann-Arbor lymphoma staging system, ranging from stage I to stage IV (Carbone et al., 1971). Consistent with the IPI, this variable was dichotomized into early (stage I/II) and advanced stage (III/IV). In an effort to improve statistical power, those with missing stage data were considered in an "unknown" stage category. Because of this, stage was modeled in categorical fashion, compared to the referent group of early stage.

Serum LDH was similarly dichotomized as normal or elevated, consistent with its measurement in the international prognostic index for aggressive NHL (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993). Since a considerable number of patients were missing information on LDH at the time of diagnosis, an unknown category was added to this variable and it was considered in categorical fashion in comparison to the referent group with normal LDH.

Sex was considered in a dichotomous fashion (male and female), although based on the historical demographics of the veteran population, the vast majority of patients were male.

Data on B-symptoms were obtained directly from the VACCR. When this data point was missing, patient records were reviewed to determine physician impression of the presence or absence of B-symptoms at the time of diagnosis. Finally, all patients with historic weight data were screened for weight loss of >10% in the six months leading up to diagnosis. Those with this finding were then classified as B-symptom positive. Those without B-symptom information or

significant weight changes were classified into an unknown category. The B-symptoms were modeled as a categorical variable compared to a referent group with absent B-symptoms.

2.4.4.3 **Nontreatment Variables**

Patients were classified as HIV positive in the presence of positive HIV serologic testing at any time before or within six months after DLBCL diagnosis. The HIV status was modeled as a dichotomous variable, positive or negative.

Comorbidity score was assessed based on ICD-9 codes present at the time of diagnosis, which were used to generate a comorbidity score based on the Charlson comorbidity index (Romano et al., 1993). Details of the ICD-9 codes used, the associated comorbid diagnoses, and relative weights of each condition are provided in Table II. In contrast to other studies using a modified Charlson score, HIV status and metastatic disease were removed from the comorbidity score for this study. This decision was based on the historically negative impact HIV positivity has on OS in DLBCL, which warranted independent measurement (Dunleavy and Wilson, 2012). The "metastatic tumor" component of the Charlson score was removed from the comorbidity variable as it is also measured by the disease stage variable, and measurement twice in the model might contribute to issues of collinearity.

TABLE II

ICD-9 CODES, ASSOCIATED DIAGNOSIS, AND WEIGHTINGS IN THE MODIFIED CHARLSON SCORE

Comorbidity	ICD-9 Diagnostic Code	ICD-9 Procedure Code	Weight
Myocardial Infarction	'410','412'		1
Heart Failure	40201','40211','40291','425','428','4293','40401', '40403','40411','40413','40491','40493'		1
Peripheral Vascular Disease	440','441','442','4431','4432','4433','4434','4435', '4436','4437','4438','4439','4471', '7854'	3813','3814','3816','3818','3833','3834', 3836','3838','3843','3844','3846', '3848', '3922','3923','3924','3925','3926','3929'	1
Cerebrovascular Disease	36234','430','431','432','433','434','435','436','4370', '4371', '4379','438','7814','7843','9970	'3812','3842'	1
Dementia	'290','3310','3311','3312'		1
Chronic Pulmonary Disease	4150','4168','4169','491','492','493','494','496'		1
Rheumatic Disease	'710','714'		1
Peptic Ulcer	'531','532','533','534'		1
Mild Liver Disease	'5712','5715','5716','5718','5719'		1
Severe Liver Disease	'5722','5723','5724','4560','4561','4562'	'391','4291'	3
Diabetes	'2500', '2501','2502','2503'		1
Complicated Diabetes	'2504', '2505','2506','2507','2508','2509'		2
Hemi- or Paraplegia	'342','344'		2
Renal Disease	'585','586','V420','V451','V56'	'3927','3942','3993','3994','3995','5498'	2
Other Malignancy	14','15','16','170','171','174','175','176','179','18', 190','191','192','193','194','195','201','203', '204','205','206','207','209','2730', '2733','V1046'	'605','6240','6241'	2
HIV/AIDS	'042','043','044'		6

Socioeconomic status was estimated based on zip code of patient residence at the time of treatment, using the median household income within that zip code in the year 2000 as defined by the 2000 United States Census (United Status Census Bureau, 2010). As a cohort study with diagnoses occurring between 1998 and 2008, the 2000 census data were believed to be a closer approximation for most patients than data from the 2010 census. Median household income was divided into quartiles for all analyses and compared to the lowest quartile, which served as the referent group.

The teaching intensity of each VHA hospital was estimated based upon the ratio of residency positions divided by the number of hospital beds. Hospitals were categorized as very major academic (resident-to-bed ratio ≥.6), major (ratio 0.599 to 0.25), minor (ratio 0.249 to 0.001), and none (ratio=0), consistent with previous studies evaluating care quality and outcomes in VHA hospitals (Volpp et al., 2007). To determine the teaching intensity ratio, the number of residency positions at each medical center in the 2010–2011 academic year was first ascertained from the VHA allocation resource center (United States Department of Veterans Affairs, 2014). Next, the number of active inpatient beds was determined with the ProClarity software system, available behind the VHA firewall. Then the number of residency positions was divided by the number of active inpatient beds to determine the ratio.

Weight at the time of treatment initiation was used for BMI calculations along with the modal observation of height measurement. A standard formula was used to calculate BMI (weight (kg) ÷ [height (m)]^2) and patients were stratified into BMI groups as defined by the World Health Organization (underweight=BMI <18.5, normal weight=BMI 18.5 to <25, overweight=BMI 25 to <30, obese=BMI ≥30) (World Health Organization, 2011). While members of the dissertation committee suggested evaluating different BMI categories due to the

generally higher mean BMI observed in the United States, no precedent could be found for such an approach on additional literature review.

2.5 **Primary Analyses**

For the primary outcome measure, age-adjusted two-year and five-year OS, stratified by race, was assessed using the methods of Kaplan and Meier with statistical significance measured by the log-rank test (Mantel, 1966). Age-adjustment is required since black patients are diagnosed at a younger mean age than white patients, masking the race-based outcome disparity in unadjusted models (Shenoy et al., 2011a). Univariate comparisons were performed to identify differences in treatment and other prognostic variables between race groups. Student's t-test was used for comparison of mean values of continuous variables between race groups (Student, 1908). Chi-square testing was used to compare proportions for dichotomous variables. The Cochran-Mantel-Haenszel row mean score test was used to evaluate for significant differences in variables such as BMI (Wallenstein and Wittes, 1993).

Cox proportional hazards modeling was then used to evaluate the significance of race as a predictor of survival over a five-year time frame, while controlling all of th*e* a priori selected variables, with the exception of ARDI. The HRs and CIs were calculated for all independent variables. Interaction variables were inserted into the model to screen for interactions between independent variables. In addition, the proportional hazards assumption was tested using Schoenfeld residuals and through insertion of time-dependent covariates for all significant independent variables. When variables violated the proportional hazards assumption, time-stratified analyses were presented, dichotomized at a clinically rational time frame (i.e., 12 months instead of 10.3 months) that still met the proportional hazards assumption, as opposed to stratification at the statistically optimal time.

A second set of Cox analyses was performed to evaluate the influence of race on OS while controlling for ARDI. Since doxorubicin is considered as dichotomous variable, and is a significant component of the ARDI variable, analyses of ARDI were performed only on the subset of patients who received doxorubicin. By definition, patients who did not receive doxorubicin could not receive more than 50% ARDI, which could lead to collinearity between the doxorubicin and ARDI variables. Furthermore, since patients who died during therapy could not complete the expected number of treatment cycles, a landmark analysis was required to reduce the risk of immortal time bias among those receiving higher ARDI (Lévesque et al., 2010). Patients surviving for five months beyond the first treatment were included in the landmark analysis, a time interval that roughly corresponds to the end of treatment for most patients (Dafni, 2011).

While the a priori expectation was that ARDI ≥85% would be optimal based upon previous literature, this is not a settled matter. Therefore, sensitivity analyses were performed dichotomizing ARDI at ≥80%, ≥85%, ≥90% and also considering ARDI as a continuous variable. The model that minimized the -2 log likelihood value presented by SAS was selected as the final model.

2.6 **Secondary Analyses**

The overarching rationale for this dissertation is to determine if race-based differences in treatment patterns explain the observed outcome disparity between black and white patients with DLBCL. At the same time, disease prognostic factors may influence treatment selection, so-called confounding by indication (Hak et al., 2002). Previous work has demonstrated that significant differences in baseline characteristics between newly diagnosed black and white DLBCL patients exist (Shenoy et al., 2011a). For this reason, additional logistic regression

analyses were performed to determine the degree to which race was independently associated with the use of rituximab, doxorubicin, MGFs, and the achievement of ARDI ≥80%, while controlling for baseline patient characteristics.

Following a univariate comparison of the patients diagnosed after January 1, 2002 who did and did not receive rituximab, logistic regression was used to identify factors significantly associated with rituximab use in a multivariable fashion. Results are presented as ORs with associated CIs. Using logistic regression, similar analyses were repeated across the entire study time frame to determine if race was independently associated with use of doxorubicin, or MGFs. Finally, logistic regression was performed to evaluate the association between race and achieving ARDI ≥80% in the subset of patients treated with CHOP chemotherapy with or without rituximab.

Since a significant number of patients had no records of therapy and there is previous evidence that black patients are less likely to receive therapy, univariate comparison was performed to determine if race may be associated with no treatment.

2.7 **Execution of Analyses**

The alpha significance level considered statistically significant in all analyses was 0.05, while an alpha significance level of 0.1 was considered consistent with a statistical trend. In Cox and logistic regression analyses, HRs and ORs with CIs not crossing one were considered statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

2.8 **Limitations of This Cohort**

There are several limitations of this cohort that should be acknowledged early to preempt concerns regarding some of the variables that were not considered in all analyses. First, two components of the IPI—physical performance status and number of extranodal sites of disease—were not routinely measured in this cohort. Second, men have historically been more likely to serve in the military (the primary mechanism to obtain VHA benefits). This resulted in a very small number of women in the patient cohort, limiting the statistical power of analyses around this variable, which was therefore dropped from all of the multivariate analyses. Third, the VHA population has only a small number of patients of races other than white or black, limiting the utility of separate analyses of patients from other racial backgrounds, again due to issues with statistical power. Finally, data on ethnicity (e.g., Hispanic ethnicity) are not routinely captured in VHA records. These variables were therefore not captured or used in the multivariate analyses.

3. RESULTS OF PRIMARY ANALYSES

3.1 Univariate Comparisons of Primary Cohort

3.1.1 Non-Modifiable Variables

After exclusion of ineligible patients as described in the methods section, univariate comparisons were made between white and black patients who received treatment within the VHA health system (Table III). Consistent with previous observations from SEER, black patients in the VHA cohort were typically younger and were more likely to have systemic B-symptoms at the time of diagnosis (Shenoy et al., 2011a). Though not statistically significant, a trend was observed toward higher-stage disease in black patients at the time of diagnosis. In one finding that has not been described previously, likely due to limitations of datasets containing large numbers of DLBCL patients, we found that black patients were significantly more likely to have an elevated LDH (64% versus 54%, p=.003) compared to white patients. Finally, there was no significant difference in the proportion of men in the black and white patient groups, so this variable was not included in the multivariate analyses.

