Impact of Donor and Center Attributes on Outcomes of Hematopoietic Cell Transplantation

A DISSERTATION

SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL

OF THE UNIVERSITY OF MINNESOTA

BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

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September 2013

Acknowledgements

I greatly appreciate all of the guidance offered by my dissertation committee. I am especially grateful for the extensive data cleaning and preparation by Center for International Blood and Marrow Transplant Research (CIBTMR). I am also thankful for the helpful and supportive faculty, staff and students in the University of Minnesota School of Public Health, particularly those in the Department of Health Policy and Management.

I am forever indebted to all of my family, friends and classmates, who accompanied me for all or part of this journey and especially to my sister, Gila, for her encouragement. Tamar, my work would have been fruitless without your endless insight, support and encouragement. You are my partner and the source of my strength and inspiration. Ce qui embellit le désert, c'est qu'il cache un puits quelque part.

Dedication

This dissertation is dedicated to the memory of my parents. On ne voit bien qu'avec le cœur. L'essentiel est invisible pour les yeux.

Abstract

Hematopoietic stem cell transplantation (HCT) is the transplantation of stem cells or blood from a donor and an effective treatment for many hematologic malignancies. After an initially slow evolution, HCT has seen rapid expansion over the last two decades and major changes in technology use. HCT is a costly procedure ranked as one of the five most expensive medical procedures that generally exceed $140,000 for allogeneic (using stem cells from a donor) HCT and has a median length of stay of 35 days. HCT care provides an important opportunity to identify how center attributes can impact outcomes. Specifically, results can inform how payers, providers and policymakers can achieve high quality outcomes in the context of accreditation, the management of patient case mix and distance to facility. Using data from the Center for International Blood & Marrow Transplant Research (CIBMTR), a registry that collects transplant essential data (TED) data that includes disease type, age, sex, pre-transplant disease stage, date of diagnosis, graft type and cause of death. This research evaluates the current gaps in knowledge by 1) evaluating the mechanism between patient case mix and overall HCT center quality (survival) 2) identifying if centers of excellence and accreditation could explain differences in outcomes overall center quality and patient outcomes for complex HCT 3) understanding the impact of distance on overall survival and further evaluating the impact of distance on complex HLA mismatched patients. Overall, this research provides significant evidence for future recommendations surrounding the relative impact of risk stratification, center accreditation and distance on HCT survival.

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Chapter 1: Specific Aims

Hematopoietic stem cell transplantation (HCT) is the transplantation of stem cells or blood from a donor and an effective treatment for many hematologic malignancies. Each year, approximately 17,000 patients receive HCT in the U.S. This number has steadily increased since 2000, and there are no signs of this trend abating.[1] More than fifty years have passed since the first reports of successful bone marrow transplants from human leukocyte antigen (HLA) identical siblings for patients with immune deficiency disorders.[2] After an initially slow evolution, HCT has seen rapid expansion over the last two decades and major changes in technology use. HCT is a costly procedure ranked as one of the five most expensive medical procedures that generally exceed $140,000 for allogeneic (using stem cells from a donor) transplantation and have a median length of stay of 35 days.[3] In 2005, underscoring the importance of quality improvement and efficiency for HCT, the Stem Cell Therapeutic and Research Act (SCTRA) was passed by the U.S. Congress.[4] The SCTRA legislated that outcome data be collected on all recipients of stem cell therapeutic products. As resources are limited and health expenditures continue to increase dramatically, reducing HCT costs and increasing HCT quality and effectiveness deserves critical examination. HCTs are typically conducted in centers of excellence and the literature has shown that as patient complexity increases, transplant-related morbidity and mortality also increases but has paid little attention to specific center characteristics to broaden our understanding of this relationship.[5-18] Identifying center focused pathways for improved survival and treatment is critical for increasing quality of care and reducing costs. There is wide variation in outcomes by center. To date, the literature lacks concensus on the driving force behind this center variation.[6] Current research evaluating the ability of patient complexity to significantly impact survival is limited both in the extent to which potential confounders

are addressed and in discussion of how other factors (such as transplant center characteristics and distance to facility) influence survival and complications. This gap in knowledge presents an opportunity to further evaluate the predictors of the performance of centers prepared to perform complex HCT. Moreover, the current research is limited in the extent to which transplant center factors drive the risk-survival relationship.[19-20]

In order to further understand the relationship between HCT survival and center quality I will use the Center for International Blood & Marrow Transplant Research (CIBMTR) data, a registry that collects transplant essential data (TED) data that includes disease type, age, sex, pre-transplant disease stage, date of diagnosis, graft type and cause of death from HCT centers in the United States. If center factors such as center accreditation, center case mix and distance are the predominant forces that drive HCT center quality we should see a relationship between center characteristics and survival. Therefore, the specific aims of my proposed research are to:

Specific Aims

(1) Evaluate differences in outcomes among lower risk HCT patients by centers that transplant high risk patients versus centers that do not.

(2) Determine whether there are differences in outcomes among HLA matched and mismatched HCT by centers that obtain the Foundation for the Accreditation of Cellular Therapy (FACT) and Blood and Marrow Transplant Clinical Trials Network (CTN) status.

(3) Determine if the travel time to the nearest transplant center moderates the center quality relationship with HCT survival and post-transplant complications.

Understanding the mechanisms that influences HCT survival and lead to improved overall outcomes will be instrumental in the design of future quality

improvement programs for HCT. Identifying and understanding the best combined components that significantly improve cancer outcomes in the U.S. is imperative for the overall improvement of HCT care.

Chapter 2: Statement of Purpose and Background

Over the past several decades, the development of quality guidelines and recommendations for HCT center care has become a priority for payers, providers and policy makers. [21] With rising health care costs, the rapidly aging population and complexity of care the optimizing of care through identifying centers of excellence has become an area of substantial interest to policy makers as it identifies effective, appropriate and affordable therapeutic care. The Patient Protection and Affordable Care Act (ACA) was passed in March 2010 and the full implementations of the key elements of the reform strategy are scheduled for 2014. [22] The ACA has created an opportunity to advance delivery and payment system reform. A major component of the ACA emphasizes the improvement of quality as a means to reduce costs. The ACA further expands the use of quality measures and metrics to identify centers that achieve high quality care and specifically rewards centers that achieve the highest levels of excellence. Identifying pathways for improved center quality has become an area of substantial interest to policy makers as it identifies specific factors that could be introduced to all centers to improve treatment, survival and long term outcomes.

HCT care provides an important opportunity to identify centers of excellence and how quality outcomes can be achieved for complex, resource intensive specialty care. Over the last two decades, practice groups and accrediting bodies such as the Foundation for the Accreditation of Cellular Therapy (FACT) a non-profit entity co-founded by the International Society for Cellular Therapy and the American Society of Blood and Marrow Transplantation in 1996 [23] have published standards of excellence that are readily available to all centers. The guidelines are still widely recognized and utilized as standards of excellence set by clinical experts in the field of transplantation medicine, surgery, nursing and pharmacy. Payers and providers have encouraged HCT

quality improvement through the use and adoption of FACT guidelines as they are thought to be centers of excellence. Although many patient factors account for variation in outcomes there is no clear consensus opinion on the center level factors that can account for HCT center quality variation.

From the perspective of policy makers and payers and in the context of rapidly rising health care costs, identifying centers that are most likely to provide effective and beneficial care remains an important goal. Cost effectiveness is especially important for HCT in light of a recent report from the Agency for Healthcare Research and Quality highlighted that despite being a relatively uncommon procedure, HCT was among the top ten procedures with the highest increase in hospital costs from 2004 to 2007 in the United States in which the total national costs of HCT hospitalization increased from $694 million to $1.3 billion over this time period. [24] Therefore, understanding where to focus quality guidelines and how to identify the components of HCT centers of excellence that are most effective in instigating quality for both complex and lower risk patients remains important for minimizing health care costs and optimizing outcomes.

In order to further understand the relationship between complex, resource intensive specialty HCT care and outcomes, several studies have indicated several patient characteristics that are clinically important to the long term survival of HCT recipients. To determine patient risk and complexity, four characteristics have been consistently reported across studies to be associated with survival following HCT: age at transplant, HLA match status, Karnofsky performance score and comorbidities.[5-18]Little attention has been paid to overall patient complexity and center characteristics over time. Further understanding the mechanism between HCT center survival and complexity will help focus future HCT quality guidelines. If there is indeed no advantageous “spillover” impact that occurs for the low risk, less complex HCT patient

population as a result of having HCT in a center that treats patients with higher risk, payers, patients and providers might restrict travel to centers of excellence. Furthermore, the case mix of a center should not necessarily be viewed as a sign of excellence by payers, patients, providers, and HCT center administrators. If complex patient volume is indeed an indicator of center excellence and elevates quality outcomes for all patients, all centers should increase patient complexity to achieve excellence and improve overall quality.

The HCT literature that focuses on centers of excellence and the management of patient complexity is limited. Although several transplant center characteristics have been associated with increased survival such as workforce and volume, no studies have systematically evaluated differences in centers' characteristics and accreditation status and the resulting impact on outcomes. Majhail et al. found that practice variation, such as physician staffing, transplant capacity, clinician approach to transplantation for hematologic disorders and choice of graft source, can impact the quality of care for transplant recipients. [19] Using Center for International Blood & Marrow Transplant Research data from 1998-2000, Loberiza et al. found significant survival differences for patients receiving allogeneic HCT in centers with one or more favorable center related factors such as lower physician caseload, contact for afterhours call and medical school affiliation. [6] However, Loberiza did not find an association between factors that might be expected to correlate with increased levels of survival such as FACT accreditation (yes/no) and NCICCC designation.

In order to further understand the impact of distance and geographical location on HCT outcomes, several studies have examined rural/urban distinctions and distance to HCT for single center analyses. Although there is an extensive literature that observes distinct disparities in cancer outcomes and survival based on the distance to the

treatment center[25-32], few have focused on nationwide U.S. HCT. Previous findings of Abou-Nassar et al. showed inferior outcomes for patients that resided 160-360 minutes driving time from the Dana-Farber/Brigham and Women's Cancer Center. [33] In a study at the University of Nebraska Medical Center between 1983 and 2004, primary area of residence was used to classify patients as either rural or urban. [34] Results were mixed. Among the autologous HCT patients, those from rural areas were found to have a higher mortality versus patients from urban areas but this difference was not evident for patients undergoing allogeneic HCT. A registry study from Canada found that there were no significant survival differences between urban and rural patients undergoing autologous or allogeneic HCT. [35]

Overall, the proposed research will evaluate the current gaps in the knowledge surrounding the impact of centers of excellence and distance to center for HCT care by 1) Evaluating the mechanism between patient case mix and overall HCT center quality (survival) 2) Identifying if centers of excellence could explain differences in outcomes and further evaluating the mechanism between HCT center accreditation and overall center quality and patient outcomes for complex HCT 3) Understanding the impact of distance on overall survival and further evaluating the impact of distance on complex HLA mismatched patients. The current lack of consensus on where to focus HCT quality improvement efforts suggests that the proposed research will provide timely and significant evidence for future recommendations.

Relationship between Patient Characteristics and HCT Outcomes

The literature indicates several patient characteristics are clinically important to the long term survival of HCT recipients. To determine patient risk, four characteristics have been consistently reported across studies to be associated with survival following

HCT: age at transplant, HLA match status, Karnofsky performance score and comorbidities.[5-18]

Age, Karnofsky Performance Score and Coexisting Disease at Transplant

The literature has shown that the median age of transplanted patients has increased continuously over the past few decades. While the upper age limit for HCT for many years was 50 or 55 years, recent reports include patients in their 70s. The Center for International Blood and Marrow Transplantation Research (CIBMTR) database shows a median patient age of 25 years in the 1980s, 39 in the 1990s, and 46 over the past decade. From 2002 to 2009, 44% of patients were older than 50, and 20% older than 60 years.[36] Transplant recipients over the age of 40 were considered to be higher risk than their younger counterparts.[37]Although older age is considered to be a higher risk indicator for HCT, research by McClune et al. showed that there is only a limited effect of age on outcomes of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome.[37] They conclude that age over 40 alone should not be considered a contraindication to HCT.

The Karnofsky performance status is used to determine the functional status of a recipient and can range from 0-100.[38] A Karnofsky performance score of 90-100 categorizes patients with the ability to carry on normal activity and no special care is needed (see appendix for a full list of Karnofsky performance scoring). In a single center Canadian study, the Karnofsky performance score was determined to be an independent indicator of survival. Karnofsky performance status was found to be a useful in predicting overall survival and in assisting treatment decisions.[39] Additionally, Sorror et al. found that coexisting disease and Karnofsky performance status assess different

levels of medical health status and that merging the information attained by the 2 scoring systems refined the outcome predictions for patients given nonmyeloablative HCT.[13]

Coexisting disease is another important predictor of HCT outcomes and measurement of pre-transplant risk and complexity. The literature has consistently shown that coexisting disease adversely impacts outcomes. In addition to using coexisting disease as a binary variable (yes/no), coexisting disease HCT index scores have been developed in order to more accurately capture comorbidity. Sorror et al. modified the established and more broadly applicable HCT index score by incorporating additional parameters with greater relevance in HCT and by assigning scores (1, 2, or 3) with better discriminating power to individual parameters. [11] The HCT-CI strictly considers only pre-transplantation patient characteristics, in particular cardiovascular, gastrointestinal, hepatic, and renal dysfunction along with antecedent solid cancer. Numerous reports have shown increased mortality and lower survival with increasing HCT-CI scores. Patients with scores of 3 or higher generally had significantly inferior survival, often half the probability of patients without comorbidities. [11-13]

Although the above mentioned studies that have used age, Karnofsky performance score and coexisting disease at transplant have all found these measures useful in assessing survival probability and post HCT outcomes at the patient level, few have used these measures to assess and stratify overall center risk. In addition to age, Karnofsky performance score and coexisting disease, HLA match status is also considered an important predictor of HCT survival.

HLA Match Status

Allogeneic hematopoietic cell transplantation (HCT) is a complex treatment for several hematological disease groups and involves the infusion of donor hematopoietic stem cells into a recipient. In the past several decades, human leukocyte antigen (HLA)

matching capabilities and refined methodology has buttressed clinical abilities to increase the successful performance of HCT. For example, donor and recipient HLA matches can be made on an 8 of 8 (match) or 7/8 (mismatched) HLA level for unrelated donor HCT. A 6/8 or lower donor recipient match is generally considered unacceptable for successful HCT.[40]

The search for a donor and recipient HLA matches begins with the patient's siblings who have the same parents as the patient. If a sibling is not a perfect match (8/8 loci are matched), the search moves to other immediate family members and possibly unrelated donors creating four total categories; HLA matched related, HLA mismatched related, HLA matched unrelated and HLA mismatched unrelated transplants.[15, 41] Finding suitable related or unrelated donors has increasingly become more common in the last decade. It is widely accepted that match quality is an essential component of higher survival rates and improved long term outcomes among HCT recipients. [15-16, 40-42] Clinical best practice dictates that whenever possible, HLA matched donors are preferable in regulating responses between donor and recipient, reducing the risk of post-transplant complications and infections and improving the chances for long term survival. [15-16, 40-42]

A matched transplant offers a greater chance of eradicating malignancy. Allogeneic HCT also confers a higher risk of transplant-related mortality due to slower hematopoietic and immunologic recovery and graft-versus-host disease (GvHD). Typically, a matched sibling donor is available for only 20-30 percent of the patients in need of a transplant. [40] The remainder of the recipients in need of transplants must rely on an unrelated donor bank population. The ideal unrelated donor for HCT has alleles matched at the HLA-A, -B, -C and DRB1 level. Under the assumption that a patient's condition is stable a patient must decide if the benefits of waiting for a more suitable

match to be recruited outweigh the risks of waiting when no suitable donor is imminently available.

The literature has shown that high resolution matching is a necessary component for survival of HCT. [15-16, 40-42] However, this does not imply that the availability of partially HLA matched donors is a contraindication to transplantation. The National Marrow Donor Program HLA-Matching guidelines for unrelated marrow transplants focus on three large contemporary studies that evaluated most of the HLA loci by using DNA testing to resolve alleles. The guidelines focused on survival as opposed to other outcomes such as engraftment and GvHD. Table 1 identifies the positions of the three sets of studies evaluating the relationship between HLA-matching levels and survival. The data sources for the three studies are (1) The Japanese Marrow Donor Program[16-17] (2) Fred Hutchinson Cancer Research Center (FHCRC) [15, 41] (3) The National Marrow Donor Program.[42] These three sets of studies differ in their designs and conclusions. However, they all suggest that matching for HLA-A, -B, -C and DRB1 are integral for survival. This group of literature also emphasizes that matching at the allele, high-resolution levels, provides a superior benefit to the recipient. In contrast, matching at the antigen level, information available through serological or low level molecular typing provides a less superior match. Overall, this set of literature agrees that the paradigmatic match quality level is the donor whose alleles match the recipient at HLA-A, -B, -C and DRB1. There is currently insufficient evidence for matching at HLA-DQ, -DP levels. The differences amongst the studies are attributed to several factors that include the concern of generalizability of the Japanese studies and immunological factors that vary across racial groups that could influence the relationship between HLA matching and transplantation outcomes. Results from Petersdorf and Flomenberg indicate that survival worsened with an increase in allelic donor mismatch. [15, 41-42] Additionally,

differing sample sizes amongst the studies limited how mismatches were classified across multiple loci and the 3 studies collapsed the loci differently. Although methodologies are variable between the three groups of studies, each of the studies demonstrates that outcomes can be improved by matching strategies and HLA matching at higher levels.[43]

Overall, the four critical components of predicting HCT survival that have been consistently reported across studies to be associated with patient risk and assessing survival probability and post HCT outcomes at the patient level following HCT are age at transplant, HLA match status, Karnofsky performance score and comorbidities.[5-18]Although the above mentioned literature has found utility in using these characteristics to stratify patient risk few have used these measures to assess and stratify overall center risk.

Table 1: Studies Evaluating the Association between Human Leukocyte Antigen (HLA) Matching and Survival

Population	Eligible Diagnosis	Study Design	Comparison	Outcomes	Timing	Study
1249 patients Data source: (FHCRC)	Treatment for leukemia or myelodysplastic syndrome (MDS)	Retrospective Cohort	Matched, one mismatch, two or more mismatches groups compared on survival.	Single mismatches in low risk patients were associated with a statistically significant risk with no difference on match for high risk patients.	1985-2003	Petersdorf[15, 41]
1298 patients	AML, ALL, CML, MDS, SAA, others	Retrospective Cohort	Collapsed mismatches on A and B together and on DR and DQ together to get a larger sample size for detecting differences among groups.	Identified the combined A/B groups as having a stronger effect on survival than the other loci	1993-1998	Morishima[16]
440 patients	80% of the population had leukemia and the remaining 20% had a diagnosis of lymphoma, marrow failure or a congenital disorder.	Retrospective Cohort	Donor mismatching was compared. For each donor-recipient pair the. Donors were classified as matched, mismatched or no match.	Mismatching of HLA-A but not HLA-C alleles was an independent risk factor of survival ($p<.001$). DRB-1 showed no effect. (DR+DQ combined)	Retrospective DNA typing	Sasazuki[17]

Table 1 Continued Population	Eligible Diagnosis	Study Design	Comparison	Outcomes	Timing	Study
423 patients	CML, AML, ALL, other malignant, nonmalignant	Retrospective Cohort	Of the 423 pairs, 282 pairs (67%) were matched for 5 classic HLA loci (HLA-A, -B, -C, -DRB1, -DQB1; ie, 10 of 10 matched) and 141 were mismatched. Of the 141 pairs, 111 were class I mismatched only, 19 were class II (DRB1, DQB1) mismatched only, and 11 were mismatched at class I and class II	Results indicate the presence of DPB1 allele incompatibility resulted in significant differences in the incidence of GvHD and disease relapse.	1996-2003	Shaw[44]
3857 patients	ALL/AML/ CML/MDS	Retrospective Cohort	8/8,7/8,6/8,5/8. Mismatches compared at specific loci	Adverse effects of either allele or antigen mismatching on outcomes with 9-10% lower 1 year survival for each additional mismatch. 6-7/8 v 8/8	1983-2003	Lee[18]
1874 patients Data source: National Marrow Donor Program)	CML/AML/ALL/nonmalignant disorders	Retrospective Cohort	Two levels of DNA based HLA matching were considered in the analyses- High resolution and low resolution for each locus- HLA/B/C/DRB1.	Single mismatches at these loci were associated with significant decrements in survival, and the presence of multiple mismatches was even worse.	1988-1996	Flomenberg[42]
14,797 unrelated patient donors	CML/ MDS/ NHL/HL Myeloma/SAA/Inherited abnormalities of erythrocytes/SCID and other immune disorders/inherited disorder of metabolism/ histolytic disorders/Other malignancies	Retrospective Cohort	Disease status at transplant and survival after URD HCT by MLA match classification. Well matched/ partially matched/mismatched grouped into 21 possible match categories.	URD HCT 83% had high resolution typing of all 4 loci-of those, 65% were well matched, 26% partially matched and 6% mismatched. Earlier clinical reports may have obscured differences in outcomes that might have been attributable to incomplete HLA matching.	1665-2006	Weisdorf[45]

Potential Confounders in the HLA Match Quality-Survival Relationship
Patient Factors

The observational studies reviewed in Table 1 examine the relationship between HLA match quality and survival and adjust for differing combinations of patient characteristics and hospital factors. The literature incorporates these factors as they might influence the relationship between match quality and outcomes. The literature often includes and adjusts patient factors such as patient age, gender, race, extent of disease, and severity (Table 2). Current literature has evaluated HCT access by gender, age, race/ethnicity, insurance coverage, disease type and education. For example, Mehta et al. estimated the ratio of HCT transplantations for male and female allogeneic patients versus disease incidence and found no association between gender and the rates of HCT for individuals with AML and CML. [46] Hwang et al. evaluated Medicare beneficiaries in Texas and found that elderly women were significantly less likely to undergo HCT than elderly men.[9] Hwang also evaluated insurance status and did not find a significant association between HCT and ethnicity or insurance coverage. Mitchell et al. found substantial variation for leukemia and lymphoma patients in access to HCT.[47] This difference was particularly significant amongst Black patients, those enrolled in HMOs, Medicaid patients and self-pay HCT recipients. The current HLA match quality literature has not fully evaluated and included socioeconomic status, transplant center characteristics or other factors that might influence survival in their survival models. As a result, these studies may not fully capture the true relationship between center characteristics, patient complexity and survival.

Table 2: HLA Match Quality-Survival Studies- Patient and Center Characteristic Confounders Included

Study	Age	Gender	Co-morbidity	Race & Ethnicity	Socio-economic status	Transplant Center Characteristics	Distance to Transplant Center	Insurance
Petersdorf	✓	✓	✓	✓	X	X	X	X
Morishima	✓	✓	✓	X	X	X	X	X
Sasazuki	✓	✓	✓	X	X	X	X	X
Shaw	✓	✓	✓	✓	X	X	X	X
Lee	✓	✓	✓	✓	X	X	X	X
Flomenberg	✓	✓	✓	✓	X	X	X	X
Weisdorf	✓	✓	✓	✓	X	X	X	X

Relationship between Center Case Mix and HCT Outcomes and Survival

As discussed above, there is a well-documented body of HCT literature that indicates certain patient characteristics such as HLA matching, co-morbidities, age and Karnofsky performance score are determinants of a patient's pre-transplant risk level and survival rates.[5-18] The literature has not used this patient stratification to stratify centers and determine the impact of risk management on overall center outcomes. There are several ways that patient case mix and risk can impact overall center performance. Variation in HCT patient characteristics in centers that treat higher risk patients could deplete resources for lower risk patients. Alternatively, the challenge of successfully managing high risk patients could benefit lower risk patients thereby increasing quality and lowering the procedural mortality for all patients.

Relationship between Center Volume and HCT Outcomes and Survival

There is a large literature that documents a positive correlation between hospital volume and good outcomes.[48-59] Typically, morbidity and mortality is found to be lowest in centers that perform the most of any given procedure. These results have been shown for multiple conditions, procedures and environments including cancer.[60-61] There are almost always numerous low-volume providers with average or exceptional outcomes,

although these outcomes are not always reliable estimates of true performance because they are based on small sample sizes. There are two ways in which volume can be thought to impact outcomes. The “learning by doing” hypothesis argues that large centers or hospitals are more apt to provide higher quality care which thus improves overall outcomes. Alternatively, hospitals that offer superior quality care attract higher demand for services and thus have higher volume levels. In other words, high volume centers are rewarded based on perceived quality or expertise. The direction of this volume relationship is important. If volume per se is the important parameter, one can make a strong case for restricting transplants to large centers. If, on the other hand, volume is a surrogate for other factors that are more common in large versus small centers, but which could be introduced into small centers, the appropriate course of action would be to set standards for these factors to be adhered to by large and small centers. For instance, if studies substantiate that patient complexity and accreditation impacts survival in the HCT setting, then it may be possible for small centers to optimize other operational and organizational management features to ensure good outcomes, rather than attempt to increase procedure volume.

Center Accreditation Status and HCT Survival

Certifying and accrediting centers of excellence are not novel approaches to oversee and underscore standards of excellence and health care quality and outcomes. There is a broad literature exploring whether there are differences in process and outcomes at academic health centers, accredited centers of excellence, teaching hospitals and the National Cancer Institute’s Comprehensive Cancer Centers (NCICCC).[62-72] Results have been mixed. For example, using the national Medicare database, Birkmeyer et al. conducted an analysis of 51 NCICCC and six cancer procedures, cystectomy, colectomy, pulmonary resection, pancreatic resection, gastrectomy, and

esophagectomy cancer.[62] Although Birkmeyer did not fully account for selection bias, she found that NCI designated cancer centers had lower surgical mortality rates than those treated at comparably high-volume hospitals, but had similar long-term survival rates. [62] Meguid et al. found that in-hospital outcomes are superior for patients undergoing lung cancer resections at teaching hospitals, with results prominent at all but the highest volume institutions.[63]

Another body of literature that analyzed either process measures of care or that assessed risk-adjusted mortality rates found differences in quality between major teaching hospitals and nonteaching hospitals across several cancer groups.[64-68]These differences have been reported in combined analyses of multiple conditions but have not always been consistent in finding significant results and rarely do these analyses control for center volume.

The HCT literature that focuses on center characteristics and FACT certification is limited. Several transplant center characteristics have been associated with increased survival. Majhail et al. found that practice variation, such as physician workforce, transplant capacity, clinician approach to transplantation for hematologic disorders and choice of graft source can impact the quality of care for transplant recipients. [19] Using Center for International Blood & Marrow Transplant Research data from 1998-2000, Loberiza et al. found significant survival differences for patients receiving allogeneic HCT in centers with one or more favorable center related factors such as physician caseload, contact for afterhours call and medical school affiliation.[20] However, Loberiza did not find an association between factors that might be expected to correlate with increased levels of survival such as FACT accreditation (yes/no) and NCICCC designation.

Despite numerous studies that have evaluated the FACT accreditation status, the literature has not stratified centers by patient risk to determine differences. Furthermore, since FACT's inception, nearly two decades ago, FACT accreditation has become ubiquitous among HCT centers and it is possible that HCT techniques have consistently improved across all centers irrespective of accreditation status.

Relationship between Distance to Facility and HCT Survival and Post-Transplant Complications

Since distance is an important determinant of the location of treatment for emergent conditions, increased travel times may increase the likelihood of an adverse health outcome for such conditions. Acute myocardial infarction (AMI) and acute stroke are two common diagnoses where time to treat is an important determinant of health outcomes. [73-76] For HCT distance to facility is important for expediting the process that leads to the donor recipient match, diagnostic screening and for post-transplant care. As explained above, the complexity of HCT requires patients to remain in close proximity to the transplant center post-transplant. Patients that travel long distances or that opt to receive post-transplant care from physicians in non-urban locations may receive suboptimal care. Physicians located in non-urban areas that are poorly trained for post-transplant complexity may provide inadequate treatment and be bereft of advanced techniques necessary for HCT patients.

The General Accounting Office estimates that in the United States, only one third of patients who need transplants from unrelated donors have preliminary searches requested from the National Marrow Donor Registry.[77] For some conditions the importance of travel time likely outweighs the benefits of receiving care at a higher quality facility. AMI and acute stroke are two of our study conditions that likely fall into that category. However, for conditions that are less time sensitive the benefits of receive care at higher quality facilities likely outweighs the disadvantages of increased travel

times in impacting health outcomes.[32] Congestive heart failure and hip fracture are two conditions that may fall into that category. Finally, for some conditions like pneumonia, there is evidence that smaller hospitals provide higher quality care than their larger counterparts.[25] HCT remains a risky procedure with many possible complications; it has traditionally been reserved for patients with life-threatening diseases. Distance to facility is of particular importance for both pre and post HCT care.

Although HCT now save thousands of lives each year, 70% of those needing a HCT using donor marrow are unable to have one because a suitable bone marrow donor cannot be found.[23] This barrier to care is for potential recipients that are already in the registry and is not a product of distance. However, HCT patients that are in the registry may potentially travel further to go to receive potentially inferior care. Ultimately, access to transplants and geographic barriers to HCT contribute to a patient's decision to be treated. There are certainly socioeconomic and health insurance factors that contribute to the eligible transplant recipient (these variables are not collected in the registry). However, often transplantation is considered only after transplantation is no longer a viable and safe alternative. Distance delays diagnosis and potentially terminates any necessary care before being started. For a transplant recipient patient the potential benefit of transplantation often occurs if the patient resides in close proximity to the transplant center. Although there is an extensive literature that observes distinct disparities in cancer outcomes and survival based on the distance to the treatment center[26-32], few have focused on nationwide U.S. HCT. Previous findings of Abou-Nassar et al. showed inferior outcomes for patients that resided 160-360 minutes driving time from the Dana-Farber/Brigham and Women's Cancer Center.[33] In a study at the University of Nebraska Medical Center between 1983 and 2004, primary area of residence was used to classify patients as either rural or urban. Results were mixed.

Among the autologous HCT patients, those from rural areas were found to have a higher mortality versus patients from urban areas but this difference was not evident for patients undergoing allogeneic HCT. [34]A registry study from Canada found that there were no significant survival differences between urban and rural patients undergoing autologous or allogeneic HCT. [35]

Limitations to Current Research

The current literature that evaluates HCT does little to incorporate center attributes to their exploration of HCT variation. The gap in knowledge presents an opportunity to further evaluate predictors of patient and center variation. Further, current research is limited in the extent to which center factors drive survival and post-transplant outcomes for HCT patients. Studies fully incorporating these confounding factors may demonstrate that the survival relationship is more likely attributable to HCT center quality and centers of excellence.

Conceptual Model

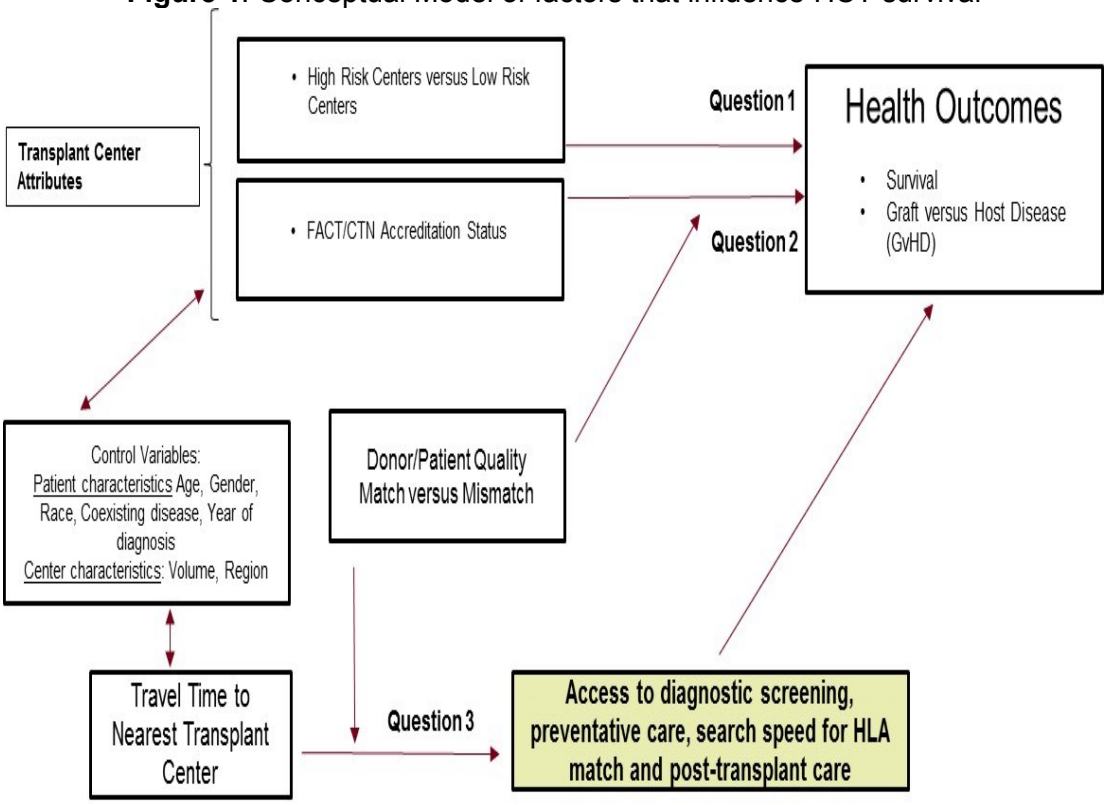
As seen in the literature review, three main groups of factors can influence the survival of HCT patients: patient, provider and transplant center characteristics (Figure 1: Conceptual Model). Although the transplant physician is ultimately responsible for the HCT treatment and success to the transplant, multiple patient characteristics can influence the HCT. In addition to specific patient biological characteristics, patient factors such as age, gender and extent of comorbidities can all impact survival. In addition to patient factors, provider characteristics and factors significantly influence technique, knowledge and experience, which all differentially influence the likelihood of superior HCT outcomes. Specifically, a surgeon's specialty, professional certification, years in practice and HCT volume all influence the ability to treat high risk HCT recipients. Although a HCT physician's ability to treat a lower risk transplant recipient should be

independent of patient characteristics, disease characteristics or unmeasured biological changes may influence a provider's ability to achieve favorable outcomes.

The willingness to care for high risk HCT recipients can also be significantly influenced by hospital characteristics, which can influence the culture or expectations of transplant center superiority and the overall perception of quality. These factors include those characteristics that are known to influence other cancer quality outcomes such as survival. Such characteristics include hospital volume for HCT procedures, type of ownership, teaching status and NCI/FACT designation.

Receipt of adequate post-transplant care, while also influenced by patient, provider and hospital characteristics, is modified by initial HLA match quality. In other words, individuals that are low risk HCT recipients are more likely to receive quality care along the HCT continuum. Once they enter a high quality system, they continue to receive appropriate therapy in a timely manner. Using a transplant recipient risk level as an initial surrogate for center risk levels-we are able to ascertain if transplant centers are able to sustain high levels of quality as risk tolerance evolves. The current literature has not yet explored the influence of patient and transplant center characteristics on the HCT continuum for various risk levels.

Figure 1: Conceptual Model of factors that influence HCT survival



Contribution of the Dissertation to Previous Work

Understanding the mechanism that influences HCT survival will be instrumental in the design of future quality improvement programs that focus on implementing more transparent HCT results. While center characteristics, HCT match quality, patient complexity, center case mix and travel distance for HCT may not drive improved survival, identifying and understanding the best combined components that significantly improve cancer outcomes in the U.S. is imperative for the overall improvement of HCT care.

Chapter 3: Do Hematopoietic Cell Transplantation Centers that Perform Higher Risk Hematopoietic Cell Transplantation have Superior Survival Outcomes for Lower Risk Transplants?

Background: Allogeneic hematopoietic cell transplantation (HCT) is the transplantation of stem cells from a donor and an effective treatment for many hematologic malignancies. Although major progress has been made in pre-transplant patient risk assessment, the research has typically used risk scores to measure differences in HCT survival outcomes without identifying or aggregating results to the transplant center at the U.S. national level. Given the lack of a center based approach in the literature we sought to compare allogeneic HCT survival outcomes and hazard of death amongst U.S. centers that treat higher risk patients versus lower risk centers that do not.

Methods: To further evaluate the association between pre-transplant risk and HCT survival by transplant center, we utilized January 1, 2008-December 31, 2010 Center for International Blood & Marrow Transplant Research (CIBMTR) data. We categorized patients into 4 risk categories (RC) that align with factors shown to be associated with HCT survival: (a) age, (b) Karnofsky performance scoring, (c) co-existing disease and (d) the human leukocyte antigen (HLA) match status of transplant donors. We stratified centers into those that conduct high pre-transplant risk HCT and examined the association between risk category score and hazard of death using Cox proportional hazard modeling.

Results: There were 12,264 HCT recipients at 147 transplant centers from 2008-2010 in the cohort. Of the 147 centers, 74 centers performed HCT for patients ranging from the lowest risk category (RC=0) to the highest level category (RC=4) and 73 centers that performed only lower risk HCT (RC=0-3). With the exception of the lowest risk category patients (RC=0), we observed an increase in HCT in all risk categories from 2008-2010. After adjusting for race, sex, year of transplant, HHS region and broad disease categories, we found that our high pre-transplant risk categories were all significantly

associated with higher relative hazard of death versus lower pre-transplant risk groups. Controlling for all other factors, we found that lower risk patients that underwent transplants in lower or higher risk centers had similar relative hazard of death.

Conclusions: Research has previously shown that providers with more experience ('learning by doing') produce better outcomes. Although the surgical literature has shown a direct relationship between procedure volume and survival 19-25, our results point to the fact that higher procedure volume, and a willingness to take on riskier transplants does not directly translate into improved outcomes for all other patients. Low risk patients had similar survival outcomes irrespective of whether they are transplanted at higher or lower risk centers. There was no apparent benefit or harm for lower risk patients receiving HCT at higher risk centers. Patient and payer policy implications could include initiatives that reduce travel for low risk patients. Similarly, HCT center administrators and providers that manage higher risk patients need not expect benefits in survival for lower risk patients. The number of HCTs performed has markedly increased in the past several decades. While centers continue to explore and expand the possibilities of HCT for higher risk transplants there should be sustained emphasis on maintaining proficiency and superior outcomes for lower risk recipients.

Background

Hematopoietic cell transplantation (HCT) is a complex treatment procedure for various hematologic malignancies and other conditions that are often otherwise are incurable. Each year, approximately 17,000 patients receive HCT in the United States. This number has been steadily increasing since 2000. [1] HCT is performed using hematopoietic progenitor cells from the patient (autologous transplant) or a human leukocyte antigen (HLA) matched related or unrelated donor (allogeneic transplant) to reestablish function in patients with damaged or defective bone marrow or immune systems. Advances in transplantation over the last four decades have resulted in an increasing number of centers that are more willing to perform more complex and higher risk transplants. While mortality is a common and useful measure of transplant center quality, comparing outcomes between centers is challenging if estimates do not take differences in transplant populations into account. [78-79] For instance, centers that transplant a relatively larger percentage of high risk patients with an intrinsically higher risk of mortality may be potentially perceived as poor performers in comparison to centers that transplant a lower percentage of such patients.

There are several ways that patient case mix and risk can impact overall center performance. Variation in HCT patient characteristics in centers that treat higher risk patients could deplete resources for lower risk patients. For example, a common argument made for case mix adjustment is that a centers' overall performance should be adjusted for underlying differences in patient population characteristics that directly and adversely impacts performance. [80-82] Alternatively, the challenge of successfully managing high risk patients could benefit lower risk patients thereby increasing quality and lowering the procedural mortality for all patients. For example, there is a literature that supports the hypothesis that when complex surgical oncologic procedures are

provided by surgical teams in hospitals with specialty expertise, overall mortality rates are lower. There is a well-documented body of HCT literature that indicates certain patient characteristics such as HLA matching, co-morbidities, age and Karnofsky performance score are determinants of a patient's pre-transplant risk level and survival rates.[5-18]

In this paper we explore the effects on survival for lower risk HCT patients being transplanted at HCT centers that do or do not perform high risk transplants. We also explore the effect of HCT risk management on centers. Specifically, we focus on potential spillover effects and benefits of higher risk HCT performance on the low risk patient population of centers. Under the Stem Cell Therapeutic and Research Act (SCTRA) of 2005 there has been a strengthened clinical and health policy emphasis for increased transplant survival outcomes transparency, including the dissemination of research and the effectiveness of transplant program operations. Our work focuses on determining a center's deftness to successfully transplant the full spectrum of recipients regardless of the levels of patient complexity. We sought to evaluate differences in outcomes among lower risk HCT patients by risk stratifying centers that transplant high risk patients versus centers that do not perform high risk HCT.