TABLE III

BASELINE CHARACTERISTICS OF US VETERANS WITH DLBCL DIAGNOSED AND TREATED 1998 TO 2008

	Race (N=2,163)		
	White (n=1,906)	**Black (n=257)**	**P-value**
Age (mean years)	66.0	57.6	<0.0001‡
Sex (Male %)	97.3	96.9	0.6864*
BMI groups (%)			
Underweight	2.0	5.5	
Normal weight	34.2	39.7	
Overweight	36.7	35.0	
Obese	24.5	17.9	
Unknown	2.6	2.0	0.0005†
Stage (%)			
I/II	42.1	34.6	
III/IV	57.2	61.9	
Unknown	0.7	3.5	0.0509†
LDH (%)			
Elevated	53.5	63.8	
Normal	35.2	26.9	
Unknown	11.3	9.3	0.0030†
B-symptoms (%)			
Yes	49.7	55.6	
No	46.0	37.4	
Unknown	4.3	7.0	0.0212*
Comorbidity score (mean)	2.3	1.9	0.0010‡
HIV+ (%)	3.5	21.0	<0.0001*
Doxorubicin use (%)	87.1	89.9	0.2054*
Rituximab use (%)	73.7	70.4	0.2714*
Myeloid Growth Factor use (%)	61.3	69.7	0.0098*
Teaching Intensity (%)			
Major academic	55.6	61.5	
Minor academic	22.5	24.1	
Insufficient or nonacademic	12.3	4.7	
Unknown	9.7	9.7	0.0024†
SES (%)			
Income quartile I	22	39.7	
Income quartile II	25.1	17.5	
Income quartile III	25.3	17.9	
Income quartile IV	24.9	19.8	
Unknown	2.7	5.1	<0.0001†

‡ t-test
* Chi-square test
† Cochran-Mantel-Haenszel (row mean score) test

3.1.2 **Treatment Variables**

There were no significant differences in rituximab or doxorubicin use between black and white patients, and no difference in ARDI. Use of MGFs was significantly higher in black patients than white patients (69.7% versus 61.3%, p=.01).

3.1.3 **Nontreatment Variables**

A major finding of this study is the significantly higher prevalence of HIV (21% versus 3.5%, p<.001) in black patients compared to white patients. Black patients were also more likely to be underweight or normal weight, compared to white patients (45.2% versus 36.3%, p=.005). After removing HIV from the comorbidity score, black patients had a lower average score at the time of diagnosis (1.9 versus 2.3, p=.001), compared to white patients. Black patients with DLBCL were also more likely to be in lower socioeconomic strata than white patients, consistent with previous literature (Wang, M. et al., 2008). Finally, black patients were significantly more likely to receive care at VHA medical centers with the highest level of teaching intensity.

3.1.4 **Discussion of Univariate Comparisons**

There are several novel findings from this analysis that augment findings from other authors using other datasets. First, among the non-modifiable baseline factors, black patients were more likely to have an elevated LDH, a finding suggesting more aggressive disease and poorer prognosis (The International Non-Hodgkin's Lymphoma Prognostic Factors Project., 1993). Second, the prevalence of HIV was six times higher in black patients in this cohort. This finding—while intuitive based upon a prevalence of HIV that is nearly eight times higher in blacks than whites—has potential major implications for both prognosis and treatment selection (Dunleavy and Wilson, 2012; Moore, 2011). Third, black patients were more likely to be underweight or normal weight at the time of diagnosis, which has previously been associated with worse OS within this patient cohort (Carson et al., 2012).

There were also several unexpected findings in the initial analysis. On average, black patients had a lower comorbidity score than white patients. This is likely explained in part by the lower age of black patients at the time of diagnosis, as well as the removal of HIV from the comorbidity score. Similarly, more frequent use of MGFs in black patients is likely explained in part by the higher prevalence of HIV, which likely influenced treatment decisions. While there was no observed difference in the use of rituximab, doxorubicin, or the achievement of ARDI ≥80%, this univariate analysis does not rule out the possibility that a difference may be unmasked after controlling for other variables in a multivariate analysis that will be described later. Furthermore, while there was no difference in the use of rituximab when the entire study time frame was examined, rituximab use became standard of care only during the last six years of that time frame. Thus, additional analyses are required to examine the cohort of patients treated in 2002 and after.

3.2 **Kaplan-Meier Analyses**

All Kaplan-Meier analyses were age-adjusted based on the observation in the univariate analysis that black patients were, on average, significantly younger than white patients.

3.2.1 **Kaplan-Meier Analyses of Progression-Free Survival**

Two- and five-year age-adjusted Kaplan-Meier curves for PFS are presented in Figures 2 and 3, respectively. Both were statistically significant (log-rank p=.04 at 2 years, and p=.03 at 5 years). The median PFS time for the combined cohort of white and black patients was 29 months, with 52% and 41% without progression or death at two and five years, respectively. At five years there were a total of 1,282 progression events, of which 774 were deaths and 508 were disease progression.

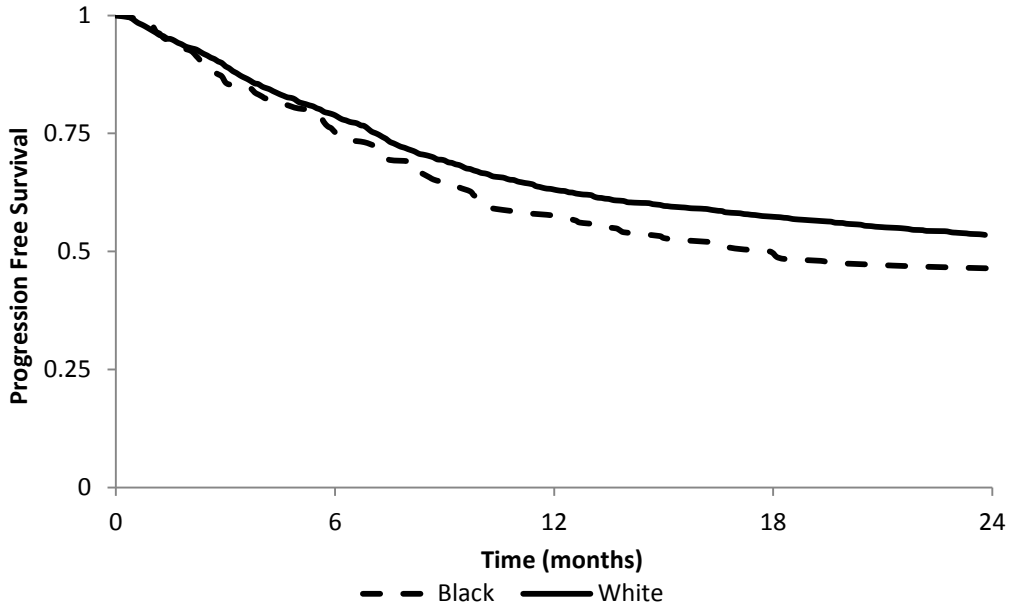

Figure 2. Age-adjusted two-year PFS in US Veterans with DLBCL diagnosed and treated 1998 to 2008, stratified by race.

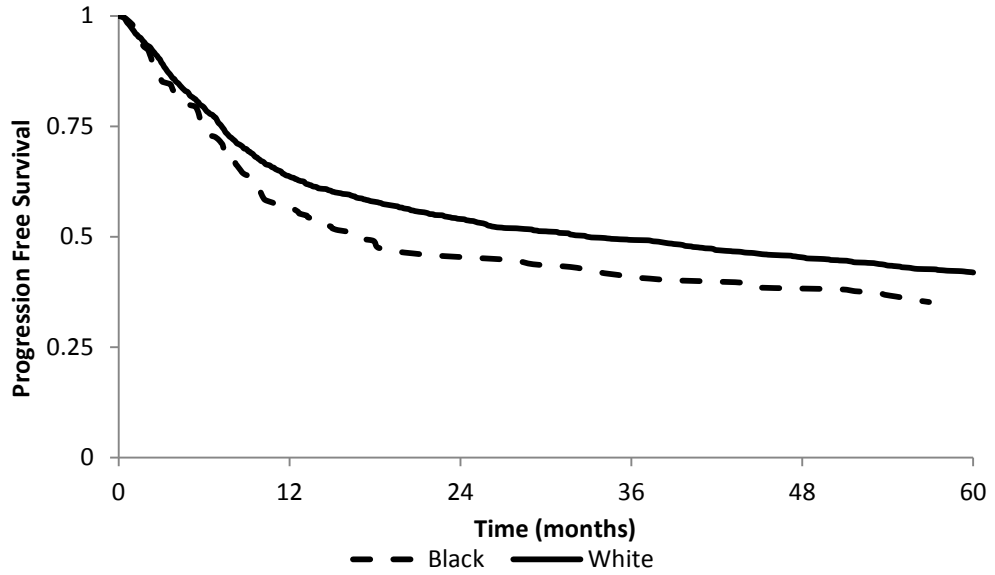

Figure 3. Age-adjusted five-year PFS in US Veterans with DLBCL diagnosed and treated 1998 to 2008, stratified by race.

3.2.2 **Kaplan-Meier Analyses of Overall Survival**

Two- and five-year age-adjusted Kaplan-Meier curves for OS are presented in Figures 4 and 5, respectively. Race was significantly associated with OS (log-rank p=.03 at 2 years, and p=.04 at 5 years). The median OS time for white and black patients combined was 51 months, with 60% and 47% alive at two and five years, respectively. At five years, there was a total of 1,142 deaths in the cohort.

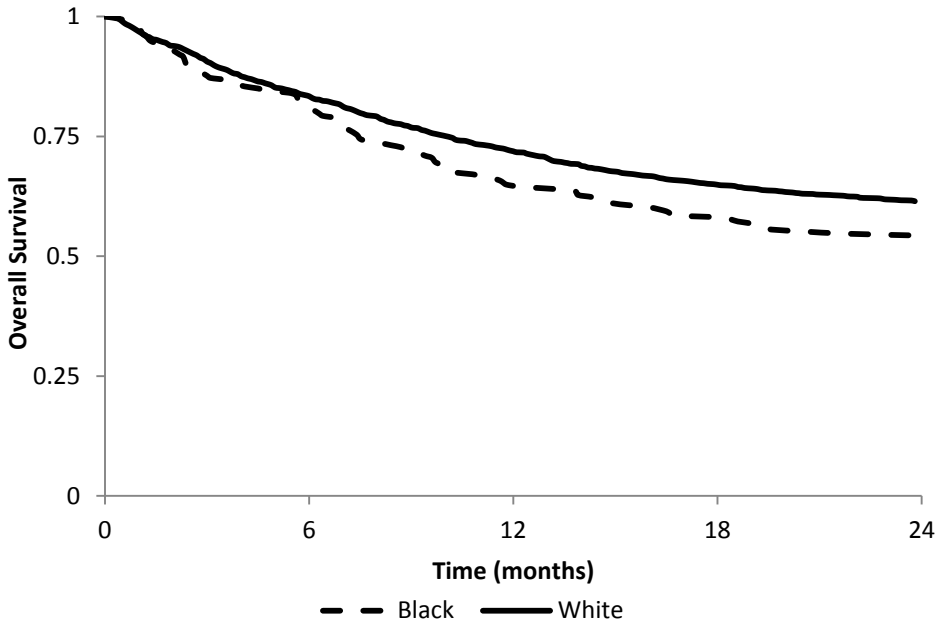

Figure 4. Age-adjusted two-year OS in US Veterans with DLBCL diagnosed and treated 1998 to 2008, stratified by race.

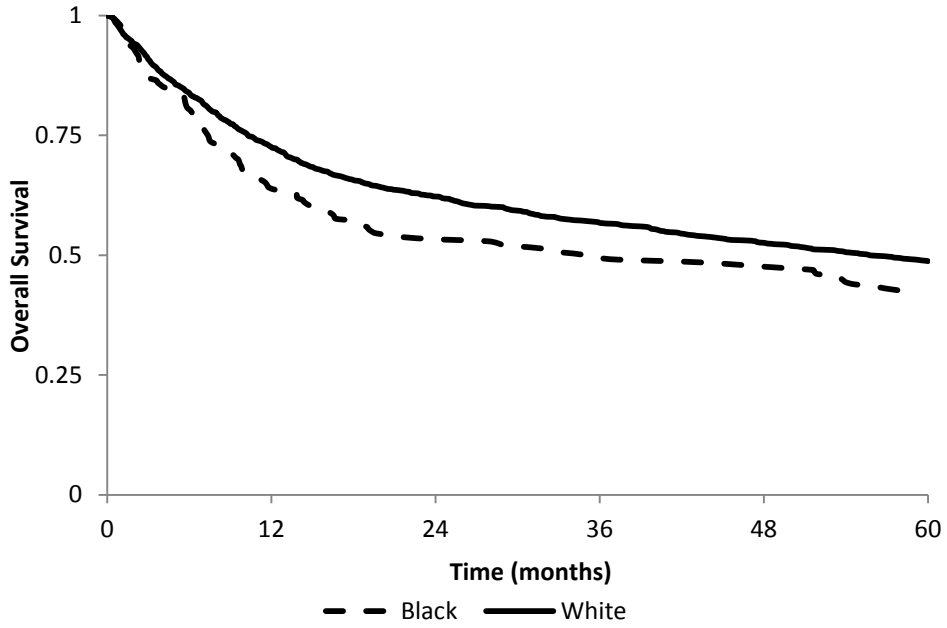

Figure 5. Age-adjusted five-year OS in US Veterans with DLBCL diagnosed and treated 1998 to 2008, stratified by race.

3.2.3 **Discussion of Kaplan-Meier Analyses**

The steep downward slope followed by a more gradual downward slope noted in both the PFS and OS curves noted in the first one to two years after diagnosis is consistent with what would be expected in this disease. Treatment-related deaths will tend to occur within the first six months of diagnosis and even in the clinical trial setting were often in the 6% to 8% range during initial treatment (Coiffier et al., 2002; Pfreundschuh et al., 2008). Then a significant majority of the relapse and death events will occur within the first two years (Larouche et al., 2010). The gradual decline in PFS and OS noted after the first two years will then largely be due to causes other than lymphoma.

An important finding from the Kaplan-Meier analysis was that only 140 of the 508 patients (28%) who relapsed within the first five years were alive at the end of five years. This resulted in a relatively small absolute difference between PFS and OS at five years of only 6%. Survival after relapse in this population is worse than what might be expected based upon clinical trial data (Gisselbrecht et al., 2010; Philip et al., 1995). This likely reflects the older age and higher comorbidities of the VHA population compared to those enrolled in randomized trials, which may preclude intensive salvage treatment options such as autologous stem cell transplantation (Wang et al., 2012). An unplanned, post-hoc analysis of survival among the black and white patients with relapsed disease demonstrated that 23/63 (37%) and 117/445 (26%), respectively, were alive five years after diagnosis (chi-square p=.09). Taken together, these findings suggest that differences in the application salvage treatments such as autologous stem cell transplantation will be not a significant contributor to the lower age-adjusted survival noted in black patients within this cohort.

Overall, the similarities between PFS and OS at two and five years support the a priori desire to focus the primary analyses on overall survival.

3.3 **Cox Analysis of Entire Treated Cohort**

Results of the Cox analysis are presented in ≤. After controlling for other variables, black race was no longer significantly associated with increased risk of death after DLBCL diagnosis (HR=1.02, 95% CI 0.83–1.25). All of the other non-modifiable variables (age, stage, LDH, B-symptoms) were statistically significant except for sex, and where necessary, HRs were stratified into two time intervals to meet the proportional hazards assumption. Patients with unknown LDH and stage had significantly worse survival, suggesting that patients who did not have these variables assessed had a poorer prognosis.

TABLE IV

HAZARD RATIOS AND 95% CIS FOR MORTALITY OF US VETERANS WITH DLBCL DIAGNOSED AND TREATED 1998 TO 2008

Variable	Hazard Ratio	95% CI	
Black Race	1.01	0.83	1.24
Age			
≤30 months			
Age	1.02	1.01	1.03
>30 months			
Age	1.06	1.05	1.08
Stage			
≤12 months			
Stage III \ IV	1.60	1.34	1.91
Stage unknown	2.55	1.29	5.06
>12 months			
Stage III \ IV	1.47	1.22	1.78
Stage unknown	0.80	0.25	2.55
LDH			
≤18 months			
LDH elevated	2.63	2.19	3.17
LDH unknown	1.57	1.20	2.07
>18 months			
LDH elevated	1.26	1.00	1.59
LDH unknown	0.96	0.68	1.37
B-symptom			
≤12 months			
B-symptom yes	1.44	1.21	1.71
B-symptom unknown	1.03	0.69	1.52
>12 months			
B-symptom yes	1.05	0.87	1.27
B-symptom unknown	1.64	1.13	2.37
Rituximab use, yes	0.60	0.52	0.69
Doxorubicin use, yes	0.57	0.49	0.67
HIV, yes	1.67	1.27	2.20
Comorbidity score	1.10	1.07	1.12

HAZARD RATIOS AND 95% CIS FOR MORTALITY OF US VETERANS WITH DLBCL DIAGNOSED AND TREATED 1998 TO 2008

Variable	Hazard Ratio	95% CI	
MGF			
≤3 months			
MGF use yes	0.74	0.56	0.98
>3 months			
MGF use yes	1.04	0.90	1.21
SES			
Quartile II	1.10	0.93	1.30
Quartile III	1.02	0.85	1.21
Quartile IV	1.05	0.89	1.25
Quartile Unknown	1.23	0.87	1.76
Teaching intensity			
≤3 months			
Very major academic	0.79	0.51	1.22
Major academic	0.69	0.42	1.14
Academic Unknown	1.73	1.06	2.84
>3 months			
Very major academic	0.98	0.79	1.22
Major academic	0.99	0.78	1.26
Academic Unknown	1.01	0.75	1.37
BMI groups			
Underweight	1.47	1.06	2.03
Overweight	0.82	0.72	0.95
Obese	0.78	0.66	0.92
Unknown	1.04	0.71	1.51

Among the treatment variables considered in the analysis performed on the entire cohort, doxorubicin use (HR=.57, 95% CI 0.49–0.67) and rituximab use (HR=.6, 95% CI 0.52–0.69), were both strongly associated with a reduced risk of death. Use of MGF was associated with decreased mortality in the first three months after diagnosis (HR=.74, 95% CI 0.56–0.98), but after that was not related to outcome (HR=1.04, 95% CI 0.9–1.21).

The nontreatment variables HIV positive (HR=1.67, 95% CI 1.27–2.2) and comorbidity score (HR=1.1, 95% CI 1.07–1.12) were each significantly associated with increased mortality. As previously published in this patient population, obese or overweight BMI at the time of diagnosis was associated with decreased mortality (Carson et al., 2012). Teaching intensity and SES were not significantly associated with mortality.

3.3.1 **Discussion of Cox Analysis of Entire Treated Cohort**

The loss of significance of the race variable during the Cox analysis suggests that differences in the remaining variables were responsible for the survival difference noted between race groups in the previous Kaplan-Meier analysis. Candidate variables would include all that were significant in this analysis except for age, comorbidity, and MGF use, as each of these variables favored black DLBCL patients compared to white patients.

Elevated LDH was the variable with the highest associated hazard of death in this analysis and black patients were more likely to have an elevated LDH at the time of diagnosis. This suggests that black DLBCL patients may have a more aggressive disease process at presentation, which may be responsible for the observed increase in mortality. The B-symptoms were also significantly higher in black patients and remained significantly associated with mortality in the Cox model, suggesting this may also be partially responsible for the increased mortality in black patients.

As might be expected, all of the treatment variables were significantly associated with improved survival. Since MGFs only reduce the risk of treatment-related complications, it is also not surprising that the benefits from their use are seen only within the first three months after diagnosis when treatment-related complications would be most common. Given the importance of the treatment variables for the reduction in mortality (the only independent variables in the survival analysis that were statistically significant and had an HR below one), the additional planned analyses of the factors associated with use of the various treatments is warranted.

Patients who were HIV positive had a significantly increased risk of death. The marked increase in the risk of death and the fact that black patients were six times more likely to have HIV suggest that this is the single biggest explanatory factor for the survival disparity noted in this population. Due to the relationship between both death and black race, HIV positivity is a major confounder in survival analyses of racial disparities in DLBCL. None of the previously published literature on racial disparities in DLBCL identified in the literature review evaluated HIV status due to limitations of the various datasets.

In contrast to previous studies noted in the literature review, SES did not appreciably influence survival. This could be due to the limited power in this relatively small cohort and it does not prove that SES is not associated with a difference in survival. However, the absence of a significant finding provides some modest indirect evidence that SES is less important in a health system that provides universal access.

There were no significant differences in survival based upon the teaching intensity of the institutions where patients received care. At the same time, patients treated at facilities with an unknown degree of affiliation had a significantly worse survival. The unknown category was necessary to protect statistical power for other variables in the cohort and was utilized for a small

number of patients early in the study time period without complete records of the treating station number. The clinical significance of this finding is unclear.

Finally, black patients were more likely to be underweight or normal weight at diagnosis compared to white patients. This is associated with poorer overall survival in DLBCL patients and may represent yet another sign of higher disease aggressiveness or differences in patient ability to tolerate chemotherapy.

3.4 **Univariate Analysis of Dose Intensity**

The baseline characteristics of the cohort of 1,575 patients who received doxorubicin treatment and survived at least five months after treatment initiation, stratified by race, are presented in Table V. Overall, this sub-cohort of patients has similar characteristics to the overall cohort in Table III.

TABLE V

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF US VETERANS DIAGNOSED WITH DLBCL DIAGNOSED 1998 TO 2008 INCLUDED IN LANDMARK ANALYSIS OF ARDI STRATIFIED BY RACE

	Race (N=1,575)		
Demographic and Clinical Characteristics	**White (n=1,384)**	**Black (n=191)**	**P-value**
Age (mean years)	64.5	56.6	<0.0001‡
Sex (Male %)	97.3	95.8	0.2670*
BMI groups (%)			
Underweight	1.5	4.7	
Normal weight	32.9	39.8	
Overweight	38.3	37.2	
Obese	27.3	18.3	0.0004†
Stage (%)			
I/II	45.4	37.2	
III/IV	54.6	62.8	0.0325†
LDH (%)			
Elevated	50.4	60.7	
Normal	38.6	32.5	
Unknown	11.0	6.8	0.0317†
B-symptoms (%)			
Present	47.9	52.4	
Absent	48.3	41.9	
Unknown	3.8	5.8	0.1454*
Comorbidity score (mean)	2.1	1.7	0.0046‡
HIV+ (%)	3.3	19.9	<0.0001*
Rituximab use (%)	76.8	73.8	0.3622*
MGF use (%)	63.7	73.3	0.0089*
Dose intensity (%)			
≥80%	53.5	46.1	
<80%	46.5	53.9	0.0528†
Teaching intensity (%)			
Very Major	55.9	64.4	
Major academic	23.3	25.1	
Minor	12.6	4.7	
Unknown	8.2	5.8	0.0044†

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF US VETERANS DIAGNOSED WITH DLBCL DIAGNOSED 1998 TO 2008 INCLUDED IN LANDMARK ANALYSIS OF ARDI, STRATIFIED BY RACE

Demographic and Clinical Characteristics	Race (N=1,575) White (n=1,384)	Black (n=191)	P-value
SES (%)			
Income quartile I	21.6	37.7	
Income quartile II	24.4	19.4	
Income quartile III	26.1	17.3	
Income quartile IV	25.3	20.4	
Unknown	2.6	5.2	<0.0001†

‡ t-test
* Chi-square test
† Row mean score test

There are significant differences for all of the non-modifiable variables except for sex and B-symptoms. Among the treatment variables, there was significantly increased use of MGFs in black patients and a nonsignificant trend toward decreased dose intensity in black patients. There was no difference in rituximab use. Also consistent with the larger cohort of all treated patients, black patients were more likely to be receive treatment at a VHA facility with the highest level of teaching intensity and were more likely to be in a lower estimated socioeconomic stratum.