Methods

Data Source

The Center for International Blood & Marrow Transplant Research (CIBMTR) is a research affiliation of the International Bone Marrow Transplant Registry, Autologous Blood and Marrow Transplant Registry, and National Marrow Donor Program (NMDP) that was established in 2004. CIBMTR is comprised of a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive HCT to a Statistical Center at the Medical College of Wisconsin in Milwaukee, WI and the NMDP Coordinating Center in Minneapolis, MN. In addition, the

CIBMTR holds the contract for the Stem Cell Therapeutic Outcomes Database part of the CW Bill Young Transplantation Program from the Human Resources and Services Administration. As part of this Program, all transplant centers in the US are mandated to report clinical outcomes data for allogeneic HCT to the CIBMTR. All CIBMTR teams contribute registration data (also called transplant essential data (TED)). These data include disease type, age, sex, pre-transplant disease stage, date of diagnosis, graft type, conditioning regimen, post-transplant disease progression and survival, development of a new malignancy, and cause of death. TED level data are collected before transplant, 100 days and 6 months after transplant, and annually thereafter or until death. We obtained a de-identified dataset from CIBTMR. Our study was deemed exempt from review by the Human Subjects Committee of the University of Minnesota's Institutional Review Board.

Patients

We included transplant recipients 18 years or older who received transplants between January 1, 2008, through December 31, 2010 and were reported to the CIBTMR. We included patients who received peripheral blood stem cells or bone marrow graft from HLA-matched or mismatched, related or unrelated donors. All diagnoses were included. We excluded patients missing any of the four risk category criteria (N=406 patients, see below for risk category derivation) and centers that reported only one transplant from 2008-2010 (N=15 Centers).

Derivation and Definition of the Patient Risk Categories

The literature indicates several patient characteristics are clinically important to the long term survival of HCT recipients. To determine patient risk, we chose four characteristics that have been consistently reported across studies to be associated with survival following HCT: age at transplant, HLA match status, Karnofsky performance score and comorbidities.[5-18]

We used binary risk indicators for the four patient characteristics to create a risk score for overall mortality that ranged from 0-4. Transplant recipients over the age of 40 (score of 1) were considered to be higher risk than their younger counterparts (score of 0). [6] The Karnofsky performance status is used to determine the functional status of a recipient and can range from 0-100. A Karnofsky performance score of 90-100 categorizes patients with the ability to carry on normal activity and no special care is needed (see appendix 1 for a full list of Karnofsky performance scoring). CIBTMR categorizes the Karnofsky performance score as a dichotomous variable of 90-100 (score of 0) and ≤ 80 (score of 1). Coexisting disease is a binary category of diseases collected by CIBMTR. CIBMTR codes HCT patients with any of 18 comorbidities as coexisting disease present (score of 1). The HLA match status of donors describes the degree of immunologic similarity between recipients and donors. HLA 8/8 match or well matched unrelated, and HLA matched sibling or synergenic HCTs were scored as 0 and any mismatched unrelated (HLA 6/8, or 7/8 matched, partially matched, or mismatched) or mismatched related HCTs were scored as 1. Prior to consolidating the related and unrelated HLA matched HCT groups within our risk category we created separate risk categories for each transplant group and independently verified our models for each group (Appendix 3).

We considered patients with all four risk components {(a) HLA mismatch, (b) coexisting disease, (c) age >40, and (d) Karnofsky performance score<80)} to be the highest pre-transplant risk within our analytical cohort (scored with a risk category of 4). Conversely, transplant recipients with a risk category score of 0 {(a) HLA match, (b) no coexisting disease, (c) age ≤40, and (d) Karnofsky performance score ≥90)} were considered to have the lowest risk within our cohort. Patients with a risk category score

of 1, 2 and 3 were considered to have moderate pre-HCT risk. Figure 1 is a summary of characteristics included in the risk categories.

{Figure 2 Here}

Overall survival for patients with scores of 1 and 2 were similar and hence, we combined them into a single group. We had a total of four risk groupings. A risk score of (a) 0, (b) combined 1 and 2, (c) 3 and (d) 4. Based on our pre HCT patient risk score categories, we categorized centers into either high or low risk centers. Centers that performed HCTs with only lower risk patients (risk score=0-3) were considered to be low risk centers. Of the 147 centers, 73 centers (N=1,984 transplants) performed only lower risk HCT (risk score=0-3). To confirm that our risk categories were illustrative of distinct patient risk we used Kaplan-Meier methods to illustrate the difference in survival probability for our risk categories and observed distinct differences between all four groups.

{Figure 3 Here}

Center Characteristics

High risk centers were categorized as any center that performed HCT for patients with the highest risk category score of 4 (N=74 high risk centers). Low risk centers were categorized as centers that did not perform HCT for the highest risk category score (N=73 low risk centers). Using organizational lists we linked the CIBTMR data to publically available center characteristics. Center accreditation characteristics included Foundation for the Accreditation of Cellular Therapy (FACT) organizational, Academic Health Centers, National Cancer Institute Comprehensive Cancer centers and core clinical trial network certified (CTN) center status. We also created a binary indicator (yes/no) of centers that performed Cord Blood transplants which are considered to be higher risk transplants. In addition to the accreditation status of centers we recorded

several other center characteristics including 10 Department of Health and Human Services (HHS) regions and we created a high volume center (>mean transplants) indicator. To adjust for possible high risk center effects and the inclusion of unrelated donors in our cohort, a transplant center and related/unrelated donor indicator was added to all multivariate models as frailty variables.

Statistical Analysis

We evaluated differences in risk categories and patient characteristics across all years. We further tested for trends in the proportion of patients in each risk category. To assess whether pre-transplant risk trends changed over time, we used the Cochrane-Armitage trend test. Additionally, we evaluated differences in risk categories and patient characteristics using the chi-square test.

After assessing the unadjusted relationship we evaluated the association between our risk categories and 3 year hazard of death using Kaplan-Meier methods and Cox proportional hazards modeling. Separate Kaplan-Meier curves were used to estimate the 3 year cumulative mortality across the risk categories for patients within centers that performed high risk transplants (n=74 centers) and for transplant centers that did not perform high risk transplants (n=73 centers) within our analytical period. Three separate multivariable Cox models were used to compare the impact of pre-transplant risk factors independently for high and low risk centers and an overall combined models. The combined Cox model, in which patients from high and low risk centers were included together, adjusted for patient factors as well as a bivariate high risk center indicator (yes/no) and the inclusion of higher risk unrelated donors.

In all models, we performed several sensitivity analyses such as the removal of non-statistically significant factors and to ensure that the observed effects were not a product of our risk categories and modeling decisions. We compared models with our risk score and those that included each risk component measured separately to verify

that there was statistical benefit to the creation and inclusion of our risk scores (appendix 2, 4, 7). Prior to consolidating related and unrelated transplant groups within our risk category, we created separate risk categories for each transplant group and independently verified our models for each group (appendix 3). In addition to using coexisting disease as a binary variable (yes/no), coexisting disease HCT index scores have been developed in order to more accurately capture comorbidity. Sorror et al. modified the established and more broadly applicable HCT index score by incorporating additional parameters with greater relevance in HCT and by assigning scores (1, 2, or 3) with better discriminating power to individual parameters. [11-13] While we acknowledge that the HCT comorbidity index (CI) and the Sorror comorbidity score are more accurate representations of patient comorbidities, the variable was underreported by centers relative to patient co-existing disease. Nevertheless, we conducted sensitivity analyses utilizing the sorror comorbidity score that did not produce results of different magnitude or direction (appendix 8). We conducted separate survival analyses with the use of hierarchical linear models to verify that accounting for transplant recipients being nested in centers did not produce results of different magnitude or direction (appendix 5). We performed separate Cox analyses to verify that our proportional hazard ratios were not a product of our high risk cohort (appendix 6) and volume. Under all assumptions, conclusions remain unchanged. See appendix for complete descriptions of sensitivity analysis results. SAS version 9.3 (SAS Institute) was used for all analyses. P values were 2 sided with a level of significance of ≤.05.

Results

Our cohort included 12,436 allogeneic transplants conducted in 147 centers. This consisted of 5,708 (46%) related transplants and 6,728 unrelated transplant recipients (54%). Of the related transplants 5,082 were from a HLA identical related (89%) and 92

(2%) were syngeneic transplants, whereas 532 (9%) of the related transplants were performed using a mismatched relative. Within our unrelated transplant cohort, 5,131 (76%) underwent transplantation from HLA-matched, unrelated donors**,** and 1,597 (24%) received HLA-mismatched transplantation (≤7/8, partially matched or mismatched unrelated donor). Our total cohort consisted of 6,026 recipients (48%) with acute myelogenous leukemia (AML) and myelodysplastic syndromes (MDS), 2,174 (17%) patients with hodgkin lymphoma (HL) or non-hodgkin lymphoma (NHL) and 1,736 (14%) patients with other leukemia or myeloproliferative syndromes (MPS). The frequency of other diseases is shown in Table 3.

Over the half of our patient cohort was over the age of 40, and 36 percent of our cohort were determined to carry on normal activity with special care needed prior to transplantation (Karnofsky performance scoring <80). Nearly 66% of our population was classified by CIBMTR to have coexisting disease prior to transplant. The annual volume of total HCT increased from 3,712 in 2008 to 4,458 in 2010.

{Table 3 Here}

Over the 2008-2010 period, the annual volume of patients in all risk categories increased from 2008 to 2010 with the exception of our lowest risk patients (risk category=0). To investigate the differences between centers that perform higher risk transplants versus centers that accommodate a lower risk transplant population we evaluated the trends in risk category distribution. Of particular interest, within centers that performed higher risk transplants the proportion of the lowest risk transplant recipients (age 18-40, Karnofsky performance score lower than 90, no comorbidity, and HLA matched related or unrelated donor) decreased significantly by 28% from 6.8 percent in 2008 to 4.9 percent in 2010 (p= 0.0005).

Characteristics by Type of Center: Disease groups, Regional and Volume Differences for High and Low Risk Centers

The disease group distribution of patients by their risk category components in high and low risk centers was similar. The distribution of AML and MDS from 2008-2010 represented the largest cohort of patients receiving HCT in both types of centers. In high risk centers, 5,101 (49%) of the patient population had AML and MDS while the patient population of low risk centers were composed of 47% (N=925) of patients with AML and MDS. NHL and HL was the second most common diagnosis amongst both low and high risk centers with 18 percent of the high risk center patients diagnosed with NHL and HL and 17 percent of low risk centers. The frequency of other diseases stratified by high and low risk center is shown in Table 2A-2C.

{Table 4A-4C Here}

HCTs were performed in all 10 HHS regions. Overall, we found the highest concentration of HCT centers in Region 4 (AL, FL, GA, KY, MS, NC, SC, TN) and Region 5 (IL, IN, MI, MN, OH, WI) with 27 and 25 centers respectively. Nearly 70% of centers within each region performed moderate risk HCT (RC=1/2/3). Of centers that performed moderate risk HCT, most were Academic Health Centers, Core Clinical Trial Network centers, and National Cancer Institute Comprehensive Cancer Centers (NCICCC). Of the 74 centers performing high risk transplants nearly all performed transplants in all risk category categories, with the exception of five centers that did not perform any lowest risk level transplants.

We further observed the frequency of center accreditation characteristics amongst our low risk and high risk centers, including the frequency of, Foundation for the Accreditation of Cellular Therapy (FACT) Centers, NCICCC, Academic Health Centers, Core Clinical Trial Network Center and Cord Blood Transplant Centers. We found that low risk centers were less likely to be FACT accredited (63% of low risk

centers were non-FACT centers), NCICCC (11 centers) and participate as a core clinical trial network center (6 centers). Conversely 81% of high risk centers were core clinical trial network centers and 72% were designated as NCICCC.

{Figure 4 Here}

In addition to being well accredited, high risk centers were generally higher volume centers. The mean HCT volume per center performed from 2008-2010 was 85 transplants (Range 2 transplants-529 transplants). The mean transplant volume per center in high risk centers was 141 transplants, while low volume centers had a mean transplant volume per center of 27 transplants from 2008-2010. Higher volume in high risk centers was not driven by high risk patients. Instead, high risk centers primarily focused on the lowest and moderate risk population (risk categories=0/1/2).

Association between Risk Category and Mortality

Unadjusted Kaplan Meier mortality estimates showed significantly higher 3 year overall mortality among patients in risk category=4 (Figure 3). When we stratified high and low risk transplant centers we found our Kaplan Meier mortality estimates unchanged. Specifically, our estimates showed that patients with RC=0 had the lowest 3 year overall mortality (median survival: 942 days), while the high risk (RC=4) group had significantly higher mortality (median survival: 243 days). We also found similar 3 year survival results for low risk patients in high risk centers (62% survival probability) and low risk patients in low risk centers (61% survival probability).

{Figure 5A-5B Here}

After adjusting for race, sex, year of transplant, HHS region and broad disease categories we found that, our pre-transplant risk groups were all significantly associated with higher relative hazard of death (adjusted hazard ratio (HR): 1.72; 95% Confidence Interval (1.51-1.96) for RC=1 & 2 vs. 0, adjusted HR: 2.55; 95% Confidence Interval

(2.227-2.92) for RC=3 vs. 0 and adjusted HR: 3.37; 95% Confidence Interval (2.835-4.016) for RC=4 vs. 0).

{Table 5 Here}

In all centers, race, hematological condition, region (region 2, region 3, region 4, region 6, and region 7) and volume were all associated with 3 year relative hazard of death ($p<0.05$ for all).

When we stratified centers by risk type we observed similar patterns. In high risk centers, after adjusting for race, sex, year of transplant, HHS region and broad disease categories we found that, our pre-transplant risk groups were all significantly associated with relative hazard of death relative to risk score=0 (adjusted hazard ratio (HR): 1.6; 95% Confidence Interval (1.404-1.902) RC=1 & 2 vs. 0, adjusted HR: 2.464; 95% Confidence Interval (2.107-2.881) RC=3 vs. 0 and adjusted HR: 3.2; 95% Confidence Interval (2.674-3.904) RC=4 vs. 0).

Low risk patients in low risk centers had similar relative hazard of death estimates compared to low risk patients in high risk centers. Specifically, in our cohort of lower risk centers, after adjusting for race, sex, year of transplant, HHS region and broad disease categories we found that, our pre-transplant risk groups were all significantly associated with higher relative hazard of death (adjusted hazard ratio (HR): 1.97; 95% Confidence Interval (1.523-2.552) RC=1 & 2 vs. 0, adjusted HR: 2.77; 95% Confidence Interval (2.069-3.702) RC=3 vs. 0).

Discussion

The last several decades has witnessed a remarkable expansion of HCT use both in the U.S. and globally. We find it noteworthy that while half our cohort of centers continues to explore new clinical successes with higher risk patients they do not demonstrate superior results for low and moderate risk patients. Relative to centers that

avoid the highest risk patients, we observed lower risk patients in high risk centers to have comparable outcomes.

Our risk groups are consistent with the pre-transplant risk literature that finds age, coexisting disease, Karnofsky score and HLA match levels to be significant indicators of overall HCT survival. Our risk category score allowed us to stratify low and high risk centers and to explore differences in survival for lower risk HCT patients. We sought to illustrate potential center level benefits of performing high risk HCT for overall center performance. We did not find any obvious differences or advantages for lower risk patients in high risk centers.

Our study builds upon previous studies examining the implications of pre-transplant risk on overall survival. Much of the literature has focused on validating various pre-HCT risk groupings. We use the literature as a starting point for our analysis and based on the established assumption that HCT survival varies by pre-transplant risk groupings.

Our analysis begins to move beyond the validation process of risk groups and focuses on the value of stratifying risk by centers both willing and unwilling to perform high risk transplants. Higher volume centers were more likely to perform higher risk transplants. However, higher risk volume did not drive overall patient volume in higher risk centers. Instead, our results indicate that higher risk centers focused most of their HCT procedures on the lower risk population. To a certain extent, this leads us to believe that the resources to treat lower risk patients in high risk centers are depleted. Research has previously shown that providers with more experience ('learning by doing') produce better outcomes. Although the surgical literature has shown a direct relationship between procedure volume and survival [19-25], our results point to the fact that higher procedure volume, and a willingness to take on riskier transplants does not directly

translate into improved outcomes for all other patients. Our results indicate that the fact that larger higher volume centers appeared to be more likely to take on pre-transplant risk cannot simply be a product of clinical expertise (more procedures increases experience). If indeed volume was a surrogate for HCT expertise we would expect higher risk centers to have superior outcomes for all risk categories.

This finding has important policy implications. What distinguishes risk taking centers from other centers is simply that a portion of their procedure population has higher pre-transplant risk and not that they perform all other transplants with equal dexterity. HCT center administrators and managers need not expect that the performance of higher risk HCT provides benefits in survival for lower risk patients.

Although our results cannot provide insight into the factors that patients may consider prior to considering a transplant center, including other clinical factors, cost and insurance coverage, our results point to the fact that higher volume centers attract various pre-transplant risk recipients to their centers and that there are other unmeasured factors that are common in both large versus small centers that provide similar outcomes. For lower risk patients, this is an important distinction that can help guide their decision to transplant at a lower volume and lower risk centers and expect similar rates of survival. More research is needed to determine if designated centers of excellence offer substantial benefits over other centers for lower risk or less complex patients. Patient and payer policy implications could include initiatives that reduce travel for low risk patients.

Although our study provides further insight into the relationship between risk stratification and HCT center specific survival we acknowledge data related limitations. The data we received from CIBMTR did not include post-transplant complications. We are unable to comment on post-transplant care and complications differences between

high and low risk centers. Additionally, our analysis only included three years of data. This limited our ability to measure a risk category trend over time or observe centers that crossed over from being low risk centers to high risk centers.

There are additional factors that may explain survival that we did not include in our model. For example, we did not include the CMV serostatus of donor and recipient, GVHD prophylaxis regimen, disease risk, cytogenetic and molecular prognostic factors, and whether treatment was performed on or off a clinical trial as the CIBMTR collects limited information on some of these variables at the registration level. Due to the fact that CIBMTR broadly identifies coexisting disease as either present or absent and because patient inclusion within a risk category may be a construct of a center's willingness to both over and under code the presence of a coexisting disease, we tested our risk categories with and without the inclusion of co-existing disease in our models. Despite these data limitations, we believe that our risk category groups provide practical benefit for clinicians and patients alike to stratify centers into risk categories.

The SCTRA was passed in order to establish a more transparent transplant outcomes research environment in which center results could easily be retrieved by clinicians and HCT recipients. Novel clinical approaches have expanded HCT to a more complex case mix of patients and increased risk for HCT will certainly continue to be more common in the coming decades. Still, our results show HCT remains associated with significant mortality for all pre-transplant risk categories and that there is indeed no difference between centers when stratified for risk. However, the broader relationship between a center's specific HCT survival rates remains complex, requiring a deeper understanding of the causal mechanisms involved in individual transplant centers and finding specific factors that could be introduced to all centers to improve outcomes. Particularly given the SCTRA, the increased transparency of information and stronger

ties of quality and transplant related readmission to payment provides transplant recipients with a more balanced choice of transplant center. While our work begins this stratification process, our results suggest the need for additional research using longitudinal data and corresponding methods to investigate the factors that more broadly predict the characteristics of superior centers and improve survival for all levels of pre-transplant risk.

Figure 2: Summary of Characteristics Included in the Risk Categories

Summary of Characteristics Included in the Risk Categories		
High Risk (Risk Category Score=4)	**Moderate Risk (Risk Category Score=1,2,3) Patients with 1,2 or 3 of the following:**	**Low Risk (Risk Category Score=0)**
• Age > 40	• Age > 40	• Age ≤40
• Coexisting disease	• Coexisting disease	• No Coexisting disease
• HLA Mismatch (7/8, 6/8, One locus mismatched relative, > One locus mismatched relative)	• HLA Mismatch (7/8, 6/8, One locus mismatched relative, > One locus mismatched relative)	• HLA Match (8/8, Matched sibling, Syngeneic, Matched relative)
• Karnofsky Performance Status score at transplant (10 to 80)	• Karnofsky Performance Status score at transplant (10 to 80)	• Karnofsky Performance Status score at transplant (90 to 100)

Figure 3: Unadjusted Kaplan Meier Overall 3 Year Mortality Estimates by Risk categories for all Transplant Centers 2008-2010

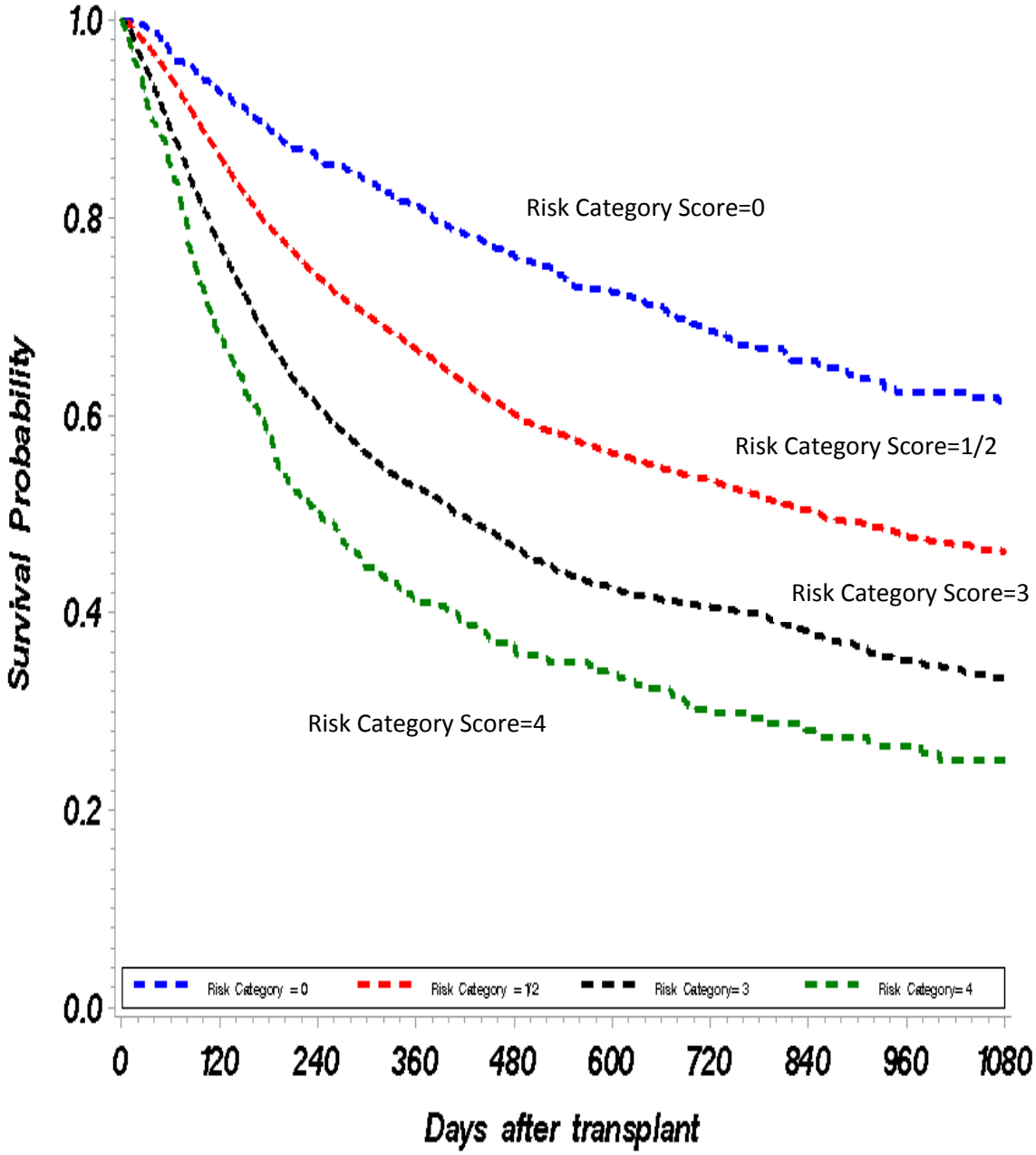
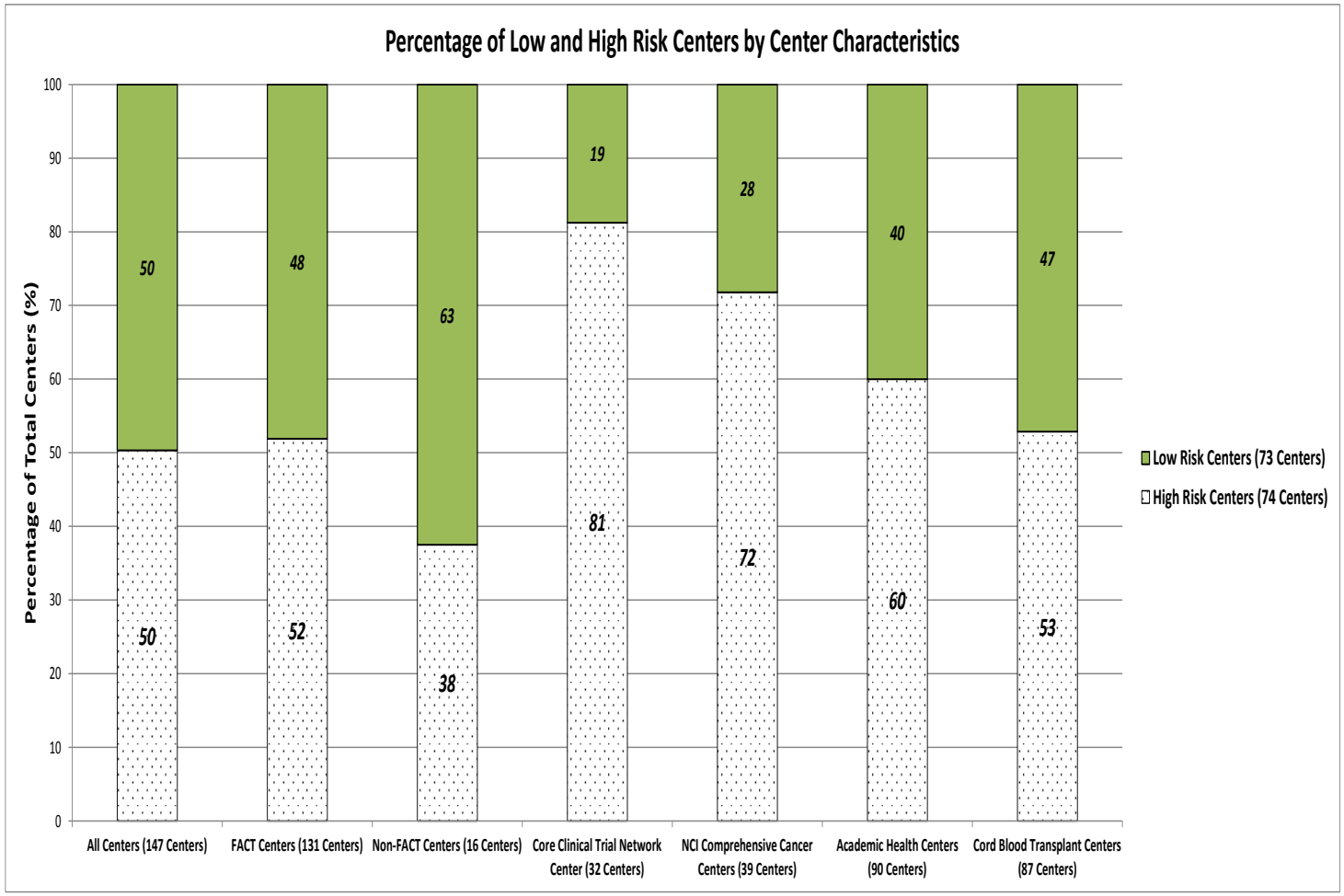
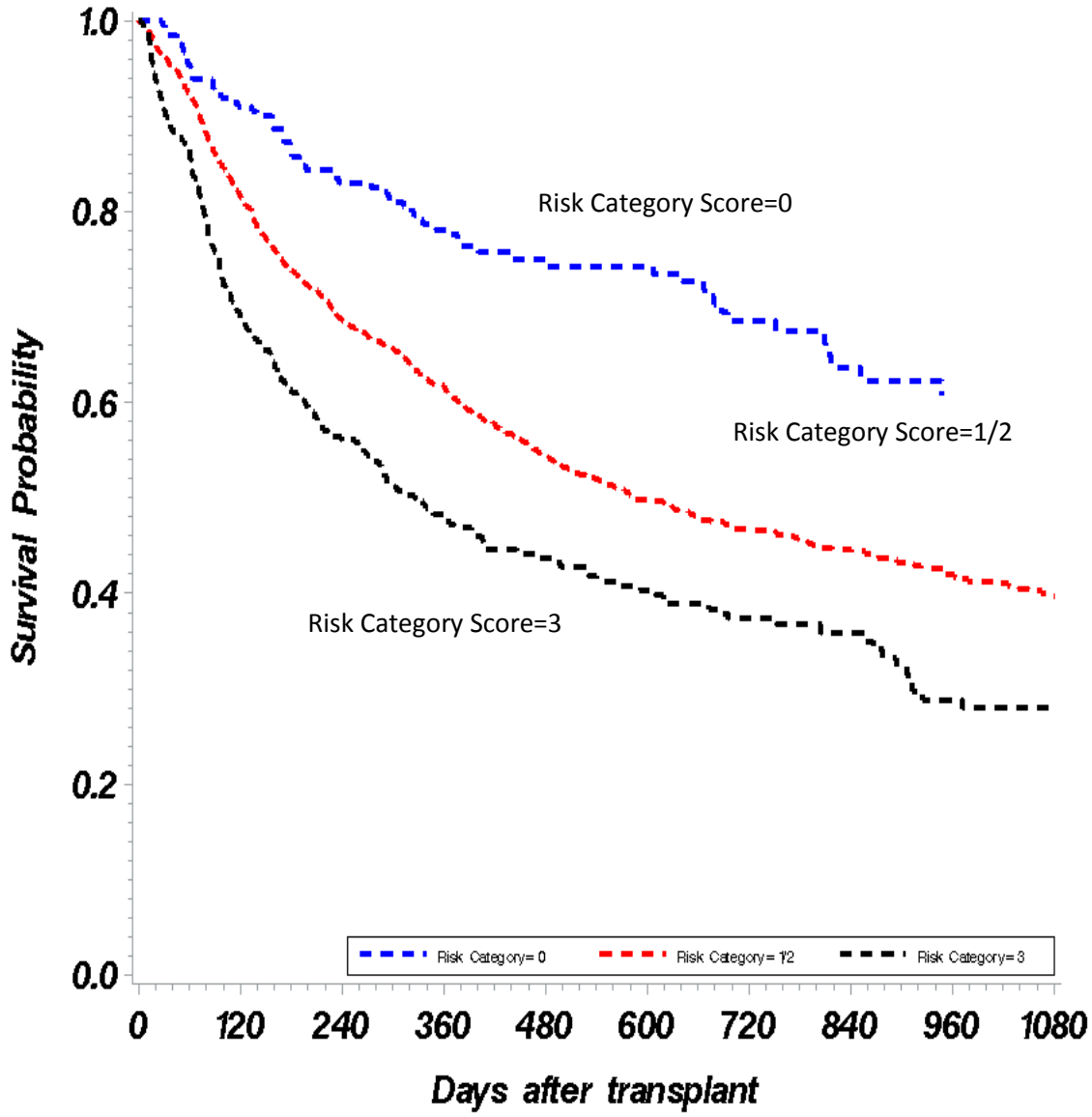


Figure 4: Center Charachtersitics of Low and High Risk Centers 2008-2010*



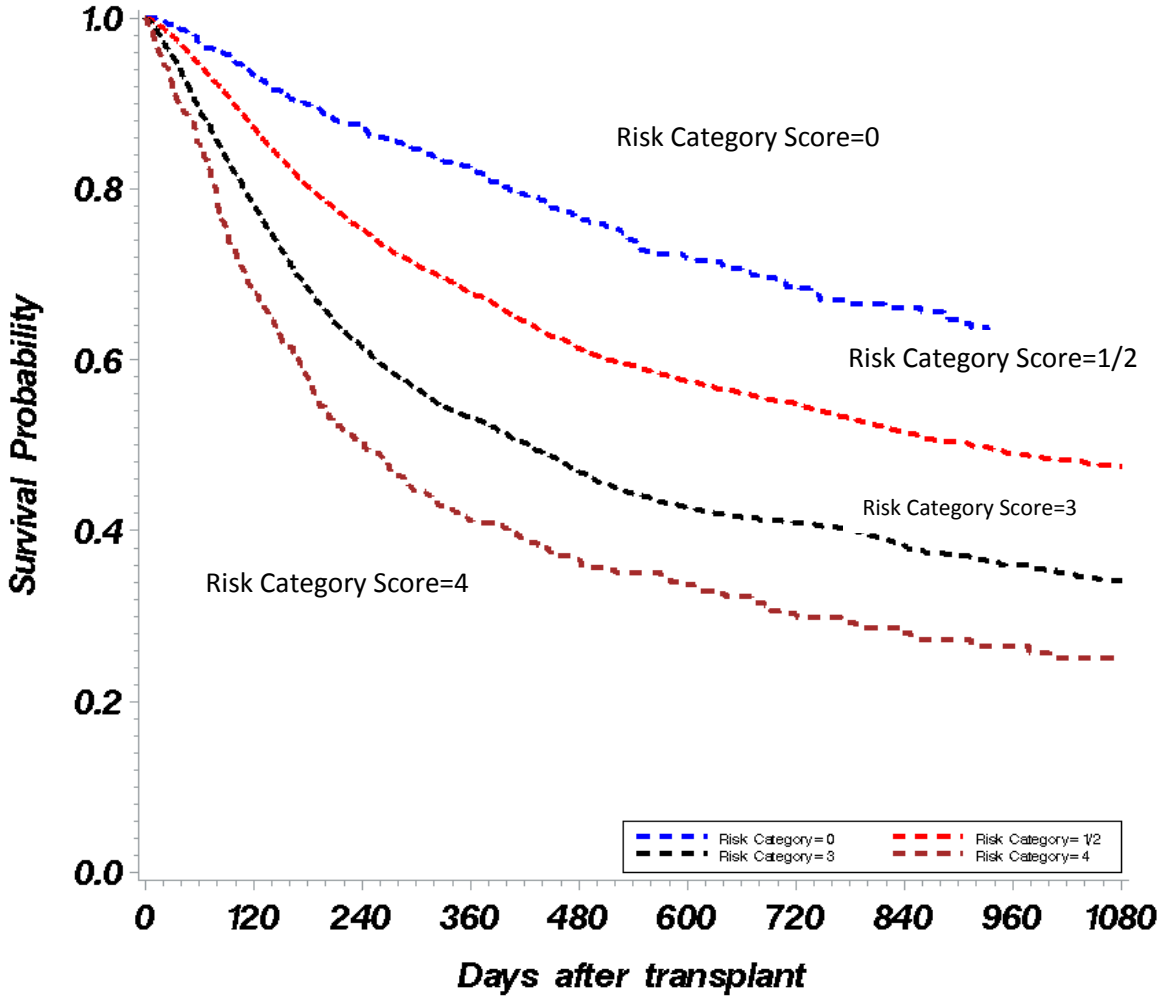
*Centers can be in more than 1 Characteristic Grouping.

Figure 5A: Adult Unrelated and Related Overall Survival in Low Risk Centers by Risk Categories 2008-2010



		240 Days	365 Days	1080 Days
Risk Category=0				
Number at Risk	212	176	165	147
Survival Probability		83%	78%	61%
Risk Category=1/2	146			
Number at Risk		1003	892	722
Survival Probability		69%	61%	39%
Risk Category=3				
Number at Risk	310	174	147	114
Survival Probability		56%	48%	23%

Figure 5B: Adult Unrelated and Related Overall Survival in High Risk Centers by Risk Categories 2008-2010



		240 Days	365 Days	1080 Days
Risk Category=0				
Number at Risk	586	510	482	411
Survival Probability		87%	82%	62%
Risk Category=1/2				
Number at Risk	6698	5041	4533	3802
Survival Probability		75%	68%	48%
Risk Category=3				
Number at Risk	2749	1689	1462	1180
Survival Probability		61%	53%	31%
Risk Category=4				
Number at Risk	419	210	172	131
Survival Probability		50%	41%	20%

Table 3: Basic Characteristics of Related and Unrelated Transplant Recipients by Risk Category (2008-2010)

	All		Risk Bundle=0		Risk Bundle= 1&2		Risk Bundle=3		Risk Bundle=4		P-Value
	N	%	N	%	N	%	N	%	N	%	
Number of Transplant Recipients Total	12436		798	6	8160	66	3059	25	419	3	
Transplant Year											
2008	3764	30	284	36	2483	30	885	29	112	27	0.0087
2009	4149	33	246	31	2716	33	1031	34	156	37	
2010	4523	36	268	34	2961	36	1143	37	151	36	
Gender											
Male	5218	42	320	40	3388	42	1334	44	176	42	0.1578
Female	7218	58	478	6	4772	66	1725	25	243	3	
Patient Race											
Non-Hispanic White	10230	82	563	71	6709	82	2605	85	353	84	<.0001
Hispanic	976	8	126	16	657	8	176	6	17	4	
Black/African American	666	5	36	5	410	5	183	6	37	9	
Other/Multiple Race/Unknown	564	5	73	9	384	5	95	3	12	3	
Disease Group											
Acute Myelogenous Leukemia & Myelodysplastic Disorders	6026	48	298	37	3825	47	1657	54	246	59	<.0001
Acute Lymphoblastic Leukemia	1523	12	201	25	1023	13	270	9	29	7	
Other Leukemia & Myeloproliferative Syndromes	1736	14	77	10	1158	14	434	14	67	16	
Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	2174	17	140	18	1508	18	473	15	53	13	
Other Malignancy	565	5	8	1	385	5	156	5	16	4	
Severe Aplastic Anemia	320	3	58	7	193	2	61	2	8	2	
Other Non-Malignant Disease	92	1	16	2	68	1	8	0	0	0	
Centers by Department of Health and Human Services Regions											
Region 1: (CT, ME, MA, NH, RI, & VT)	1025	8	73	9	712	9	205	7	35	8	<.0001
Region 2: (NJ, NY)	1132	9	74	9	709	9	291	10	58	14	
Region 3: (DE, DC, MD, PA, VA, WV)	1329	11	104	13	873	11	316	10	36	9	
Region 4: (AL, FL, GA, KY, MS, NC, SC, TN)	1937	16	74	9	1214	15	576	19	73	17	

Region 5: (IL, IN, MI, MN, OH, WI)	2262	18	127	16	1471	18	575	19	89	21	
Region 6: (AR, LA, NM, OK, TX)	1322	11	80	10	814	10	384	13	44	11	
Region 7: (IA, KS, MO, NE)	618	5	18	2	384	5	190	6	26	6	
Region 8: (CO, MT, ND, SD, UT, WY)	385	3	22	3	254	3	99	3	10	2	
Region 9:(AZ, CA, HI, NV)	1687	14	203	25	1205	15	251	8	28	7	
Region 10 (AK, ID, OR, WA)	739	6	23	3	524	6	172	6	20	5	
Patient Age at Transplant											
18 to 29	1562	13	352	56	974	13	66	2	0	0	<.0001
30 to 39	1392	11	0	44	1693	12	684	2	0	0	
40 to 49	2487	20	0	0	2557	21	1193	22	143	26	
50 to 59	3893	31	0	0	1725	31	970	39	152	34	
60 to 69	2847	23	0	0	148	21	93	32	14	36	
>70	255	2	0	0	148	2	93	3	14	3	
Patient Karnofsky Performance Status score at transplant											
90-100	7997	64	798	100	6556	80	643	21	0	0	<.0001
≤80	4439	36	0	0	1604	20	2416	79	419	100	
Coexisting Disease											
Absent	4516	36	798	100	3576	44	142	5	0	0	<.0001
Present	7920	64	0	0	4584	56	2917	95	419	100	
HLA Matching Unrelated Donor											
Matched Unrelated	5131	76	0	100	3589	86	1067	62	23	0	<.0001
Mismatched Unrelated	1597	24	29	0	303	14	245	38	73	100	
HLA Matching Related Donor											
Mismatched Relative	532	9	0	0	189	5	247	19	96	100	<.0001
Matched Relative	5176	91	408	100	3703	95	1065	81	0	0	

Table 4A: Disease Groups of Related and Unrelated Transplant Recipients by Risk Category for All Centers (2008-2010)

	All		Risk Category=0		Risk Category=1&2		Risk Category=3		Risk Category=4	
Disease Group	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Acute Myelogenous Leukemia & Myelodysplastic Disorders	6026	48	298	37	3825	47	1657	54	246	59
Acute Lymphoblastic Leukemia	1523	12	201	25	1023	13	270	9	29	7
Other Leukemia & Myeloproliferative Syndromes	1736	14	77	10	1158	14	434	14	67	16
Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	2174	17	140	18	1508	18	473	15	53	13
Other Malignancy	565	5	8	1	385	5	156	5	16	4
Severe Aplastic Anemia	320	3	58	7	193	2	61	2	8	2
Other Non-Malignant Disease	92	<1	16	2	68	<1	8	<1	0	0

Table 4B: Disease Groups of Related and Unrelated Transplant Recipients by Risk Category for High Risk Centers (2008-2010)

	All		Risk Category=0		Risk Category=1&2		Risk Category=3		Risk Category=4	
Disease Group	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Acute Myelogenous Leukemia & Myelodysplastic Disorders	5101	49	234	40	3145	47	1476	54	246	59
Acute Lymphoblastic Leukemia	1229	12	140	24	825	12	235	9	29	7
Other Leukemia & Myeloproliferative Syndromes	1496	14	59	10	978	15	392	14	67	16
Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	1830	18	100	17	1242	19	435	16	53	13
Other Malignancy	493	5	7	1	320	5	150	5	16	4
Severe Aplastic Anemia	248	2	39	7	147	2.19	54	2	8	2
Other Non-Malignant Disease	55	<1	7	1	41	<1	7	<1	0	0