3.5 **Cox Analysis of Dose Intensity**

Results of the Cox analysis evaluating survival starting five months after treatment initiation are presented in Table VI. After controlling for baseline variables and ARDI, race was not significantly associated with survival. Patients who received ARDI ≥80% had significantly lower mortality than those who did not (HR=.58; 95% CI 0.47–0.71). The non-modifiable variables (LDH, disease stage, B-symptoms) continued to be associated with increased mortality, while rituximab was associated with decreased mortality. After controlling for ARDI and other variables, there was no difference in survival associated with treatment at an academic center or with SES. In addition, HIV was no longer significantly associated with survival in this model.

TABLE VI

HAZARD RATIOS AND 95% CIS FOR MORTALITY FOR US VETERANS WITH DLBCL DIAGNOSED FROM 1998 TO 2008 AND TREATED WITH DOXORUBICIN

Variable	Hazard Ratio	95% CI	
Race			
White	Reference	------	
Black	1.01	0.83	1.24
Age			
≤24 months			
Age	1.01	1.00	1.02
>24 months			
Age	1.05	1.04	1.07
Stage			
I\II	Reference	------	
III \ IV	1.56	1.32	1.86
LDH			
Normal	Reference	------	
≤24 months			
LDH elevated	2.14	1.71	2.69
LDH unknown	1.36	0.96	1.94
>24 months			
LDH elevated	1.12	0.83	1.51
LDH unknown	1.08	0.68	1.72
B-symptom			
Absent	Reference	------	
≤12 months			
B symptom present	1.58	1.25	2.00
B symptom unknown	1.44	0.88	2.36
>12 months			
B symptom present	0.90	0.71	1.14
B symptom unknown	1.47	0.89	2.42
Rituximab use, yes	0.53	0.44	0.64
ARDI			
ARDI <80%	Reference	------	
≤24 months			
ARDI ≥80%	0.58	0.47	0.71
>24 months			
ARDI ≥80%	0.99	0.74	1.32
MGF use yes	1.12	0.94	1.34

HAZARD RATIOS AND 95% CIS FOR MORTALITY FOR US VETERANS WITH DLBCL DIAGNOSED FROM 1998 TO 2008 AND TREATED WITH DOXORUBICIN

Variable	Hazard Ratio	95% CI	
HIV yes	1.00	0.68	1.47
≤24 months			
Comorbidity score	1.07	1.02	1.11
>24 months			
Comorbidity score	1.18	1.10	1.26
SES			
Income Quartile II	1.07	0.86	1.33
Income Quartile III	1.06	0.84	1.32
Income Quartile IV	1.01	0.81	1.27
Unknown	1.34	0.85	2.13
Teaching Intensity			
Minor	Reference	------	
Very major	0.96	0.74	1.24
Major	0.97	0.73	1.28
Unknown	0.84	0.58	1.23
BMI groups			
Normal weight	Reference	------	
Underweight	1.42	0.89	2.26
Overweight	0.79	0.66	0.95
Obese	0.82	0.66	1.00

3.5.1 **Discussion of Cox Analysis of Dose Intensity**

Many of the associations in this Cox analysis are not unexpected. The ARDI would not be expected to change the associations of rituximab and the non-modifiable baseline variables on mortality. While achieving ARDI ≥80% is important and clearly associated with decreased mortality, even after a landmark analysis there is likely some residual confounding by indication, whereby patients who were healthier tended to receive a higher dose intensity of therapy. While consideration was given to use of methods such as inverse probability weighting and propensity score matching to address these concerns (Cook et al., 2009), these attempts were frustrated by limitations of these methods. For example, while reasonable matching along potentially confounding variables was possible using propensity score methods, doing so markedly decreased the size of the study sample from 1,884 to 1,004, with concurrent decreases in statistical power.

One finding that must be interpreted with caution is the loss of significance of the association between HIV and increased mortality in this model, which will be further discussed in the overall conclusions of the dissertation.

3.6 **Sensitivity Analyses of Dose Intensity**

Additional analyses were performed to evaluate ARDI as a continuous variable and dichotomized at 80%, 85%, and 90%. Ultimately, dichotomization at 80% was chosen for the survival and logistic regression models.

While the negative log-likelihood function was lowest using a continuous ARDI variable, suggesting it was the best fit model, the implicit assumption that one unit of change in ARDI is equally associated with survival regardless of the total treatment dose is counterintuitive. For example, increasing ARDI from 10% to 20% would likely have a different effect than increasing

from 75% to 85%, and previous literature suggests a threshold effect of ARDI on survival in patients with DLBCL (Bosly et al., 2008). Furthermore, use of ARDI as a continuous variable required stratification of the variable at multiple time points, markedly complicating interpretation of results.

When comparing the three dichotomous ARDI variables, the best fitting model was seen with an ARDI cut point of 80%, based on the lowest negative log-likelihood value. While 90% might be expected to be better predictive of survival, relatively few patients achieved this level of treatment intensity in this patient cohort. The a priori thought had been that 85% would be the optimal point for dichotomization, though after this analysis, all analyses of ARDI dichotomized at 80%.

4. RESULTS OF SECONDARY ANALYSES

4.1 Influence of Race on Treatment versus No Treatment

As described in the literature review, Griffiths et al. (2010) reported that black DLBCL patients were less likely to receive treatment than white patients in an analysis of SEER-Medicare linked data. In an effort to ensure that lack of treatment is not a major factor in the survival disparity noted between white and black patients (something not addressed in the survival analyses performed in the preceding section), the baseline characteristics of the 2,163 patients who received treatment within the VHA system were compared to the 449 who had no documentation of treatment inside or outside the VHA system (Table VII). Patients who received no treatment were on average older, and had a higher comorbidity score. They were also more likely to be underweight and have higher LDH. There was no relationship observed between race and treatment in this cohort, suggesting that this is not a major contributor to the survival disparity. Teaching intensity could not reliably be assessed in patients who received no treatment, as treatment location was obtained in conjunction with chemotherapy records. Based on these univariate comparisons, it is unlikely that there are racial disparities in the provision of treatment within the VHA health system.

TABLE VII

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS STRATIFIED BY TREATMENT AMONG US VETRANS DIAGNOSED WITH DLBCL FROM 1998 TO 2008

	Treatment (N=2,612)		
Demographic and Clinical Characteristics	**Yes (n=2,163)**	**No (n=449)**	**P-value**
Age (mean years)	65.0	74.2	<0.0001‡
Sex (Male %)	97.3	97.6	0.7401*
Race (%)			
White	88.1	90	
Black	11.9	10	0.2622*
BMI groups (%)			
Underweight	2.5	7.4	
Normal weight	34.8	37.2	
Overweight	36.5	32.1	
Obese	23.7	15.8	
Unknown	2.5	7.6	<0.0001†
Stage (%)			
I/II	41.2	39.6	
III/IV	57.7	56.6	
Unknown	1.1	3.8	0.8681†
LDH (%)			
Elevated	54.7	43.7	
Normal	34.2	17.8	
Unknown	11.1	38.5	0.0023*
B-symptoms (%)			
Present	50.4	50.1	
Absent	45	37.9	
Unknown	4.6	12	0.1320*
Comorbidity score (mean)	2.3	3.6	<0.0001‡
HIV+ (%)	5.6	4.7	0.4355*
SES (%)			
Income quartile I	24.1	27.4	
Income quartile II	24.2	24.1	
Income quartile III	24.4	23.2	
Income quartile IV	24.3	23.2	
Unknown	3.0	2.2	0.2169†

‡ t-test

* Chi-square test

† Row mean score test

4.2 Influence of Race on Doxorubicin Use

4.2.1 Doxorubicin Background

Doxorubicin is an anthracycline chemotherapeutic agent that has been used in the treatment of DLBCL since the 1970s (McKelvey et al., 1976). While it is still considered one of the most important drugs in the curative intent therapy of this disease, the use of cumulative doses above 450mg/m^2 is associated with nonischemic cardiomyopathy, a serious long-term toxicity (Armitage, 2012). Even at lower doses, some patients will develop cardiomyopathy, particularly those with preexisting cardiac dysfunction (Hershman et al., 2008). Despite this known toxicity, anthracyclines are used in most patients with DLBCL as the benefits of treatment outweigh the long-term risks of cardiac dysfunction.

Another major toxicity associated with doxorubicin (and many chemotherapy drugs) is a temporary reduction in the number of neutrophils, a type of white blood cell (Rabinowitz et al., 2006). Neutrophils are an important component of the immune defense against bacterial infections, and patients with a neutrophil count less than 500/microliter have a significantly increased risk of developing life-threatening infections (Kuderer et al., 2006). To reduce the risk of prolonged neutropenia and subsequent infection, MGFs such as filgrastim are often used to reduce the duration of neutropenia (Crawford et al., 1991). The use of MGFs will be considered further in a subsequent section. Since doxorubicin is a major factor influencing the use of MGFs and they are administered after doxorubicin, we did not consider MGF use in the logistic regression analysis to avoid associations based upon reverse causality (Flegal et al., 2011).

On average, black patients have a lower “normal” range of their neutrophil count in the absence of chemotherapy, though the impact of this on risk of severe infection is unknown (Bain, 1996). It is conceivable that there would be different patterns of use of severely

myelosuppressive agents, such as doxorubicin, in black patients due to concerns about enhanced myeloid toxicity.

4.2.2 **Results of Doxorubicin Analyses**

Univariate comparisons of those who did and did not receive doxorubicin are presented in Table VIII. Patients who did not receive doxorubicin were more likely to be older and have a higher comorbidity score compared to those who did get doxorubicin. Surprisingly, patients who received doxorubicin were also significantly more likely to be HIV positive. There was also a nonsignificant trend toward higher BMI in the patients who received doxorubicin. In addition, patients who received doxorubicin were more likely to receive MGFs. Race was not a significant factor associated with doxorubicin use in the univariate analysis.

TABLE VIII

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS STRATIFIED BY DOXORUBICIN USE AMONG TREATED PATIENTS WITH DLBCL AMONG US VETERANS FROM 1998 TO 2008

	Doxorubicin Use (N=2,163)		
Demographic and Clinical Characteristics	**Yes (n=1,891)**	**No (n=272)**	**P-value**
Age (mean years)	63.9	72.1	<0.0001‡
Sex (Male %)	97.3	97.4	0.8674*
Race (%)			
White	87.8	90.4	
Black	12.2	9.6	0.2054*
BMI groups (%)			
Underweight	2.4	2.2	
Normal weight	34.0	40.8	
Overweight	36.8	34.6	
Obese	24.2	20.6	
Unknown	2.6	1.8	0.0626†
Stage (%)			
I/II	41.5	39.0	
III/ IV	57.3	60.7	
Unknown	1.2	0.4	0.3678†
LDH (%)			
Elevated	54.8	54.0	
Normal	34.6	31.3	
Unknown	10.6	14.7	0.5382*
B-symptoms (%)			
Present	49.9	53.7	
Absent	45.3	43.0	
Unknown	4.8	3.3	0.3517*
Comorbidity score (mean)	2.1	3.4	<0.0001‡
HIV+ (%)	6.0	2.6	0.0204*
Rituximab use (%)	73.6	71.3	0.4360*
MGF use (%)	65.3	41.9	<0.0001*
Teaching Intensity (%)			
Very major	56.4	55.5	
Major	23.0	21.0	
Minor	11.3	12.1	
Unknown	9.4	11.4	0.8643

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS STRATIFIED BY DOXORUBICIN USE AMONG TREATED PATIENTS WITH DLBCL AMONG US VETERANS FROM 1998 TO 2008

	Doxorubicin Use (N=2,163)		
Demographic and Clinical Characteristics	**Yes (n=1,891)**	**No (n=272)**	**P-value**
SES (%)			
Income quartile I	24.1	24.6	
Income quartile II	23.5	29.0	
Income quartile III	24.7	22.4	
Income quartile IV	24.6	21.7	
Unknown	3.1	2.2	0.2†

‡ t-test
* Chi-square test
† Row mean score test

Results of the logistic regression analysis are presented in Table IX. Age and comorbidity score continued to be significantly negatively associated with doxorubicin use. Patients who did not have LDH measurements available for analysis were also less likely to receive doxorubicin. All of the other variables were not significant.