Table 4C: Disease Groups of Related and Unrelated Transplant Recipients by Risk Category for Low Risk Centers (2008-2010)

	All		Risk Category=0		Risk Category=1&2		Risk Category=3	
Disease Group	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Acute Myelogenous Leukemia & Myelodysplastic Disorders	925	47	64	30	680	47	181	58
Acute Lymphoblastic Leukemia	294	15	61	29	198	14	35	11
Other Leukemia & Myeloproliferative Syndromes	240	12	18	8	180	12	42	14
Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	344	17	40	19	266	18	38	12
Other Malignancy	72	4	1	0	65	4	6	2
Severe Aplastic Anemia	72	4	19	9	46	3	7	2
Other Non-Malignant Disease	37	2	9	4	27	2	1	<1

Table 5: Factors Associated with 3 Year Relative Hazard of Death among HCT Patients, Cox Proportional Hazard Models, Hazard Ratio, 95% CI

	Cox Model ALL				Cox Model High Risk Centers				Cox Model Low Risk Centers			
	Hazard Ratio	95% CI		P Value	Hazard Ratio	95% CI		P Value	Hazard Ratio	95% CI		P Value
Risk Categories												
0	REF				REF				REF			
1/2	1.721	1.51	1.961	<.0001	1.634	1.404	1.902	<.0001	1.971	1.523	2.552	<.0001
3	2.552	2.227	2.925	<.0001	2.464	2.107	2.881	<.0001	2.768	2.069	3.702	<.0001
4	3.374	2.835	4.016	<.0001	3.231	2.674	3.904	<.0001	-	-	-	-
Gender												
Male	REF				REF				REF			
Female	0.914	0.868	0.963	0.0007	0.923	0.872	0.977	0.0058	0.871	0.766	0.99	0.035
Patient Race												
Non-Hispanic White	REF				REF				REF			
Hispanic	1.055	0.954	1.166	0.2955	1.072	0.956	1.201	0.2327	1.004	0.811	1.244	0.9697
Black/African American	1.16	1.038	1.296	0.0087	1.056	0.927	1.203	0.4094	1.552	1.247	1.932	<.0001
Other/Multiple Race/Unknown	0.993	0.871	1.133	0.9215	0.964	0.835	1.112	0.611	1.216	0.874	1.692	0.2456
Transplant Year												
2008	REF				REF				REF			
2009	1	0.939	1.064	0.9877	0.977	0.913	1.046	0.5083	1.115	0.956	1.302	0.1663
2010	1.007	0.942	1.076	0.8375	0.99	0.92	1.066	0.7955	1.093	0.929	1.287	0.2834
Disease Group												
Acute Myelogenous Leukemia & Myelodysplastic Disorders	REF				REF				REF			
Acute Lymphoblastic Leukemia	0.992	0.915	1.077	0.8562	0.96	0.876	1.052	0.3805	1.129	0.94	1.357	0.1949
Other Leukemia & Myeloproliferative Syndromes	0.763	0.704	0.827	<.0001	0.749	0.686	0.818	<.0001	0.849	0.693	1.04	0.1143
Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	0.829	0.771	0.892	<.0001	0.823	0.76	0.892	<.0001	0.865	0.722	1.037	0.1165
Other Malignancy	0.929	0.822	1.05	0.2371	0.926	0.811	1.056	0.252	0.926	0.666	1.288	0.6496
Severe Aplastic Anemia	0.548	0.445	0.675	<.0001	0.644	0.514	0.806	0.0001	0.296	0.17	0.516	<.0001
Other Non-Malignant Disease	0.627	0.436	0.901	0.0116	0.712	0.441	1.15	0.1647	0.526	0.3	0.923	0.0251

	Cox Model ALL				Cox Model High Risk Centers				Cox Model Low Risk Centers			
	Hazard Ratio	95% CI		P Value	Hazard Ratio	95% CI		P Value	Hazard Ratio	95% CI		P Value
Centers by Department of Health and Human Services Regions												
Region 1: (CT, ME, MA, NH, RI, & VT)	REF				REF				REF			
Region 2: (NJ, NY)	1.146	1.013	1.298	0.0308	1.126	0.988	1.283	0.0751	1.422	0.935	2.164	0.0999
Region 3: (DE, DC, MD, PA, VA, WV)	1.203	1.066	1.357	0.0027	1.209	1.06	1.379	0.0047	1.235	0.848	1.797	0.2709
Region 4: (AL, FL, GA, KY, MS, NC, SC, TN)	1.124	1.005	1.257	0.0403	1.134	1.007	1.277	0.0379	1.136	0.787	1.639	0.4969
Region 5: (IL, IN, MI, MN, OH, WI)	1.082	0.968	1.209	0.1655	1.072	0.953	1.207	0.2465	1.183	0.812	1.723	0.3818
Region 6: (AR, LA, NM, OK, TX)	1.194	1.059	1.346	0.0037	1.24	1.092	1.409	0.0009	1.074	0.729	1.582	0.7174
Region 7:(IA, KS, MO, NE)	1.287	1.117	1.482	0.0005	1.295	1.118	1.5	0.0006	1.408	0.807	2.456	0.2286
Region 8:(CO, MT, ND, SD, UT, WY)	1.083	0.911	1.288	0.3634	1.081	0.907	1.287	0.3849	0	0	4E+154	0.9531
Region 9:(AZ, CA, HI, NV)	1.062	0.943	1.196	0.3225	1.016	0.896	1.153	0.8032	1.338	0.9	1.988	0.1498
Region 10 (AK, ID, OR, WA)	1.057	0.918	1.218	0.439	1.052	0.911	1.214	0.4935	0.952	0.128	7.065	0.9617
Center Characteristics												
Low Volume Indicator (≤55 Transplants)	REF				REF				REF			
High Volume Indicator (>55 Transplants)	1.205	1.099	1.322	<.0001	1.333	1.171	1.518	<.0001	1.184	1.024	1.368	0.0226
Related Donor Indictor	REF				REF				REF			
Unrelated Donor Indicator	1.151	1.092	1.214	<.0001	1.142	1.078	1.211	<.0001	1.202	1.056	1.369	0.0054
FACT Status (no)	REF				REF				REF			
FACT Status (yes)	0.958	0.843	1.088	0.5050	1.128	0.943	1.351	0.1883	0.865	0.702	1.065	0.1714
Low Risk Center Indicator	REF											
High Risk Center Indicator	1.136	1.048	1.232	0.002	-	-	-	-	-	-	-	-

Chapter 4: The Impact of Center Accreditation on Hematopoietic Cell Transplantation (HCT): Should HLA Mismatched HCT be Restricted to Foundation for the Accreditation of Cellular Therapy (FACT) Centers and Core Clinical Trial Network Centers?

Background: Hematopoietic cell transplantation (HCT) is the transplantation of stem cells from a related or unrelated donor for the treatment of many hematologic malignancies. The choice of donor is based on compatible human leukocyte antigen (HLA). HLA match quality (8/8 loci) is an essential component of higher survival rates among HCT recipients and whenever possible, HLA mismatching (7/8 loci) is avoided. There are two voluntary center accrediting organizations, The Foundation for the Accreditation of Cellular Therapy (FACT) and core clinical trial network certification (CTN) that are thought to improve and ensure HCT center quality care, engage in rigorous donor and cell selection criteria and certify clinical excellence. We sought to observe whether there are differences in outcomes among HLA matched and mismatched HCT by CTN and FACT status.

Methods: Using the 2008-2010 Center for International Blood & Marrow Transplant Research (CIBMTR) data we created three center categories (a) non-FACT centers (n=24 centers) (b) FACT-only certified centers (N=106 centers) and (c) FACT and core clinical trial network (FACT/CTN) certified centers (N=32 centers). We identified HLA match categories and patient characteristics within our centers and the relationship between FACT certification and survival. The association between our center categories and hazard of death was evaluated using Cox proportional hazard modeling.

Results: Our transplant cohort consisted of 12,993 transplants conducted in 162 centers. The number of total HCTs increased from 3,984 in 2008 to 4,639 in 2010. Over time, the number of patients in all categories (related and unrelated, HLA matched and mismatched) increased. After adjusting for patient and center characteristics we found that FACT/CTN centers had consistently superior results relative to non-FACT and FACT only centers ($p<0.05$). However, non-FACT centers were comparable to FACT-

only centers for matched related and unrelated patients. FACT/CTN centers showed particular superiority for more complex HCT.

Conclusions: Current attempts to improve and ensure HCT quality care and certify clinical excellence include voluntary center participation in FACT. Our findings imply that FACT/CTN centers have better survival rates than other accredited and non-accredited centers and are particularly superior at treating more complex HLA mismatched HCTs. However, we do not see fundamental differences in survival between FACT and non-FACT centers in the less complex matched cohort. Although FACT status is an important standard of quality control that begins to define improved overall survival our results indicate that FACT status alone is not an indicator for superior outcomes.

Background

Allogeneic hematopoietic cell transplantation (HCT) is a complex treatment for several hematological disease groups and involves the infusion of donor hematopoietic stem cells into a recipient. In the past several decades, human leukocyte antigen (HLA) matching capabilities and refined methodology has buttressed clinical abilities to increase the successful performance of HCT. For example, donor and recipient HLA matches can be made on an 8 of 8 (match) or 7/8 (mismatched) HLA level for unrelated donor HCT. A 6/8 or lower donor recipient match is generally considered unacceptable for successful HCT. [40]

The search for a donor and recipient HLA match begins with the patient's siblings who have the same parents as the patient. If a sibling is not a perfect match (8/8 loci are matched), the search moves to other immediate family members and possibly unrelated donors creating four total categories; HLA matched related, HLA mismatched related, HLA matched unrelated and HLA mismatched unrelated transplants.[15-41]Finding suitable related or unrelated donors has increasingly become more common in the last decade with the proliferation of HCT centers and ease of access to donor registries. It is widely accepted that match quality is an essential component of higher survival rates and improved long term outcomes among HCT recipients.[15-16, 40-42] Clinical best practice dictates that whenever possible, HLA matched donors are preferable in regulating responses between donor and recipient, reducing the risk of post-transplant complications and infections and improving the chances for long term survival.[15-16, 40-42]

The Foundation for the Accreditation of Cellular Therapy (FACT) is a non-profit entity co-founded by the International Society for Cellular Therapy and the American Society of Blood and Marrow Transplantation in 1996. [23] Its core mission is to certify the clinical excellence in process and outcomes of transplant centers. In addition to facility

certification, FACT publishes standards of excellence that are readily available to all centers. Specific standards include minimum of 5 HCTs annually, guidelines for HCT center laboratories and clinical oversight and methodologies for HLA typing and processing. The first edition of the FACT standards was published in 1996, and the first center was accredited in 1998. Accreditation is awarded after successful documentation of compliance with the current FACT standards and an annual fee is paid. Annual on-site inspections are carried out by a team of clinical inspectors. [23]

FACT centers are thought to be centers of excellence that engage in rigorous donor and cell selection criteria and exert adequate quality control over the entire HCT process. Non-FACT centers may adhere to evidence based practice and levels of non-accredited levels of excellence in process and outcomes. However, it is assumed that payers and providers do not recognize non-FACT accredited centers in the U.S. as experienced centers with fully developed clinical treatment protocols.[6, 21, 23]There is a core assumption that FACT centers adhere to standards of excellence set by clinical experts in the field of transplantation medicine, surgery, nursing and pharmacy that is unattainable by other non-accredited centers.[23]

Certifying and accrediting centers of excellence are not novel approaches to oversee and underscore standards of excellence and health care quality and outcomes. There is a broad literature exploring whether there are differences in process and outcomes at academic health centers, accredited centers of excellence, teaching hospitals and the National Cancer Institute's Comprehensive Cancer Centers (NCICCC). [21, 48, 63-67, 71] Results have been mixed. For example, using the national Medicare database, Birkmeyer et al. conducted an analysis of 51 NCICCC and six cancer procedures, cystectomy, colectomy, pulmonary resection, pancreatic resection, gastrectomy, and esophagectomy cancer. [48] Although Birkmeyer did not fully account for

differences in patient population, she found that NCI designated cancer centers had lower surgical mortality rates than those treated at comparably high-volume hospitals, but had similar long-term survival rates.[48] Meguid et al. found that in-hospital outcomes are superior for patients undergoing lung cancer resections at teaching hospitals, with results prominent at all but the highest volume institutions.[63]Other literature that analyzed either process measures of care or that assessed risk-adjusted mortality rates found differences in quality between major teaching hospitals and nonteaching hospitals across several cancer groups.[68-72]These differences have been reported in combined analyses of multiple conditions but have not always been consistent in finding significant results and rarely do these analyses control for center volume.

The HCT literature that focuses on center characteristics and FACT certification is limited. Several transplant center characteristics have been associated with increased survival. Majhail et al. found that practice variation, such as physician workforce, transplant capacity, clinician approach to transplantation for hematologic disorders and choice of graft source can impact the quality of care for transplant recipients. [19] Using Center for International Blood & Marrow Transplant Research data from 1998-2000, Loberiza et al. found significant survival differences for patients receiving allogeneic HCT in centers with one or more favorable center related factors such as physician caseload, contact for afterhours call and medical school affiliation. [20] However, Loberiza did not find an association between factors that might be expected to correlate with increased levels of survival such as FACT accreditation (yes/no) and NCICCC designation.

In addition to FACT accreditation, centers hold a variety of other credentials including NCICCC, Academic Health Center status, Accreditation Council for Graduate Medical Education-approved centers and Center of Excellence Designation by Medical Insurance Plans. These are highly correlated to each other. In 2001, With the support of

the National Cancer Institute and the National Heart, Lung, and Blood Institute, the Blood and Marrow Transplant Clinical Trials Network (CTN) was established.[38] Currently, there are 32 centers that participate as "core" centers within the U.S. with the goal of conducting phase II and III multicenter trials to address clinical issues in HCT and offer trial participation to patients in all regions of the United States. For this study we created three center categories that included non-FACT centers, FACT-only accredited centers and FACT and core CTN centers (FACT/CTN).

The literature has previously found no significant differences between FACT and non-FACT centers. As FACT accreditation has become more common among centers (approximately 90% of U.S. HCT centers are accredited), we created a third center category in order to determine if FACT accreditation and clinical trial participating centers demonstrated a high level of excellence. Additionally, in order to account for patient complexity, we sought to determine if accreditation had any impact on the survival of HLA mismatched HCT. Specifically, our goal is to broaden the scope of the accreditation and HCT literature by assessing if there are differences in outcomes among HLA matched and mismatched HCT by FACT and CTN status.

Methods

Data Source

The Center for International Blood & Marrow Transplant Research (CIBMTR) is a research affiliation of the International Bone Marrow Transplant Registry, Autologous Blood and Marrow Transplant Registry, and National Marrow Donor Program (NMDP) that was established in 2004. CIBMTR is comprised of a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive HCT to a Statistical Center at the Medical College of Wisconsin in Milwaukee, WI and the NMDP Coordinating Center in Minneapolis, MN. In addition, the CIBMTR holds the contract for the Stem Cell Therapeutic Outcomes Database part of

the CW Bill Young Transplantation Program from the Human Resources and Services Administration; as a part of this Program, all transplant centers in the US are mandated to report clinical outcomes data for allogeneic HCT to the CIBMTR. All CIBMTR teams contribute registration data (also called transplant essential data (TED)). These data include disease type, age, sex, pre-transplant disease stage, date of diagnosis, graft type, conditioning regimen, post-transplant disease progression and survival, development of a new malignancy, and cause of death. TED level data are collected before transplant, 100 days and 6 months after transplant, and annually thereafter or until death. We obtained a de-identified dataset from CIBTMR. Our study was deemed exempt from review by the Human Subjects Committee of the University of Minnesota's Institutional Review Board.

FACT Center Categories and Center Characteristics

We linked our CIBMTR data to a publically available FACT organizational list and the core clinical trial network certified (CTN) center status list[38,83]and created three center categories (a) non-FACT centers (n=24 centers) (b) FACT-only accredited centers (N=106 centers) and (c) FACT and core clinical trial network certified centers (FACT/CTN) (N=32 centers). FACT/CTN centers are accredited by FACT but are also part of HCT leadership as they conduct multicenter trials to address clinical issues in HCT. FACT/CTN centers are assumed by our study to adhere to a higher form of excellence in relation to other centers. In addition to FACT and CTN status we recorded several other center characteristics including 10 Department of Health and Human Services (HHS) regions and center volume quartiles.

Patient Variables

We included transplant recipients 18 years or older who received transplants between January 1, 2008, through December 31, 2010 and were reported to the CIBTMR. We included patients who received peripheral blood stem cells or bone

marrow graft from HLA-matched or mismatched, related or unrelated donors. All diagnoses, the 4 level recipient and transplant donor match category (matched related, mismatched related, matched unrelated and mismatched unrelated), coexisting disease, and patient Karnofsky score were included.

The Karnofsky performance status is used to determine the functional status of a recipient and can range from 0-100. A Karnofsky performance score of 90-100 categorizes patients with the ability to carry on normal activity and no special care is needed. [84] CIBMTR categorized Karnofsky scoring as a dichotomous variable of 90-100, and ≤ 80. Coexisting disease is a binary category of diseases collected by CIBMTR. CIBMTR codes HCT patients with any of 18 comorbidities as coexisting disease present. [85] We included patients that had missing coexisting disease information (N=406). We combined our matched related and unrelated patients into one category and our mismatched related and unrelated patients into a second category. Prior to consolidating related and unrelated transplant groups we created separate categories for each transplant group and independently verified our models for each group.

Statistical Analysis

We evaluated differences in FACT center status and patient characteristics across all years of transplantation. To assess whether the performance of mismatched HLA HCTs changed over time, we used the Cochrane- Armitage trend test. Additionally, we evaluated the differences in FACT center status and patient characteristics using the chi-square test.

After assessing unadjusted relationships we used logistic regression to examine the association between the relative odds of mismatched related or unrelated HCT (yes/no), patient demographics and FACT/CTN status. Finally, we evaluated the association between FACT certification and 3 year hazard of death using Kaplan-Meier

methods and Cox proportional hazards modeling. Kaplan-Meier methods were used to estimate unadjusted 3 year cumulative mortality by transplant center FACT status and HLA match type categories within our analytical period. In order to capture the interaction between both FACT status and HLA match category we created an HLA match category by FACT status variable. To adjust for possible high volume center effects in our cohort a high volume transplant center indicator was added to all multivariate models as a frailty variable.

In all models, we performed several sensitivity analyses to ensure that the observed effects were not a product of our FACT center classification and modeling decisions. We modeled our cohort with and without the inclusion of non-FACT centers in order to ensure that these centers did not distort our results for the two other FACT categories, in which the majority of transplants were performed. We did not observe a change in the magnitude or direction of our results. We performed several survival analyses on separate sub-cohorts to ensure that various severity distinctions and disease groups did not alter our results. We also performed separate survival analyses to verify that our proportional hazard ratios were not a product of transplant volume and center regions and measured proportional hazard ratios for low and high volume centers and higher HCT concentration regions (appendix 9 and 10). Finally, we conducted separate analyses for related and unrelated cohorts (appendix 11a-11e). Under all assumptions, conclusions remain unchanged. See appendix for complete descriptions of sensitivity analysis results.

SAS version 9.3 (SAS Institute) was used for all analyses. P values were 2 sided with a level of significance of ≤.05.

Results

Our final cohort consisted of 12,993 transplants conducted in 162 centers. Of these, 24 centers were non-FACT certified (N=559 transplants), 106 centers were

FACT-only certified (N=5,655 transplants), and 32 centers had FACT/CTN status (N=6,779 transplants). Between 2008-2010, the annual number of total transplants increased for all types of centers. Most of the patient cohort was classified with a coexisting disease (64%, N=8,279) and 62% had a Karnofsky score above 90 (N=8,014). The majority of the patients (66%) were diagnosed with AML and MDS (N=6,263 transplants) or NHL and HL (N=2,320 transplants).

{Table 6 HERE}

We found that matched and mismatched unrelated HCT increased significantly over time ($p<.05$) while transplants in the related HCT category did not experience a significant increase. Matched related donors (N=5,349 transplants) or matched unrelated donors (N=5,419 transplants) accounted for 83% of HCTs. The percentage of unrelated transplants ranged from 45% within FACT/CTN centers to 48% in non-FACT centers. Similarly, nearly half of the transplants performed in FACT-only and non-FACT centers were related HCTs (47% related FACT-only HCT and 52% related non-FACT HCT). When the transplant population was broken down by FACT status and HLA matched or mismatched status, non-FACT centers performed the highest percentage of matched related or unrelated HCT (86%) and FACT/CTN centers performed the highest percentage of mismatched related and unrelated transplants (18%). FACT only and non-FACT centers performed a similar proportion of mismatched related/unrelated transplants (16% and 14% respectively).

{Figure 6A and 6B Here}

Association between Receipt of HLA Mismatch HCT and FACT Status

In our study, 17% of HCT patients received a mismatched related or unrelated transplant. We used multivariate analyses in order to examine the association between the relative odds of mismatched related or unrelated HCT and FACT status and the

likelihood of HLA mismatched HCT at non-FACT, FACT-only or FACT/CTN certified facilities. After adjusting for center and clinical variables, patients were significantly more likely to have HLA mismatched HCT at FACT/CTN certified facilities (adjusted odds ratio (OR) FACT/CTN versus Non-FACT, 1.43; p-value <.0001). Additional factors significantly associated with the increased likelihood of HLA mismatched HCT included race (Hispanic, African American, multiple race versus non-Hispanic white), and region (DHS Region 2, Region 3, and Region 9 versus Region 1).

{Table 7 HERE}

There were also factors significantly associated with a decreased likelihood of HLA mismatched HCT including, older age categories 40-69 (relative to ages 18-29). Acute Lymphoblastic Leukemia and SAA were disease categories significantly associated with a decreased likelihood of HLA mismatched relative to AML and MDS. Although transplant year was not significantly associated with mismatched HCT, the likelihood of mismatched transplants decreased over time.

Association between FACT Status and Mortality

Unadjusted Kaplan Meier mortality estimates showed significantly higher 3 year overall mortality among all patients in both non-FACT and FACT-only centers relative to FACT/CTN.

{Figure 7A-7C HERE}

When we stratified matched and mismatched transplant recipients by center certification status we found that FACT/CTN centers had the lowest 3 year overall mortality among HLA matched related patients. However, non-FACT and FACT certified centers showed strikingly similar curves for HLA matched related recipients. Unadjusted Kaplan Meier mortality estimates showed significantly higher 3 year overall mortality among mismatched related HCTs within FACT-only centers. For the unrelated matched

HCT cohort both non-FACT and FACT-only centers had lower 3 year overall mortality than mismatched unrelated HCT recipients. These results were unchanged when we further restricted our cohort to high volume centers.

Adjusted Association between FACT Status and Hazard of Death

In order to capture the interaction between both FACT status and HLA match category we created an HLA match category by FACT status variable. After adjusting for patient and center characteristics we found that our non-FACT/mismatched HCT patients had the highest adjusted relative hazard of death (adjusted hazard ratio (HR): 2.05; p-value<.0001 non-FACT/Any Mismatch vs. non-FACT/Matched). However, FACT/Matched patients had a higher relative hazard of death relative to Non-FACT/Matched HCT (adjusted HR: 1.138; p-value .075 FACT/Matched vs. Non-FACT/Matched).

{Table 8 HERE}

The FACT/CTN superiority trend persisted for mismatched HCT. However, our non-FACT centers performed remarkably similarly to our FACT-only centers for both matched and mismatched patients. Overall, our FACT/CTN centers consistently showed superior results for more complex mismatched HCT.

There were also factors significantly associated with hazard of death including race, older age, recipient Karnofsky performance status score at transplant, and coexisting disease ($p<0.05$ for all). For disease groups, NHL and HL, Other Leukemia and Myeloproliferative Syndromes, Severe Aplastic Anemia and Other non-malignant disease (versus Acute Myelogenous Leukemia & Myelodysplastic Disorders) were all associated with lower 3 year relative hazard of death ($p<0.05$ for all). We also saw some regional variation. Region 3, 4, 6 and 7 showed higher relative hazard of death versus Region 1 (CT, ME, MA, NH, RI, & VT) ($p<0.05$).

Discussion

In this study of 162 centers, we found that FACT/CTN accreditation was most strongly associated with superior overall 3 year survival. Differences in survival by FACT accreditation status were most apparent for more complex HCTs. Non-FACT and FACT-only centers were less likely to perform mismatched HCT relative to FACT/CTN centers. After stratifying our transplant recipients by related and unrelated match categories we found that FACT/CTN centers were more capable of performing complex mismatched HCTs compared to centers with FACT-only and non-FACT accreditation status.

Despite the inferior outcomes of mismatched HCT patients in non-FACT centers relative to FACT only and FACT/CTN centers, Non-FACT and FACT only centers performed similarly overall in the HLA matched HCT category. These results suggest that since FACT's inception nearly two decades ago, FACT accreditation has become ubiquitous among HCT centers and that HCT techniques have consistently improved across all centers irrespective of accreditation status.

Our findings are consistent with previous center accreditation literature that finds mixed results among accredited centers of excellence. Our findings indicate that when FACT centers are stratified into distinct categories, FACT/CTN accreditation status does imply superior overall results in the matched transplants category as compared to non-FACT or FACT alone accredited centers irrespective of transplant volume. These differences are further highlighted among mismatched related and unrelated HCTs. This finding also implies that FACT/CTN centers are particularly superior at treating more complex HLA mismatched HCTs. However, we do not see fundamental differences between FACT and non-FACT centers in the matched cohort. We are limited in our ability to comment on the apparent superiority of FACT/CTN centers because we cannot completely rule out explanations such as observed higher transplant volume or patient case mix. However, based on our sensitivity analysis we do not believe that FACT/CTN

centers' superior results are due to higher transplant volume or favorable patient case mix. We hypothesize that one explanation for FACT/CTN superiority is the nature of the clinical trials conducted in FACT/CTN centers that require higher levels of national clinical collaboration and standardization of protocols.

There are several components of FACT accreditation that should in theory explain transplant patients' superior results. FACT requirements are updated regularly with the contributions of the most innovative minds in cellular therapy and the wider transplant community. These organizations engage in a more transparent and open environment in which donor and cell selection standards are adhered to at the highest levels. [6, 21, 23] Although FACT accreditation sets an important center standard that begins to define improved overall survival, our results indicate that FACT status alone is not an indicator of superior outcomes.

Our study builds upon previous studies examining the implication of FACT accreditation. Although Loberiza et al. did not find differences in survival between FACT centers vs. non-FACT centers[21] we found that the differences in centers was within the FACT category and that not all FACT centers perform equally. Although the majority of our centers are FACT-only centers (106 centers), we find that non-FACT centers have similar relative hazard of death results to FACT-only centers.

While our study provides important implications for center certification initiatives, we acknowledge several data related limitations. First, there are additional factors that may explain survival that we did not included in our model. For example, we did not include the regimen; therapy related or transformed disease, and whether treatment was performed on or off a clinical trial. Our FACT/CTN accredited centers were unquestionably more likely to perform clinical trials. The data does not indicate which of our centers participated in trials or which patients were enrolled in trials. Additionally, we

are not able to obtain detailed patient comorbidity information. Due to the fact that CIBMTR broadly identifies coexisting diseases as either present or absent we may underestimate the severity of patient complexity in certain FACT center status categories. We are also limited by not knowing the clinical decision pathway in which providers and patients sought to find a mismatched related or mismatched unrelated donor. For example, some centers may choose a matched unrelated donor immediately after not finding a suitable matched related donor while others may search instead for a mismatched related donor. This decision making process would provide additional insight into our ability to further identify particularities in center differences for the mismatched related and unrelated HLA cohort. Despite these data limitations we believe that our results highlight differences between FACT centers and the need for additional research to explain the causal mechanisms involved in FACT/CTN superiority.

In conclusion, our study has important implications for providers, policy makers and patients seeking a transplant center. The Stem Cell Therapeutic and Research Act was enacted by Congress in order to establish a more transparent transplant outcomes research environment in which center results could easily be retrieved by clinicians and HCT recipients. For nearly two decades, FACT accreditation has been promoted as measure of center excellence. For example, FACT accreditation is a factor in the ranking of “America’s Best Hospitals,” and “America’s Best Children’s Hospitals,” published annually by U.S. News and World Report. Our results begin to illustrate the variation within FACT categories and also underscore the notion that FACT accreditation alone is not enough of an indicator to differentiate transplant centers. However, the broader relationship between FACT status and a center’s specific HCT survival rate remains complex, requiring a deeper understanding of the causal mechanism involved and finding specific factors that could be introduced to all centers to improve outcomes.

Learning from the evolution of accredited centers over time will provide policy makers, administrators and payers with information to guide future resource planning and areas to focus future quality improvement efforts.

Table 6: Basic Patient Characteristics by FACT Center Status: 2008-2010

		All		No FACT Certification (24 Centers)		FACT Certification Only (106 Centers)		FACT and Core Clinical Trial Network (32 Centers)		P-Value
		N	%	N	%	N	%	N	%	
Number of Transplants		12993		559	4	5655	44	6779	52	
Transplant Year										0.0116
	2008	3984	31	154	28	1803	32	2027	30	
	2009	4370	34	185	33	1810	32	2375	35	
	2010	4639	36	220	39	2042	36	2377	35	
HLA Matching Related/Unrelated Donor										<.0001
	Matched Related Donor	5419	42	287	51	2488	44	2644	39	
	Mismatched Related Donor	570	4	5	1	171	3	394	6	
	Matched Unrelated Donor	5349	41	197	35	2256	40	2896	43	
	Mismatched Unrelated Donor	1655	13	70	13	740	13	845	12	
Gender										0.1947
	Male	7543	58	345	62	3280	58	3918	58	
	Female	5450	42	214	38	2375	42	2861	42	
Patient Race										<.0001
	Non-Hispanic White	10669	82	444	79	4856	81	5639	83	
	Hispanic	1018	8	52	9	505	9	461	7	
	Black/African American	704	5	30	5	347	6	327	5	
	Other/Multiple Race/Unknown	602	5	33	6	217	4	352	5	
Patient Age at Transplant										0.0499
	18 to 29	1630	13	80	14	750	13	800	12	
	30 to 39	1450	11	65	12	657	12	728	11	
	40 to 49	2586	20	108	19	1098	19	1380	20	
	50 to 59	4075	31	184	33	1770	31	2121	31	
	60 to 69	2983	23	117	21	1262	22	1604	24	
	≥80	269	2	5	1	118	2	146	2	
Patient Karnofsky Performance Status Score at Transplant										<.0001
	90-100	8014	62	292	52	3448	61	4274	63	
	≤80	4445	34	264	47	20666	37	2115	31	
	Missing	534	4	3	1	141	2	390	6	
Coexisting Disease										<.0001
	Absent or Missing	4714	36	272	49	2144	38	2298	34	
	Present	8279	64	287	51	3511	62	4481	66	
Disease Group										<.0001
	Acute Myelogenous Leukemia & Myelodysplastic Disorders	6263	48	234	42	2770	49	3259	48	
	Acute Lymphoblastic Leukemia	1566	12	69	12	743	13	754	11	
	Other Leukemia & Myeloproliferative Syndromes	1820	14	74	13	773	14	973	14	
	Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	2320	18	101	18	938	17	1281	19	
	Other Malignancy	595	5	59	11	239	4	297	4	
	Severe Aplastic Anemia	332	3	13	2	154	3	165	2	
	Other Non-Malignant Disease	97	1	9	2	38	1	50	1	
Center Transplant Volume										<.0001
	Quartile I Volume Centers (1-5 Transplants)	102	1	22	4	80	1	0	0	
	Quartile II Volume Centers (6-44 Transplants)	871	7	146	26	680	12	45	1	
	Quartile III Volume Centers (45-107 Transplants)	2946	22	264	47	2337	41	345	5	
	Quartile IV Volume Centers (108-713 Transplants)	9074	70	127	23	2558	45	6389	94	
Centers by Department of Health and Human Services Regions										<.0001
	Region 1: (CT, ME, MA, NH, RI, & VT)	1066	8	25	4	313	6	728	11	
	Region 2: (NJ, NY)	1163	9	16	3	730	13	417	6	
	Region 3: (DE, DC, MD, PA, VA, WV)	1402	11	103	18	726	13	573	8	
	Region 4: (AL, FL, GA, KY, MS, NC, SC, TN)	1943	15	18	3	801	14	1124	17	
	Region 5: (IL, IN, MI, MN, OH, WI)	2341	18	141	25	1434	25	766	11	
	Region 6: (AR, LA, NM, OK, TX)	1544	12	5	1	776	14	763	11	
	Region 7:(IA, KS, MO, NE)	670	5	1	0	134	2	535	8	
	Region 8:(CO, MT, ND, SD, UT, WY)	391	3	75	13	153	3	163	2	
	Region 9:(AZ, CA, HI, NV)	1705	13	129	23	585	10	991	15	
	Region 10 (AK, ID, OR, WA)	768	6	46	8	3	0	719	11	

Table 7: Relative Odds of HLA Mismatch among HLA Mismatched HCT Patients (2008-2010)

	Related/Unrelated HLA Mismatch		
	OR	**95% CI**	
FACT Status			
No FACT Certification	REF		
FACT Only Certification	1.225	0.938	1.6
FACT/CTN Certification	**1.433**	**1.081**	**1.901**
Transplant Year			
2008	REF		
2009	1.065	0.949	1.194
2010	0.894	0.795	1.004
Gender			
Male	REF		
Female	0.956	0.869	1.051
Race			
Non-Hispanic White	REF		
Hispanic	**1.509**	**1.273**	**1.788**
Black/African American	**3.158**	**2.666**	**3.741**
Other/Multiple Race/Unknown	**1.36**	**1.098**	**1.684**
Age Categories			
18 to 29	REF		
30 to 39	0.948	0.792	1.136
40 to 49	**0.776**	**0.657**	**0.915**
50 to 59	**0.64**	**0.545**	**0.751**
60 to 69	**0.726**	**0.613**	**0.859**
≥80	0.86	0.612	1.208
Patient Karnofsky Performance Status Score at Transplant			
90-100	REF		
≤80	1.089	0.984	1.206
Missing	1.007	0.79	1.283
Coexisting Disease			
Absent or Missing	REF		
Present	**1.169**	**1.055**	**1.295**
Disease Group			
Acute Myelogenous Leukemia & Myelodysplastic Disorders	REF		
Acute Lymphoblastic Leukemia	**0.83**	**0.709**	**0.968**
Other Leukemia & Myeloproliferative Syndromes	0.89	0.766	1.023
Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	0.95	0.835	1.081
Other Malignancy	**0.737**	**0.575**	**0.945**
Severe Aplastic Anemia	**0.666**	**0.482**	**0.919**
Other Non-Malignant Disease	0.88	0.54	1.45
High Volume Quartile Indicator			
Quartile I Volume Centers (1-5 Transplants)	REF		
Quartile II Volume Centers (6-44 Transplants)	0.97	0.55	1.71
Quartile III Volume Centers (45-107 Transplants)	1.05	0.60	1.82
Quartile IV Volume Centers (108-713 Transplants)	1.106	0.636	1.921
Centers by Department of Health and Human Services Regions			
Region 1: (CT, ME, MA, NH, RI, & VT)	REF		
Region 2: (NJ, NY)	**1.426**	**1.13**	**1.799**
Region 3: (DE, DC, MD, PA, VA, WV)	**2.119**	**1.705**	**2.632**
Region 4: (AL, FL, GA, KY, MS, NC, SC, TN)	1.092	0.881	1.355
Region 5: (IL, IN, MI, MN, OH, WI)	0.985	0.792	1.224
Region 6: (AR, LA, NM, OK, TX)	0.912	0.724	1.151
Region 7:(IA, KS, MO, NE)	1.295	0.994	1.688
Region 8:(CO, MT, ND, SD, UT, WY)	0.799	0.553	1.154
Region 9:(AZ, CA, HI, NV)	**1.268**	**1.017**	**1.58**
Region 10 (AK, ID, OR, WA)	1.145	0.88	1.491

***Significant values <0.05 Bolded**

Table 8: Factors Associated with 3 Year Relative Hazard of Death Among HCT Patients, Cox Proportional Hazard models, Hazard Ratio, 95% CI

	Cox Model Related/Unrelated Mismatched			
	Hazard Ratio	95% CI		P Value
HLA Match Category by FACT Status				
No FACT Status/ Matched	REF			
FACT Only Status/ Matched	1.138	0.987	1.311	0.0757
FACT/CTN Certification/ Matched	1.008	0.868	1.172	0.9146
No FACT Status/ Mismatched	**2.058**	**1.527**	**2.772**	**<.0001**
FACT Only Status/ Mismatched	**1.713**	**1.462**	**2.007**	**<.0001**
FACT/CTN Certification/ Mismatched	**1.266**	**1.073**	**1.495**	**0.0052**
Transplant Year				
2008	REF			
2009	0.998	0.939	1.06	0.9451
2010	0.992	0.929	1.059	0.8031
Gender				
Male	REF			
Female	**0.929**	**0.883**	**0.978**	**0.0046**
Patient Race				
Non-Hispanic White	REF			
Hispanic	1.056	0.956	1.166	0.2815
Black/African American	**1.149**	**1.031**	**1.281**	**0.0119**
Other/Multiple Race/Unknown	1.001	0.882	1.136	0.9844
Patient Age Category				
18-29	REF			
30-39	1.04	0.929	1.164	0.4953
40-49	**1.21**	**1.096**	**1.337**	**0.0002**
50-59	**1.32**	**1.201**	**1.451**	**<.0001**
60-69	**1.516**	**1.374**	**1.671**	**<.0001**
≥80	**1.682**	**1.406**	**2.012**	**<.0001**
Patient Karnofsky Performance Status Score at transplant				
90-100	REF			
≤80	**1.496**	**1.419**	**1.578**	**<.0001**
Missing	**1.26**	**1.109**	**1.431**	**0.0004**
Coexisting Disease				
Absent or Missing	REF			
Present	**1.188**	**1.124**	**1.255**	**<.0001**
Disease Group				
Acute Myelogenous Leukemia & Myelodysplastic Disorders	REF			
Acute Lymphoblastic Leukemia	1.027	0.945	1.115	0.5314
Other Leukemia & Myeloproliferative Syndromes	**0.776**	**0.717**	**0.839**	**<.0001**

Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	**0.837**	**0.78**	**0.899**	**<.0001**
Other Malignancy	0.948	0.842	1.068	0.381
Severe Aplastic Anemia	**0.574**	**0.467**	**0.706**	**<.0001**
Other Non-Malignant Disease	**0.676**	**0.471**	**0.969**	**0.0333**
	Cox Model Related/Unrelated Mismatched			
Centers by Department of Health and Human Services Regions	**Hazard Ratio**	**95% CI**		**P Value**
Region 1: (CT, ME, MA, NH, RI, & VT)	REF			
Region 2: (NJ, NY)	1.089	0.963	1.231	0.172
Region 3: (DE, DC, MD, PA, VA, WV)	**1.127**	**1.001**	**1.269**	**0.0483**
Region 4: (AL, FL, GA, KY, MS, NC, SC, TN)	**1.118**	**1.001**	**1.248**	**0.0478**
Region 5: (IL, IN, MI, MN, OH, WI)	1.06	0.949	1.184	0.3004
Region 6: (AR, LA, NM, OK, TX)	**1.132**	**1.009**	**1.271**	**0.0354**
Region 7:(IA, KS, MO, NE)	**1.322**	**1.152**	**1.516**	**<.0001**
Region 8:(CO, MT, ND, SD, UT, WY)	1.001	0.842	1.191	0.9887
Region 9:(AZ, CA, HI, NV)	1.059	0.942	1.191	0.3374
Region 10 (AK, ID, OR, WA)	1.127	0.978	1.297	0.0977
High Volume Quartile Indicator				
Quartile I Volume Centers (1-5 Transplants)	REF			
Quartile II Volume Centers (6-44 Transplants)	1.23	0.878	1.721	0.2283
Quartile III Volume Centers (45-107 Transplants)	1.032	0.743	1.435	0.8495
Quartile IV Volume Centers (108-713 Transplants)	0.918	0.66	1.277	0.612

Figure 6A: Percentages of Related and Unrelated HCT by FACT Status (2008-2010)

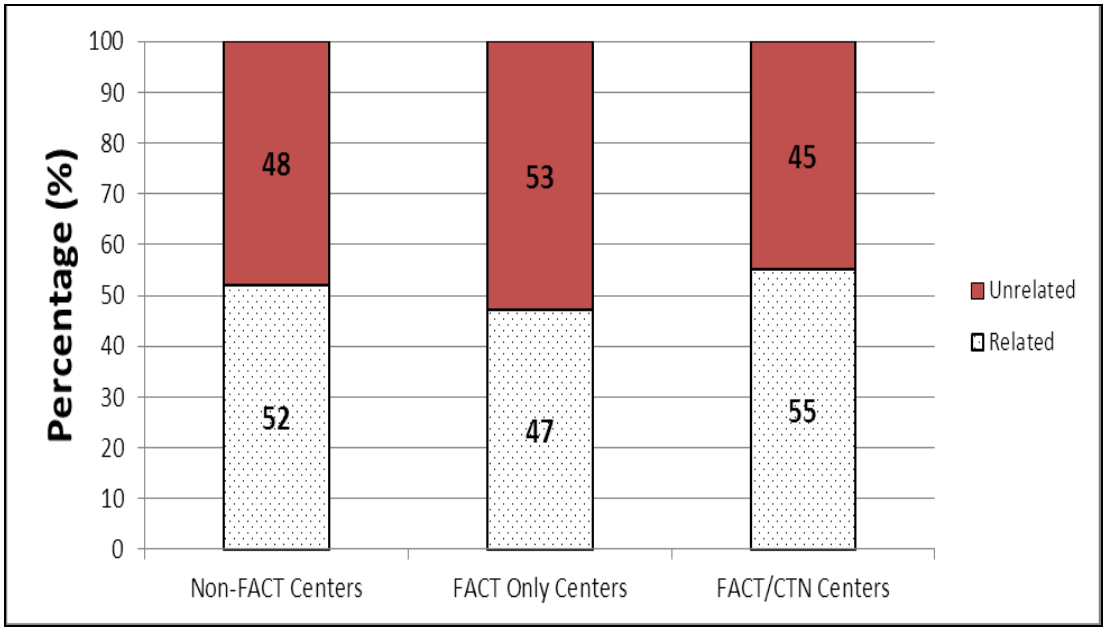


Figure 6B: Percentages of Related/Unrelated Matched or Mismatched HCT by FACT Status (2008-2010)

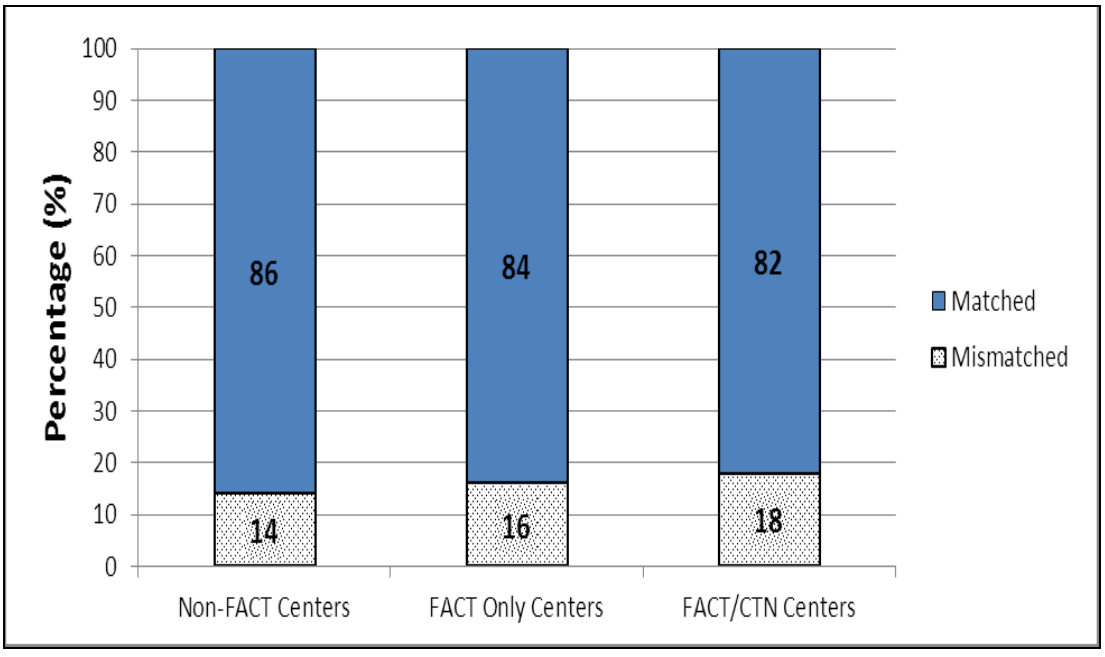


Figure 7A: Kaplan Meier: All Adult HCT Survival by FACT Status: 2008-2010

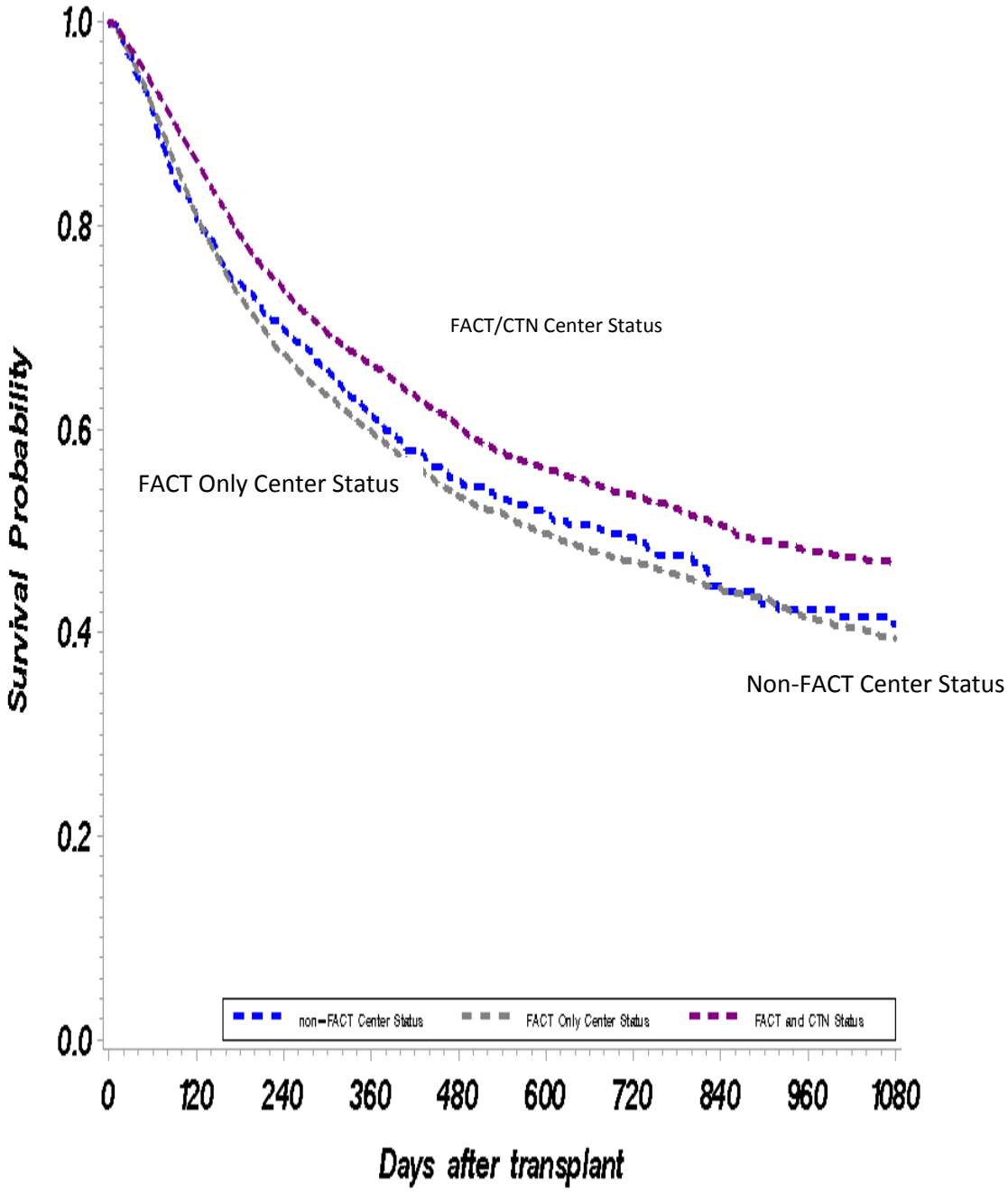


Figure 7B: Mismatched Related and Unrelated Adult HCT Survival by FACT Status: 2008-2010

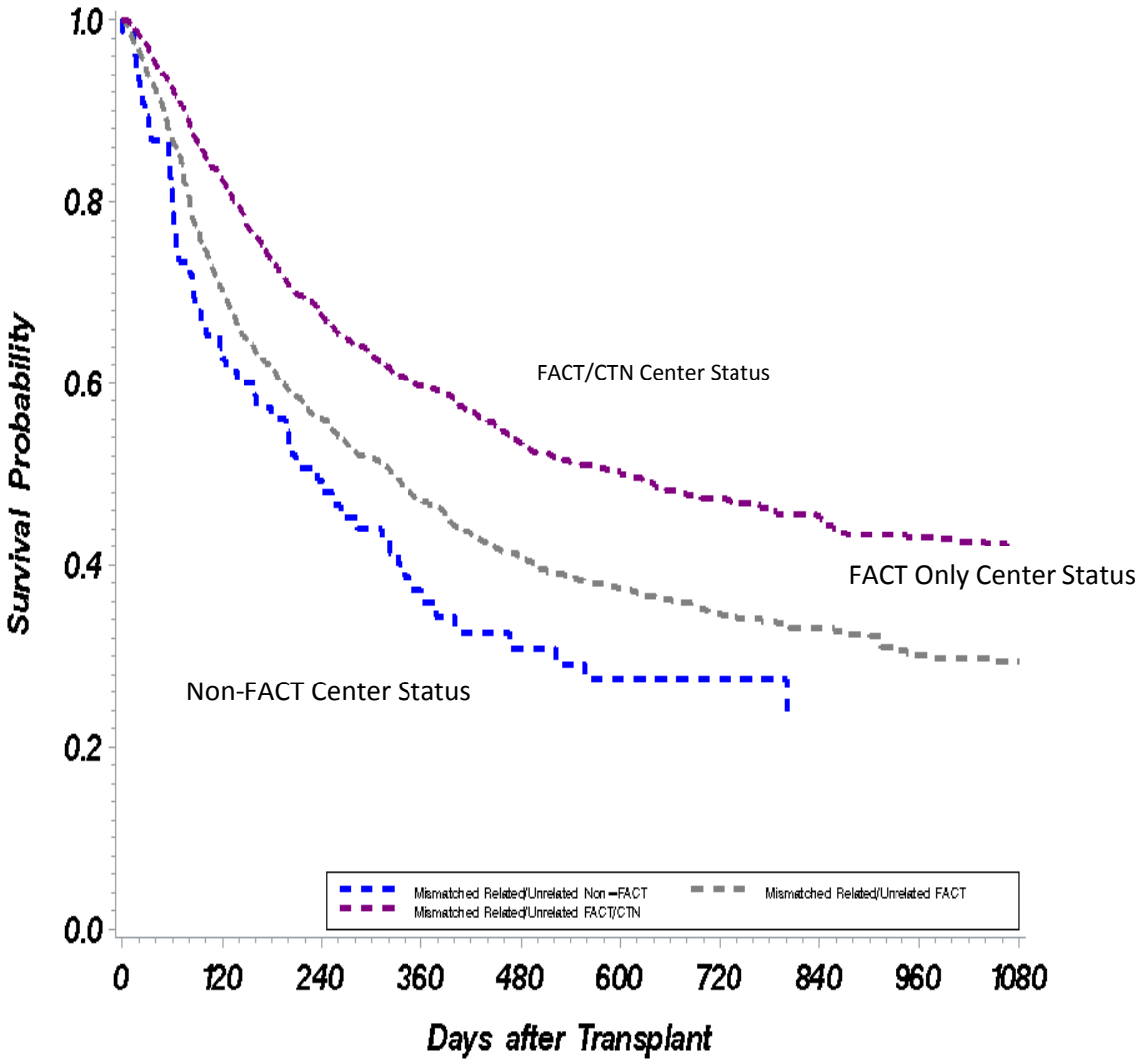
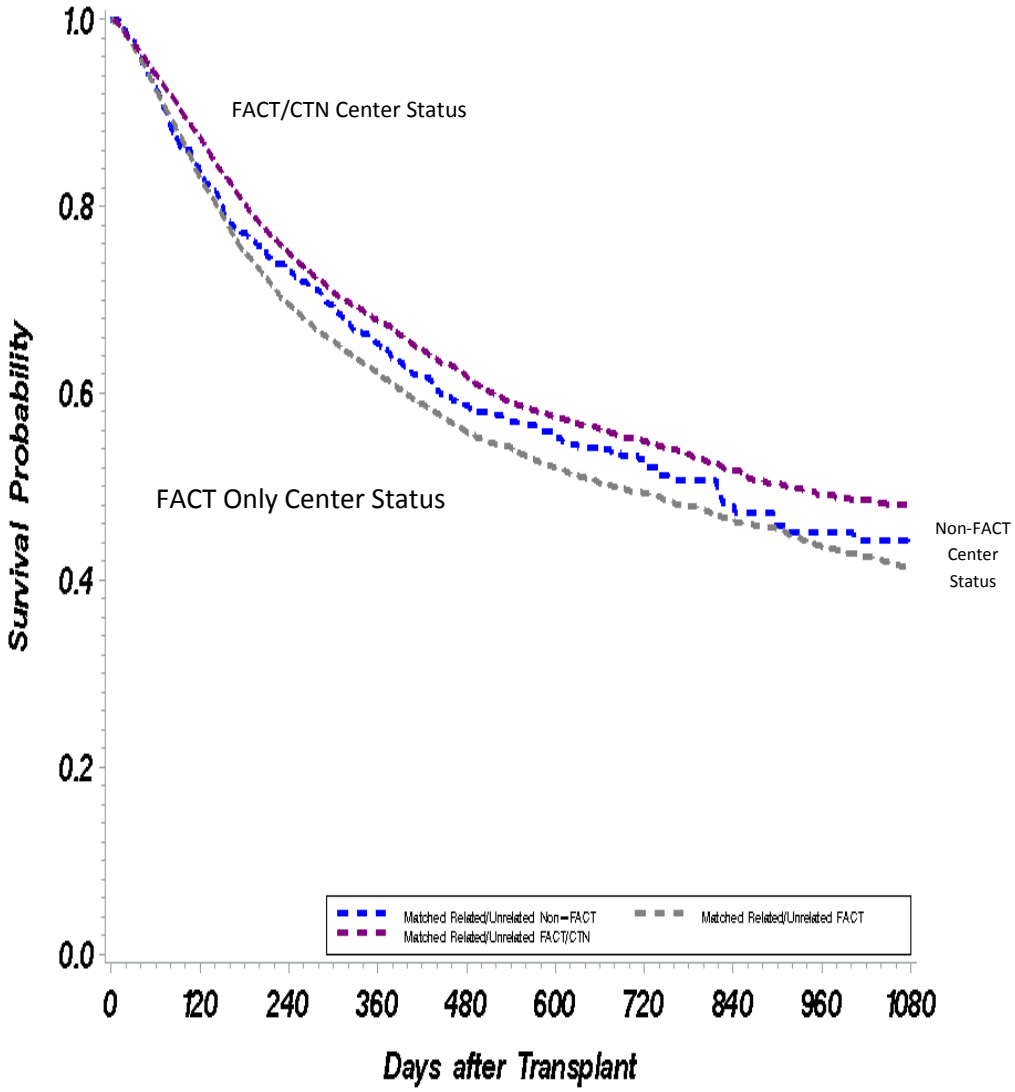


Figure 7C: Matched Related and Unrelated Adult HCT Survival by FACT Status: 2008-2010



Chapter 5: Geographic Inequality or Advantage: The Impact of Distance to Transplant Center on Outcomes after Unrelated Donor HCT in the United States

Background: Hematopoietic cell transplantation (HCT) is the transplantation of stem cells from a donor and an effective treatment for many hematologic malignancies. The complexity of HCT requires lengthy specialized care that could put patients residing in distant locations at a distinct disadvantage compared to patients that resided closer to their HCT center. We sought to evaluate the differences in survival and post-transplant complications {chronic graft-versus-host disease (cGvHD)} among HCT patients by distance to center.

Methods: To evaluate the association between distance to transplant center and HCT survival, we studied all patients reported to the Center for International Blood and Marrow Transplant Research (CIBTMR) who received transplant between January 1, 2000-December 31, 2009 data. Using Google Maps we calculated driving distance in minutes from patient zip code to transplant center. We categorized patients into distance quartiles and bifurcated our upper quartile to create a fifth category of patients who had travel times >6 hours. Utilizing our distance stratification we examined the association between distance category and hazard of death and cGvHD using Cox Proportional Hazard modeling.

Results: There were 10,068 HCT recipients at 130 transplant centers from 2000-2009 in the cohort. Median driving distance was 65 minutes (range 2 minutes- 20,820 minutes). Our patient cohort was predominately older (over the age of 40) (66%) and male (58%). Over time, patients decreased their long distance travel for HCT from a median time of 78 minutes in 2000 to 60 minutes in 2009. Unadjusted Kaplan Meier mortality estimates showed differences between 9 year overall mortality among patients in our fifth distance category and all other distance categories. After adjusting for patient and center characteristics we found that distance from the transplant center was not significantly associated with overall survival or disease free survival (adjusted hazard ratio (HR):

.975; 95% Confidence Interval (.884-1.075) Distance category 361-20,820 minutes vs. 2-32 minutes).

Conclusions: Our findings suggest that patients accessing HCT from longer distances need not necessarily expect inferior outcomes. This was especially apparent for more complex HLA mismatched patients. For payers and policy makers our findings indicate that, if sufficient post-transplant care is provided, there is no clear benefit to restrict the performance of HCT to the closest available center.

Background

Hematopoietic cell transplantation (HCT) is the transplantation of stem cells from a donor and is an effective treatment for many hematologic malignancies. The complexity of HCT requires lengthy specialized care and that post-transplant recovery necessitates that the transplant recipient remain in close proximity to their center for potential treatment.[86-88] There are two ways in which distance to HCT could impact outcomes. Distance to facility could be important for expediting the process that leads to the donor recipient match, diagnostic screening and for post-transplant care. Patients who travel long distances or who opt to receive recommended post-transplant screening from providers who are unfamiliar with treatment plans may receive suboptimal care from providers that lack the advanced techniques necessary for HCT patients.[88] Conversely, it is possible that patients that travel longer distances receive more vigilant specialty care prior to discharge and are ultimately healthier at discharge prior to post-transplant travel.

Health services research has shown that patients in rural areas or patients that have to travel considerably greater distances than their urban counterparts to access specialized care detrimentally impacts healthcare access and utilization.[89-92] Length of stay for HCT is particularly longer than most other conditions, such as emergent care, elective hospital care, primary care and other cancers. Geographical location (urban/rural) and their proximity to transplant centers have been hypothesized to be a predictor of successful outcomes and mitigate post-transplant complications such as graph versus host disease (GvHD). Yet, the research documenting the relationship between survival and distance is sparse. A recent study by Abou-Nassar et al. analyzed a cohort of adult patients who underwent allogeneic HCT at the Dana-Farber/Brigham and Women's Cancer Center between 1996 and 2009 and who resided within 6 hours

driving time of the institution. [88] They found that overall survival (OS) for patients stratified by driving time quartile after HCT was similar in the first year but worse after 1 year in patients in the top quartile (>160 minutes driving time). [88] In a retrospective cohort of patients undergoing HCT in Nebraska, patients from rural areas undergoing autologous stem cell transplantation were found to have inferior results compared to patients from urban areas.[34] Research by Loberiza and colleagues found that results were not inferior for rural patients and that there was no urban/rural distinction.[93]

We sought to use national U.S. data from 130 centers to evaluate the differences in survival and post-transplant complications (GvHD) among HCT patients by distance to center.

Methods

Data Source and Patients

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a research affiliation of the International Bone Marrow Transplant Registry, Autologous Blood and Marrow Transplant Registry, and National Marrow Donor Program (NMDP) that was established in 2004. CIBMTR is comprised of a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive HCT to a Statistical Center at the Medical College of Wisconsin in Milwaukee, WI and the NMDP Coordinating Center in Minneapolis, MN. In addition, the CIBMTR holds the contract for the Stem Cell Therapeutic Outcomes Database part of the CW Bill Young Transplantation Program from the Human Resources and Services Administration; as a part of this Program, all transplant centers in the US are mandated to report clinical outcomes data for allogeneic HCT to the CIBMTR. Data are collected before transplant, 100 days and 6 months after transplant, and annually thereafter or until death. Computerized checks for discrepancies, physician review of submitted data and on-site audits of participating centers ensure data quality. We obtained a de-

identified dataset from CIBTMR. Our study was deemed exempt from review by the Human Subjects Committee of the University of Minnesota's Institutional Review Board.

Patient Variables Utilized

We included transplant recipients 18 years or older who received transplants between January 1, 2000 through December 31, 2009 and were reported to the CIBTMR. We included patients who received peripheral blood stem cells or bone marrow graft from HLA-matched or mismatched unrelated donors. All diagnoses were included.

We utilized patient race, gender, the HLA match status of the patient, coexisting disease, Karnofsky score, and chronic GvHD (cGvHD) status. CIBMTR reports both the incidence of cGvHD and when it occurs. CIBMTR censored patients that died without cGvHD or second transplant (Competing risk) or were alive or had second transplant with no cGvHD event. The Karnofsky performance status is used to determine the functional status of a recipient and can range from 0-100. A Karnofsky performance score of 90-100 categorizes patients with the ability to carry on normal activity and no special care is needed. Karnofsky performance score was considered by CIBTMR as a dichotomous variable of 90-100 and ≤ 80. Coexisting disease is a binary category of diseases collected by CIBMTR. CIBMTR codes HCT patients with any of 18 comorbidities as coexisting disease present.

The HLA match status of donors describes the degree of immunologic similarity between recipients and donors. We categorized patients as HLA matched or mismatched HCTs. We excluded patients with missing HLA match information (N=718)

Length of stay (LOS) and 100 day survival has typically been used by literature as important cutoff for HCT and survival outcomes.[88, 94] Although CIBTMR does not collect LOS from transplant centers we used 100 day survival as a proxy for LOS to

determine if the difference in survival probability by distance category persisted for patients with 100 day post-transplant survival.

In order to link patient zip code with median household income, we used the most recent 2007-2011 United States Census Bureau American Community Survey (ACS), a statistical survey that samples a small percentage of the population every year, to extract median household income by ZIP code tabulation areas.[95] The 5-Digit ZIP code tabulation areas (ZCTA) geographic levels are generalized area representations of United States Postal Service (USPS) ZIP Code service areas. [96] In most instances, an address ZIP code will also be the ZCTA in which that address falls.[97] However, an address's ZIP code does not consistently match the ZCTA it falls into and conversely that ZIP code may not match the ZCTA (N=178 patients).

Distance Defined

Using Google Maps we calculated driving distance in minutes from patient zip code to transplant center zip code. [98] This approach produced comparable estimates with the SAS 9.3 ZIPCITY function. [99] We divided our cohort into quartiles and subdivided the upper quartile into a group of patients that resided more than 6 hours driving time from the transplant center. Patients with invalid zip codes, foreign zip codes and patient zip codes that matched identically with transplant center zip codes were excluded (N=843 patients, 7% of total).

Transplant Center Characteristics

We also utilized several transplant center characteristics in our models, including center volume (quartiles), The Foundation for the Accreditation of Cellular Therapy center (FACT), Core Blood and Marrow Transplant Clinical Trial Network (CTN) status and center geographic location (Department of Health and Human Services (HHS) regions). Based on the literature, we found benefit in categorizing centers with non-FACT, FACT Only or FACT/CTN status. [100]

Statistical Analysis

The primary objective of this retrospective study was to examine if geographic proximity affects overall survival (OS) of HCT patients from 2000-2009 and post-transplant complications such as cGvHD. We compared the relationship between distance categories using chi-square tests. Overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan-Meier method with significance testing using log rank tests. OS was defined as the time from stem cell infusion to death from any cause. Patients lost to follow-up were censored at the date last known alive. DFS was defined as the time from stem cell infusion to disease relapse, progression, or death from any cause. We evaluated differences in distance categories, HLA match status, cGvHD and patient characteristics across all years of transplantation. In order to capture the interaction between distance travelled and patient complexity we created a distance to facility by HLA match category variable.

After assessing this unadjusted relationship we utilized multivariable Cox proportional hazards models to evaluate the association between distance categories and death. We then used multivariate logistic regression to determine the odds of cGvHD occurrence.

In all models, we performed several sensitivity analyses such as the removal of non-statistically significant factors and use of stratification to ensure that the observed effects were not a product of our modeling decisions (appendix 12-17). We examined the impact of alternate categories to confirm that our findings were not a product of our distance categories (appendix 12-14). Under all assumptions, conclusions remain unchanged. SAS version 9.3 (SAS Institute) was used for all analyses. P values were 2 sided with a level of significance of ≤.05.

Results

Our final cohort included 10,068 transplants conducted in 130 centers between January 1, 2000 through December 31, 2009. Median driving distance was 65 minutes (range 2 minutes- 20,820 minutes). Our patient cohort was predominately older (over the age of 40) (66%) and male (58%). Over time, patients decreased their long distance travel for HCT from a median time of 78 minutes in 2000 to 60 minutes in 2009.

Nearly half of the patient cohort consisted of HLA matched unrelated HCTs (N=6,291; 46%) and the remainder were mismatched HCTs (3,147; 54%). There was no apparent difference in travel time for mismatched HCT. The median travel time for HCT mismatched patients was 60 minutes and the median time for matched patients was 68 minutes. Over 31% of our cohort was unable to carry on normal activity with no special care needed prior to transplantation (Karnofsky scoring ≤80) and 61% of our population was classified by CIBMTR as having coexisting disease prior to HCT. We observed variation in median travel time by disease group. Median travel time for AML and MDS was 65 minutes, 59 minutes for ALL and 77 minutes for CML, other Leukemia and MPS.

There was a strong correlation between income and travel time. Of the 2,482 patients in the upper quartile of median household income ($73,258-$242,188) only 30% travelled beyond the median driving distance for receipt of HCT (64 minutes). Of patients in the lower quartile of median household income ($10,055-$43,796), 68% travelled beyond 64 minutes for their transplants.

{Table 9A-91B Here}

Association between Driving Distance Category and Mortality

Unadjusted Kaplan Meier mortality estimates showed differences between 9 year overall mortality among patients in our fifth distance category and all other distance categories. Although patients in the first four categories had similar OS, our fifth distance category showed higher survival than our other distance categories. In order to observe

whether survival differs between groups once patients are discharged from the transplant center we used 100 day survival as a proxy for LOS and excluded patients with ≤100 days of survival. After this exclusion, we observed similar patterns in our unadjusted Kaplan Meier mortality estimates when we plotted curves with patients living >6 hours away vs. all others.

{Figure 8A and 8B Here}

However, after adjusting for patient and center characteristics we found that our upper quartile distance groups were not significantly associated with lower relative hazard of death (adjusted hazard ratio (HR): .975; 95% Confidence Interval (.884-1.075) Distance category 361-20,820 minutes vs. 2-32 minutes).

{Table 10 Here}

Earlier year of transplant (2009 versus 2000), gender (female versus male), Karnofsky performance stratus score <80, other malignancies, and Severe Aplastic Anemia (versus AML and MDS) were all associated with lower 9 year relative hazard of death ($p<0.05$ for all). The results of our DFS models showed similar patterns. Namely, patients that lived 6 hours or more away from their transplant centers had lower 9 year hazard of death or relapse versus all other distance categories.

Association between Driving Distance Category and HLA Match and Mismatch HCT

When we grouped our distance categories by HLA matched and mismatched HCT and plotted Kaplan Meier curves we observed an advantage for mismatched HLA unrelated patients living >6 hours away vs. all others. We did not observe this long distance travel advantage when we grouped our distance categories by HLA matched.

{Figure 9A and 9B Here}

After adjusting for patient and center characteristics we found that the more complex, HLA mismatched patients that resided 6 hours or more from the HCT center were significantly associated with lower relative hazard of death (adjusted hazard ratio

(HR): .79; 95% Confidence Interval (.67-.95) Distance category 361-20,820 minutes vs. 2-32 minutes).

{Table 11 Here}

Earlier year of transplant (2009 versus 2000), gender (female versus male) Karnofsky performance stratus score <80, disease groups (other leukemia and MPS, other malignancies and SAA versus AML and MDS) were all associated with lower 9 year relative hazard of death ($p<0.05$ for all) for the HLA mismatched cohort.

Association between Driving Distance Category and Post-Transplant Complications: cGvHD

Unadjusted Kaplan Meier estimates showed only small differences between cGvHD probability among patients in our fifth distance category and all other distance categories. Although patients in the first, second, third and fourth categories had similar cGvHD after 1 year, our fifth distance category showed a lower probability of cGvHD diagnosis before 1 year (78% for patients that travelled >6 hours compared to 93% for patients travelling <6 hours).

{Figure 10 Here}

After adjusting for patient and center characteristics we found that HLA mismatched patients that travelled more than 6 hours were significantly associated with higher odds of cGvHD (adjusted OR: 1.545; Confidence Interval (1.19- 2.01) Distance category 4 (150-360 minutes) vs. 1 (2-32 minutes)). Less complex, HLA matched patients showed lower but not significant odds of cGvHD.

{Table 12 Here}

Other covariates that were associated with higher odds of cGvHD estimates included year of transplant (2003+ versus 2000) and patient Karnofsky performance status score at transplant ($p<0.05$ for all).

Discussion

The last several decades has witnessed a remarkable expansion of HCT use both in the U.S. and globally. Although HCT centers continue to explore new clinical successes we observed that patients are decreasing their long distance travel for HCT. Our data does not allow us to explain this decline in travel. However, we suspect that in addition to the increase in the number of HCT centers within markets, the decline in travel for HCT can also partially be attributed to a confluence of events including, more restrictive managed care plans and patient and provider caution at increased travel. Despite potential motivations that would restrict travel for HCT, our findings suggest that long distance travel to HCT center is not a cause of inferior results. Moreover, the potential precautions that are taken with long distance travelling for HCT may produce advantages that modestly improve OS and cGvHD outcomes for patients that travel 6 hours or more.

We observed the clearest distance benefit for the most complex HLA mismatched patients living 6 or more hours from their transplant center. This benefit was not evident for HLA matched patients. We did not observe significant differences between driving distance and median household income. These results imply that in addition to the precautions taken at the treatment center with long distance patients there is additional caution taken for complex HCT that may include prolonged LOS. The advantage for complex patients persisted for the entire study period implying that post-transplant care has improved beyond the HCT center of origin. Furthermore, patients living 6 or more hours from their transplant center might intensify the caution taken by provider and request a delay in their discharge.

Our findings have important policy implications for patients, providers, payers and policy makers. Patients accessing HCT from longer distances need not necessarily expect inferior outcomes. This expectation is applicable for complex HLA mismatched

and simpler HLA matched patients. For providers, the precautions taken for long distance patients seem to be not only justified but necessary for OS and the prevention of GvHD occurrence. It has previously been hypothesized that the patients in upper distance categories have limited access to post-HCT specific care and are more prone to HCT complications such as infections and GVHD that should ideally be managed by providers with HCT specific expertise. However, based on our findings it would appear that HCT centers are able to ensure the success of transplants for patients who reside long distances from transplant centers perhaps by effectively disseminating advanced post-transplant care techniques to non-specialized clinicians providing post-transplant care. For payers and policy makers our findings indicate that, if sufficient post-transplant care is provided, there is no risk to patients who need to travel to receive care. However, other work by Marmor et al. suggests that while low risk patients need not travel for HCT and can expect to receive comparable HCT care at low risk centers, there is an advantage for complex patients to travel to centers of excellence for HCT. [100] Indeed, we did observe a driving distance advantage for our complex patients.

Although there is an extensive literature that observes distinct disparities in cancer outcomes and survival based on the distance to the treatment center[25-32, 101], few have focused on nationwide U.S. HCT. Previous findings of Abou-Nassar et al. showed inferior outcomes for patients that resided 160-360 minutes driving time from the Dana-Farber/Brigham and Women's Cancer Center.[88] In a study at the University of Nebraska Medical Center between 1983 and 2004, primary area of residence was used to classify patients as either rural or urban. Results were mixed. Among the autologous HCT patients, those from rural areas were found to have a higher mortality versus patients from urban areas but this difference was not evident for patients undergoing allogeneic HCT.[34] A registry study from Canada found that there were no significant survival

differences between urban and rural patients undergoing autologous or allogeneic HCT.[35]

Our study builds upon previous studies examining the implications of distance on overall HCT survival and complications. Our analysis moves beyond a rural versus urban distinction. Additionally, in contrast to Abou-Nassar, we included patients residing > 6 hours away from their transplant centers in our analyses. [88] We recognize that patients residing 6 or more hours away from their HCT center would often use other modes of transportation to reduce their travel time and facilitate access that could also contribute to superior transplant results. Our results persisted even after restricting our sample to patients that had survived >100 days post HCT.

Although our study provides further insight into the relationship between patient distance to HCT center and post-transplant outcomes we acknowledge several data related limitations. CIBTMR did not provide detailed post-transplant care including the frequency of follow up care visits and the types of providers that were available to patients after HCT. However, even after we restricted our cohort to >100 days survival our results persisted suggesting that some aspect of clinical decision making is different for long distance patients. Our observed differences in OS by driving time did not appear to be directly attributable to measurable differences in patient baseline characteristics that the literature has previously established as important predictors of risk such as age, Karnofsky performance status, HLA matching category and coexisting disease.[7-9, 13-18] We cannot exclude possible confounding by unmeasured socioeconomic variables and reporting error due to our use of the median income 2007-2011 ACS variables. However, median household income did not appear to be directly attributable to survival and GvHD complications. Lastly, our analysis was restricted to unrelated transplants. We do not know if our results are generalizable to related

transplants. Despite these limitations we found significant distinctions between our distance categories that indicate that long distance HCT patients may indeed expect comparable survival and outcomes results compared to other patients.

Although our findings suggest that long distance HCT offer modestly superior results versus other patients that reside closer to their treatment center, the broader relationship between a patients' distance and survival and complications rate remains complex. A deeper understanding of the causal mechanisms involved is required to find specific factors that could be introduced to all centers to improve outcomes for all long distance patients. While our work begins to distinguish differences in patient distance, our results suggest the need for additional research using longitudinal data and corresponding methods to investigate the factors that more broadly predict the characteristics of superior results for long distance related and unrelated HCT patients and ultimately improve survival for all patients regardless of distance and complexity.

Table 9A: Basic Characteristics of Unrelated Transplant Recipients by Driving Distance Category (2000-2009)											
	Time Distance (2-32 min)		**Time Distance (33-64 min)**		**Time Distance (65-149 min)**		**Time Distance (150-360 min)**		**Time Distance (361-20,820 min)**		**P-Value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
	2489	25	2512	25	2573	26	1425	14	1069	11	
Transplant Year											
											<.0001
2000	157	24	132	20	162	24	105	16	107	16	
2001	146	23	163	25	158	25	80	12	97	15	
2002	186	24	195	25	185	24	104	14	100	13	
2003	227	24	218	23	255	27	116	12	117	13	
2004	282	26	260	24	261	24	163	15	128	12	
2005	297	25	289	24	294	25	188	16	112	9	
2006	315	24	338	26	350	26	195	15	124	9	
2007	361	26	371	26	367	26	177	13	137	10	
2008	263	25	277	26	280	26	159	15	83	8	
2009	255	26	269	27	261	26	138	14	64	6	
Gender											
											0.2517
Female	1096	26	1040	25	1078	25	593	14	435	10	
Male	1393	24	1472	25	1495	26	832	14	634	11	
Patient Race											
											<.0001
Non-Hispanic White	1986	23	2198	25	2344	27	1284	15	952	11	
Hispanic	193	35	142	26	88	16	82	15	40	7	
Black/African American	185	46	74	18	86	21	32	8	27	7	
Other/Multiple Race/Unknown	125	35	98	28	55	15	27	8	50	14	
Recipient Age at Transplant											
											0.0013
18 to 29	485	27	428	24	482	27	256	14	153	8	
30 to 39	396	25	381	24	394	25	234	15	162	10	
40 to 49	532	24	516	23	617	28	318	14	241	11	
50 to 59	658	23	730	26	716	25	395	14	314	11	
60 to 64	266	26	280	27	230	22	133	13	119	12	
65+	152	24	177	28	134	21	89	14	80	13	

Recipient Karnofsky Performance Status score at transplant											
											<.0001
90-100	1532	25	1525	25	1552	26	841	14	591	10	
10-80	774	25	787	25	832	26	454	14	305	10	
Missing	183	21	200	23	189	22	130	15	173	20	
Coexisting Disease											
											0.0949
Absent or Missing	1001	26	924	24	980	25	571	15	418	11	
Present	1488	24	1588	26	1593	26	854	14	651	11	
Disease Group											
											<.0001
Acute Myelogenous Leukemia & Myelodysplastic Disorders	1281	25	1289	25	1353	26	716	14	506	10	
Acute Lymphoblastic Leukemia	367	26	388	27	355	25	187	13	123	9	
Other Leukemia & Myeloproliferative Syndromes	448	22	461	23	490	24	336	17	286	14	
Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	263	26	263	26	264	26	134	13	91	9	
Other Malignancy	33	30	22	20	22	20	12	11	20	18	
Severe Aplastic Anemia	83	28	78	27	75	26	35	12	23	8	
Other Non-Malignant Disease	14	22	11	17	14	22	5	8	20	31	
HLA Matching Donor											
											<.0001
Matched	1638	24	1716	25	1828	26	965	14	774	11	
Mismatched	851	27	796	25	745	24	460	15	295	9	
Median Household Income Quartile Categories											
											<.0001
Quartile 1 ($10,055-$43,796)	502	20	293	12	842	34	555	23	268	11	
Quartile 2 ($43,797-$55,702)	531	21	497	20	723	29	470	19	262	11	
Quartile 3 ($55,703-$73,257)	675	27	728	30	578	23	238	10	246	10	
Quartile 4 ($73,258-$242,188)	748	30	962	39	378	15	135	5	259	10	
Missing	33	19	32	18	52	29	27	15	34	19	
Centers by Department of Health and Human Services Regions											
											<.0001
Region 1: (CT, ME, MA, NH, RI, & VT)	188	24	234	30	198	25	131	17	33	4	
Region 2: (NJ, NY)	360	43	238	29	172	21	48	6	11	1	
Region 3: (DE, DC, MD, PA, VA, WV)	239	26	314	34	289	31	66	7	13	1	
Region 4: (AL, FL, GA, KY, MS, NC, SC, TN)	209	16	245	19	484	38	294	23	51	4	
Region 5: (IL, IN, MI, MN, OH, WI)	529	27	529	27	535	28	238	12	108	6	

Region 6: (AR, LA, NM, OK, TX)	301	22	255	19	232	17	248	18	331	24	
Region 7:(IA, KS, MO, NE)	157	26	129	21	191	31	121	20	14	2	
Region 8:(CO, MT, ND, SD, UT, WY)	63	26	73	30	48	20	44	18	14	6	
Region 9:(AZ, CA, HI, NV)	265	23	380	33	317	28	117	10	69	6	
Region 10 (AK, ID, OR, WA)	178	19	115	12	107	11	118	13	425	45	
High Volume Quartile Indicator											
											<.0001
Quartile I Volume Centers (1-9 Transplants)	35	30	31	27	32	28	14	12	4	3	
Quartile II Volume Centers (10-48 Transplants)	336	38	236	27	159	18	85	10	65	7	
Quartile III Volume Centers (49-93 Transplants)	631	30	576	27	617	29	240	11	70	3	
Quartile IV Volume Centers (94-681 Transplants)	1487	21	1669	24	1765	25	1086	16	930	13	
FACT Status											
											<.0001
No FACT Certification	103	38	49	18	50	18	31	11	40	15	
FACT Only Certification	1377	31	1257	28	1155	26	484	11	174	4	
FACT/CTN Certification	1009	19	1206	23	1368	26	910	17	855	16	

Table 9B: Total Basic Characteristics of Unrelated Transplant Recipients by Driving Distance Category (2000-2009)		
	N	**%**
Total	10,068	100
Transplant Year		
2000	663	7
2001	644	6
2002	770	8
2003	933	9
2004	1094	11
2005	1180	12
2006	1322	13
2007	1413	14
2008	1062	11
2009	987	10
Gender		
Female	4242	42
Male	5826	58
Patient Race		
Non-Hispanic White	8764	87
Hispanic	545	5
Black/African American	404	4
Other/Multiple Race/Unknown	355	4
Patient Age at Transplant		
18 to 29	1804	18
30 to 39	1567	16
40 to 49	2224	22
50 to 59	2813	28
60 to 64	1028	10
65+	632	6
Recipient Karnofsky Performance Status score at transplant		
90-100	6041	60
10-80	3152	31
Missing	875	9
Coexisting Disease		
Absent or Missing	3894	39
Present	6174	61
Disease Groups		
Acute Myelogenous Leukemia & Myelodysplastic Disorders	5145	51
Acute Lymphoblastic Leukemia	1420	14
Other Leukemia & Myeloproliferative Syndromes	2021	20
Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	1015	10
Other Malignancy	109	1
Severe Aplastic Anemia	294	3
Other Non-Malignant Disease	64	1
HLA Matching Donor		
Matched	6921	69
Mismatched	3147	31
Median Household Income Quartile Categories		
Quartile 1 ($10,055-$43,796)	2460	24
Quartile 2 ($43,797-$55,702)	2483	25
Quartile 3 ($55,703-$73,257)	2465	24
Quartile 4 ($73,258-$242,188)	2482	25
Missing	178	2