TABLE IX

ODDS RATIOS AND 95% CIS FOR DOXORUBICIN USE AMONG PATIENTS WITH DLBCL DIAGNOSED AMONG US VETERANS FROM 1998 TO 2008

Variable	Odds ratio	95% CI	
Race			
White	Reference	------	
Black	0.80	0.50	1.29
Age	0.95	0.93	0.96
Stage			
I/II	Reference	------	
III/IV	0.89	0.67	1.19
Unknown	2.00	0.26	15.46
BMI groups			
Normal weight	Reference	------	
Underweight	1.19	0.48	2.96
Overweight	1.29	0.95	1.77
Obese	1.26	0.87	1.83
Unknown	1.39	0.51	3.77
Comorbidity score	0.83	0.79	0.88
HIV yes	0.85	0.37	1.99
LDH			
Normal	Reference	------	
Elevated	0.89	0.65	1.21
Unknown	0.59	0.38	0.91
B-symptoms			
Absent	Reference	------	
Present	0.91	0.68	1.20
Unknown	1.20	0.57	2.55
Teaching Intensity			
Minor	Reference	------	
Very major	1.05	0.68	1.62
Major	1.28	0.79	2.08
Unknown	0.84	0.48	1.47
SES			
Income quartile I	Reference	------	
Income quartile II	0.84	0.58	1.22
Income quartile III	1.07	0.73	1.59
Income quartile IV	1.16	0.78	1.73
Unknown	1.28	0.51	3.20

4.2.3 **Discussion of Doxorubicin Results**

Despite previous evidence that black patients may have a higher risk of doxorubicin associated cardiomyopathy (Hershman et al., 2008), we found no evidence of a systematic difference in the use of doxorubicin based upon race. The statistically significant finding in this cohort that older patients and those with a higher comorbidity score were less likely to receive doxorubicin was not surprising, as these factors weigh heavily in clinical decisions to use doxorubicin (Pfreundschuh, 2010). Previous literature has demonstrated that at the time of DLBCL diagnosis black patients generally are younger than white patients (Shenoy et al., 2011a). A similar observation was made in this cohort, as highlighted in Table III. In addition, after excluding HIV, black patients in this cohort had a lower mean comorbidity score. Considering the significant inverse relationship between age and comorbidities and the use of doxorubicin, it is not surprising that there was no observed difference in doxorubicin use based upon race. Based on anecdotal observation that many of the patients who received doxorubicin were treated with the CHOP regimen, an additional analysis was performed to confirm that 1,774 of the 1,891 doxorubicin treated patients (94%) received CHOP. Thus, doxorubicin use is a reasonable surrogate for CHOP treatment in this population.

4.3 **Influence of Race on Myeloid Growth Factor Use**

4.3.1 **Background on Myeloid Growth Factors**

The MGFs filgrastim and sargramostim were approved by the Food and Drug Administration in 1991 to reduce the risk of febrile neutropenia when administered after chemotherapy. In 2002, a sustained release formulation of filgrastim was also approved, simplifying administration (United States Food and Drug Administration, 2013). There is little evidence to support use of one drug over another, so for the purposes of this analysis they were

considered interchangeably as a drug class that will be described as the MGFs. While there is no single study that supports a survival advantage for lymphoma patients who receive MGFs, data from a meta-analysis of 61 trials supports a modest survival benefit in patients with cancer (Lyman et al., 2013). As a patented biologic medication produced with recombinant DNA technology, these drugs add significantly to the cost of care for patients, with an average sales price of $3,120.22 to $4,585.07 for the approved doses of the MGFs (Centers for Medicare and Medicaid Services, 2013), which are often delivered with each cycle of chemotherapy (Rabinowitz et al., 2006).

Given the high cost of the MGFs, clinical practice guidelines suggest their use should be considered in patients receiving CHOP-based chemotherapy, but is not recommended for all patients uniformly (National Comprehensive Cancer Network, 2013). Thus, the decision is left to the patient and his or her physician, potentially allowing the development of bias in the use of these drugs.

Since MGFs are prescribed after chemotherapy treatment, choice of chemotherapy may have a significant influence on the decision to use MGFs. Thus, doxorubicin and rituximab use were considered in both the univariate and logistic regression analyses of MGF use.

4.3.2 **Results of Myeloid Growth Factor Analyses**

Among the 2,163 patients who received treatment, 1,348 (62%) received MGFs. Baseline characteristics of these patients stratified by MGF use are presented in Table X. On univariate analysis, compared to patients who did not receive MGFs, patients who received MGFs tended to have the following characteristics: older age, more advanced stage, black race, elevated LDH, B-symptoms present, higher comorbidity score, more likely to receive rituximab, more likely to receive doxorubicin, and HIV positive. Patients who received MGFs were also more likely to have a lower BMI and come from a higher estimated socioeconomic quartile.

TABLE X

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS STRATIFIED BY MGF USE AMONG TREATED PATIENTS WITH DLBCL AMONG US VETERANS FROM 1998 TO 2008

	MGF (N=2,163)		
Demographic and Clinical Characteristics	**Yes (n=1,348)**	**No (n=815)**	**P-value**
Age (mean years)	65.6	64.0	0.0035‡
Sex (Male %)	97.3	97.3	0.9499*
Race (%)			
White	86.7	90.4	
Black	13.3	9.6	0.0098*
BMI groups (%)			
Underweight	2.7	2.0	
Normal weight	35.8	33.3	
Overweight	37.6	34.7	
Obese	22.0	26.6	
Unknown	1.9	3.4	0.0190†
Stage (%)			
I/II	37.2	47.7	
III/ IV	61.4	51.7	
Unknown	1.3	0.6	<0.0001†
LDH (%)			
Elevated	58.5	48.5	
Normal	32.0	37.9	
Unknown	9.6	13.6	0.0002†
B-symptoms (%)			
Present	53.4	45.4	
Absent	42.3	49.5	
Unknown	4.3	5.2	0.0005*
Comorbidity score (mean)	2.3	2.1	0.0339‡
Rituximab use (%)	77.7	66.0	<0.0001*
Doxorubicin use (%)	91.5	80.6	<0.0001*
HIV+ (%)	7.6	2.3	<0.0001*
Dose intensity (%)			
≥ 80%	39.5	37.6	
<80%	57.2	58.9	
Unknown	3.3	3.6	0.3802†
Teaching Intensity (%)			
Very Major	58.7	52.3	
Major academic	24.9	19.0	
Minor	11.4	11.3	
Unknown	5.0	17.4	0.9768†

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS STRATIFIED BY MGF USE AMONG TREATED PATIENTS WITH DLBCL AMONG US VETERANS FROM 1998 TO 2008

Demographic and Clinical Characteristics	MGF (N=2,163) Yes (n=1,348)	No (n=815)	P-value
SES (%)			
Income quartile I	24.1	24.2	
Income quartile II	22.6	26.9	
Income quartile III	23.4	26.0	
Income quartile IV	27.0	20.0	
Unknown	2.8	3.2	0.0156†

‡ t-test
* Chi-square test
† Row mean score test

Results of the logistic regression analysis are presented in Table XI. Positive associations with MGF use were seen with higher age, advanced stage, higher comorbidity score, HIV positive, elevated LDH. The only variable significantly associated with reduced odds of receiving MGF was receipt of care at a facility where the teaching intensity could not be determined. A nonsignificant trend toward greater MGF use was seen in black patients (OR=1.34, p=.07) those from the highest estimated socioeconomic quartile (OR=1.3, p=.07), and those with systemic B-symptoms (OR=1.21, p=.06).

TABLE XI

ODDS RATIOS AND 95% CIS FOR MGF USE AMONG PATIENTS WITH DLBCL DIAGNOSED AMONG US VETERANS FROM 1998 TO 2008

Variable	Odds ratio	95% CI	
Race			
White	Reference	------	
Black	1.34	0.98	1.86
Age	1.02	1.02	1.03
Stage			
I/II	Reference	------	
III/IV	1.33	1.09	1.62
Unknown	2.38	0.83	6.84
BMI groups			
Normal weight	Reference	------	
Underweight	1.07	0.56	2.06
Overweight	0.99	0.79	1.24
Obese	0.83	0.65	1.07
Unknown	1.03	0.56	1.90
Comorbidity score	1.06	1.01	1.12
HIV yes	4.86	2.80	8.42
LDH			
Normal	Reference	------	
Elevated	1.31	1.06	1.62
Unknown	0.87	0.64	1.20
B-symptoms			
Absent	Reference	------	
Present	1.21	0.99	1.48
Unknown	0.94	0.58	1.51
Doxorubicin use yes	3.45	2.58	4.59
Rituximab use yes	1.57	1.25	1.97
Teaching Intensity			
Minor	Reference	------	
Very major	0.93	0.69	1.26
Major	1.12	0.80	1.58
Unknown	0.30	0.20	0.45
SES			
Income quartile I	Reference	------	
Income quartile II	0.83	0.63	1.08
Income quartile III	0.91	0.70	1.19
Income quartile IV	1.30	0.98	1.71
Unknown	0.82	0.46	1.46

4.3.3 **Discussion of Myeloid Growth Factor Analyses**

Some of the factors associated with MGF are relatively intuitive, based on existing notions of those who are at greatest risk for the development of infectious complications following chemotherapy administration. The variables most strongly associated with MGF use were HIV positivity and doxorubicin use. This suggests a rational heightened concern about infectious toxicity in those known to be immune suppressed by HIV and those receiving doxorubicin as part of their treatment regimen. Similarly, those with elevated LDH, advanced stage, and higher comorbidity score were more likely to receive MGF, suggesting that those with a more severe disease presentation and worse overall clinical status were also more likely to receive MGF. Finally, advanced age was associated with MGF use. This suggests adherence to treatment guidelines that recommend MGFs for patients over age 65 receiving R-CHOP (National Comprehensive Cancer Network, 2013).

Two additional findings of interest were the nonsignificant associations between black race, higher SES, and MGF use. There was no race-based bias against black patients in the use of MGFs, though it is unclear why race might be independently associated with increased MGF utilization. One possible explanation is the lower mean neutrophil count observed in the black population, as this might heighten concern for the development of febrile neutropenia (Bain, 1996). An association between higher MGF use and higher SES is more easily explained by the known relationship between SES and cancer treatment selection (Greenberg et al., 1988). What is interesting about this finding is that it persists even in an equal-access setting like the VHA, suggesting that unequal provision of care may persist even after full implementation of legislation designed to provide equal access, such as the Affordable Care Act.

The reason that unknown teaching intensity may be associated with decreased MGF utilization may be related to an artifact in the dataset. The station number where each patient

received treatment was obtained in conjunction with administrative data on chemotherapy administration, available only after October 2002. While individual chart review allowed collection of this information for some of the patients diagnosed from 1998 to 2002, in some cases a reliable match could not be made with the affiliate inpatient treatment facility. Thus, the patients who received care at institutions with unknown teaching intensity were largely ones who were treated early in the study time frame. In the early part of the study, prophylaxis was typically recommended when the expected risk of febrile neutropenia was 40% (Calhoun et al., 2005). In 2006, this standard was relaxed to a 20% risk (Smith et al., 2006). Thus, this finding may be related to a more liberal standard for the use of MGF over time that resulted in increased use for patients diagnosed and treated later in the study time frame, when complete information on the treating station was available.