Centers by Department of Health and Human Services Regions		
Region 1: (CT, ME, MA, NH, RI, & VT)	784	8
Region 2: (NJ, NY)	829	8
Region 3: (DE, DC, MD, PA, VA, WV)	921	9
Region 4: (AL, FL, GA, KY, MS, NC, SC, TN)	1283	13
Region 5: (IL, IN, MI, MN, OH, WI)	1939	19
Region 6: (AR, LA, NM, OK, TX)	1367	14
Region 7:(IA, KS, MO, NE)	612	6
Region 8:(CO, MT, ND, SD, UT, WY)	242	2
Region 9:(AZ, CA, HI, NV)	1148	11
Region 10 (AK, ID, OR, WA)	943	9
High Volume Quartile Indicator		
Quartile I Volume Centers (1-9 Transplants)	116	1
Quartile II Volume Centers (10-48 Transplants)	881	9
Quartile III Volume Centers (49-93 Transplants)	2134	21
Quartile IV Volume Centers (94-681 Transplants)	6937	69
FACT Status		
No FACT Certification	273	2.7
FACT Only Certification	4447	44
FACT/CTN Certification	5348	53

Table 10: Factors Associated with 9 Year Relative Hazard of Death (OS and DFS) Among HCT Patients by Distance Categories, Cox Proportional Hazard models, Hazard Ratio, 95% CI

		Cox Model OS Unrelated Transplants Distance Quartiles 2000-2009				Cox Model DFS Unrelated Transplants Distance Quartiles 2000-2009			
		Hazard Ratio	95% CI		P Value	Hazard Ratio	95% CI		P Value
Time Quartile Indicator	Time Distance (2-32 min)	REF				REF			
	Time Distance (33-64 min)	1.024	0.956	1.097	0.499	1.01	0.942	1.083	0.777
	Time Distance (65-149 min)	1.066	0.994	1.143	0.0732	1.056	0.983	1.134	0.1363
	Time Distance (150-360 min)	1.009	0.926	1.099	0.8461	0.982	0.9	1.072	0.6861
	Time Distance (361-20820 min)	0.984	0.897	1.08	0.7326	0.958	0.872	1.054	0.379
Transplant Year	2000	REF				REF			
	2001	0.993	0.875	1.127	0.9101	0.98	0.863	1.114	0.7602
	2002	0.924	0.817	1.046	0.2107	0.969	0.856	1.097	0.6218
	2003	0.822	0.73	0.927	0.0014	0.829	0.734	0.936	0.0024
	2004	0.818	0.728	0.919	0.0007	0.775	0.688	0.873	<.0001
	2005	0.709	0.63	0.797	<.0001	0.69	0.612	0.777	<.0001
	2006	0.738	0.658	0.828	<.0001	0.752	0.669	0.845	<.0001
	2007	0.686	0.611	0.77	<.0001	0.699	0.622	0.784	<.0001
	2008	0.616	0.545	0.697	<.0001	0.636	0.562	0.719	<.0001
	2009	0.626	0.552	0.711	<.0001	0.633	0.558	0.718	<.0001
Gender	Male	REF				REF			
	Female	0.907	0.863	0.952	<.0001	0.898	0.854	0.944	<.0001
Age Groups	18 to 29	REF				REF			
	30 to 39	1.099	1.007	1.199	0.0351	1.078	0.985	1.18	0.1024
	40 to 49	1.246	1.148	1.352	<.0001	1.208	1.111	1.313	<.0001
	50 to 59	1.399	1.291	1.517	<.0001	1.403	1.292	1.524	<.0001
	60 to 64	1.546	1.397	1.71	<.0001	1.578	1.424	1.749	<.0001
	65+	1.665	1.482	1.87	<.0001	1.666	1.48	1.875	<.0001
Patient Race	Non Hispanic White	REF				REF			
	Hispanic	1.15	1.03	1.284	0.0132	1.068	0.951	1.2	0.2676
	Black/African American	1.315	1.166	1.482	<.0001	1.257	1.109	1.425	0.0003
	Other/Multiple Race/Unknown	1.089	0.953	1.244	0.2095	1.057	0.918	1.216	0.4418
Disease Group	Acute Myelogenous Leukemia & Myelodysplastic Disorders	REF				REF			
	Acute Lymphoblastic Leukemia	1.144	1.063	1.231	0.0003	1.134	1.053	1.222	0.0009
	Other Leukemia & Myeloproliferative Syndromes	0.796	0.746	0.85	<.0001	1.016	0.953	1.083	0.6278
	Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	0.925	0.851	1.005	0.0658	1.024	0.936	1.12	0.6057
	Other Malignancy	1.303	1.061	1.6	0.0116	1.665	1.287	2.155	0.0001
	Severe Aplastic Anemia	0.54	0.449	0.648	<.0001	.	.	.	.
	Other Non-Malignant Disease	1.093	0.803	1.488	0.5733	.	.	.	.
Coexisting Disease	Absent or Missing	REF				REF			
	Present	1.14	1.08	1.201	<.0001	1.088	1.031	1.148	0.0022
HLA Matching Donor	Matched	REF				REF			
	Mismatched	1.326	1.259	1.397	<.0001	1.224	1.160	1.292	<.0001
Pateint Karnofsky Performance Status Score	90-100	REF				REF			
	≤80	0.72	0.68	0.758	<.0001	0.727	0.689	0.768	<.0001
	Missing	0.856	0.78	0.941	0.0013	0.884	0.803	0.973	0.0119
Median Household Income Quartile Categories	Quartile 1 ($10,055-$43,796)	REF				REF			
	Quartile 2 ($43,797-$55,702)	0.966	0.90	1.034	0.3165	0.954	0.889	1.023	0.1829
	Quartile 3 ($55,703-$73,257)	0.968	0.90	1.039	0.3630	0.972	0.904	1.045	0.4359
	Quartile 4 ($73,258-$242,188)	0.927	0.86	1	0.0492	0.944	0.874	1.019	0.1415
	Missing	0.996	0.83	1.2	0.9690	0.959	0.795	1.157	0.6615
FACT/Core Clinical Trial Network Center Indicator	No FACT Affiliation	1.191	1.014	1.398	0.0328	1.096	0.928	1.295	0.2782
	FACT Only	1.152	1.082	1.227	<.0001	1.094	1.026	1.166	0.0063
	FACT/CTN	REF				REF			
Centers by Department of Health and Human Services Regions	Region 1: (CT, ME, MA, NH, RI, & VT)	REF				REF			
	Region 2: (NJ, NY)	1.025	0.904	1.162	0.7005	1.029	0.906	1.169	0.6625
	Region 3: (DE, DC, MD, PA, VA, WV)	1.335	1.186	1.502	<.0001	1.39	1.234	1.565	<.0001
	Region 4: (AL, FL, GA, KY, MS, NC, SC, TN)	1.194	1.066	1.338	0.0022	1.135	1.012	1.274	0.0311
	Region 5: (IL, IN, MI, MN, OH, WI)	1.116	1.004	1.24	0.0419	1.104	0.993	1.228	0.0679
	Region 6: (AR, LA, NM, OK, TX)	1.084	0.97	1.212	0.1558	1.121	1.002	1.254	0.0468
	Region 7:(IA, KS, MO, NE)	1.152	1.011	1.314	0.0343	1.186	1.039	1.353	0.0112
	Region 8:(CO, MT, ND, SD, UT, WY)	1.083	0.903	1.299	0.3891	1.178	0.981	1.414	0.0788
	Region 9:(AZ, CA, HI, NV)	1.035	0.921	1.162	0.567	1.088	0.967	1.223	0.1607
	Region 10 (AK, ID, OR, WA)	1.008	0.888	1.144	0.9056	1.004	0.883	1.141	0.9513
Volume Quartile Indicator	Quartile I Centers (1-5 Transplants)	REF				REF			
	Quartile II Centers (6-44 Transplants)	1.093	0.858	1.392	0.473	1.072	0.837	1.373	0.582
	Quartile III Centers (45-107 Transplants)	1.059	0.839	1.338	0.6286	1.055	0.831	1.338	0.662
	Quartile IV Centers (108-713 Transplants)	0.942	0.746	1.191	0.6192	0.958	0.755	1.216	0.7237

Table 11: Factors Associated with 9 Year Relative Hazard of Death Among HCT Patients by Distance/Match Categories, Cox Proportional Hazard models, Hazard Ratio, 95% CI

	Cox Model: Matched Unrelated Transplants by Distance Categories 2000-2009				Cox Model: Mismatched Unrelated Transplants by Distance Categories 2000-2009			
	Hazard Ratio	95% CI		P Value	Hazard Ratio	95% CI		P Value
Time Quartile Indicator								
Time Distance (2-32 min)	REF				REF			
Time Distance (33-64 min)	1.036	0.95	1.129	0.4222	1.026	0.912	1.155	0.6688
Time Distance (65-149 min)	1.044	0.958	1.139	0.3266	1.046	0.924	1.184	0.4788
Time Distance (150-360 min)	1.028	0.926	1.14	0.6086	0.91	0.785	1.055	0.2093
Time Distance (361-20820 min)	1.072	0.952	1.208	0.2496	0.786	0.652	0.946	0.0111
Transplant Year								
2000	REF				REF			
2001	1.123	0.933	1.352	0.2196	0.888	0.743	1.061	0.191
2002	1.01	0.849	1.2	0.914	0.885	0.731	1.072	0.2123
2003	0.901	0.759	1.069	0.2308	0.776	0.648	0.93	0.0059
2004	0.89	0.755	1.049	0.1656	0.721	0.601	0.865	0.0004
2005	0.806	0.684	0.951	0.0104	0.563	0.466	0.68	<.0001
2006	0.821	0.699	0.964	0.0163	0.69	0.572	0.831	<.0001
2007	0.753	0.641	0.884	0.0005	0.647	0.537	0.78	<.0001
2008	0.702	0.593	0.832	<.0001	0.565	0.464	0.689	<.0001
2009	0.694	0.584	0.826	<.0001	0.592	0.48	0.73	<.0001
Gender								
Male	REF				REF			
Female	0.87	0.818	0.925	<.0001	0.954	0.874	1.04	0.2847
Age Groups								
18 to 29	REF				REF			
30 to 39	1.104	0.985	1.237	0.0899	1.117	0.966	1.291	0.1355
40 to 49	1.265	1.138	1.407	<.0001	1.254	1.094	1.436	0.0011
50 to 59	1.442	1.302	1.598	<.0001	1.369	1.19	1.575	<.0001
60 to 64	1.593	1.407	1.802	<.0001	1.572	1.303	1.896	<.0001
65+	1.814	1.58	2.082	<.0001	1.244	0.975	1.588	0.0795
Patient Race								
Non-Hispanic White	REF				REF			
Hispanic	1.176	1.005	1.375	0.043	1.044	0.881	1.238	0.6163
Black/African American	1.417	1.182	1.699	0.0002	1.142	0.959	1.359	0.1352
Other/Multiple Race/Unknown	1.056	0.879	1.268	0.5603	1.053	0.847	1.308	0.6428
Disease Group								
Acute Myelogenous Leukemia & Myelodysplastic Disorders	REF				REF			

Acute Lymphoblastic Leukemia	1.111	1.012	1.22	0.0274	1.188	1.051	1.343	0.006
Other Leukemia & Myeloproliferative Syndromes	0.77	0.71	0.835	<.0001	0.991	0.886	1.108	0.8684
Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	0.9	0.813	0.995	0.0391	0.989	0.835	1.172	0.9013
Other Malignancy	1.332	1.028	1.726	0.0302	1.639	1.033	2.603	0.0361
Severe Aplastic Anemia	0.51	0.4	0.649	<.0001	.	.	.	.
Other Non-Malignant Disease	0.927	0.587	1.463	0.744	.	.	.	.
Coexisting Disease								
Absent or Missing	REF				REF			
Present	1.108	1.04	1.183	0.0021	1.158	1	1.271	0.0020
Patient Karnofsky Performance Score								
90-100	REF				REF			
≤80	0.715	1	0.764	<.0001	0.75	1	0.823	<.0001
Missing	0.868	1	0.974	0.0157	0.852	1	1.017	0.0763
Median Household Income Quartile Categories								
Quartile 1 ($10,055-$43,796)	REF				REF			
Quartile 2 ($43,797-$55,702)	0.881	0.81	0.96	0.0036	1.139	1.01	1.285	0.0343
Quartile 3 ($55,703-$73,257)	0.915	0.84	0.999	0.0472	1.059	0.93	1.2	0.3705
Quartile 4 ($73,258-$242,188)	0.864	0.79	0.948	0.0021	1.018	0.89	1.165	0.7996
Missing	0.952	0.76	1.198	0.6757	0.984	0.71	1.373	0.9245
FACT/Core Clinical Trial Network Center Indicator								
No FACT Affiliation	1.224	1.008	1.486	0.041	1.153	0.844	1.576	0.371
FACT Only	1.152	1.065	1.245	0.0004	1.119	0.998	1.254	0.0543
FACT/CTN	REF				REF			
Centers by Department of Health and Human Services Regions								
Region 1: (CT, ME, MA, NH, RI, & VT)	**REF**				**REF**			
Region 2: (NJ, NY)	1.077	0.918	1.264	0.36	0.999	0.804	1.24	0.9892
Region 3: (DE, DC, MD, PA, VA, WV)	1.366	1.178	1.584	<.0001	1.44	1.175	1.766	0.0004
Region 4: (AL, FL, GA, KY, MS, NC, SC, TN)	1.278	1.11	1.471	0.0006	1.092	0.889	1.341	0.4018
Region 5: (IL, IN, MI, MN, OH, WI)	1.183	1.036	1.35	0.0129	1.047	0.871	1.259	0.6259
Region 6: (AR, LA, NM, OK, TX)	1.127	0.981	1.295	0.0919	1.093	0.897	1.333	0.3774
Region 7:(IA, KS, MO, NE)	1.263	1.069	1.493	0.0061	1.146	0.92	1.427	0.2236
Region 8:(CO, MT, ND, SD, UT, WY)	1.155	0.926	1.439	0.2005	1.009	0.715	1.424	0.9596
Region 9:(AZ, CA, HI, NV)	1.113	0.962	1.287	0.1518	1.001	0.818	1.224	0.9942
Region 10 (AK, ID, OR, WA)	1.032	0.883	1.207	0.6908	1.063	0.845	1.338	0.6004
Volume Quartile Indicator								
QI Centers (1-5 Transplants)	**REF**				**REF**			
Q II Centers (6-44 Transplants)	1.162	0.838	1.611	0.3674	0.998	0.674	1.478	0.9913
Q III Centers (45-107 Transplants)	1.153	0.841	1.583	0.3767	0.938	0.643	1.37	0.7421
QIV Centers (108-713 Transplants)	1.02	0.743	1.4	0.9011	0.878	0.602	1.281	0.5007

Table 12: Factors Associated with Odds of cGvHD Among HCT Patients by Distance Categories

		HLA Matched			HLA Mismatched		
		Odds Ratio	95% CI		Odds Ratio	95% CI	
Distance Indicator	Below 6 Hour Driving Distance	REF			REF		
	Above 6 Hours Driving Distance	0.91	0.78	1.07	**1.55**	**1.19**	**2.01**
Transplant Year	2000	REF			REF		
	2001	1.20	0.87	1.64	1.56	1.12	2.17
	2002	1.29	0.96	1.73	**1.64**	**1.16**	**2.31**
	2003	**1.43**	**1.07**	**1.90**	**1.56**	**1.13**	**2.15**
	2004	**1.38**	**1.05**	**1.82**	**1.91**	**1.38**	**2.65**
	2005	**1.70**	**1.29**	**2.24**	**2.28**	**1.65**	**3.15**
	2006	**1.63**	**1.24**	**2.13**	**1.88**	**1.35**	**2.61**
	2007	**1.61**	**1.23**	**2.10**	**2.14**	**1.54**	**2.98**
	2008	**1.58**	**1.19**	**2.08**	**2.78**	**1.96**	**3.94**
	2009	**1.54**	**1.16**	**2.03**	**2.17**	**1.50**	**3.12**
Gender	Male	REF			REF		
	Female	0.92	0.83	1.01	1.05	0.90	1.21
Patient Race	Non-Hispanic White	REF			REF		
	Hispanic	1.01	0.78	1.31	1.23	0.94	1.61
	Black/African American	0.76	0.55	1.04	**0.64**	**0.47**	**0.87**
	Other/Multiple Race/Unknown	1.18	0.88	1.58	1.09	0.77	1.53
Recipient Age Category	18-29	REF			REF		
	30-39	**1.27**	**1.06**	**1.52**	0.98	0.77	1.25
	40-49	1.12	0.94	1.32	1.03	0.82	1.29
	50-59	0.87	0.74	1.03	0.87	0.69	1.11
	60-69	0.87	0.71	1.06	**0.70**	**0.51**	**0.98**
	70-81+	0.81	0.64	1.02	1.06	0.71	1.59
Patient Karnofsky Performance Score	90-100	REF			REF		
	≤80	**1.52**	**1.36**	**1.70**	**1.52**	**1.29**	**1.79**
	Missing	1.18	0.97	1.42	0.99	0.73	1.34
Coexisting disease	Absent	REF			REF		
	Present	1.03	0.92	1.14	**0.84**	**0.72**	**0.99**
Disease Group	Acute Myelogenous Leukemia & Myelodysplastic Disorders	REF			REF		
	Acute Lymphoblastic Leukemia	**0.81**	**0.69**	**0.94**	0.87	0.70	1.08
	Other Leukemia & Myeloproliferative Syndromes	**1.36**	**1.19**	**1.55**	**1.21**	**1.00**	**1.47**
	Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	1.04	0.88	1.23	1.01	0.77	1.32
	Other Malignancy	1.51	0.92	2.46	0.64	0.31	1.33
	Severe Aplastic Anemia	0.77	0.57	1.05	1.05	0.68	1.61
	Other Non-Malignant Disease	0.64	0.32	1.29	**0.32**	**0.13**	**0.83**
Median Household Income Quartile Categories	Quartile 1 ($10,055-$43,796)	REF			REF		
	Quartile 2 ($43,797-$55,702)	**1.23**	**1.07**	**1.42**	0.94	0.77	1.16
	Quartile 3 ($55,703-$73,257)	**1.23**	**1.06**	**1.41**	1.06	0.86	1.30
	Quartile 4 ($73,258-$242,188)	1.14	0.99	1.31	1.07	0.86	1.32
	Missing	0.98	0.67	1.43	1.04	0.59	1.86
FACT/Core Clinical Trial Network Center Indicator	No FACT Affiliation	1.17	0.84	1.61	0.98	0.59	1.64
	FACT Only	**0.85**	**0.75**	**0.95**	**0.62**	**0.52**	**0.74**
	FACT/CTN	REF			REF		
Volume Quartile Indicator	QI Centers (1-5 Transplants)	REF			REF		
	Q II Centers (6-44 Transplants)	1.34	0.79	2.27	1.56	0.76	3.23
	Q III Centers (45-107 Transplants)	1.13	0.68	1.89	1.51	0.75	3.06
	QIV Centers (108-713 Transplants)	**2.02**	**1.21**	**3.37**	2.01	0.99	4.06

Figure 8A: Unadjusted Kaplan Meier 9 Year Mortality Estimates for all Distance Categories 2000-2009

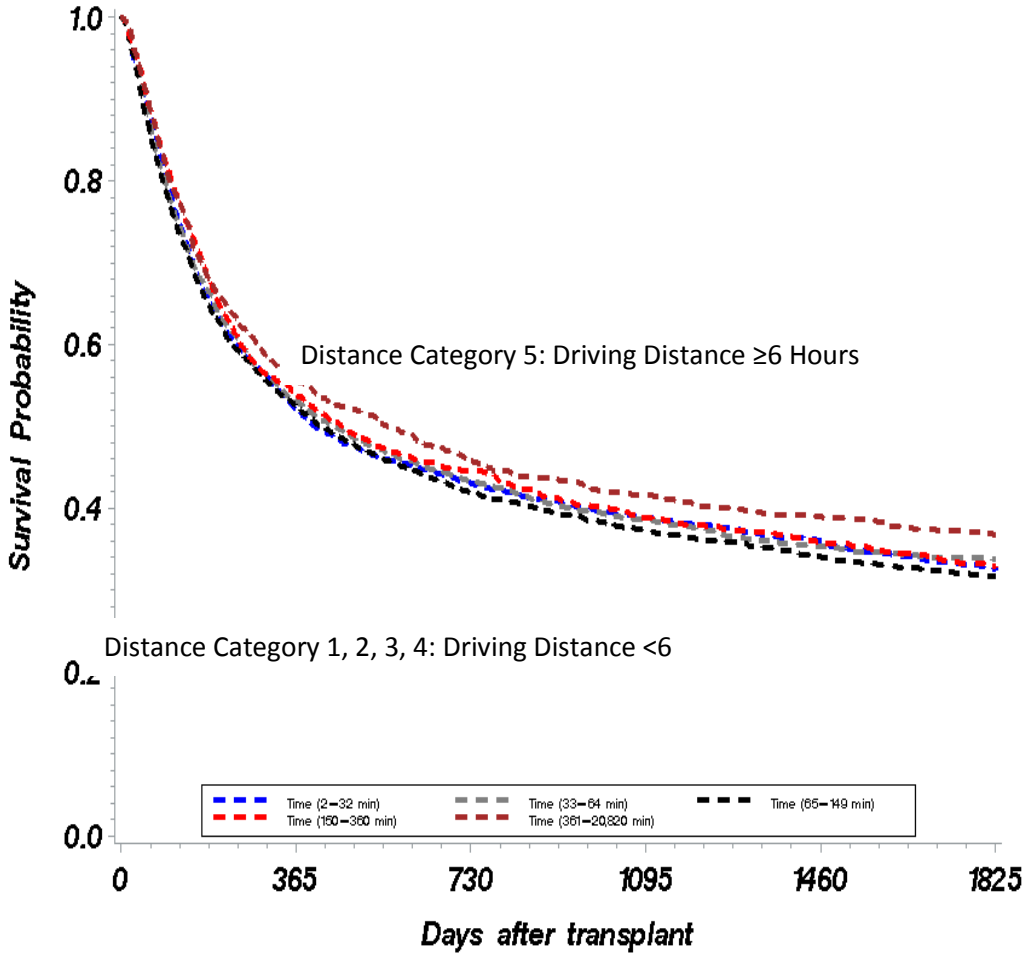


Figure 8B: Unadjusted Kaplan Meier 9 Year Mortality Estimates for all Distance Categories 2000-2009 (Survival >100 Days)

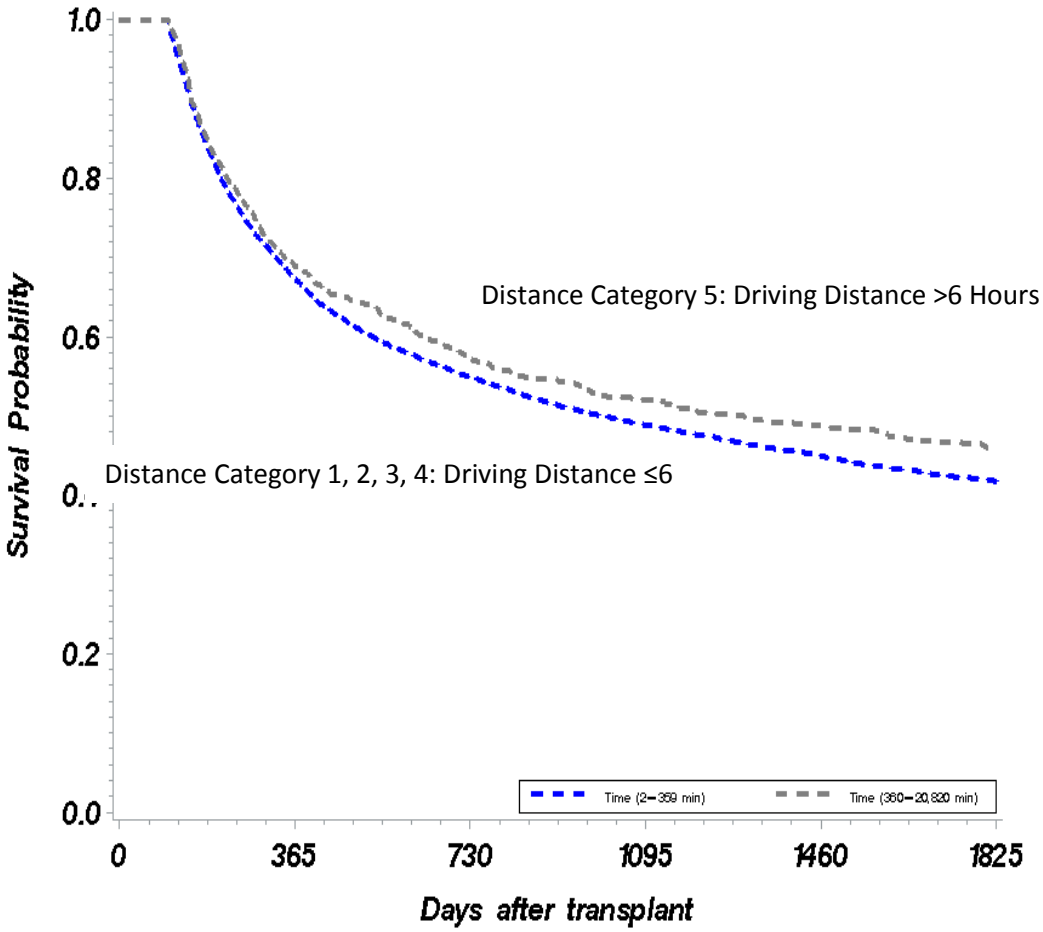


Figure 9A: Unadjusted Kaplan Meier 9 Year Mortality HCT Mismatched Estimates for all Distance Categories 2000-2009

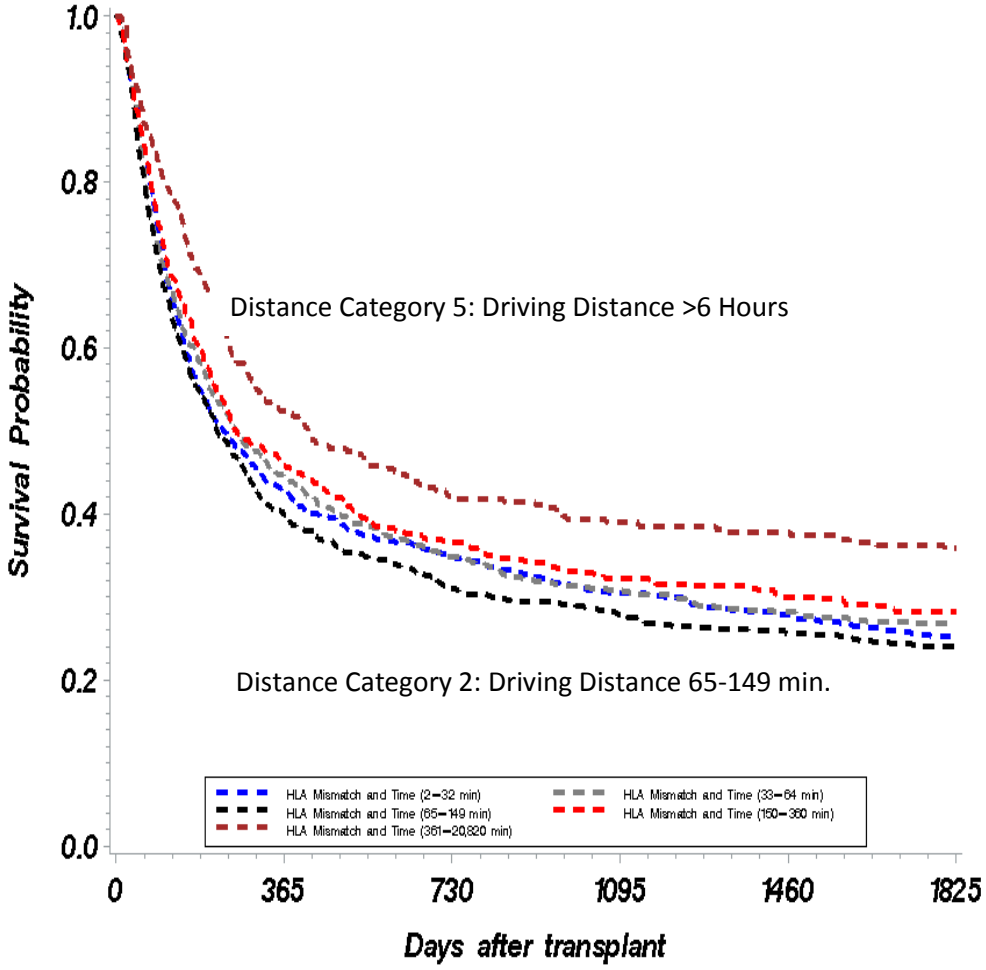


Figure 9B: Unadjusted Kaplan Meier 9 Year Mortality Estimates for Matched HCT by Distance Categories 2000-2009

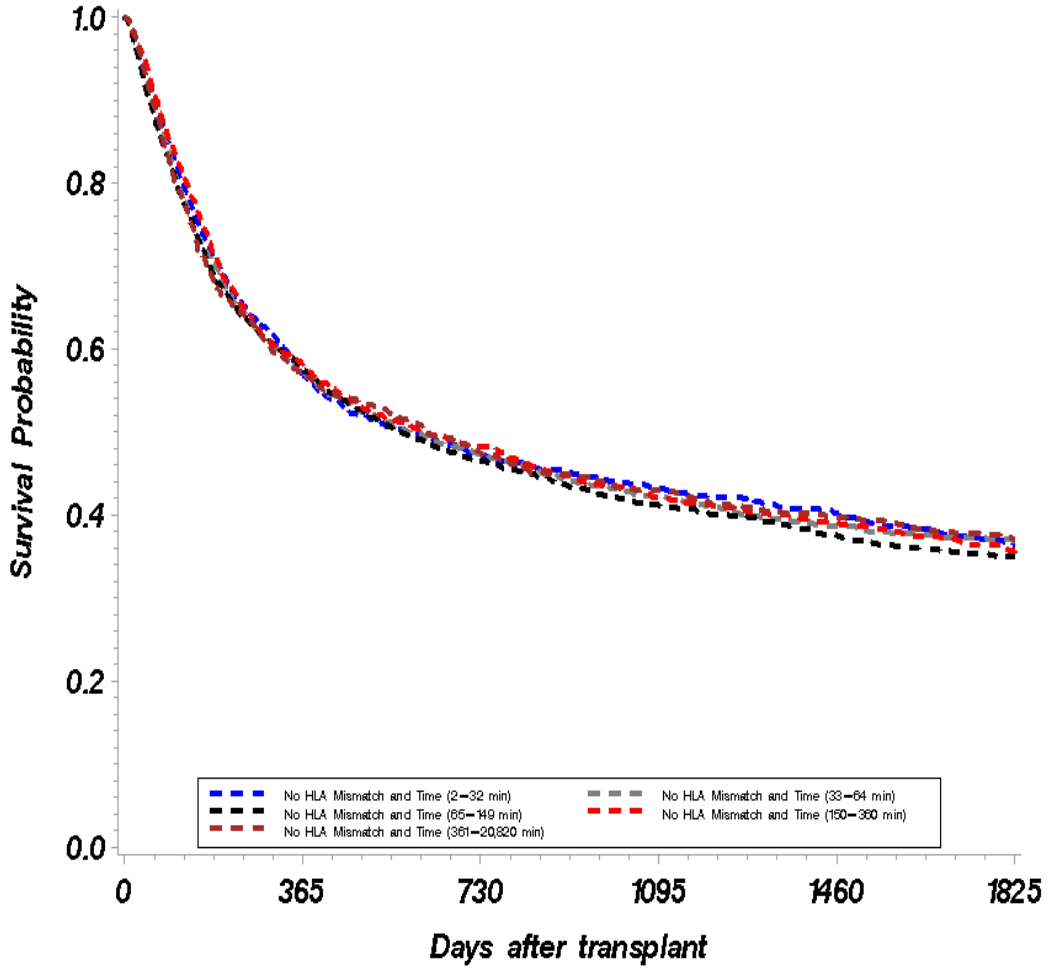
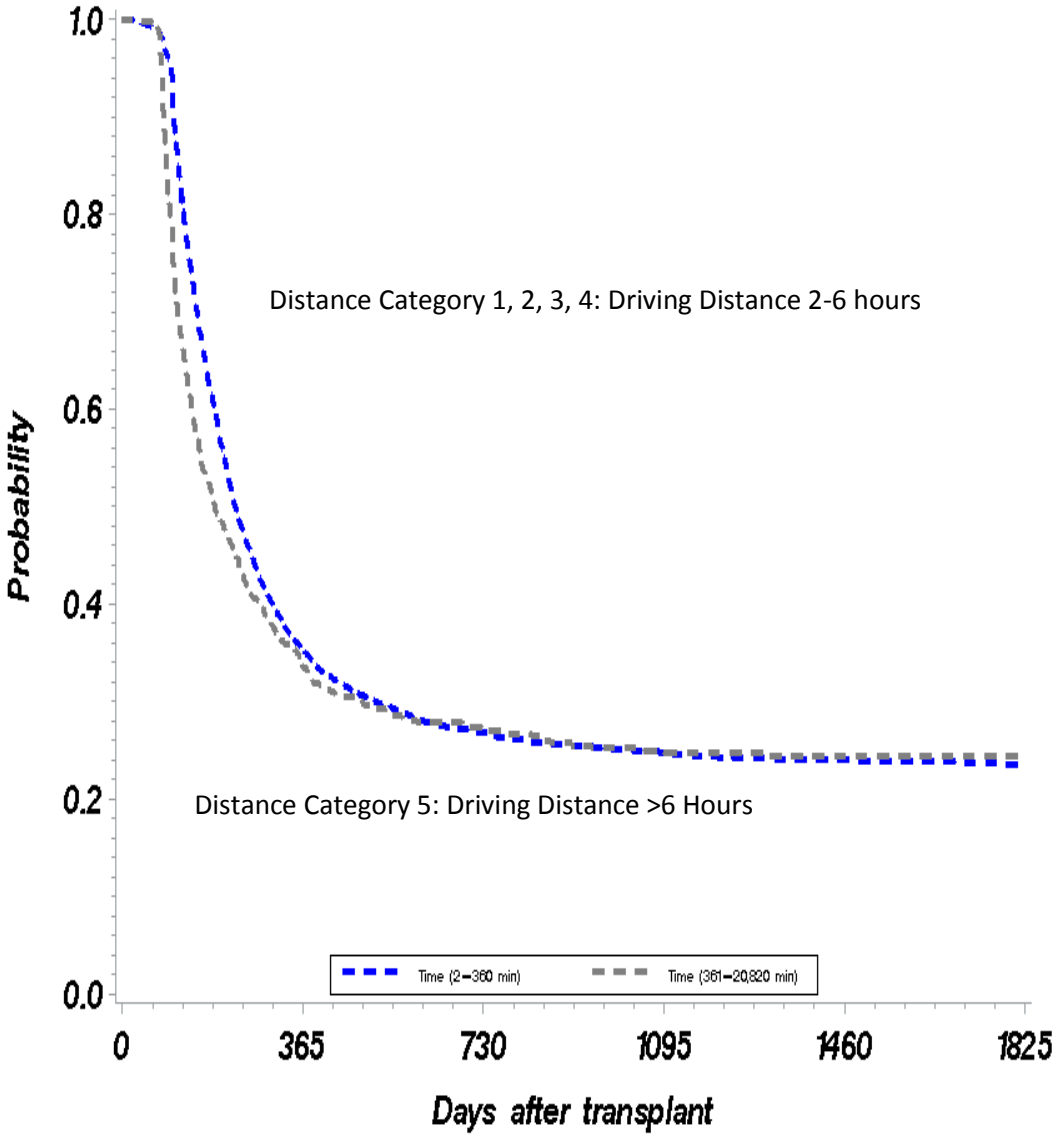


Figure 10: Kaplan Meier Probability of cGvHD for Unrelated HCT by Distance Category



		100 Days	365 Days	730 Days	1825 Days
Distance Group 1,2,3,4 (≤360 Minutes) Number at Risk	8873	8363	5092	4753	4655
Ø cGvHD Probability		93%	35%	27%	23%
Distance Group 5 (≥360 Minutes) Number at Risk	1023	838	533	501	490
Ø cGvHD Probability		78%	34%	27%	23%

Conclusion and Future Implications

This 3-paper dissertation examined the relationship between several determinants of HCT survival. HCT care provides an important opportunity to identify how payers, providers and policymakers can achieve high quality outcomes in the context of accreditation, the management of patient case mix and distance to facility. Previous studies have identified that patient risk stratification in centers of excellence and patient distance to HCT centers are important factors in improved overall HCT outcomes. This research identified the current gaps in the knowledge surrounding the impact of high risk patient management, FACT and CTN accreditation, and distance on survival and outcomes.

Overall, this research provides significant evidence for future guideline recommendations surrounding the relative impact of HCT risk management at high or low risk centers, FACT/CTN certified centers of excellence and HCT for long distance travelers. However, the exact mechanism behind identifying the best combined mechanisms for overall quality could significantly improve HCT care in the US and influence HCT providers' abilities to achieve more favorable outcomes. Using data from the Center for International Blood & Marrow Transplant Research (CIBMTR), a registry that collects transplant essential data (TED) data that includes disease type, age, sex, pre-transplant disease stage, date of diagnosis, graft type and cause of death, this research evaluated the current gaps in knowledge by 1) Evaluating the mechanism between patient case mix and overall HCT center quality (survival) 2) Identifying if centers of excellence and accreditation could explain differences in outcomes overall center quality and patient outcomes for complex HCT 3) Understanding the impact of distance on overall survival and further evaluating the impact of distance on complex HLA mismatched patients. Overall, this research provides significant evidence for future

recommendations surrounding the relative impact of risk stratification, center accreditation and distance on HCT survival.

Risk Stratification of Centers and HCT Quality

Chapter 3 of this dissertation calls into question the notion that a transplant centers' management of higher risk patients could impact and improve the survival of lower risk patients. The number of HCTs increased dramatically over the last decade and novel clinical approaches have expanded HCT to a more complex case mix of patients. An increase in overall HCT risk will likely continue to be a more common trend in the coming decades. Nevertheless, the fact that HCT centers transplant higher risk patients does not imply that they are able to treat their lower risk patient population with improved quality. There is indeed no overwhelmingly advantageous "spillover" effect that occurs for the low risk HCT patient population as a result of having HCT in a center that treats patients with higher risk. The case mix of a center should not necessarily be viewed as a sign of excellence by payers, patients, providers, and HCT center administrators. From the payers' perspective, HCT center case mix should not be a determinant of centers of excellence and low risk patient access should not be restricted to high risk centers. This might imply decreasing patient travel for lower risk HCT. Additionally, pay for performance initiatives should not simply reward high risk centers on the basis of case mix volume. For lower risk patients, our results can help guide their decision to transplant at a lower volume and lower risk centers and expect similar rates of survival. Finally, HCT center administrators and providers should not presume that augmenting higher risk patient volume case mix could improve overall outcomes for all patients, especially patients with lower risk. Combined these findings suggest that case mix cannot be a driving mechanism that maximizes HCT quality.

Overall, these findings may bring insight to policy guidelines in other cancers. Future research should continue to evaluate the presumed mechanism of "learning by

doing" and examine how higher risk volume and patient management might improve outcomes in other cancers. For example, does high volume in higher risk patient population result in better outcomes for lower risk patients? Such studies might evaluate the relationship between the performance of treatment for higher risk patients and the resulting effect on overall outcomes for the entire patient population and particularly the lower risk patients. Other research might evaluate the types of centers that are most able to demonstrate high levels of quality with both low and high risk patients. These studies might also evaluate alternative mechanisms for evaluating the case mix of cancer centers. As healthcare resources are limited and persistent efforts to promote efficient, effective evidence based practice becomes widespread, these studies will become crucial for identifying guidelines that will likely have the largest impact on overall outcomes. Continued research in this area will further encourage effective use of healthcare resources, the promotion or effective risk management and the adoption of promising quality improvement strategies.

Accredited Centers of Excellence and Quality Outcomes

Chapter 4 further evaluates the mechanism between HCT risk and complexity and survival by examining whether this relationship could be partially explained by HCT center accreditation. This second study demonstrates that FACT/CTN centers are more adept at performing complex HLA mismatched HCT versus FACT-only and non-FACT accredited centers. These findings also illustrate the variation within the FACT category and also underscore the notion that FACT accreditation alone is not enough of an indicator to differentiate transplant centers. Although FACT/CTN centers consistently showed superior outcomes, for lower risk HLA matched patients, accreditation alone does not impact survival and does not appear to be the sole mechanism for improved survival. However, there were survival advantages in HCT at FACT-only centers versus non-FACT centers for more complex HCT mismatched patients.

These findings present two key opportunities of research. First, for nearly two decades, FACT accreditation has been acknowledged to be an accurate publicly available center indicator of excellence. For example, FACT accreditation is a factor in the ranking of "America's Best Hospitals," and "America's Best Children's Hospitals," published annually by U.S. News and World Report. These organizations presumably engage in a more transparent and open environment in which donor and cell selection standards are adhered to at the highest levels. Although FACT status is an important standard that begins to define improved overall survival, our results indicate that FACT status alone is not an indicator of superior outcomes. Further research is needed to identify the components of quality that the FACT accreditation and publicly available guidelines have been able to disseminate to non-FACT centers. Additional research could identify specific factors that are implemented at FACT/CTN centers that could be introduced to all centers to improve outcomes. For example, additional analyses could find specific improvements implemented by early FACT adopters versus late adopting centers. Moreover, learning from the evolution of accredited centers over time will provide policy makers, administrators and payers with information to guide future resource planning and areas to focus future quality improvement efforts.

Second, these findings bring scrutiny to the importance of accreditation. As evidenced by high levels of voluntary center FACT participation, accreditation has widely been viewed as an important gateway to ensure higher levels of quality. Further organizational research is needed to ascertain if the accreditation process is simply a fad or fashion in which HCT centers imitate the behavior of their counterparts through the accreditation process but experience no actual advantage in having FACT status. Other similar research might explore if the pressures to adopt accreditation policies and conforming to the market norms increases according to the number of other HCT

centers that have already adopted them and explore differences in early and late adopters of accreditation.

The broader relationship between FACT status and a center's specific HCT survival rate remains complex, requiring a deeper understanding of the causal mechanism involved and finding specific factors that could be disseminated to all centers to improve outcomes. Learning from the evolution of accredited centers over time will provide policy makers, administrators and payers with information to guide future resource planning and areas to focus future quality improvement efforts. This relationship should be examined in other cancers, particularly those that heavily rely on the accreditation process to support guideline and evidence based practice. Understanding how to identify those centers that adopt accreditation policy and simultaneously improve overall outcomes for all patients will be important for improving care and disseminating effective quality guidelines to all centers.

Distance and HCT Outcomes

Finally, chapter 5 examined distance to HCT centers and the impact on survival and post-transplant complications. Results showed that between 2001-2009 patients accessing HCT from longer distances could expect comparable survival and outcomes results compared to other patients. This was especially apparent for more complex patients. After adjusting for patient and center characteristics we observed a distinct significant advantage for more complex, HLA mismatched patients that traveled distances greater than 6 hours. These results suggest that HCT centers are able to ensure the success of transplants for patients who reside long distances from transplant centers perhaps by effectively disseminating advanced post-transplant care techniques to non-specialized clinicians providing post-transplant care. Additionally, our results imply that in addition to the precautions taken at the treatment center with long distance

patients there is additional caution taken for complex HCT that may include prolonged length of stay and resistance by both patient and provider to discharge too early.

Overall, this research provides important insights into the potential implications for future research that explores the impact of distance and outcomes. Additionally, researchers should focus on identifying the most important early care components that most influence mortality and comorbidity within the HCT population. Further research with augmented datasets that include length of stay and post-transplant care variables could help determine the specific factors that should be introduced to all centers to improve outcomes for all long and short distance patients.

In conclusion, understanding the mechanism that influences the relationship between complex HCT and improved center outcomes will be instrumental in the design of future quality improvement programs and the design and designation of centers of excellence. While center characteristics, HCT match quality, patient complexity, center case mix and travel distance for HCT are not the exclusive determinants of improved survival, identifying and understanding the best combined components that significantly improve cancer outcomes in the U.S. is imperative for the overall improvement of HCT care.

Bibliography

1. Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2010. Available at: http://www.cibmtr.org.

2. Thomas, E. Donnall. A history of haemopoietic cell transplantation. British journal of haematology 105.2 (1999): 330-339. A history of haemopoietic cell transplantation. British Journal of Haematology, 105: 330–339. doi: 10.1111/j.1365-2141.1999.01337.

3. Agency for Healthcare Research and Quality (AHRQ), Nationwide Inpatient Sample (NIS), 2003. Accessed from: hcup.ahrq.gov/HCUPnet.asp

4. Stem Cell Therapeutic and Research Act of 2005. H.R. 2520 (109th): http://www.govtrack.us/congress/bills/109/hr2520/text. Accessed July 1, 2013

5. Gratwohl, Alois, et al. Risk score for outcome after allogeneic hematopoietic stem cell transplantation. Cancer 115.20 (2009): 4715-4726.

6. Loberiza Jr, Fausto R., et al. Association of transplant center and physician factors on mortality after hematopoietic stem cell transplantation in the United States. Blood 105.7 (2005): 2979-2987.

7. Armand, Philippe, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. Blood 120.4 (2012): 905-913.

8. Mitchell, J.M. et al. Access to Bone Marrow Transplantation for Leukemia and Lymphoma: The Role of Sociodemographic Factors. J Clin Oncol, v.15 (1997):2644-2651.

9. Hwang, J.P. et al. Hematopoietic Stem Cell Transplantation Among Patients with Leukemia of All Ages in Texas. Cancer, v.101:2230-2238, 2004.

10. Appelbaum FR. Hematopoietic-cell transplantation at 50. N Engl J Med. 2007;357:1472-1475.

11. Sorror, M. L., Maris, M. B., Storb, R., Baron, F., Sandmaier, B. M., Maloney, D. G., & Storer, B. (2005). Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood, 106(8), 2912-2919.

12. Sorror M, Storer B, Sandmaier BM, et al. Hematopoietic cell transplantation-comorbidity index and Karnofsky performance performance status are independent predictors of morbidity and mortality after allogeneic nonmyeloablative hematopoietic cell transplantation. Cancer. 2008;112:1992-2001.

13. Sorror ML, Sandmaier BM, Storer BE, et al. Comorbidity and disease status based risk stratification of outcomes among patients with acute myeloid leukemia or myelodysplasia receiving allogeneic hematopoietic cell transplantation. J Clin Oncol. 2007;25:4246-4254.

14. Wingard, John R., Majhail, N. S., Brazauskas, R., Wang, Z., et al. Long-term survival and late deaths after allogeneic hematopoietic cell transplantation. Journal of Clinical Oncology 29.16 (2011): 2230-2239.

15. Petersdorf EW, Anasetti C, Martin PJ, et al. Limits of HLA mismatching in unrelated hematopoietic cell transplantation. Blood. 2004;104:2976-2980.

16. Morishima Y, Sasazuki T, Inoko H, et al. The clinical significance of human leukocyte antigen (HLA) allele compatibility in patients receiving a marrow transplant from serologically HLA-A, HLA-B, and HLA-DR matched unrelated donors. Blood. 2002;99:4200-4206.

17. Sasazuki T, Juji T, Morishima Y, et al. Effect of matching of class I HLA alleles on clinical outcome after transplantation of hematopoietic stem cells from an unrelated donor. Japan Marrow Donor Program. N Engl J Med. 1998;339:1177-1185.

18. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood. 2007;110:4576-4583.12. Reece RL, ed. Volume-Outcome Link is Strong Indicator of Quality. The Quality Indicator Physician Resource. Morristown, NJ; Premiere Healthcare Resource Inc. April 2001.

19. Majhail, Navneet S., Murphy E. Allogenic Transplant Physician and Center Capacity in the United States. Blood. 2011;17:956-961.

20. F R Loberiza Jr, D S Serna, M M Horowitz and J D Rizzo. Transplant center characteristics and clinical outcomes after hematopoietic stem cell transplantation: what do we know? Bone Marrow Transplantation (2003) 31, 417–421.

21. Blue Cross Blue Shield Association. Blue Distinction Centers for Transplants. http://www.bcbs.com/why-bcbs/blue-distinction/blue-distinction-transplants/BMT_MidLevelCriteria.pdf. Accessed April 30, 2013.

22. Patient Protection and Affordable Care Act, P.L. No. 111-148 § 1323 Stat. 27 (2010).

23. The Foundation for the Accreditation of Hematopoietic Cellular Therapy. http://marrow.org. Accessed April 30, 2013.

24. Stranges E, Russo CA, Friedman B. Procedures with the most rapidly increasing hospital costs, 2004–2007. HCUP Statistical Brief #82. December 2009. Agency for Healthcare Research and Quality: Rockville, MD. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb82.pdf.

25. Haynes RM, Bentham CG. The effects of accessibility on general practitioner consultations, out-patient attendances and in-patient admissions in Norfolk, England. Soc Sci Med. 1982; 16:561-569.

26. Campbell NC, Elliott AM, Sharp L, Ritchie LD, Cassidy J,Little J. Rural factors and survival from cancer: analysis of Scottish cancer registrations. Br J Cancer. 2000;82:1863-1866.

27. Jack RH, Gulliford MC, Ferguson J, Moller H. Geographical inequalities in lung cancer management and survival in South East England: evidence of variation in access to oncology services? Br J Cancer. 2003;88:1025-1031.

28. French J, McGahan C, Duncan G, Lengoc S, Soo J, Cannon J. How gender, age, and geography influence the utilization of radiation therapy in the management of malignant melanoma. Int J Radiat Oncol Biol Phys. 2006;66:1056-1063.

29. Dejardin O, Bouvier AM, Herbert C, et al. Social and geographic disparities in access to reference care site for patients with colorectal cancer in France. Br J Cancer. 2005;92:1842-1845.

30. Pagano E, Di CD, Bona C, et al. Accessibility as a major determinant of radiotherapy underutilization: a population based study. Health Policy. 2007;80:483-491.

31. Kim YE, Gatrell AC, Francis BJ. The geography of survival after surgery for colo-rectal cancer in southern England. Soc Sci Med. 2000;50:1099-1107.

32. Fortney J, Rost K, Warren J. Comparing alternative methods of measuring geographic access to health services. Heath Serv Outcomes Res Methol. 2011;1:173-184.

33. Abou-Nassar, K. E., Kim, H. T., Blossom, J., Ho, V. T., Soiffer, R. J., Cutler, C. S., ... & Armand, P. (2012). The Impact of Geographic Proximity to Transplant Center on Outcomes after Allogeneic Hematopoietic Stem Cell Transplantation. Biology of Blood and Marrow Transplantation, 18(5), 708-715.

34. Rao K, Darrington DL, Schumacher JJ, Devetten M, Vose JM, Loberiza FR Jr. Disparity in survival outcome after Hematopoietic cell transplantation for hematologic malignancies according to area of primary residence. Biol Blood Marrow Transplant. 2007;13:1508-1514.

35. Paulson K, Lambert P, Bredeson C, et al. Does location matter? Rural vs urban outcomes after blood and marrow transplantation in a population-based Canadian cohort. Bone Marrow Transplant. 2010;45:1167-1173.

36. Deeg, H. Joachim, and Brenda M. Sandmaier. Who is fit for allogeneic transplantation? *Blood* 116.23 (2010): 4762-4770.

37. McClune, Brian L., et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *Journal of Clinical Oncology* 28.11 (2010): 1878-1887.

38. The National Cancer Instictute at the National Institute of Health. NCI Dictionary of Cancer Terms. http://www.cancer.gov/dictionary?CdrID=44156. Acceded July 1, 2013.

39. Guilfoyle, R., et al. Performance status, but not the hematopoietic cell transplantation comorbidity index (HCT-CI), predicts mortality at a Canadian transplant center. *Bone marrow transplantation* 43.2 (2008): 133-139.

40. National Marrow Donor Program. Be the Match. HLA Matching: Finding the Best Donor or Cord Blood Unit. http://marrow.org. Accessed April 30, 2013.

41. Petersdorf EW, Gooley TA, Anasetti C, et al. Optimizing outcome after unrelated marrow transplantation by comprehensive matching of HLA class I and II alleles in the donor and recipient. Blood. 1998;92:3515-3520.

42. Flomenberg N, Baxter-Lowe LA, Confer D, et al. Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome. Blood. 2004;104:1923-1930.

43. Hurley CK, Wagner, John, Setterholm, Michelle, et al. Advances in HLA: Practical Implications for Selecting Adult Donors and Cord Blood Units. Biology of Blood and MT. 2006.

44. Shaw BE, Marsh SG, Mayor NP, Russell NH, Madrigal JA. HLA-DPB1 matching status has significant implications for recipients of unrelated donor stem cell transplants. Blood. 2006; 107:1220-1226.

45. Weisdorf D, Spellman S, Haagenson M, et al. Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: revised definitions to predict survival. Biol Blood Marrow Transplant. 2008;14:748-758.

46. Mehta, P. et al. Access to Stem Cell Transplantation: Do Women Fare As Well As Men? Am Journal Hema, v. 72 (2003):99-102.

47. Mitchell, J.M. et al. Access to Bone Marrow Transplantation for Leukemia and Lymphoma: The Role of Sociodemographic Factors. J Clin Oncol, v.15 (1997):2644-2651.

48. Birkmeyer JD, Stukel TA, Siewers AE, et al. Surgeon volume and operative mortality in the United States. N Engl J Med. 2003;349:2117– 2127.

49. Schrag D, Panageas KS, Riedel E, et al. Surgeon volume compared to hospital volume as a predictor of outcome following primary colon cancer resection.J Surg Oncol. 2003;83:68–78.

50. Schrag D, Panageas KS, Riedel E, et al. Hospital and surgeon procedure volume as predictors of outcome following rectal cancer resection.Ann Surg . 2002; 236:583–592.

51. Ho V, Heslin MJ, Yun H, et al. Trends in hospital and surgeon volume and operative mortality for cancer surgery. Ann Surg Oncol. 2006; 13:851–858.

52. Begg CB, Cramer LD, Hoskins WJ, et al. Impact of hospital volume on operative mortality for major cancer surgery. JAMA . 1998;280:1747–1751.

53. Shahian, David M. and Normand, Sharon L. "The Volume Outcome Relationship: From Luft to Leapfrog." Annals of Thoracic Surgery, 2001, 75(3), pp. 1048-58.

54. Halm, Ethan A. "Is Volume Related to Outcome in Health Care? A Systematic Review and Methodologic Critiqueo f the Literature."A n-nals of Internal Medicine, 2002, 137(6), pp. 511-20.

55. Hillner BE, Smith TJ, Desch CE. Hospital and physician volume or specialization and outcomes in cancer treatment: importance in quality of cancer care. J Clin Oncol . 2000;18:2327–2340.

56. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. Ann Surg. 1998;228:429–438.

57. Swisher SG, Deford L, Merriman KW, et al. Effect of operative volume on morbidity, mortality, and hospital use after esophagectomy for cancer. J Thorac Cardiovasc Surg. 2000;119:1126–1132.

58. Kuo EY, Chang Y, Wright CD. Impact of hospital volume on clinical and economic outcomes for esophagectomy. Ann Thorac Surg. 2001; 72:1118–1124.

59. Harmon JW, Tang DG, Gordon TA, et al. Hospital volume can serve as a surrogate for surgeon volume for achieving excellent outcomes in colorectal resection. Ann Surg . 1999;230:404–413.

60. Greenstein AJ, Litle VR, Swanson SJ, Divino CM, Packer S, Wisnivesky JP. Effect of the number of lymph nodes sampled on postoperative survival of lymph node-negative esophageal cancer. Cancer 2008;112(6):1239-46.

61. Prandi M, Lionetto R, Bini A. Prognostic evaluation of stage B colon cancer patients is improved by an adequate lymphadenectomy: Results of a secondary analysis of a large scale adjuvant trial. Ann Surg 2002;235:458-463.

62. Birkmeyer, N. J., Goodney, P. P., Stukel, T. A., Hillner, B. E. (2005). Do cancer centers designated by the National Cancer Institute have better surgical outcomes? Cancer, 103(3), 435-441.

63. Meguid, Robert A., et al. Are surgical outcomes for lung cancer resections improved at teaching hospitals?. The Annals of thoracic surgery 85.3 (2008): 1015-1025.

64. Allison, J.J., C.I. Kiefe, N.W. Weissman, S.D. Person, M. Rousculp, J.G. Canto, S. Bae, O.D. Williams, R. Farmer, and R.M. Centor. 2000. Relationship of Hospital Teaching Status with Quality of Care and Mortality for Medicare Patients with Acute MI. Journal of the American Medical Association 284:1256–62.

65. Ayanian, J.Z., J.S.Weissman, S. Chasan-Taber, and A.M. Epstein. 1998. Quality of Care for Two Common Illnesses in Teaching and Nonteaching Hospitals. Health Affairs 17:194–205.

66. Keeler, E.B., L.V. Rubenstein, K.L. Kahn, D. Draper, E.R. Harrison, M.J. McGinty,W.H. Rogers, and R.H. Brook. 1992. Hospital Characteristics and Quality of Care. Journal of the American Medical Association 268:1709–14.

67. Kuhn, E.M., A.J. Hartz, H. Krakauer, R.C. Bailey, and A.A. Rimm. 1994. The Relationship of Hospital Ownership and Teaching Status to 30- and 180-Day Adjusted Mortality Rates. Medical Care 32:1098–1108.

68. Rosenthal, G.E., D.L. Harper, L.M. Quinn, and G.S. Cooper. 1997. Severity-Adjusted Mortality and Length of Stay in Teaching and Nonteaching Hospitals: Results of a Regional Study. Journal of the American Medical Association 278:485–90.

69. Zimmerman, J.E., S.M. Shortell, W.A. Knaus, D.M. Roussear, D.P. Wagner, R.R. Gillies, E.A. Draper, and K. Devers. 1993. Value and Cost of Teaching Hospitals: A Prospective, Multicenter, Inception Cohort Study. Critical Care Medicine 21:1432–42.

70. Hartz, A.J., H. Krakauer, E.M. Kuhn, M. Young, S.J. Jacobsen, G. Gay, L. Muenz, M. Katzoff, R.C. Bailey, and A.R. Rimm. 1989. Hospital Characteristics and Mortality Rates. New England Journal of Medicine 321:1720–5.

71. Kuhn, E.M., A.J. Hartz, M.S. Gottlieb, and A.A. Rimm. 1991. The Relationship of Hospital Characteristics and the Results of Peer Review in Six Large States. Medical Care 29:1028–38.

72. Taylor, D.H., D.J. Whellan, and F.A. Sloan. 1999. Effects of Admission to a Teaching Hospital on the Cost and Quality of Care for Medicare Beneficiaries. New England Journal of Medicine 340:293–9.

73. McClellan, M., B. J. McNeil and J. P. Newhouse (1994). Does more intensive treatment of acute myocardial infarction in the elderly reduce mortality? Analysis using instrumental variables. Jama 272(11): 859-66.

74. Herlitz, J., M. Hartford, S. Aune, T. Karlsson and A. Hjalmarson (1993). Delay time between onset of myocardial infarction and start of thrombolysis in relation to prognosis. Cardiology 82(5): 347-53.

75. Davalos, A., J. Castillo and E. Martinez-Vila (1995). Delay in neurological attention and strokeoutcome. Cerebrovascular Diseases Study Group of the Spanish Society of Neurology. Stroke26 (12): 2233-7.

76. LaVela SL, Smith B, Weaver FM, Miskevics SA. Geographical proximity and health care utilization in veterans with SCI&D in the USA. Soc Sci Med. 2004;59:2387-2399.

77. Johansen, K. A., et al. Efforts of the United States' National Marrow Donor Program and Registry to improve utilization and representation of minority donors.Transfusion Medicine 18.4 (2008): 250-259.

78. Rubin HR, Pronovost P, Diette GB. The advantages and disadvantages of process-based measures of health care quality. Int J Qual Health Care . 2001;13:469-474.

79. Dimick, Justin B., H. Gilbert Welch, and John D. Birkmeyer. Surgical mortality as an indicator of hospital quality. JAMA: the journal of the American Medical Association 292.7 (2004): 847-851.

80. Jost TS. Health system reform: forward or backward with quality oversight? JAMA. 1994;271:1508-1511.

81. Kassirer JP. The use and abuse of practice profiles. N Engl J Med. 1994;330:634-636.

82. Kuhlthau K, Ferris TG, Iezzoni L. Risk adjustment for pediatric quality indicators. Pediatrics. 2004;113:210-216.

83. The Foundation for the Accreditation of Hematopoietic Cellular Therapy. http://www.factwebsite.org/CordSearch.aspx?&type=Cord. Accessed April 30, 2013.

84. Center for International Blood and Marrow Transplant Research. http://www.cibmtr.org/DataManagement/TrainingReference/Manuals/DataManagement/Documents/appendix-l.pdf. Accessed April 30, 2013.

85. Center for International Blood and Marrow Transplant Research. http://www.cibmtr.org/datamanagement/trainingreference/manuals/datamanagement/documents/pre-ted-instructions.pdf. Accessed April 30, 2013.

86. Rizzo JD, Wingard JR, Tichelli A, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the American Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2006;12:138-151.

87. Horowitz MM, Przepiorka D, Champlin RE, et al. Should HLA-identical sibling bone marrow transplants for leukemia be restricted to large centers? Blood. 1992;79:2771-2774.

88. Abou-Nassar, K. E., Kim, H. T., Blossom, J., Ho, V. T., Soiffer, R. J., Cutler, C. S., ... & Armand, P. (2012). The Impact of Geographic Proximity to Transplant Center on Outcomes after Allogeneic Hematopoietic Stem Cell Transplantation. Biology of Blood and Marrow Transplantation, 18(5), 708-715.

89. Chan L, Hart LG, Goodman DC. Geographic access to health care for rural Medicare beneficiaries. J Rural Health. 2006;22: 40-146.

90. Haynes RM, Bentham CG. The effects of accessibility on general practitioner consultations, out-patient attendances and in-patient admissions in Norfolk, England. Soc Sci Med. 1982; 16:561-569.

91. LaVela SL, Smith B, Weaver FM, Miskevics SA. Geographical proximity and health care utilization in veterans with SCI&D in the USA. Soc Sci Med. 2004; 59:2387-2399.

92. Moscovice, Ira S. Rural hospitals: a literature synthesis and health services research agenda. *Health Services Research* 23.6 (1989): 891.

93. Loberiza Jr, Fausto R., et al. Outcomes of hematologic malignancies after unrelated donor hematopoietic cell transplantation according to place of residence. *Biology of Blood and Marrow Transplantation* 16.3 (2010): 368-375.

94. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation. Oct 1974;18(4):295-304.

95. Minnesota Population Center. National Historical Geographic Information System: Version 2.0. Minneapolis, MN: University of Minnesota 2011.

96. US Department of Commerce. United States Census Bureau. http://www.census.gov/prod/2009pubs/acsbr08-2.pdf. Accessed April 30, 2013.

97. US Department of Commerce. United States Census Bureau. http://www.census.gov/geo/reference/zctas.html. Accessed April 30, 2013.

98. Google Maps. Google. Retrieved from http://maps.google.com/maps

99. SAS Institute Inc., SAS 9.3 Help and Documentation, Cary, NC: SAS Institute Inc., 2011.

100. Marmor, S. et al. Unpublished Dissertation. 2013.

101. Majhail, N. S., et al. Costs of autologous and allogeneic hematopoietic cell transplantation in the United States: a study using a large National Private Claims Database. Bone Marrow Transplantation 48.2 (2012): 294-300.

Appendices

Appendix 1: Karnofsky Performance Score Table

The CIBMTR uses Karnofsky/Lansky performance status to determine the functional status of a recipient. Recipient performance status is a critical data field that has been determined to be essential for all outcome-based analyses. The Karnofsky Scale is designed for recipients aged 16 years and older. The Karnofsky score runs from 100 to 0, where 100 is "perfect" health. The performance status is an attempt to quantify cancer patients' general well-being and activities of daily life and is used to measure of quality of life. CIBTMR categorizes the Karnofsky performance score as a dichotomous variable of 90-100 (score of 0) and ≤ 80 (score of 1).

Karnofsky Scale (recipient age ≥16 years)	
Able to carry on normal activity; no special care is needed	
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity
80	Normal activity with effort
Unable to work, able to live at home cares for most personal needs, a varying amount of assistance is needed	
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly	
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization indicated, although death not imminent
20	Very sick, hospitalization necessary
10	Moribund, fatal process progressing rapidly

Appendix 2: Benefit of the Risk Category Stratification: Cox Proportional Hazard Models

The following sensitivity analyses evaluate the benefit of creating a risk bundle versus testing each component (age, coexisting disease, human leukocyte antigen (HLA) match and Karnofsky score) of the risk bundle separately within our model. Utilizing cox proportional hazard models with and without our risk bundles we found no statistical benefit between the two models. Since they are nested models (one is a subset of the other) we tested whether the separate parameters significantly improve the fit using the -2 Log Likelihood.

The differences in the Log Likelihood (106913.38-106630.67=39.19) and is distributed as chi-square with 28 DF. This is a non-significant (p-value .1) indicating that including each component (age, coexisting disease, HLA match and Karnofsky score) of the risk category in the model does not lead to a better fir than the component risk category model. Although, the risk category model does not lead to a significantly better fit we found benefit to modeling the risk category variable in order to facilitate and simplify our center stratification.

a) Model fit statistic with No Risk Category DF=28

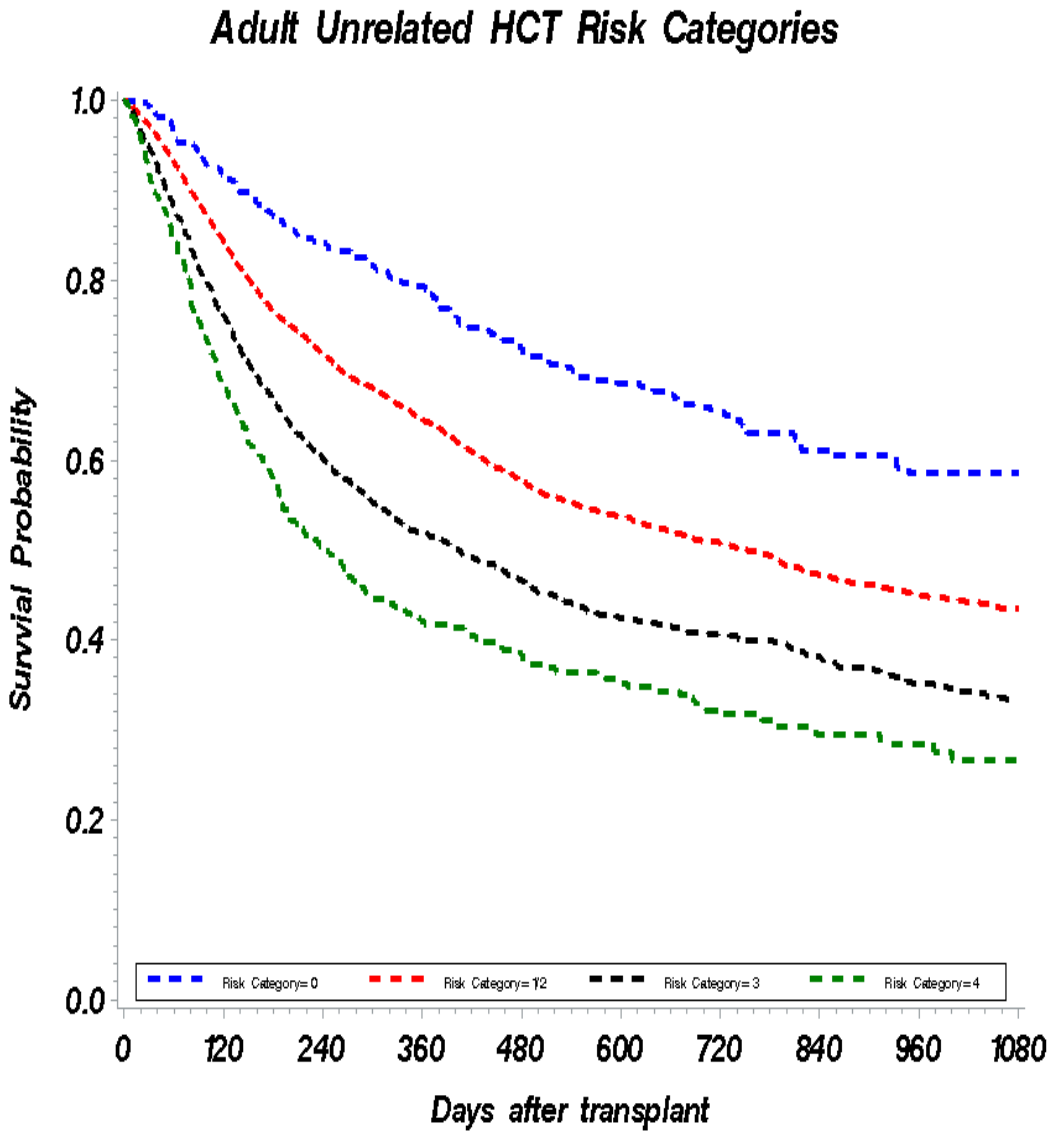
Model Fit Statistic		
Criterion	**Without Covariates**	**With Covariates**
-2Log L	**107277.67**	**106630.67**
AIC	**107277.67**	**106686.67**
SBC	**107277.67**	**106874.18**

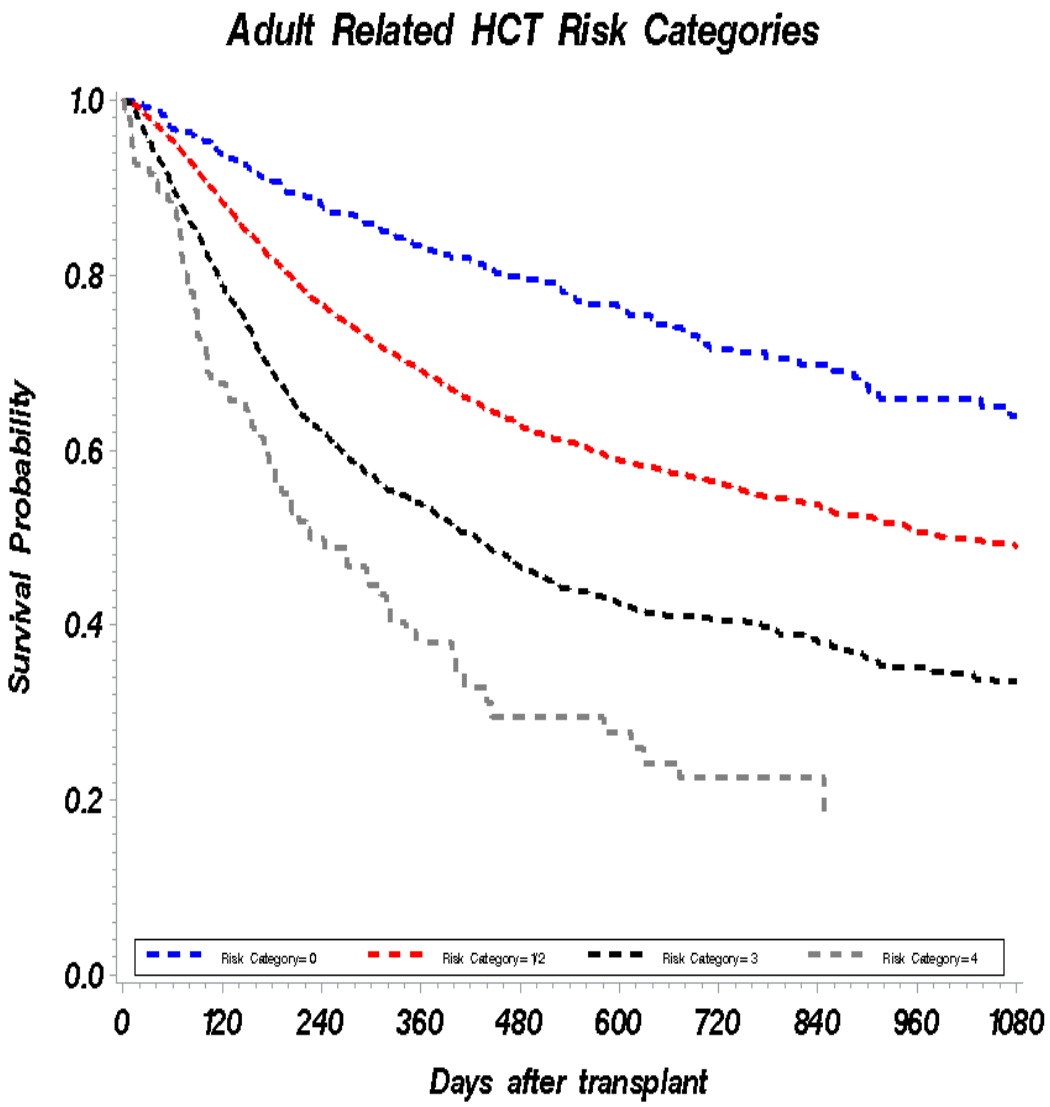
b) Model Fit Statistics with Risk Category DF=28

Model Fit Statistic		
Criterion	**Without Covariates**	**With Covariates**
-2Log L	**107277.67**	**106630.67**
AIC	**107277.67**	**106725.86**
SBC	**107277.67**	**106913.38**

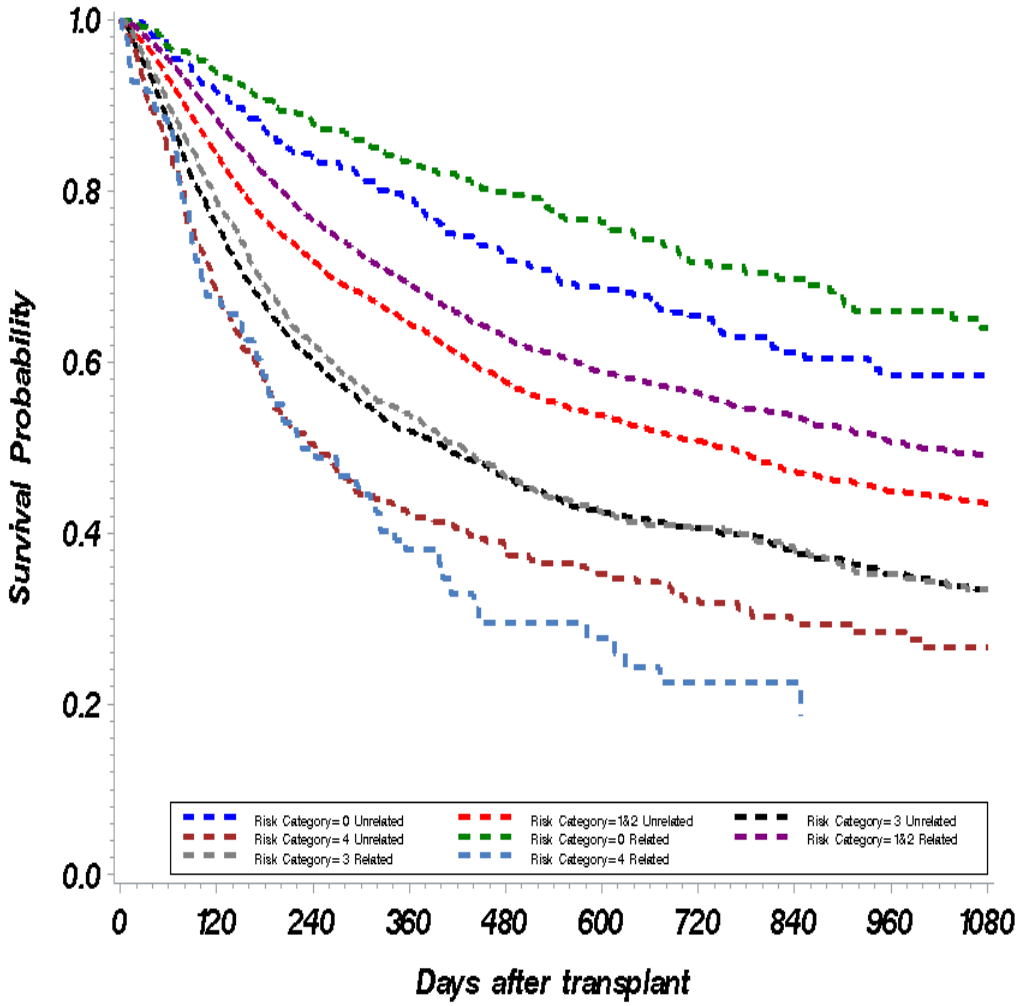
Appendix 3: Inclusion of Related and Unrelated Donor for HSCT Risk Categories

The following sensitivity analysis evaluates our consolidation of the related and unrelated donor HSCT groups within our risk categories. We created independent risk categories composed of age, coexisting disease, human leukocyte antigen (HLA) match and Karnofsky-Lansky score for each type of donor, related and unrelated. Age, coexisting disease, and Karnofsky-Lansky score were categorized identically for both the related and unrelated transplant groups. For the HLA match status of donors we created separate categories for related and unrelated HSCT. For unrelated donors an 8/8 match was categorized as (1) and any mismatch (6/8, 7/8, partially matched, mismatched) were scored with a 0. For the related group a matched relative, matched sibling, synergenic donor was scored as 1and all others were scored as a 0.



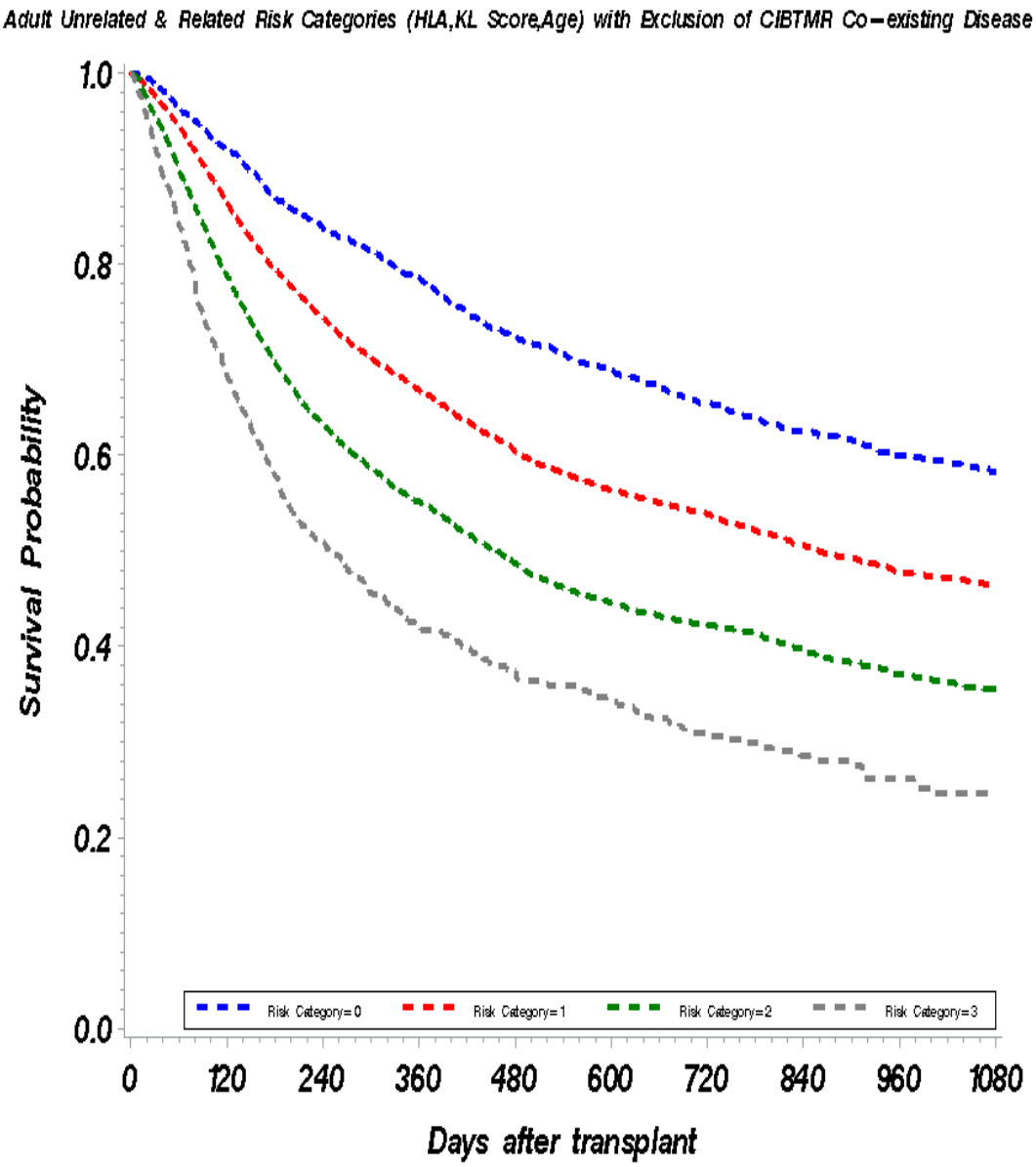

Adult Related HCT Risk Categories
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
120
240
360
480
600
720
840
960
1080
Days after transplant
Risk Category=0
Risk Category=1\2
Risk Category=3
Risk Category=4

Adult Unrelated & Related HCT Risk Categories



Appendix 4: Existence of coexisting disease with the Calculated Risk Categories

Due to the fact that CIBMTR broadly identifies coexisting disease and because patient inclusion within a risk category may be a construct of a center's willingness to both over and under code the presence of coexisting disease, we tested our risk categories with and without the inclusion of co-existing disease in our models. Using Kaplan Meir curves we determined that our risk categories that included co-existing disease were no different from our Kaplan Meir cuvees that excluded coexisting disease.



Appendix 5: Risk Bundle Stratification with Hierarchical Linear Models

The following sensitivity analysis evaluates the use of Hierarchical Linear Models (HLM) in opposition to cox proportional models. In our HLM risk categories defined patients are nested within our high and low risk centers. Below, we include the Odds Ratios of the HLM indicating that our conclusions are unchanged and that the use of HLM to verify that accounting for transplant recipients being nested in centers did not produce results of different magnitude or direction.