4.4 **Influence of Race on Rituximab Use**

4.4.1 **Rituximab Specific Background**

Rituximab is a chimeric, anti-CD20 monoclonal antibody approved in 1997 for the treatment of B-cell NHLs (Dotan et al., 2010). The first study supporting its routine use in diffuse large B-cell lymphoma was published in early 2002 (Coiffier et al., 2002). While rituximab has rarely been associated with severe toxicities (Byrd et al., 1999), the overall favorable toxicity profile and high therapeutic index have resulted in its routine incorporation into combination treatment regimens for most patients with B-cell lymphomas. One exception has been in patients with HIV, as early data suggested higher infectious toxicity in patients with HIV-related lymphomas (Kaplan et al., 2005). Subsequent literature has suggested that rituximab is effective for these patients, though rituximab is still withheld for some patients with severe preexisting immunosuppression related to HIV (Levine, 2010; Sparano et al., 2010).

As a biologic medication for which no competing generic equivalent has been approved, rituximab is the most expensive component of the R-CHOP chemotherapy regimen. As of October 2013, the Centers for Medicaid and Medicare Services payment allowance limits for Medicare part B drugs listed an upper payment limit of $678.70 for a 100mg vial of rituximab (Centers for Medicare and Medicaid Services, 2013). The standard dose of rituximab is 375mg/m^2 resulting in a total dose of approximately 700mg for an average-sized man with a body surface area of 1.9 m^2 (Sacco et al., 2010). This results in an average sales price of $4,750.90 for each dose of rituximab, or a total average sales price of $28,505.40 for the rituximab in six cycles of R-CHOP chemotherapy. In contrast, using the Centers for Medicare and Medicaid Services upper payment limit, BSA of 1.9 m^2, and standard doses of cyclophosphamide (750mg/m2), doxorubicin (50mg/m2), and vincristine (2mg flat dose), the average sales price of the infused drugs contained in six cycles of CHOP without rituximab is $3,577.74 (Centers for Medicare and Medicaid Services, 2013). Thus, each dose of rituximab is more expensive than the rest of the chemotherapy drug costs combined across all cycles.

4.4.2 **Results of Rituximab Analyses**

The baseline characteristics of the 2,163 patients who received treatment, stratified by rituximab use are presented in Table XII. Race was not significant in this analysis. Univariate analyses demonstrated that the patients who received rituximab were significantly older, had higher BMI, higher stage, and higher comorbidity score. Patients who received rituximab were also less likely to be HIV positive.

TABLE XII

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS STRATIFIED BY RITUXIMAB USE AMONG TREATED PATIENTS WITH DLBCL AMONG US VETERANS FROM 1998 TO 2008

	Rituximab Use (N=2,163)		
Demographic and Clinical Characteristics	**Yes (n=1,585)**	**No (n=578)**	**P-value**
Age (mean years)	65.5	63.6	0.0018‡
Sex (Male %)	97.3	97.2	0.9444*
Race (%)			
White	88.6	86.9	
Black	11.4	13.1	0.2714
BMI groups (%)			
Underweight	2.3	2.8	
Normal weight	34.8	35.0	
Overweight	37.4	34.1	
Obese	25.0	20.2	
Unknown	0.5	8.0	<0.0001†
Stage (%)			
I/II	39.3	46.4	
III/ IV	59.6	52.8	
Unknown	1.1	0.9	0.0036*
LDH (%)			
Elevated	54.8	54.5	
Normal	35.1	31.7	
Unknown	10.1	13.8	0.3555*
B-symptoms (%)			
Present	51.3	47.9	
Absent	46.5	40.8	
Unknown	2.2	11.3	0.5436*
Comorbidity score (mean)	2.3	2.1	0.0156‡
HIV+ (%)	3.3	11.9	<0.0001*
Doxorubicin use (%)	87.8	86.5	0.4360*
Teaching Intensity (%)			
Very Major	59.9	46.2	
Major academic	23.8	19.7	
Minor	11.7	10.4	
Unknown	4.5	23.7	0.3536†

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS STRATIFIED BY RITUXIMAB USE AMONG TREATED PATIENTS WITH DLBCL AMONG US VETERANS FROM 1998 TO 2008

	Rituximab Use (N=2,163)		
Demographic and Clinical Characteristics	**Yes (n=1,585)**	**No (n=578)**	**P-value**
SES (%)			
Income quartile I	22.7	28.0	
Income quartile II	24.6	23.2	
Income quartile III	24.9	23.2	
Income quartile IV	24.9	22.7	
Unknown	3.0	2.9	0.1563†

‡ t-test
* Chi-square test
† Row mean score test

Logistic regression was performed on the entire treated cohort and is presented in Table XIII. While advanced stage was significantly associated with rituximab use, the dominating significant variable was diagnosis after January 1, 2002 (OR=35; 95% CI 25.9–48). A nonsignificant trend associated with increased rituximab use was associated with care at centers with the highest teaching intensity (OR=1.45, p=.09). Unknown B-symptoms and unknown BMI were significantly associated with decreased odds of rituximab use.

TABLE XIII

ODDS RATIOS AND 95% CIS FOR RITUXIMAB USE AMONG PATIENTS WITH DLBCL DIAGNOSED AMONG US VETERANS FROM 1998 TO 2008

Variable	Odds ratio	95% CI	
Race			
White	Reference	------	
Black	1.25	0.81	1.93
Age	1.00	0.99	1.01
Stage			
I/II	Reference	------	
III/IV	1.41	1.06	1.87
Unknown	3.42	0.85	13.78
BMI groups			
Normal weight	Reference	------	
Underweight	1.36	0.60	3.11
Overweight	0.94	0.68	1.28
Obese	1.14	0.78	1.65
Unknown	0.28	0.10	0.76
Comorbidity score	1.00	0.93	1.07
HIV yes	0.10	0.06	0.16
LDH			
Normal	Reference	------	
Elevated	0.94	0.69	1.28
Unknown	0.79	0.51	1.24
B-symptoms			
Absent	Reference	------	
Present	0.88	0.66	1.18
Unknown	0.51	0.27	0.95
Teaching Intensity			
Minor	Reference	------	
Very major	1.45	0.95	2.22
Major	1.22	0.76	1.96
Unknown	0.80	0.45	1.41
SES			
Income quartile I	Reference	------	
Income quartile II	1.19	0.81	1.75
Income quartile III	1.16	0.79	1.71
Income quartile IV	1.15	0.78	1.69
Unknown	1.27	0.56	2.89
Diagnosis 2002 and after	35.3	25.9	48

The finding that diagnosis after 2002 was the most important variable associated with rituximab use in the entire treated cohort of 2,163 patients was anticipated a priori and prompted a preplanned subanalysis of the 1,672 patients diagnosed and treated after January 1, 2002. The baseline demographics of the sub-cohort are presented in Table XIV, stratified by rituximab use. In univariate analyses, patients who did not receive rituximab were significantly more likely to be black, younger age, have a lower BMI, higher LDH, more likely to be HIV positive, and less likely to be obese.

TABLE XIV

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS STRATIFIED BY RITUXIMAB USE AMONG TREATED PATIENTS WITH DLBCL AMONG US VETERANS FROM 2002 TO 2008

	Rituximab Use (N=1,672)		
Demographic and Clinical Characteristics	**Yes (n=1,494)**	**No (n=178)**	**P-value**
Age (mean years)	65.6	62.6	0.0065‡
Sex (Male %)	97.4	97.8	0.7723*
Race (%)			
White	88.9	81.5	
Black	11.1	18.5	0.0038*
BMI groups (%)			
Underweight	2.1	3.9	
Normal weight	34.5	40.5	
Overweight	37.6	38.2	
Obese	25.4	16.3	
Unknown	0.3	1.1	0.0036†
Stage (%)			
I/II	39.3	43.8	
III/IV	59.6	55.6	
Unknown	1.1	0.6	0.2645†
LDH (%)			
Elevated	54.0	61.8	
Normal	36.1	25.8	
Unknown	9.8	12.4	0.0102†
B-symptoms (%)			
Present	51.3	53.9	
Absent	46.7	42.1	
Unknown	2.1	3.9	0.1886*
Comorbidity score (mean)	2.3	2.1	0.1915‡
HIV+ (%)	3.4	23.6	<0.0001*
MGF use (%)	66.8	62.4	0.2630*
Doxorubicin use (%)	87.6	85.4	0.3983
Teaching Intensity (%)			
Very Major	60.8	52.8	
Major academic	24.2	24.2	
Minor	12.0	14.6	
Unknown	3.1	8.4	0.1416†

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS STRATIFIED BY RITUXIMAB USE AMONG TREATED PATIENTS WITH DLBCL AMONG US VETERANS FROM 2002 TO 2008

	Rituximab Use (N=1,672)		
Demographic and Clinical Characteristics	**Yes (n=1,494)**	**No (n=178)**	**P-value**
SES (%)			
Income quartile I	22.4	27.0	
Income quartile II	24.8	20.2	
Income quartile III	24.6	26.4	
Income quartile IV	25.3	23.0	
Unknown	3.0	3.4	0.4100†

‡ t-test
* Chi-square test
† Row mean score test

Logistic regression analysis of patients diagnosed after 2002 is presented in Table XV. After controlling for other variables, black race was no longer significant. The most striking finding was that patients who were HIV positive were 10 times less likely to receive rituximab than those who were HIV negative (OR=.1; 95% CI 0.06–0.18). Other variables significantly associated with decreased use of rituximab were elevated LDH, and treatment at a site of unknown teaching intensity. Higher stage was significantly associated with rituximab use, while treatment at a facility with the highest teaching intensity demonstrated a nonsignificant trend towards increased use of rituximab (OR=1.57, p=.07).

TABLE XV

ODDS RATIOS AND 95% CIS FOR RITUXIMAB USE AMONG PATIENTS WITH DLBCL DIAGNOSED AMONG US VETERANS FROM 2002 TO 2008.

Variable	Odds ratio	95% CI	
Race			
White	Reference	------	
Black	1.05	0.63	1.77
Age	1	0.99	1.02
Stage			
I/II	Reference	------	
III/IV	1.50	1.05	2.12
Unknown	3.61	0.41	31.63
BMI groups			
Normal weight	Reference	------	
Underweight	1.14	0.43	3.04
Overweight	0.97	0.67	1.42
Obese	1.53	0.94	2.49
Unknown	0.40	0.07	2.28
Comorbidity score	0.99	0.91	1.07
HIV yes	0.10	0.06	0.18
LDH			
Normal	Reference	------	
Elevated	0.61	0.41	0.90
Unknown	0.58	0.33	1.02
B-symptoms			
Absent	Reference	------	
Present	0.95	0.67	1.35
Unknown	0.98	0.36	2.68
Teaching Intensity			
Minor	Reference	------	
Very major	1.57	0.96	2.58
Major	1.29	0.75	2.24
Unknown	0.46	0.21	0.97
SES			
Income quartile I	Reference	------	
Income quartile II	1.34	0.82	2.18
Income quartile III	0.99	0.62	1.57
Income quartile IV	1.28	0.80	2.07
Unknown	1.09	0.41	2.90

4.4.3 **Discussion of Rituximab Results**

While the first results of clinical trials comparing R-CHOP to CHOP were presented as early as 2000 (Sehn, 2010), incorporation of rituximab into routine practice did not occur until early 2002 or even later, after the publication of several seminal articles (Coiffier et al., 2002; Habermann et al., 2006; Pfreundschuh et al., 2008). Likely due to the high cost of rituximab, wide-spread early adoption of this intervention did not occur despite the preliminary evidence supporting improved PFS and OS in DLBCL patients who received rituximab. The importance of this finding is that it demonstrates how the change in the standard of care during the study period initially masked a univariate finding of an association between race and rituximab use. Based upon the knowledge of the change in standard of care, the year of diagnosis variable was included in the analysis of the entire cohort, which was highly significant, justifying analysis of the smaller sub-cohort diagnosed after January 1, 2002.