Hierarchical Linear Model-All Centers 2008-2010				
		Odds Ratio	95% CI	
Risk Category Groups	0	REF		
	1	1.877	1.596	2.208
	2	3.213	2.694	3.831
	3	5.116	3.916	6.684
Gender	Female	REF		
	Male	1.158	1.075	1.247
Patient Race	Non-Hispanic White		REF	
	Hispanic	1.07	0.925	1.236
	Black/African American	1.205	1.02	1.423
	Other/Multiple Race/Unknown	0.963	0.803	1.154
Disease Group	Acute Myelogenous Leukemia & Myelodysplastic Disorders	REF		
	Acute Lymphoblastic Leukemia	0.956	0.85	1.075
	Other Leukemia & Myeloproliferative Syndromes	0.668	0.598	0.747
	Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	0.757	0.683	0.838
	Other Malignancy	0.938	0.784	1.122
	Severe Aplastic Anemia	0.404	0.313	0.522
	Other Non-Malignant Disease	0.499	0.315	0.79
Centers by Department of Health and Human Services Regions	Region 1: (CT, ME, MA, NH, RI, & VT)	REF		
	Region 2: (NJ, NY)	1.202	0.857	1.686
	Region 3: (DE, DC, MD, PA, VA, WV)	1.178	0.853	1.626
	Region 4: (AL, FL, GA, KY, MS, NC, SC, TN)	1072	0.791	1.452
	Region 5: (IL, IN, MI, MN, OH, WI)	0.966	0.712	1.31
	Region 6: (AR, LA, NM, OK, TX)	1.139	0.808	1.604
	Region 7:(IA, KS, MO, NE)	1.168	0.76	1.795
	Region 8:(CO, MT, ND, SD, UT, WY)	1.002	0.655	1.532
	Region 9:(AZ, CA, HI, NV)	1.016	0.734	1.408
	Region 10 (AK, ID, OR, WA)	0.867	0.547	1.375
Center Characteristics	Low Volume Indicator (2-54 Transplants)	REF		
	High Volume Indicator (>=55 Transplants)	0.785	0.646	0.955
	Unrelated Donor Indicator	REF		
	Related Donor Indicator	0.843	0.781	0.909

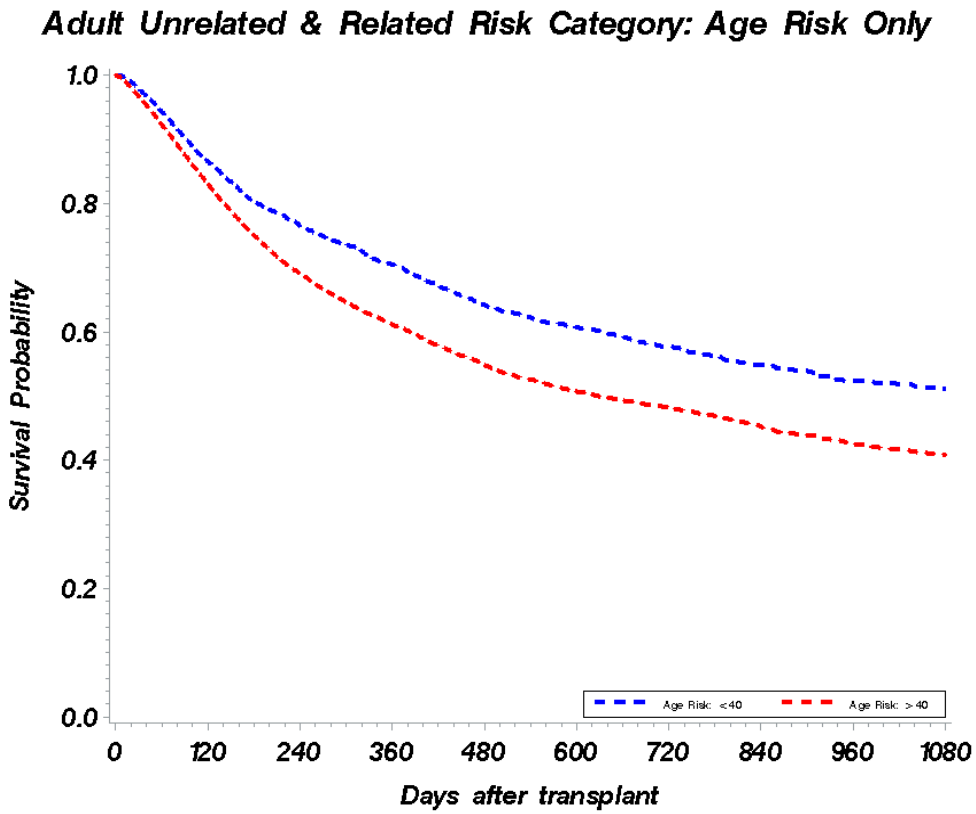
Appendix 6: Cox Proportional Hazard Models with High Risk Category Exclusion

The following sensitivity analysis evaluates the exclusion of our high risk category patients (RC=4) from our cox proportional hazard models for our high risk centers in order to verify that high risk patients do not drive our Hazard Ratio results for our lower risk patient population.

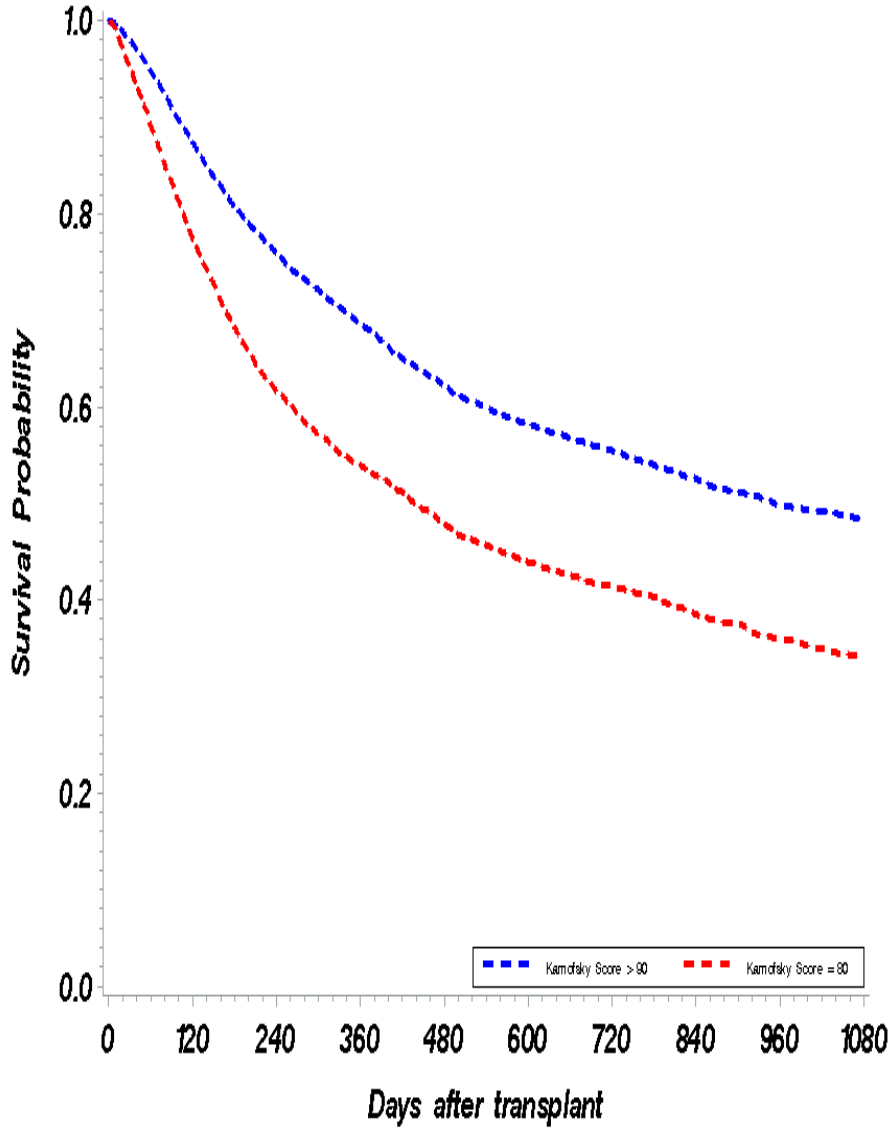
Cox Model for High Risk Centers without High Risk Patients 2008-2010					
		Hazard Ratio	95% CI		P Value
Risk Category Groups	0	REF			
	1	1.635	1.405	1.903	<.0001
	2	2.465	2.108	2.882	<.0001
Gender	Male	REF			
	Female	0.921	0.869	0.977	0.006
Patient Race	Caucasian	REF			
	Hispanic	1.066	0.949	1.197	0.2831
	Black/African American	1.069	0.932	1.225	0.3397
	Other/Multiple Race/Unknown	0.97	0.838	1.122	0.6807
Transplant Year	2008	REF			
	2009	0.978	0.912	1.049	0.5349
	2010	0.968	0.897	1.043	0.3914
Disease Group	Acute Myelogenous Leukemia & Myelodysplastic Disorders	REF			
	Acute Lymphoblastic Leukemia	0.954	0.869	1.048	0.3287
	Other Leukemia & Myeloproliferative Syndromes	0.728	0.664	0.797	<.0001
	Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	0.823	0.758	0.893	<.0001
	Other Malignancy	0.911	0.796	1.044	0.18
	Severe Aplastic Anemia	0.608	0.481	0.768	<.0001
	Other Non-Malignant Disease	0.71	0.44	1.148	0.1623
Centers by Department of Health and Human Services Regions	Region 1: (CT, ME, MA, NH, RI, & VT)	REF			
	Region 2: (NJ, NY)	1.14	0.996	1.304	0.0579
	Region 3: (DE, DC, MD, PA, VA, WV)	1.201	1.049	1.375	0.0079
	Region 4: (AL, FL, GA, KY, MS, NC, SC, TN)	1.158	1.025	1.309	0.0182
	Region 5: (IL, IN, MI, MN, OH, WI)	1.052	0.931	1.189	0.4134
	Region 6: (AR, LA, NM, OK, TX)	1.249	1.095	1.424	0.0009
	Region 7:(IA, KS, MO, NE)	1.312	1.128	1.526	0.0004
	Region 8:(CO, MT, ND, SD, UT, WY)	1.095	0.916	1.308	0.3199
	Region 9:(AZ, CA, HI, NV)	1.015	0.893	1.155	0.8155
	Region 10 (AK, ID, OR, WA)	1.035	0.893	1.199	0.6515
Center Characteristics	High Volume Indicator (>=55 Transplants)	1.378	1.203	1.578	<.0001
	Related Donor Indicator	1.156	1.089	1.227	<.0001

Appendix 7: Separate Kaplan Meir curves for Risk by Age (>40 versus ≤40), Coexisting Disease (Present versus Absent), Karnofsky Performance Score (>90 versus ≤80) and HLA Match (Match versus Mismatch)

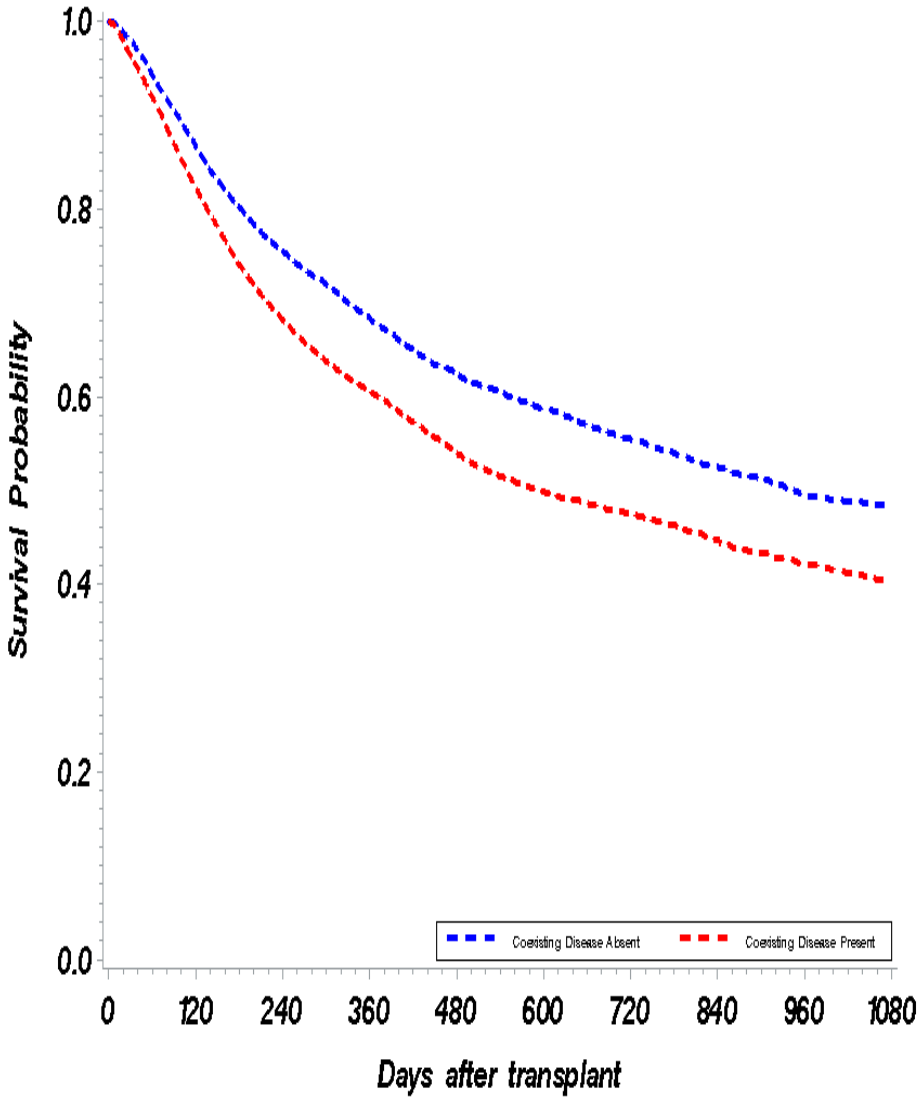
In order to ensure that our defined risk of >40, coexisting disease, Karnofsky score <90 and HLA mismatch were accurate representations of risk we tested each component of our risk categories separately using Kaplan Meir curves. Below, the set of Kaplan Meir curves indicates that our risk components are verified measures of risk.

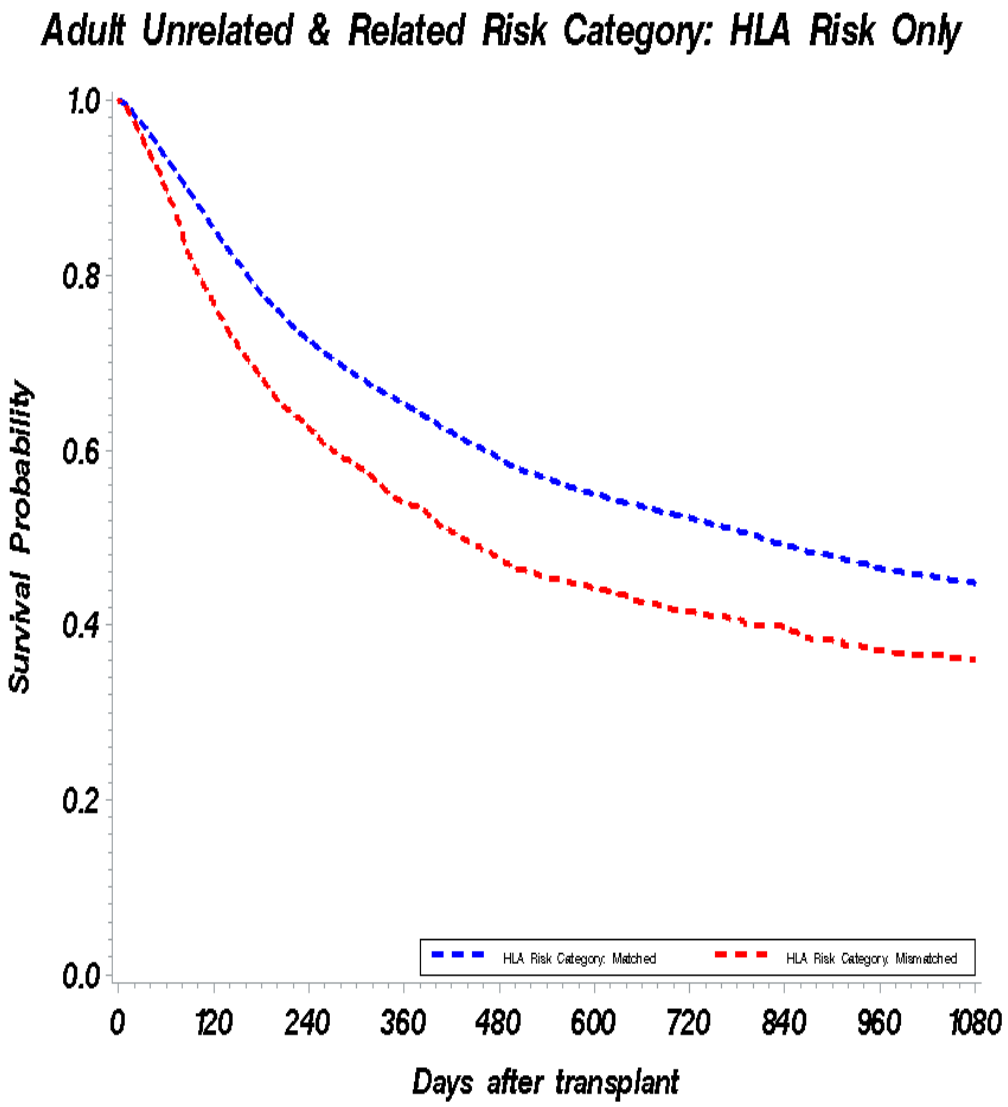


Adult Unrelated & Related Risk Category: Karnofsky Score Only



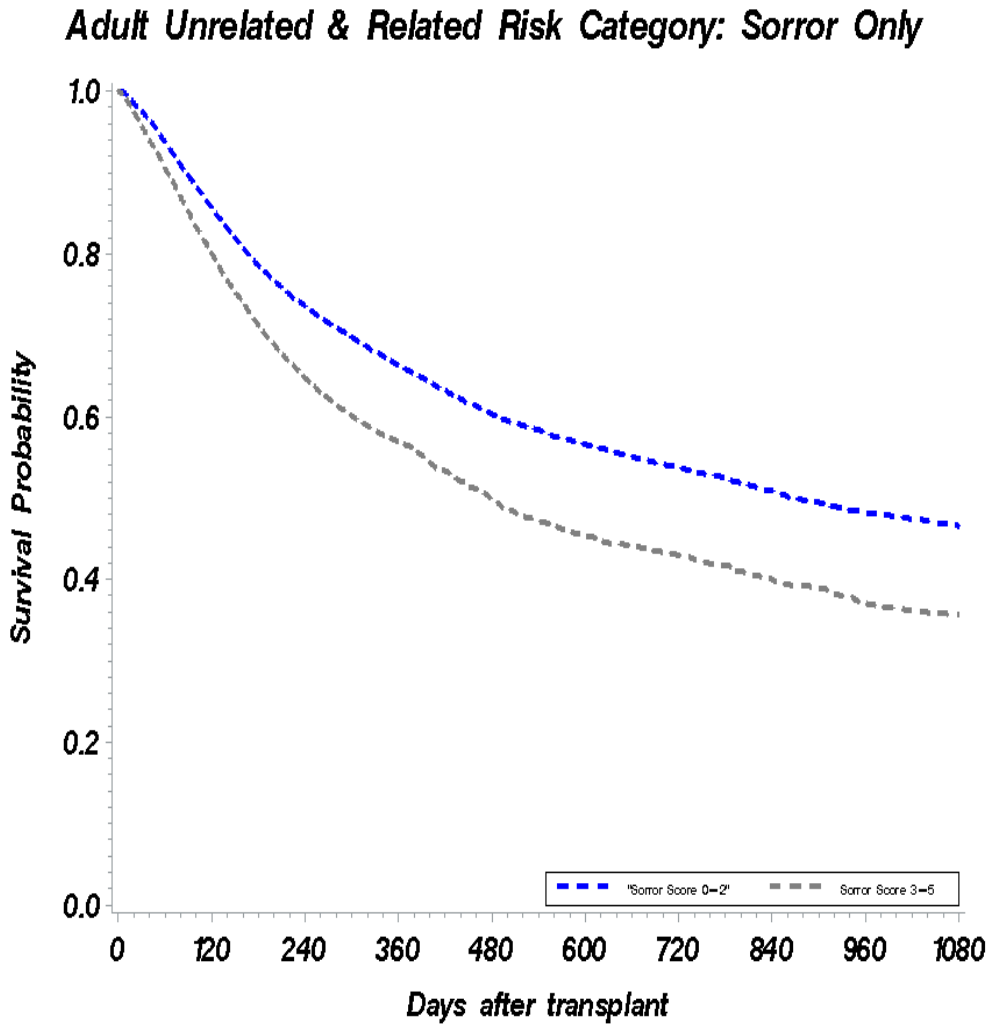
Adult Unrelated & Related Risk Category: Coexisting Disease Only



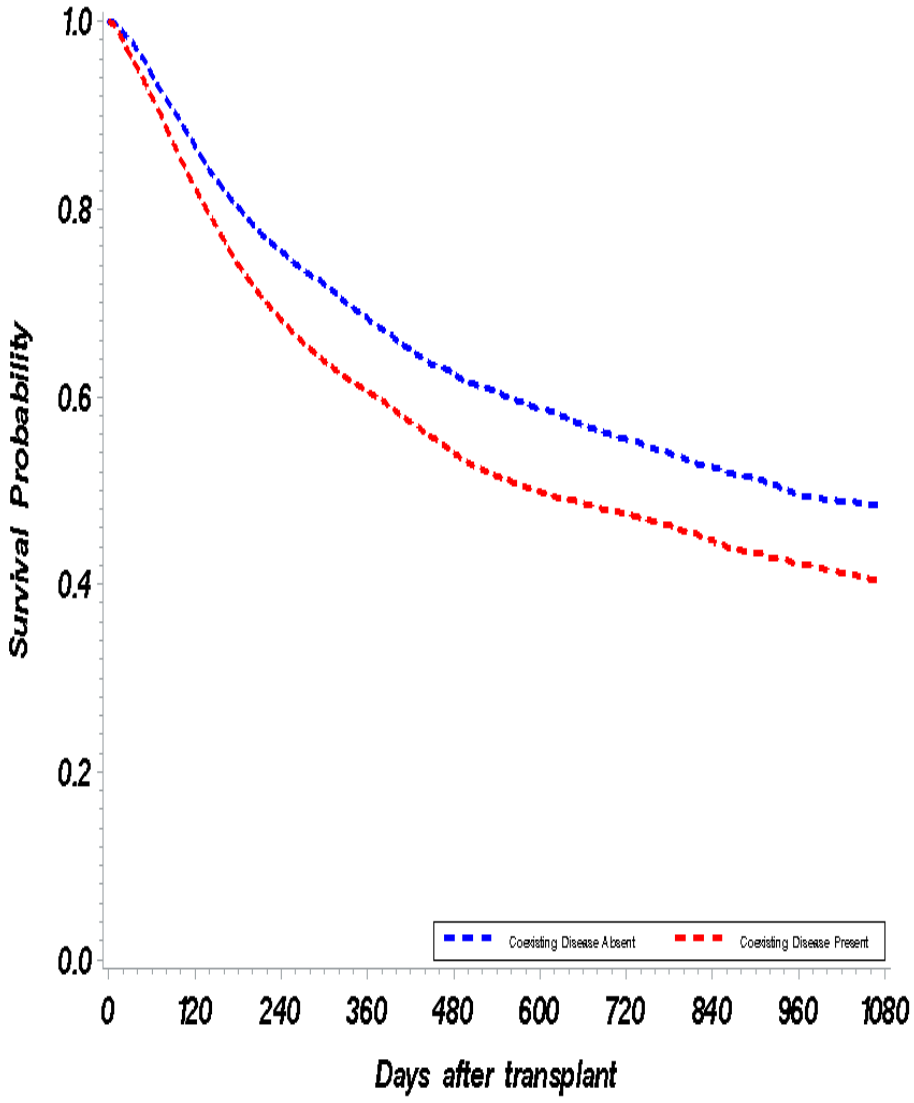

Adult Unrelated & Related Risk Category: HLA Risk Only
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
120
240
360
480
600
720
840
960
1080
Days after transplant
HLA Risk Category: Matched
HLA Risk Category: Mismatched

Appendix 8: Separate Kaplan Meir curves for Sorror Score versus Coexisting Disease

While we acknowledge that the HCT comorbidity index (CI) and the sorror comorbidity score are more accurate representations of patient comorbidities, the variable was underreported by centers relative to patient co-existing disease. [18] Nevertheless, we conducted sensitivity analyses utilizing the sorror comorbidity score that did not produce results of different magnitude or direction for our overall risk categories. Median Survival in Days for Sorror risk group =478 days 35% survival at 1080 days while the Median Survival in Days for Coexisting Disease=595 Days. 46% survival at 1080 days. Nevertheless, when we plot KM curves for our overall risk categories results are unchanged.



Adult Unrelated & Related Risk Category: Coexisting Disease Only



Appendix 9: Correlation of Risk Category Components

The following sensitivity analysis evaluates our consolidation of the risk components using Spearman correlation. Results indicate that our risk components are not highly correlated and independently measure risk.

	Median for All Centers
Coexexting Disease Risk Percentage (Present)	60.2
Karnofsky Score Risk Percentage (<90)	25.0
Age Risk Category Risk Percentage (Age>40)	13.7
HLA Mismatch Risk Percentage (Mismatched HCT)	73.9

Spearman Correlation Coefficients, N = 162

	Coexisting Disease Percentage	Karnofsky Score Percentage	Age Risk Category Percentage	HLA Mismatch Percentage
Coexisting Disease Percentage	1			
Karnofsky Score Percentage	0.24 (.002)	1		
Age Risk Category Percentage	-.06(.42)	0.16 (.04)	1	
HLA Mismatch Percentage	0.16 (.05)	0.32 (<.0001)	-0.01 (.93)	1

Appendix 10: FACT/CTN status for High and Low Risk Centers

In order to verify our Chapter 4 FACT/CTN status differences on Chapter 3 findings (High Risk Low Risk Centers). We found that high risk centers were also most likely to have FACT/CTN status. Additionally, when using our Chapter 3 Cox Models with FACT/CTN status we found our risk category findings unchanged.

	Low Risk Centers (73 Centers)	High Risk Centers (74 Centers)
FACT Status	N (%)	N (%)
Non-FACT Center (16 Centers)	10 (63)	6 (37)
FACT Only Center (99 Centers)	57 (56)	42 (44)
FACT/CTN Center (32 Centers)	6 (19)	26 (81)

Cox Model for All Centers (High and Low Risk Centers) with FACT/CTN Status 2008-2010

		Hazard Ratio	95% CI		P Value
Risk Categories	**0**	REF			
	1/2	1.719	1.508	1.959	<.0001
	3	2.543	2.219	2.914	<.0001
	4	3.360	2.823	3.999	<.0001
Gender	**Male**	REF			
	Female	0.914	0.867	0.962	0.0006
Patient Race	**Non-Hispanic White**	REF			
	Hispanic	1.051	0.950	1.162	0.3350
	Black/African American	1.168	1.045	1.305	0.0062
	Other/Multiple Race/Unknown	1.001	0.878	1.141	0.9938
Transplant Year	**2008**	REF			
	2009	1.005	0.944	1.069	0.8831
	2010	1.010	0.944	1.079	0.7792
Disease Group	**Acute Myelogenous Leukemia & Myelodysplastic Disorders**	REF			
	Acute Lymphoblastic Leukemia	0.986	0.908	1.070	0.7288
	Other Leukemia & Myeloproliferative Syndromes	0.763	0.703	0.827	<.0001
	Non-Hodgkin lymphoma (NHL) & Hodgkin Lymphoma (HL)	0.835	0.776	0.898	<.0001
	Other Malignancy	0.926	0.819	1.047	0.2173
	Severe Aplastic Anemia	0.553	0.449	0.681	<.0001
	Other Non-Malignant Disease	0.649	0.452	0.933	0.0195

		Cox Model ALL			
		Hazard Ratio	95% CI		P Value
Centers by Department of Health and Human Services Regions	Region 1: (CT, ME, MA, NH, RI, & VT)	REF			
	Region 2: (NJ, NY)	1.075	0.948	1.219	0.2581
	Region 3: (DE, DC, MD, PA, VA, WV)	1.149	1.017	1.297	0.0254
	Region 4: (AL, FL, GA, KY, MS, NC, SC, TN)	1.107	0.990	1.238	0.0746
	Region 5: (IL, IN, MI, MN, OH, WI)	1.010	0.902	1.131	0.8626
	Region 6: (AR, LA, NM, OK, TX)	1.140	1.010	1.286	0.0335
	Region 7:(IA, KS, MO, NE)	1.306	1.134	1.505	0.0002
	Region 8:(CO, MT, ND, SD, UT, WY)	1.022	0.858	1.218	0.8059
	Region 9:(AZ, CA, HI, NV)	1.042	0.925	1.174	0.4946
	Region 10 (AK, ID, OR, WA)	1.103	0.956	1.272	0.1783
Center Characteristics	Low Volume Indicator (≤55 Transplants)	REF			
	High Volume Indicator (>55 Transplants)	1.127	1.025	1.239	0.0131
	Related Donor Indictor	REF			
	Unrelated Donor Indicator	1.155	1.096	1.218	<.0001
	Non-FACT	REF			
	FACT Only	1.028	0.904	1.170	0.6714
	FACT/CTN	.841	.736	.961	0.0111
	Low Risk Center Indicator	REF			
	High Risk Center Indicator	1.079	0.994	1.170	0.0681

Appendix 11: Benefit of including Volume Quartiles for the Relative Odds of HLA Mismatch among Related and Unrelated Transplant recipients

The following sensitivity analyses evaluate the benefit of including volume in our models. Utilizing Logistic regression with and without volume we found statistical benefit between the two models. Since these are nested models (one is a subset of the other) we can test whether the separate parameters significantly improve the fit using the -2 Log Likelihood.
The difference in the Log Likelihood is (3042.038-3054.511=12.481) and is distributed as chi-square with 3 DF. This is a significant (p-value <.01), indicating that including the volume quartiles in the model does lead to a better fit compared to the model that does not include volume.

a) Model fit statistic with no volume indicator (31 DF)

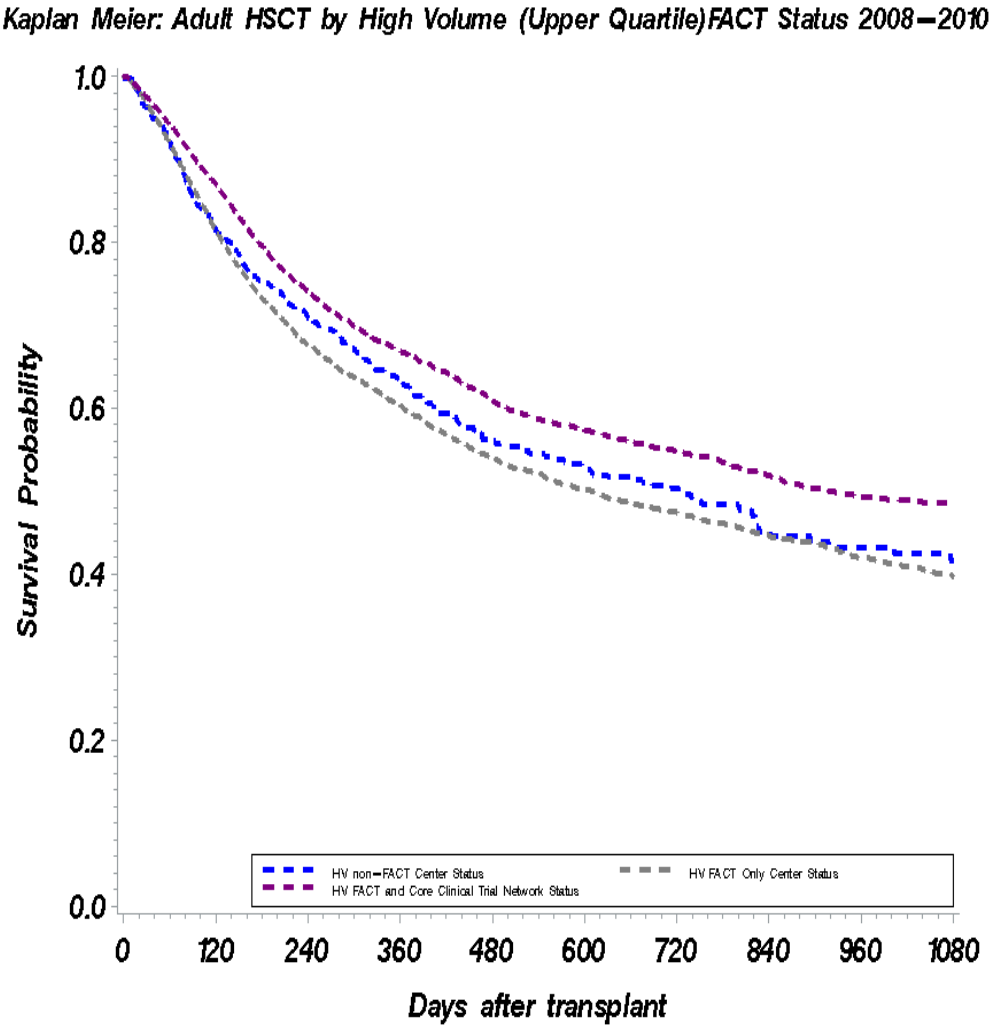
Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	3767.272	3118.511
SC	3773.970	3332.837
-2 Log L	3765.272	3054.511

b) Model fit statistics with a volume indicator (34 DF)

Model Fit Statistics		
Criterion	**Intercept Only**	**Intercept and Covariates**
AIC	3767.272	3112.038
SC	3773.970	3346.456
-2 Log L	3765.272	3042.038

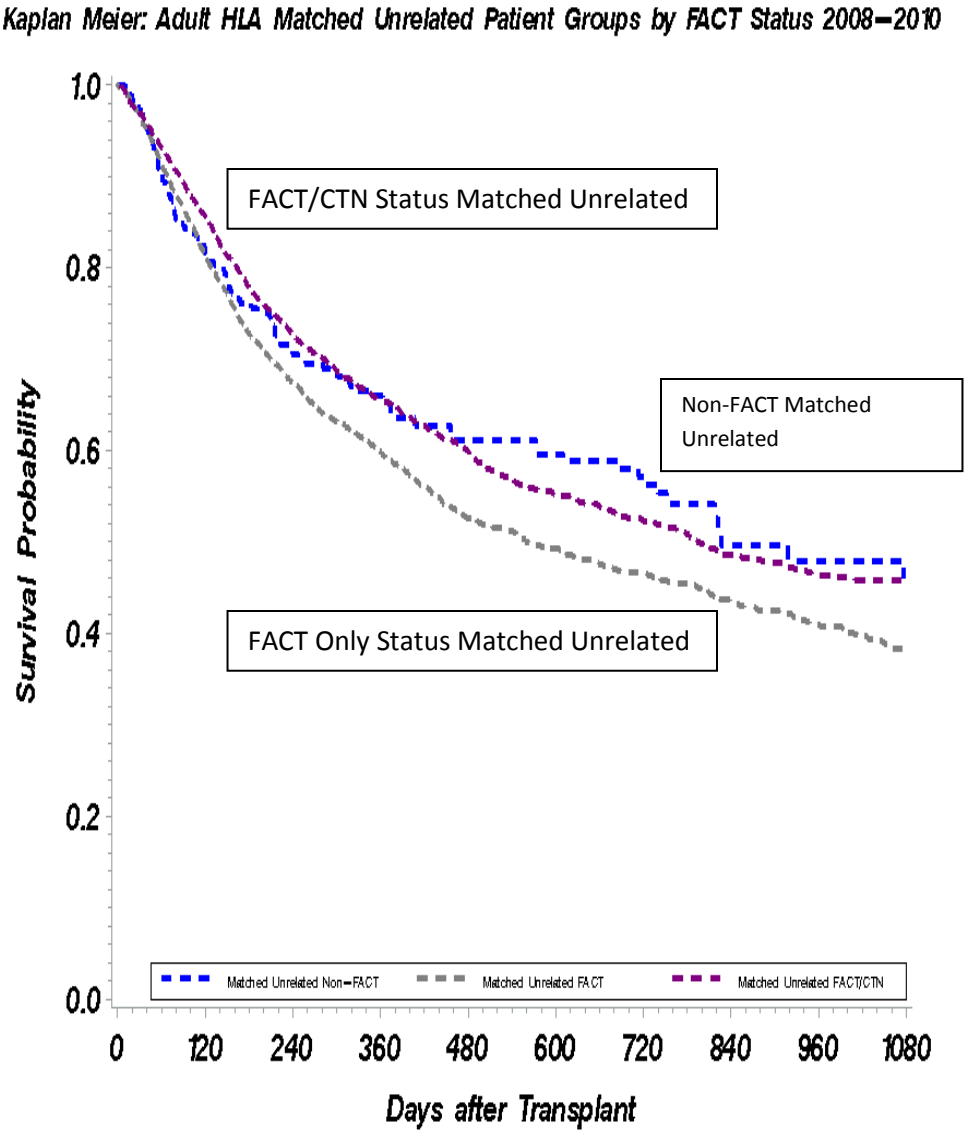
Appendix 12: High Volume Centers by FACT/CTN Status

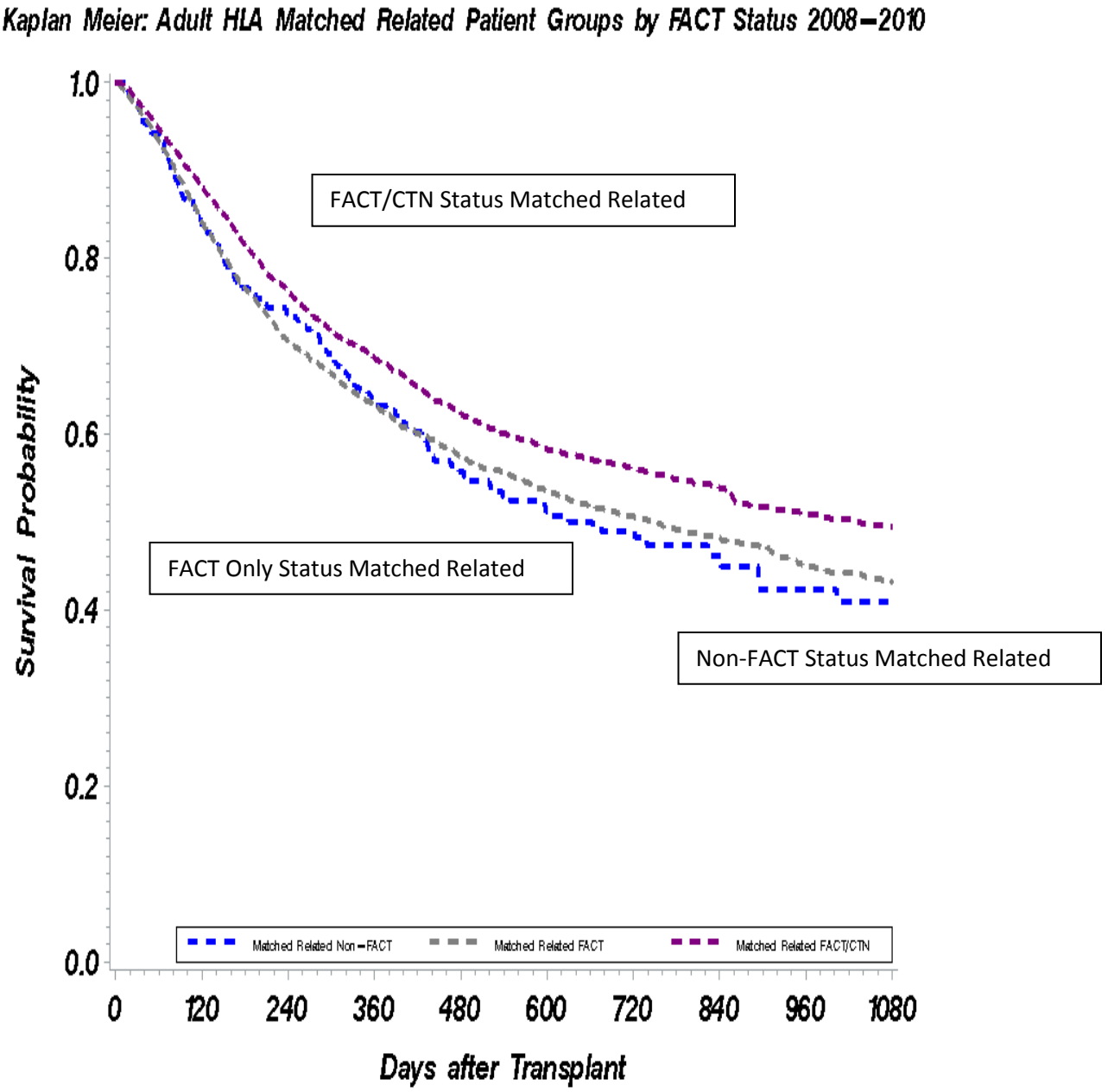
In order to ensure that our FACT/CTN findings were only a product of low HCT volume settings we tested FACT/CTN status using Kaplan Meir curves. Below, the set of Kaplan Meir curves indicates that our high volume centers show the same trends illustrated by our overall results. Namely, FACT/CTN centers show superior survival probability than FACT-only and non-FACT status centers.