Within the cohort diagnosed after January 1, 2002, race was highly significant on univariate analysis but was not significantly associated with rituximab use after controlling for other variables, most notably HIV. The higher frequency of HIV seen in black patients is likely driving the univariate finding that black patients were less likely to receive rituximab. What initially appeared to be a racial disparity in rituximab use was an artifact related to a higher prevalence of HIV in black patients diagnosed with DLBCL, which in turn is related to the higher prevalence of HIV in the African American population (Orkin and Zon, 2008). Instead of representing racial bias in rituximab use, this observation was instead due to proper application of the evidence circa 2005 that suggested worse outcomes in patients with HIV and DLBCL who were treated with rituximab and chemotherapy compared to chemotherapy alone (Kaplan et al., 2005). While these results from a system with relatively equal insurance access may not be representative of the larger population of DLBCL, this finding does suggest that the racial

disparity in the use of immunotherapy described by other authors may be attributable to race-based differences in HIV (Flowers et al., 2012; Shih et al., 2009). Attempts were made to evaluate rituximab use in patients with HIV at various points in time relative to the shifting landscape of treatment recommendations in this subpopulation, but ultimately no conclusions could be drawn due to small patient numbers.

The observed trend toward increased rituximab use in patients treated at centers with the highest teaching intensity may be explained by a more rapid implementation of new clinical findings at major academic medical centers. The significantly lower odds of rituximab use seen for those patients treated at facilities with unknown teaching intensity is likely explained by the fact that these patients were primary diagnosed between January and September of 2002, shortly after publication of the first major trial demonstrating survival benefit from rituximab in patients with DLBCL.

4.5 **Influence of Race on Treatment Dose Intensity**

4.5.1 **Background on Dose Intensity**

Previous research in a number of malignancies including breast cancer and diffuse large B-cell lymphoma has demonstrated that higher treatment dose intensity is associated with improved survival (Bosly et al., 2008). A natural extrapolation of this finding was the exploration of dose-dense chemotherapy regimens that further increased dose intensity. Dose-dense CHOP is administered every 14 days instead of every 21 days, and in the era before rituximab was associated with improved overall survival (Pfreundschuh et al., 2004). Two subsequent large randomized studies evaluating dose-dense R-CHOP (every 14 days) demonstrated no difference in PFS or OS when compared to R-CHOP given on a standard schedule (every 21 days) (Cunningham et al., 2013; Delarue et al., 2013). In the United States,

dose-dense chemotherapy for DLBCL has never been adopted as standard of care. As described in the methods, ARDI was evaluated assuming a 21-day administration schedule among the patients who received doxorubicin therapy.

4.5.2 **Results of Dose Intensity Analysis**

The baseline characteristics of the 1,575 patients who received doxorubicin and survived more than five months after treatment initiation are presented in Table XVI, stratified by ARDI. On univariate analysis, compared to patients who received ARDI ≥80%, those who received ARDI <80% were more likely to be older, have advanced-stage disease, have systemic B-symptoms, have more comorbidities, were more likely to have HIV, less likely to receive rituximab, less likely to be treated at an institution with the highest teaching intensity, and were more likely to be from lower estimated income socioeconomic strata. While not statistically significant, patients receiving lower ARDI were slightly more likely to be black.

TABLE XVI

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS STRATIFIED BY ARDI AMONG TREATED PATIENTS WITH DLBCL AMONG US VETERANS FROM 1998 TO 2008

	ARDI (N=1,575)		
Demographic and Clinical Characteristics	**≥ 0.80 (n=829)**	**<0.80 (n=746)**	**P-value**
Age (mean years)	61.2	66.1	<0.0001‡
Sex (Male %)	96.7	97.5	0.4034*
Race (%)			
White	89.4	86.2	
Black	10.6	13.8	0.0527*
BMI groups (%)			
Underweight	1.5	2.4	
Normal weight	33.4	34.1	
Overweight	39.6	36.6	
Obese	25.6	26.9	0.7713†
Stage (%)			
I/II	47.3	41.2	
III/ IV	52.7	58.9	0.0145†
LDH (%)			
Elevated	50.1	53.5	
Normal	39.8	35.7	
Unknown	10.1	10.9	0.1032*
B-symptoms (%)			
Present	45.5	51.7	
Absent	51.9	42.8	
Unknown	2.7	5.5	0.0018*
Comorbidity score (mean)	1.7	2.4	<0.0001‡
HIV+ (%)	3.3	7.5	0.0002*
Rituximab use (%)	79.1	73.5	0.0081*
MGF use (%)	63.2	66.6	0.1567*
Teaching Intensity (%)			
Very Major	60.2	53.4	
Major academic	22.8	24.3	
Minor	10.5	12.9	
Unknown	6.5	9.5	0.0241†

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS STRATIFIED BY ARDI AMONG TREATED PATIENTS WITH DLBCL AMONG US VETERANS FROM 1998 TO 2008

	ARDI (N=1,575)		
Demographic and Clinical Characteristics	**≥ 0.80 (n=829)**	**<0.80 (n=746)**	**P-value**
SES (%)			
Income quartile I	21.8	25.5	
Income quartile II	23.0	24.7	
Income quartile III	25.6	24.4	
Income quartile IV	26.3	22.9	
Unknown	3.3	2.6	0.0315†

‡ t-test
* Chi-square test
† Nonzero Correlation test

Logistic regression results are presented in Table XVII. Patients who were black, older, had advanced stage disease, HIV positive, and had systemic B-symptoms all had reduced odds of receiving treatment with ARDI ≥80%. Only treatment at a center with the highest teaching intensity was associated with significantly increased odds of receiving ARDI ≥80% (OR=1.62; 95% CI 1.15–2.28). In addition, being in the highest socioeconomic quartile was associated with a nonsignificant trend toward increased odds of receiving ARDI ≥80%.

TABLE XVII

ODDS RATIOS AND 95% CIS FOR ARDI 80 AMONG PATIENTS WITH DLBCL DIAGNOSED AMONG US VETERANS FROM 1998 TO 2008

Variable	Odds ratio	95% CI	
Race			
White	Reference	------	
Black	0.62	0.44	0.87
Age	0.96	0.95	0.97
Stage			
I/II	Reference	------	
III/IV	0.81	0.64	1.01
BMI groups			
Normal weight	Reference	------	
Underweight	0.71	0.32	1.57
Overweight	1.03	0.80	1.32
Obese	0.80	0.61	1.07
Comorbidity score	0.89	0.84	0.94
HIV yes	0.24	0.14	0.40
LDH			
Normal	Reference	------	
Elevated	0.89	0.71	1.13
Unknown	0.85	0.59	1.23
B-symptom			
Absent	Reference	------	
Present	0.74	0.59	0.93
Unknown	0.48	0.27	0.85
Teaching Intensity			
Minor	Reference	------	
Very major	1.62	1.15	2.28
Major	1.35	0.92	1.97
Unknown	0.79	0.49	1.29
SES			
Income quartile I	Reference	------	
Income quartile II	1.07	0.79	1.45
Income quartile III	1.09	0.80	1.48
Income quartile IV	1.31	0.97	1.78
Unknown	1.39	0.72	2.67

4.5.3 **Discussion of Dose Intensity Analysis**

Unlike the other treatment variables, after controlling for the a priori identified variables, black patients were significantly less likely to receive ARDI of 80%. The reasons for this difference are unclear and warrant additional investigation that goes beyond the scope of this dissertation, but this finding is consistent with previous reports in breast cancer (Griggs et al., 2003; Smith et al., 2005). In those studies, toxicities were similar in black and white patients receiving adjuvant chemotherapy for breast cancer, but dose reductions were more common in black patients. Another study in breast cancer demonstrated that black race was independently associated with nonadherence to chemotherapy (Barcenas et al., 2012). It is also possible that there is poorer tolerance of chemotherapy in black patients, resulting in dose reductions and delays. While there is no evidence to support this theory, there is evidence refuting this idea in another malignancy. Among cervical cancer patients treated with platinum-based chemotherapy, black patients tolerated chemotherapy better than white patients (Plaxe et al., 2008).

The observation that patients who were older, had more comorbidities, or had HIV were less likely to receive ARDI ≥80% is somewhat less surprising. Toxicities such as febrile neutropenia are a frequent cause of dose reduction and dose delay. Advanced age has long been associated with increased chemotherapy toxicity, secondary to age-related decline in organ function and decreased physiologic reserve (Repetto, 2003). Similarly, higher degrees of comorbidity and HIV are associated with increased chemotherapy toxicity (Lee et al., 2011; Petrich et al., 2012).

The association between advanced-stage disease and B-symptoms with lower dose intensity is also somewhat difficult to explain. In a previous large study of patients with DLBCL, advanced stage was an independent predictor of lower dose intensity (Lyman et al., 2004). Therefore it stands to reason that B-symptoms would also be associated with lower dose

intensity, as it is often a second surrogate marker of disease burden and aggressiveness. However, another study of lymphoma patients suggested that advanced-stage disease and B-symptoms are not significantly associated with the risk of febrile neutropenia, which would be the major toxicity expected to decrease dose intensity (Lyman and Delgado, 2003).

The significant association between chemotherapy ARDI and treatment at institutions with a higher degree of teaching intensity has not been reported previously. It is possible that physicians at major academic VHA medical centers may be subspecialized in the management of lymphoma and more likely to insist upon higher-dose-intensity treatment, but measurement of this would be challenging and goes beyond the scope of this dissertation.

5. CONCLUSIONS

5.1 HIV and Race-Based Survival Disparity

A major finding from this study is that the racial disparity in survival noted in the baseline analyses of the entire cohort of treated patients can be largely explained by race-based differences in HIV prevalence. This observation prompted generation of age- and HIV-adjusted survival curves, which are presented in Figure 6. After adjustment for HIV, there was no significant survival difference based upon race (HR=1.1; 95% CI 0.91–1.33). Similarly, age-adjusted survival curves stratified by race and HIV status suggest increased mortality in all those who were HIV positive, regardless of race, but no difference in outcome based upon race alone, as presented in Figure 7.

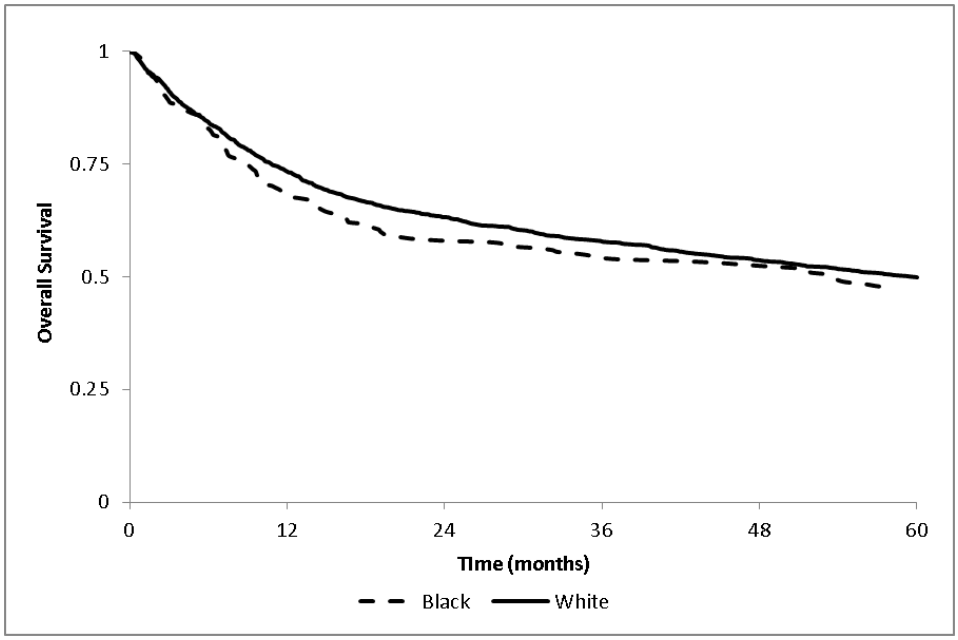

Figure 6. Age and HIV adjusted OS in US veterans with DLBCL diagnosed and treated 1998 to 2008, stratified by race.

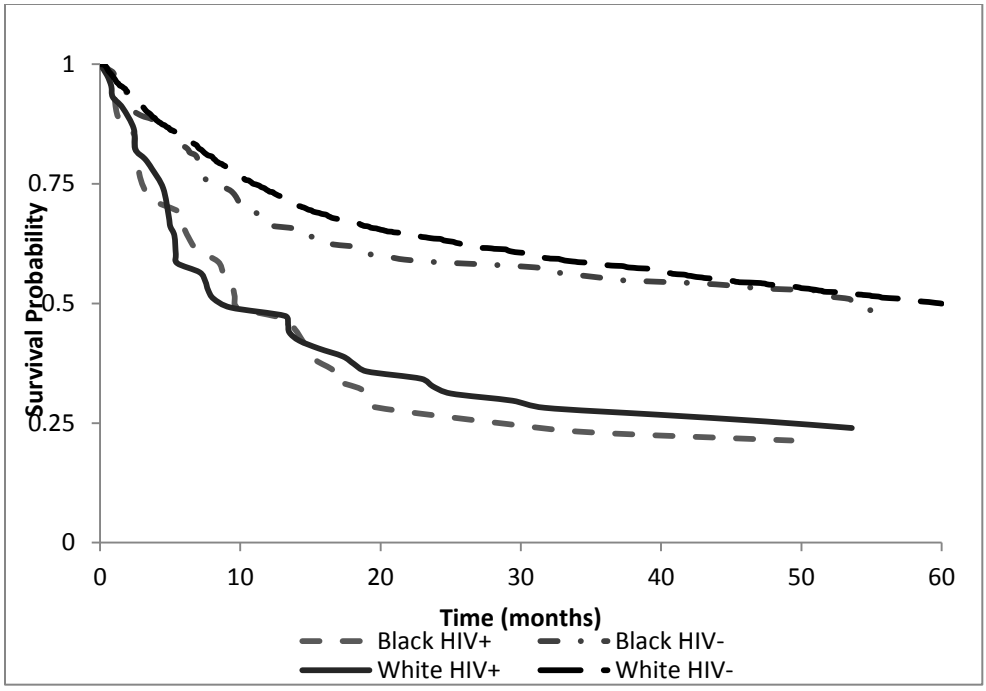

Figure 7. Age-adjusted OS in US veterans with DLBCL diagnosed and treated 1998 to 2008, stratified by race and HIV status.

Advancements in the treatment of HIV with highly active antiretroviral therapy have improved survival for patients with HIV-related lymphoma compared to patients who do not receive antiretroviral therapy (Vaccher et al., 2003). Unfortunately, survival remains worse for HIV-positive lymphoma patients who receive antiretroviral treatment compared to HIV-negative lymphoma patients (Chao et al., 2010). A diagnosis of HIV increases the risk of all-cause mortality in patients with lymphoma, and a CD4-positive lymphocyte count of <200 cells/microliter or prior Acquired Immune Deficiency Syndrome (AIDS)-defining illness are associated with an increased risk of lymphoma-specific mortality. Thus, early antiretroviral

treatment in an effort to protect CD4 counts and reduce the risk of AIDS-defining illness is essential.

Reducing the element of the race-based survival disparity in DLBCL that is directly attributable to HIV will require earlier detection and treatment of HIV. While this is being attempted with the recommendation from the US Preventive Services Task Force that all adults aged 15–65 years undergo HIV screening, benefits from the approach will likely not be evident in population-based studies for a number of years (Moyer, 2013). In a post-hoc analysis of the 121 HIV-positive patients in this cohort, 82 (68%) were diagnosed with HIV more than six months before DLBCL, 17 (14%) were diagnosed within six months before the DLBCL diagnosis, and 22 (18%) were diagnosed after the DLBCL diagnosis. Thus, up to one-third of the HIV-positive subgroup may have had a better outcome if their disease been detected earlier.

In the near term, efforts to ensure HIV screening of patients with newly diagnosed DLBCL, as supported by practice guidelines from the National Comprehensive Cancer Network, are advisable (National Comprehensive Cancer Network, 2012). Such an approach will allow for initiation of antiretroviral therapy during chemotherapy treatment, with the associated improvements in outcome (Ratner et al., 2001).

One related finding that deserves further exploration was that among the patients included in the landmark analysis of survival, controlling for ARDI made HIV a nonsignificant variable (HR=1; 95% CI 0.68–1.47). When this observation is considered prima facie, it would suggest that treatment with full-dose intensity should be recommended for patients with HIV-related lymphoma. However, given the retrospective nature of this study, there may be residual confounding by indication whereby patients with the most severe HIV and resulting greatest risk

of death were deliberately given lower doses of treatment. Furthermore, the landmark analysis may have excluded most of the patients who died from treatment-related toxicity, which is the major difficulty encountered in the treatment of HIV-positive lymphoma patients (Kaplan et al., 1989). There is no clear consensus on the issue of treatment intensity in HIV-positive patients at this time, and unfortunately most of the clinical data from randomized trials comes from the era before highly active antiretroviral therapy (Dunleavy and Wilson, 2012).

5.2 **Socioeconomic Status, Treatment, and Survival**

In the baseline comparisons contained in Table III, black patients with DLBCL were significantly more likely to be from lower socioeconomic strata. Despite previous literature suggesting that worse outcomes driven by lower SES in patients with lymphoma, this variable was not significantly associated with survival in the models presented here (Wang, M. et al., 2008). While it is conceivable that a significant association could be found with increased statistical power in a larger dataset, the HRs for each estimated income quartile were close to 1. Thus, it is unlikely that an association would be seen even in a much larger group of VHA patients.

When the association between SES and the treatment variables were considered, the only positive findings were that patients in the highest income stratum demonstrated nonsignificant trends towards increased utilization of MGFs and achievement of higher ARDI. There was no significant association between estimated income and doxorubicin or rituximab use. Increased use of MGFs among higher-income individuals may be attributable to increased willingness of

individuals from higher socioeconomic strata to ask questions of their physicians, though this cannot be fully assessed in this study (Davis et al., 2008).

The implication of this observation is that in a healthcare system that in essence provides equal insurance access, SES does not have a major influence on survival after the diagnosis of DLBCL. Healthcare access is a multifaceted variable with dimensions that are not fully addressed by equal insurance access, such as transportation access (Syed et al., 2013). While access to transportation and other dimensions of healthcare access may not be fully addressed by health insurance, it appears that equal insurance access in this population may have contributed to similar survival outcomes across socioeconomic strata. While significant controversy still surrounds the implementation of the Patient Protection and Affordable Care Act, this finding suggests that the goal of increased insurance coverage contained in this law may improve outcomes for patients with DLBCL who come from lower socioeconomic strata.

5.3 **Racial Differences in Non-Modifiable Variables**

Consistent with previous studies, black patients in this cohort were generally younger and more likely to have advanced-stage disease at the time of diagnosis. New findings from this study are that black patients typically have a lower BMI and are more likely to have an elevated LDH at the time of diagnosis, both of which are associated with a worse prognosis (The International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993; Carson et al., 2011). Taken together, these findings suggest a more aggressive disease process at the time of diagnosis in black patients compared to white patients, which has led some to suggest that there may be differences in the frequency of the DLBCL subtypes between black and white patients (Sinha et

al., 2012). There are two major subtypes of DLBCL, each associated with a distinct gene expression profile and prognosis (Rosenwald et al., 2002). Race-based differences in the incidence of these subtypes could help explain differences in baseline characteristics and prognosis. Further study of archived samples, planned as part of a recently completed trial run by the Alliance for Clinical Trials in Oncology, will answer this question.

Unfortunately, from a clinical perspective it is difficult to conceive of a way to mitigate the negative impact of these variables on prognosis. There are no widely accepted diagnostic tests to screen for lymphoma. While it could be argued that increased access to primary care might facilitate early diagnosis, as is seen with solid tumor malignancies, there is no evidence that this is true in lymphoma (Rubin et al., 2011; Wang, F. et al., 2008).

5.4 **Racial Differences in Treatment Patterns**

Despite the concerns raised in previous retrospective studies, there were no major differences in the utilization of rituximab or doxorubicin based upon race in this patient population after controlling for other variables. While it is impossible to determine the reasons for this observation in other populations, HIV status was a major factor associated with decreased utilization of rituximab in this study and it was not controlled for in other studies. That said, since the VHA provides equal access to care, a disparity in access due to inability to pay for treatment may still be present outside of the VHA system that would not be detected in this cohort.

One potential area for intervention identified in this study was the significant race-based difference in achievement of ARDI ≥80%. The ARDI was also significantly associated

with reduced mortality in the survival analysis. However, this finding must interpreted with caution for several reasons. First, the strong association with survival may be due to residual confounding by indication. Second, higher-dose intensity may also increase toxicity (and treatment-related mortality), which would be masked in the landmark analysis. Finally, this study did not directly ascertain the rationale for treatment discontinuation, dose reductions, or dose delays, all of which will influence dose intensity. Future study of the patterns of reduced ARDI—and potentially the rationale as contained in the physician notes—would help clarify if achieving ARDI ≥80% is a cause or effect in its association with survival.

5.5 **Study Limitations**

There are several limitations of this study that should be noted. First, the VHA serves a population that is largely men. The incidence of HIV is considerably higher in both white and black men compared to white and black women, respectively (Lyman et al., 2005). Therefore, these results may not be fully applicable to racial disparities in DLBCL outcomes among women. Second, nearly all of the patients in this cohort previously served in the United States military, many of whom served in the Vietnam conflict. Some soldiers in Vietnam were exposed to Agent Orange, which may influence the incidence of NHL (O'Brien et al., 1991). However, there is no reason to believe that this prior exposure will modify response to treatment. Finally, based on the retrospective nature of the study, we are unable to obtain information on the rationale for treatment decisions.

5.6 **Future Directions**

Moving forward, this project has stimulated interest in evaluation of race on the DLBCL subtype observed in patients treated on the Cancer and Leukemia Group B, 50303 clinical trial protocol. Additionally, based on the findings related to HIV and rituximab, analysis of an updated cohort will be performed in the future to determine if updated standards of care that recommend rituximab use in HIV-positive patients will increase rituximab use in these patients. The skills learned from this dissertation will also be deployed to examine treatment and survival disparities in patients with MM. Finally, additional studies will be performed to evaluate how differential incidence rates for the various subtypes of NHL, in addition to survival disparities within NHL subtypes, are influencing the overall outcome disparity in NHL.

5.7 **Overall Conclusions**

Despite the appearance of a racial disparity in both outcome and treatment in the initial analyses, the subsequent exhaustive analyses that controlled for major confounding factors demonstrated no racial disparity. The dedicated clinicians at the VHA (and this author is among them) consistently provide standard of care therapy without regard to race in this population that is frequently underserved. Future efforts to address racial disparities in lymphoma care cannot ignore the marked race-based differences in the prevalence of HIV as a source of treatment and outcome disparities in DLBCL. The similarities in the frequency of HIV infection in the general population (eight times more likely in black than white) and this study population (six times more likely in black than white) supports application of these findings to the entire United States population.

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