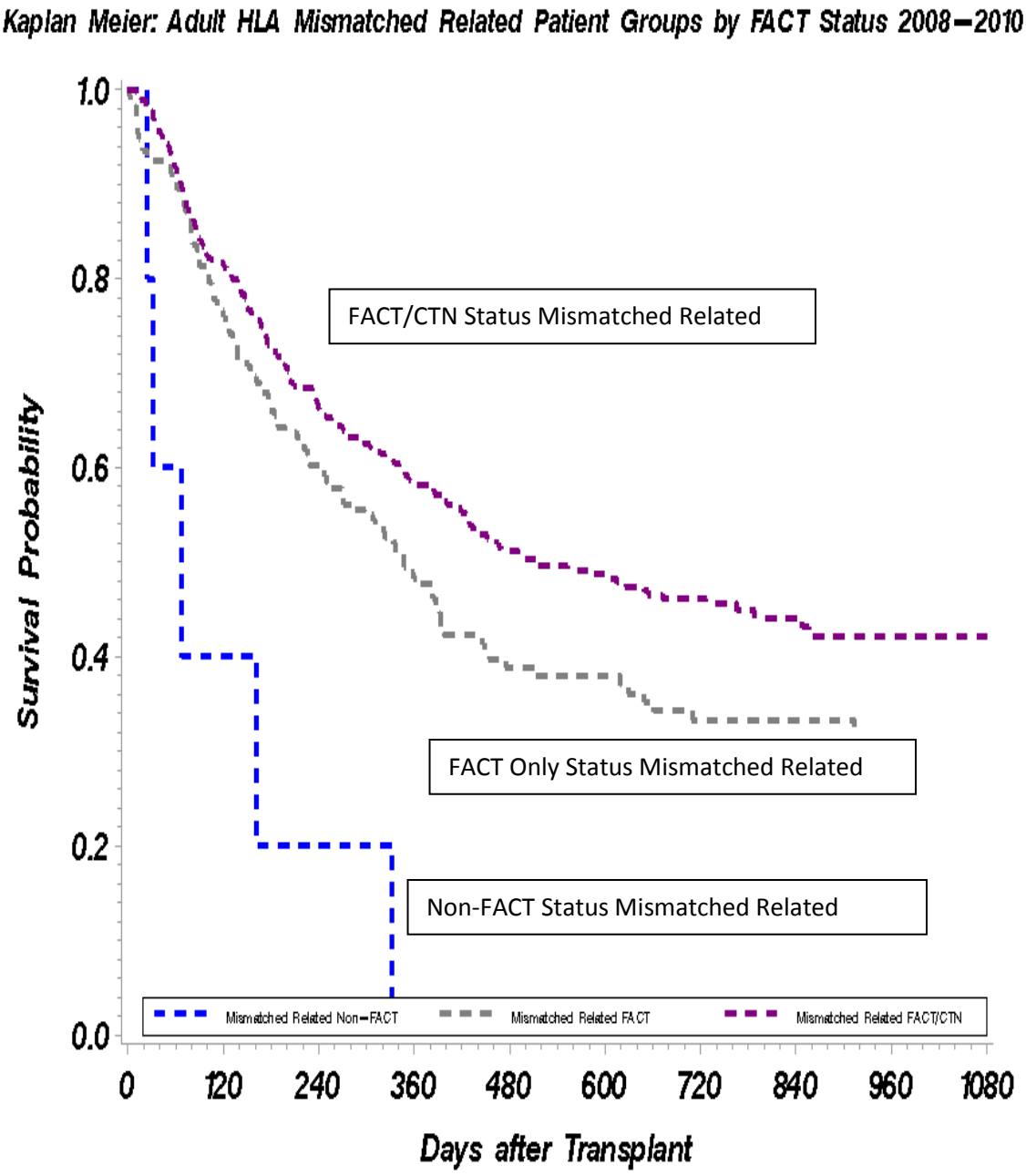


Appendix 13A-13E: FACT/CTN Status by HLA Related and Unrelated Group by FACT Status

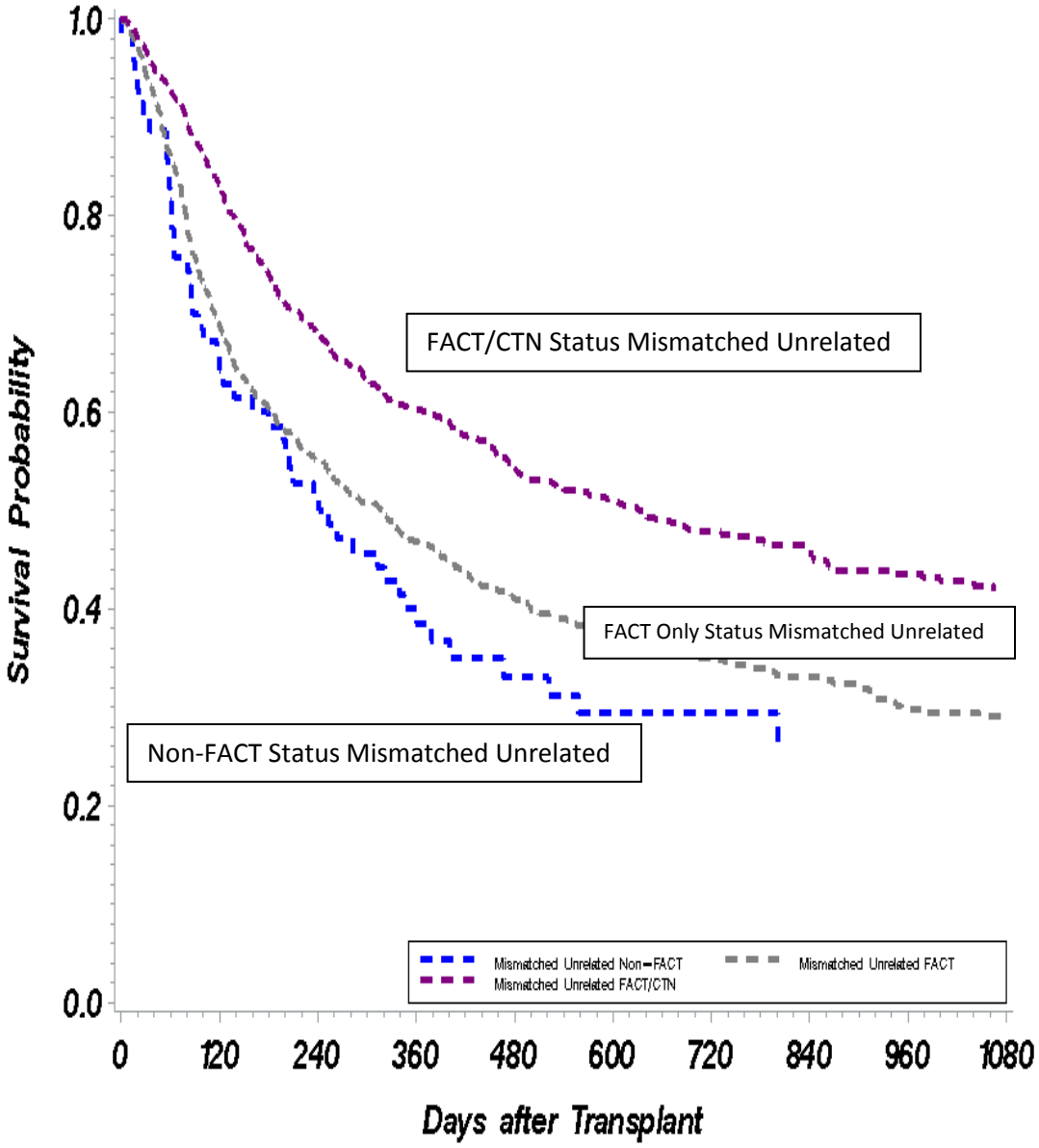
In order to justify our consolidation of (a) related and unrelated matched and (b) related and unrelated mismatched we conducted separate analyses for each individual group using Kaplan Meir curves and cox proportional models. Our results did not produce results of different magnitude or direction.




Kaplan Meier: Adult HLA Matched Related Patient Groups by FACT Status 2008–2010
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
120
240
360
480
600
720
840
960
1080
Days after Transplant
FACT/CTN Status Matched Related
FACT Only Status Matched Related
Non-FACT Status Matched Related
Matched Related Non-FACT
Matched Related FACT
Matched Related FACT/CTN

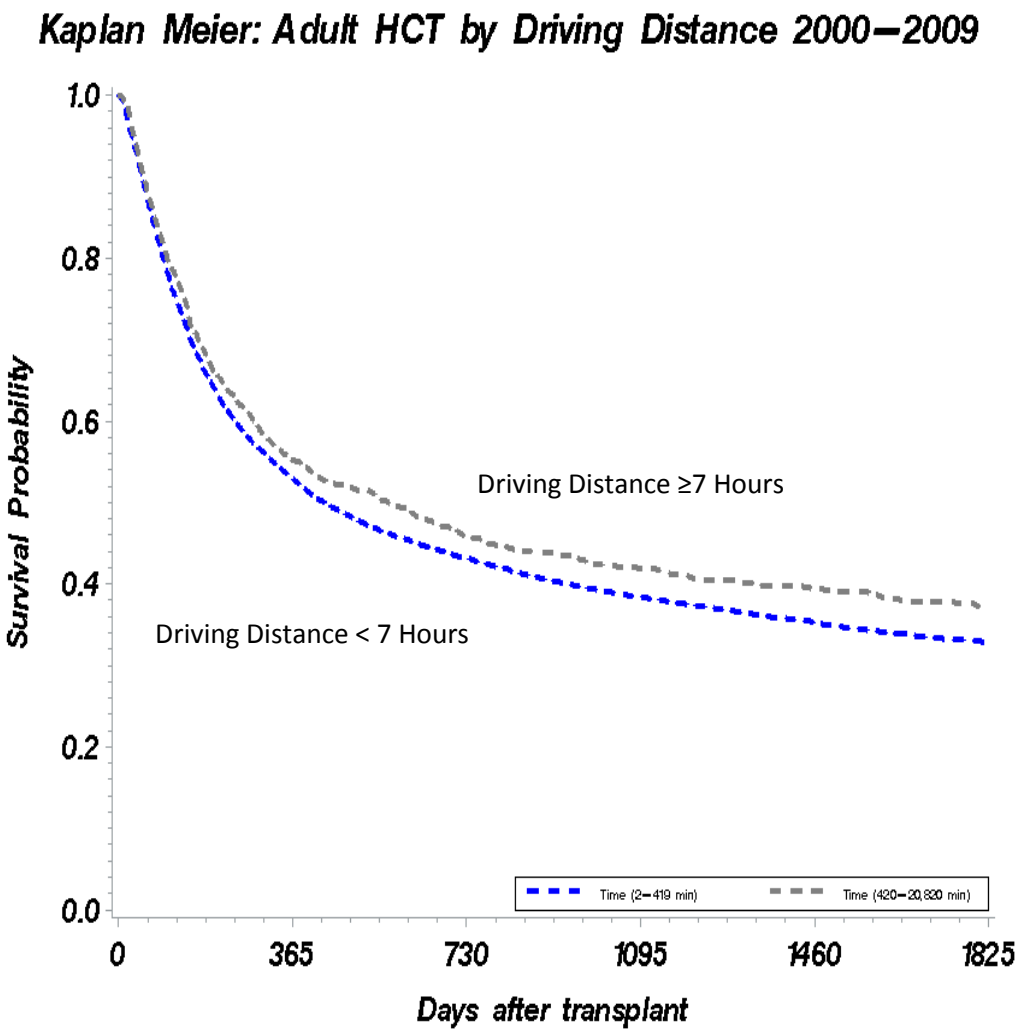

Kaplan Meier: Adult HLA Mismatched Related Patient Groups by FACT Status 2008–2010
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
120
240
360
480
600
720
840
960
1080
Days after Transplant
FACT/CTN Status Mismatched Related
FACT Only Status Mismatched Related
Non-FACT Status Mismatched Related
Mismatched Related Non-FACT
Mismatched Related FACT
Mismatched Related FACT/CTN

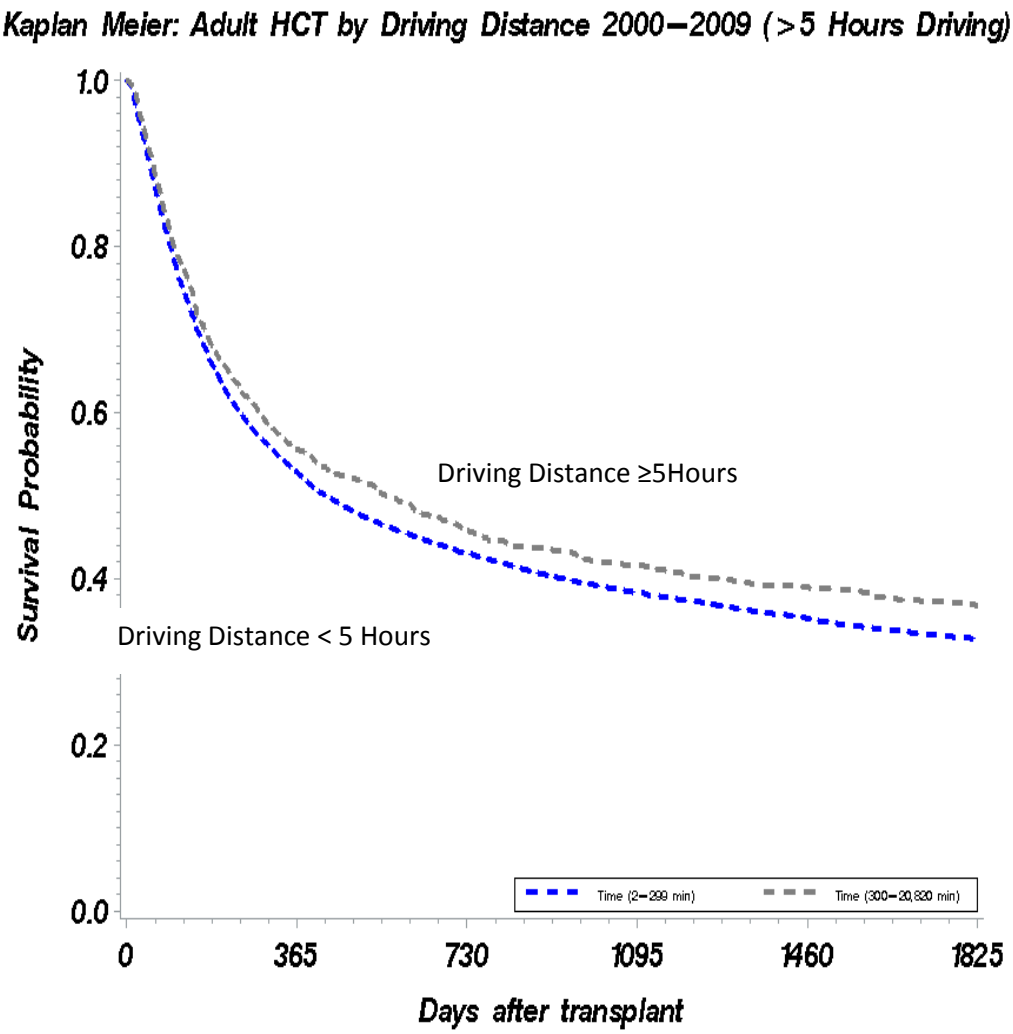
Kaplan Meier: Adult HLA Mismatched Unrelated Patient Groups by FACT Status 2008–2010

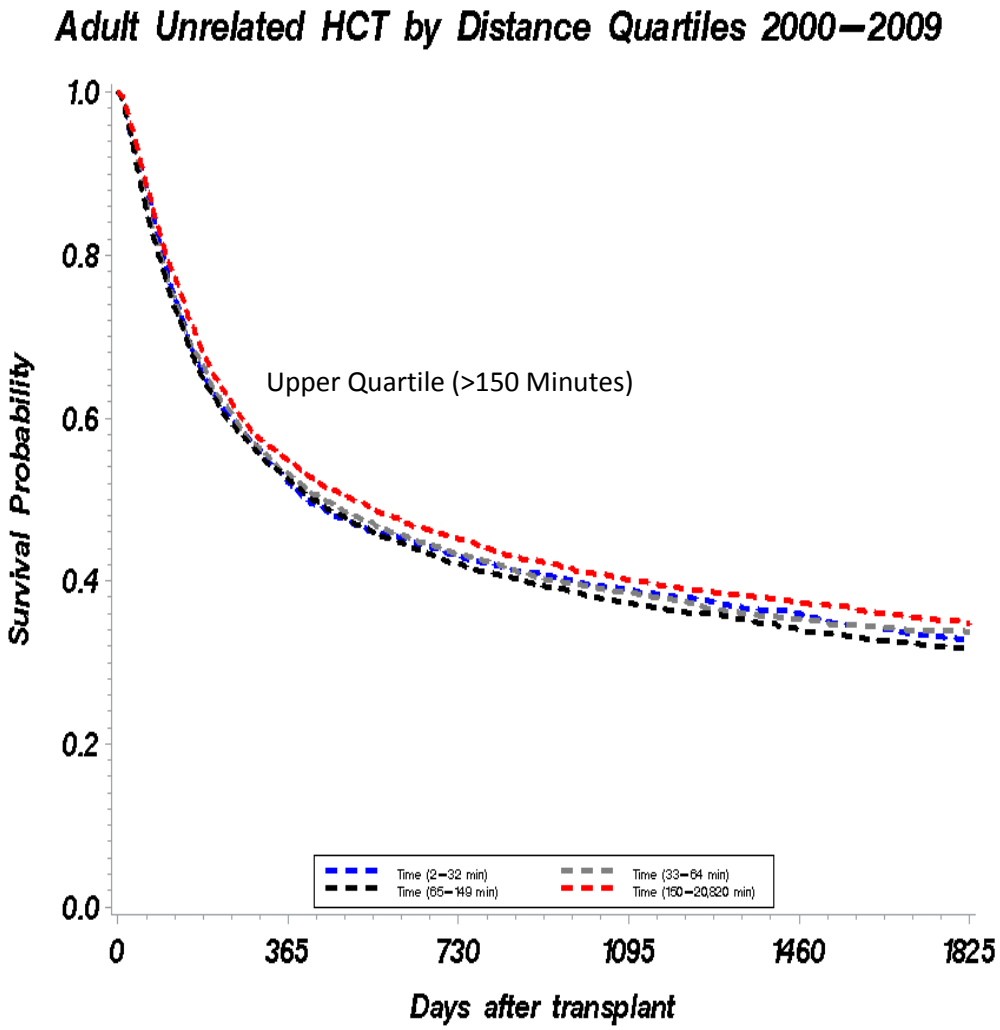


Appendix 14: Inclusion of various time Distance cut-offs

A recent study by Abou-Nassar, et al. analyzed a cohort of adult patients who underwent allogeneic HCT at the Dana-Farber/Brigham and Women's Cancer Center between 1996 and 2009 and who resided within 6 hours driving time of the institution.[3] Although Abou-Nassar et al. established 6 hour driving distance as a potential impactful distance on HCT outcomes we tested other times to ensure that our results were not a product of an arbitrary cut-off. Results from our Kaplan Meier curves for our quartiles (without dividing the upper quartile), >5 hours, >7 hours all showed similar survival trends. Namely, longer driving distances showed superior results.

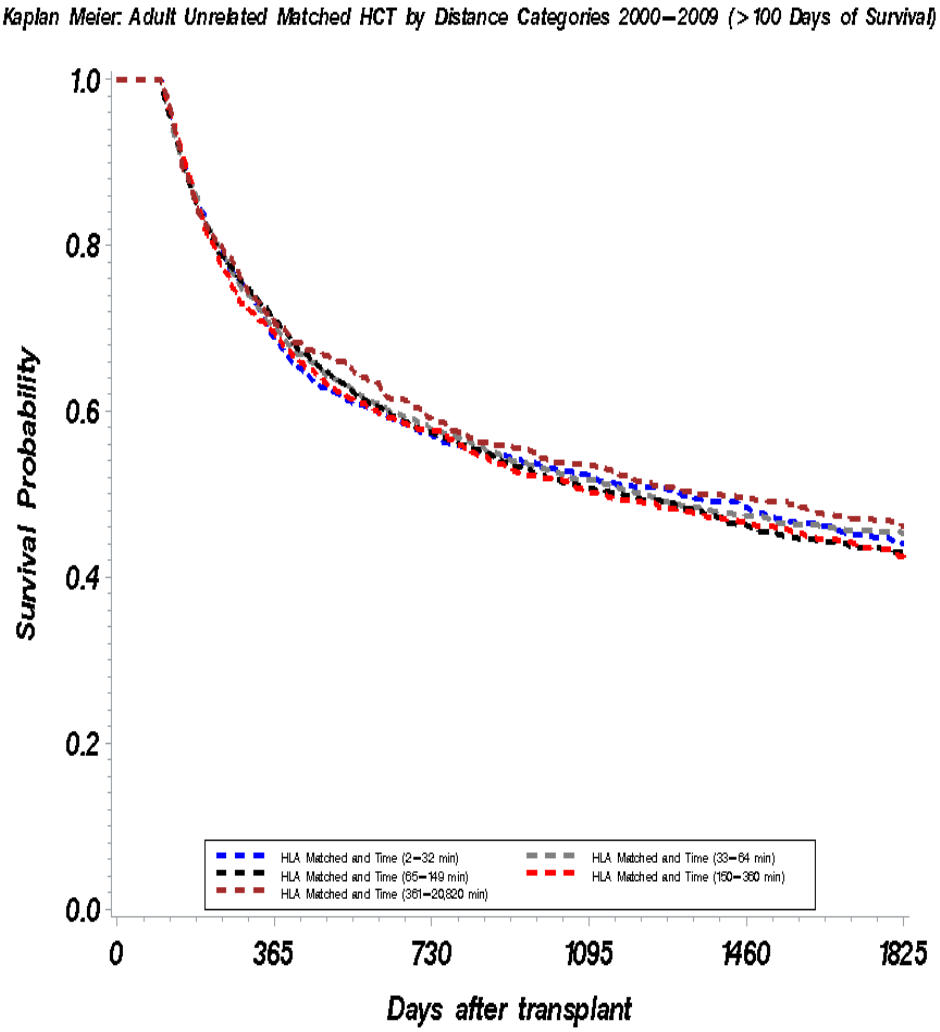


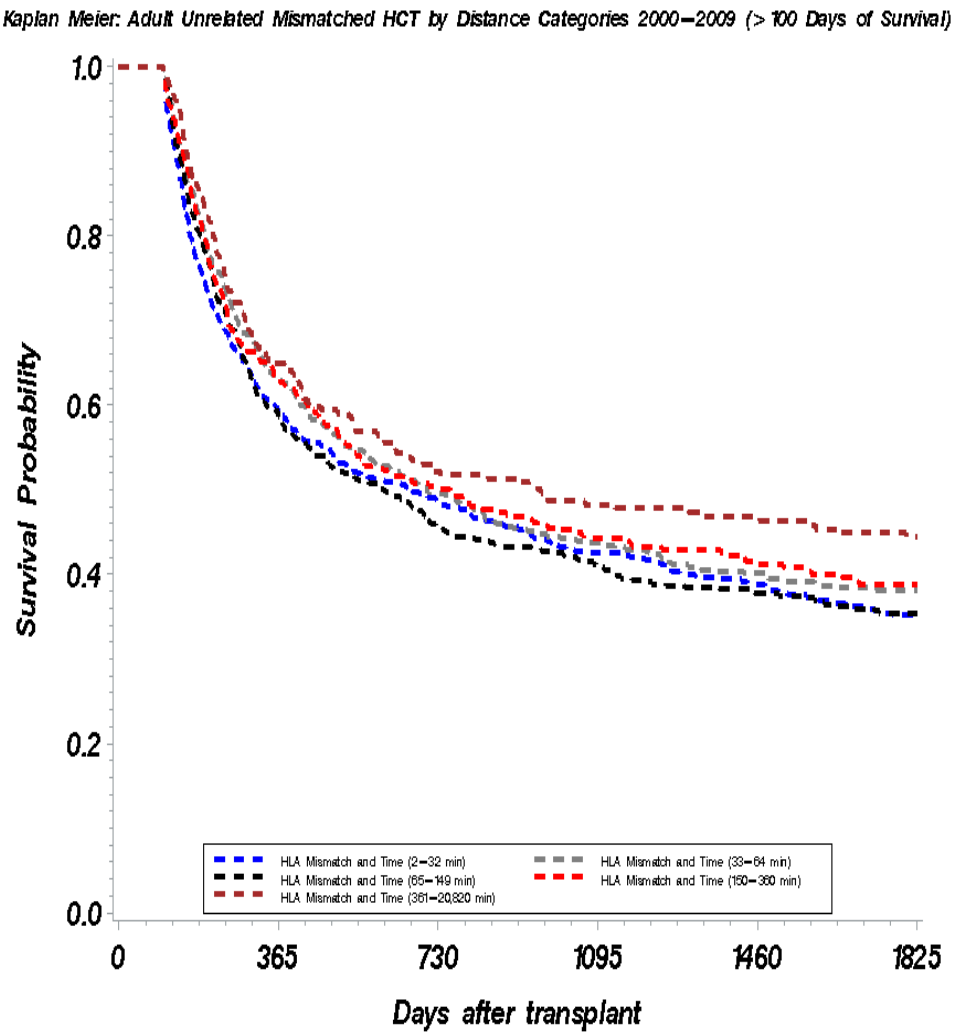

Kaplan Meier: Adult HCT by Driving Distance 2000–2009 (>5 Hours Driving)
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Driving Distance ≥5Hours
Driving Distance < 5 Hours
Time (2–299 min)
Time (300–20,820 min)
0
365
730
1095
1460
1825
Days after transplant


Adult Unrelated HCT by Distance Quartiles 2000–2009
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Upper Quartile (>150 Minutes)
Time (2–32 min)
Time (33–64 min)
Time (65–149 min)
Time (150–20,820 min)
0
365
730
1095
1460
1825
Days after transplant

Appendix 15: HLA Matched and Mismatched 100 Day cut-off

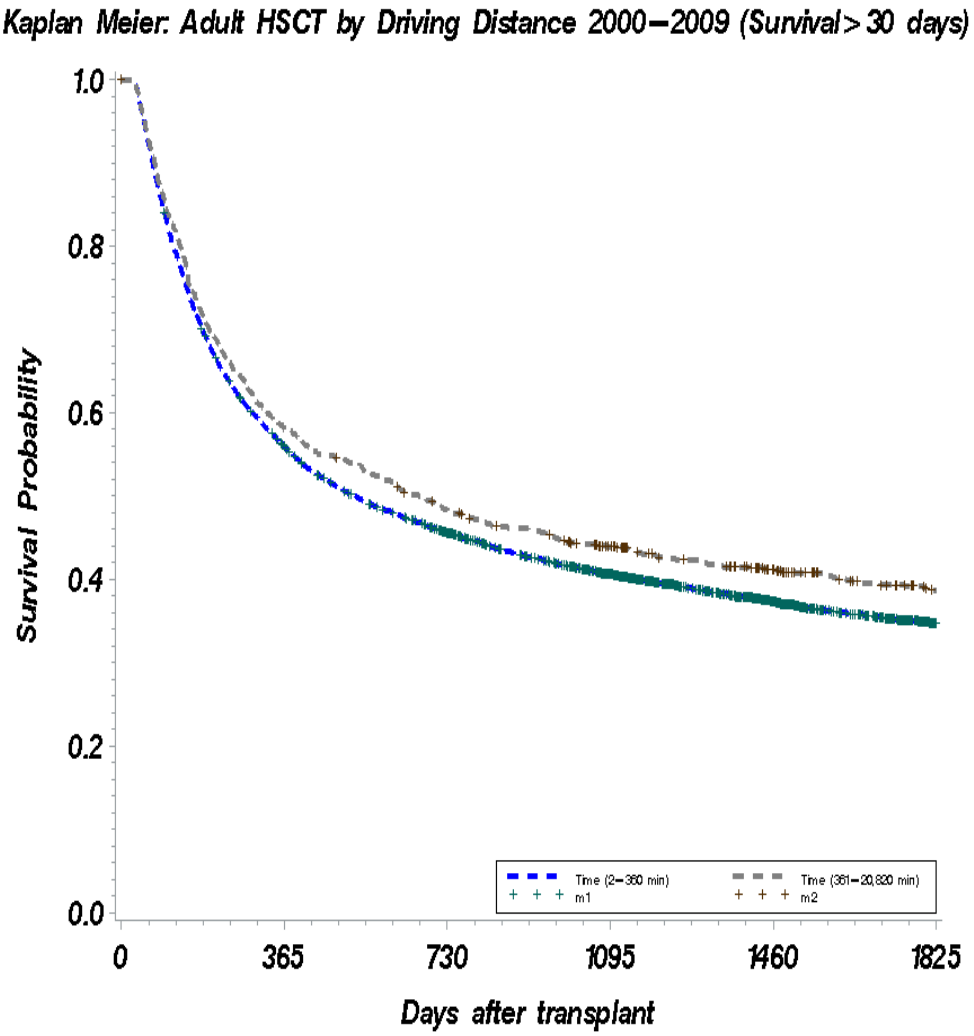
Length of stay (LOS) and 100 day survival has typically been used by literature as an important cutoff for HCT and survival outcomes. Although CIBTMR does not collect LOS from transplant centers we used 100 day survival as a proxy for LOS to determine if the difference in survival probability for HLA matched and mismatched HCT by distance category persisted and if long distance complex patients did indeed have superior OS results compared to equally complex HLA mismatched HCT patients that lived in close proximity to HCT centers. Our sensitivity analysis indicated a similar trend relative to our initial findings that complex long distance patients see an OS advantage versus other HLA mismatched HCT patients. Conversely, the trend for HLA matched patients, in which no distinction was observed by distance, also persisted.



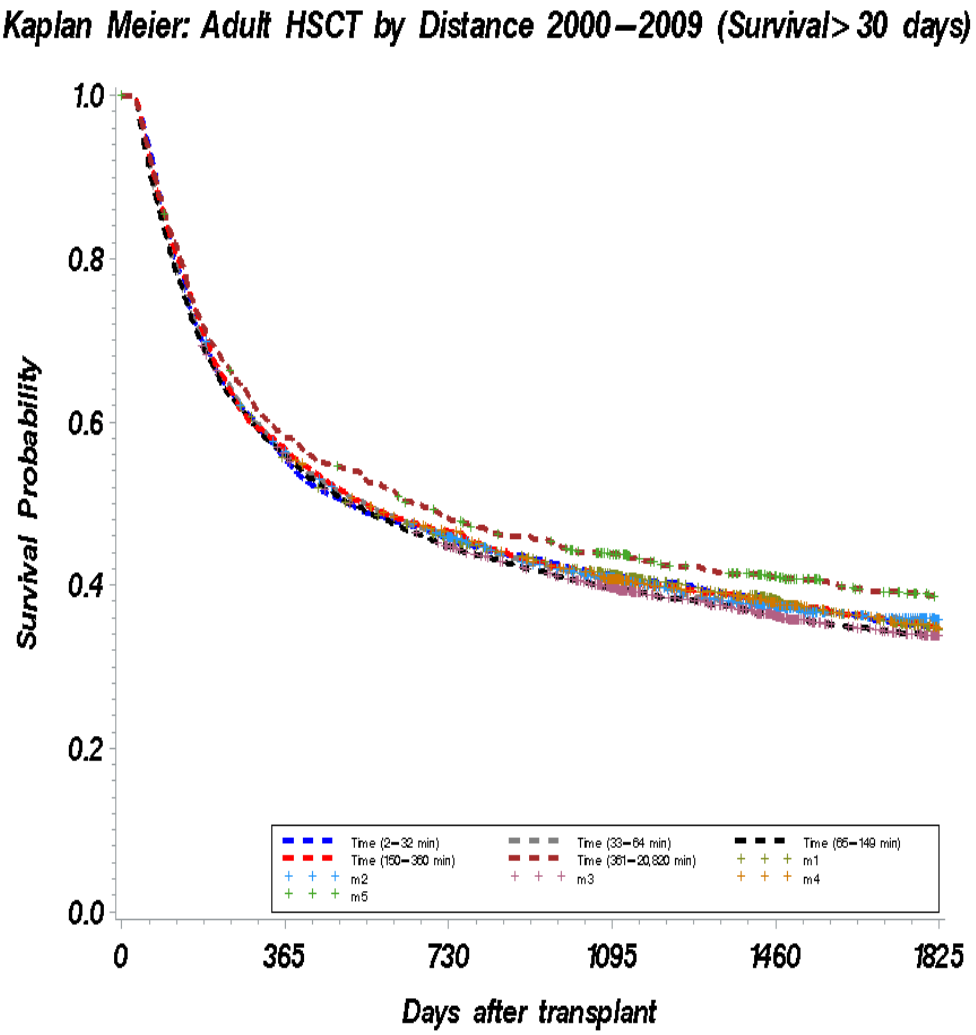

Kaplan Meier: Adult Unrelated Mismatched HCT by Distance Categories 2000–2009 (> 100 Days of Survival)
1.0
0.8
0.6
0.4
0.2
0.0
Survival Probability
0
365
730
1095
1460
1825
Days after transplant
HLA Mismatch and Time (2–32 min)
HLA Mismatch and Time (33–64 min)
HLA Mismatch and Time (65–149 min)
HLA Mismatch and Time (150–360 min)
HLA Mismatch and Time (361–20,820 min)

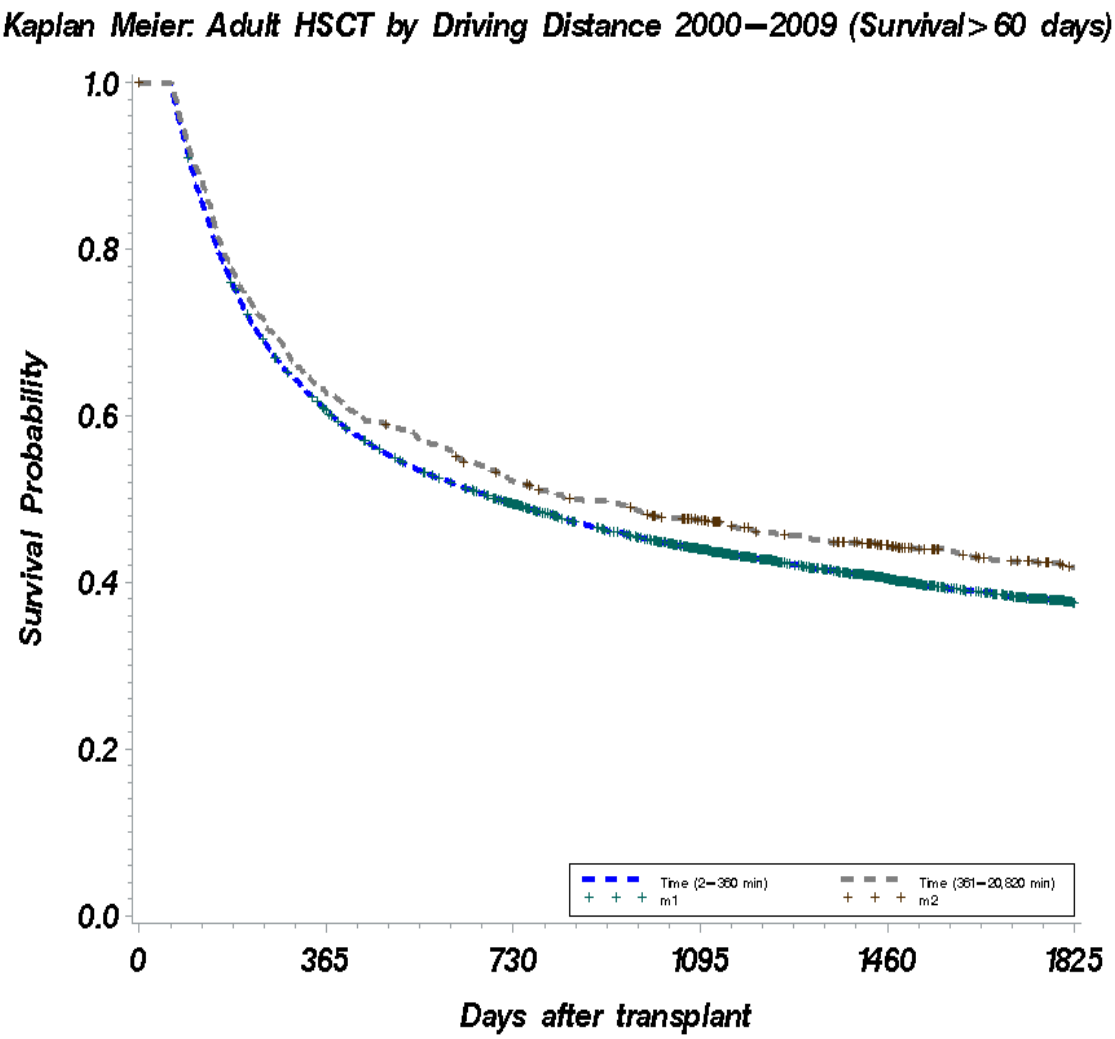
Appendix 16: Length of Stay (LOS) Proxy and Inclusion of Various Time Distances Cut-Offs

In order to ensure that our choice of 100 days was not an arbitrary proxy for LOS we used a series of survival cut-offs for LOS including, 30 days, 60 days, 90 days, 100 days, 120 days. Our Kaplan Meier curves did not produce results of different magnitude or direction.

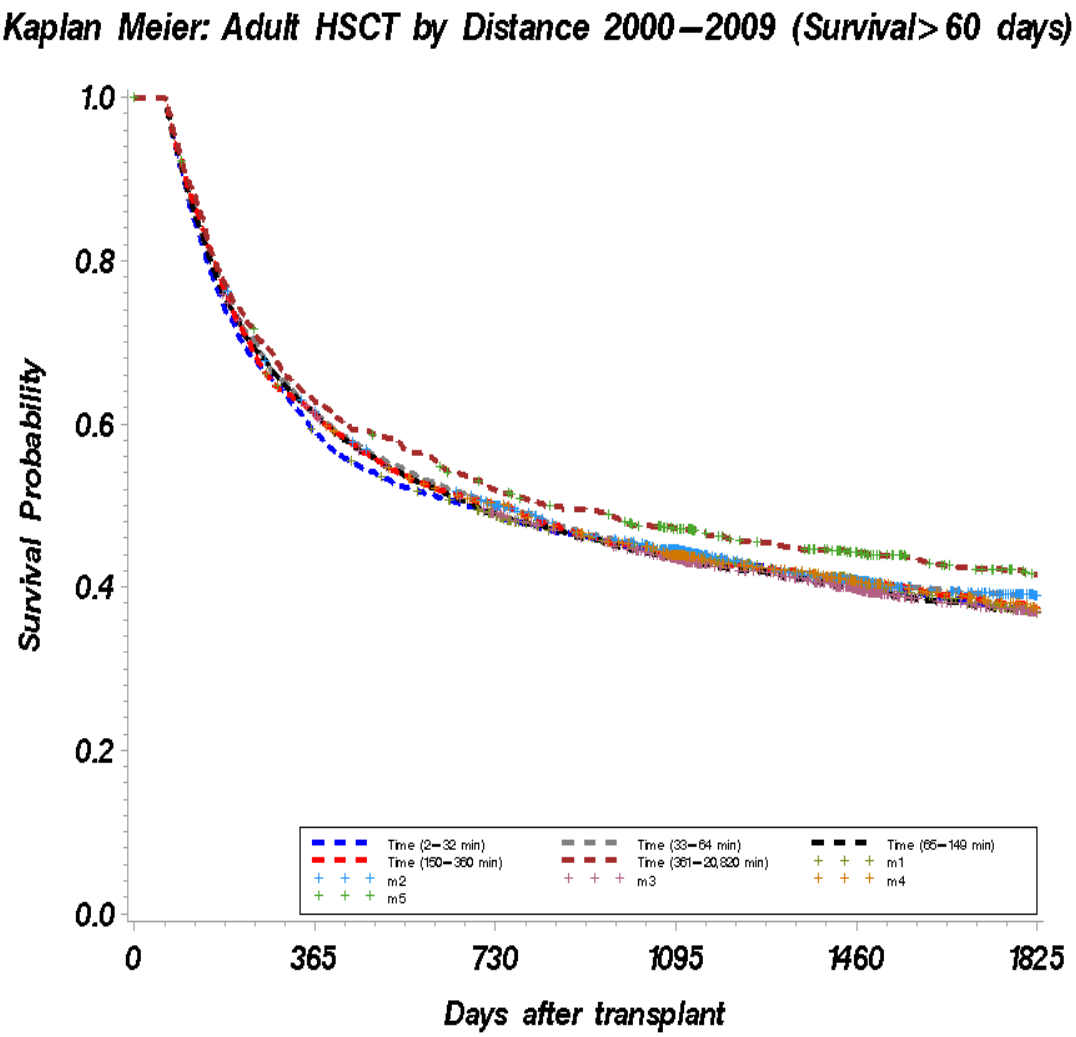


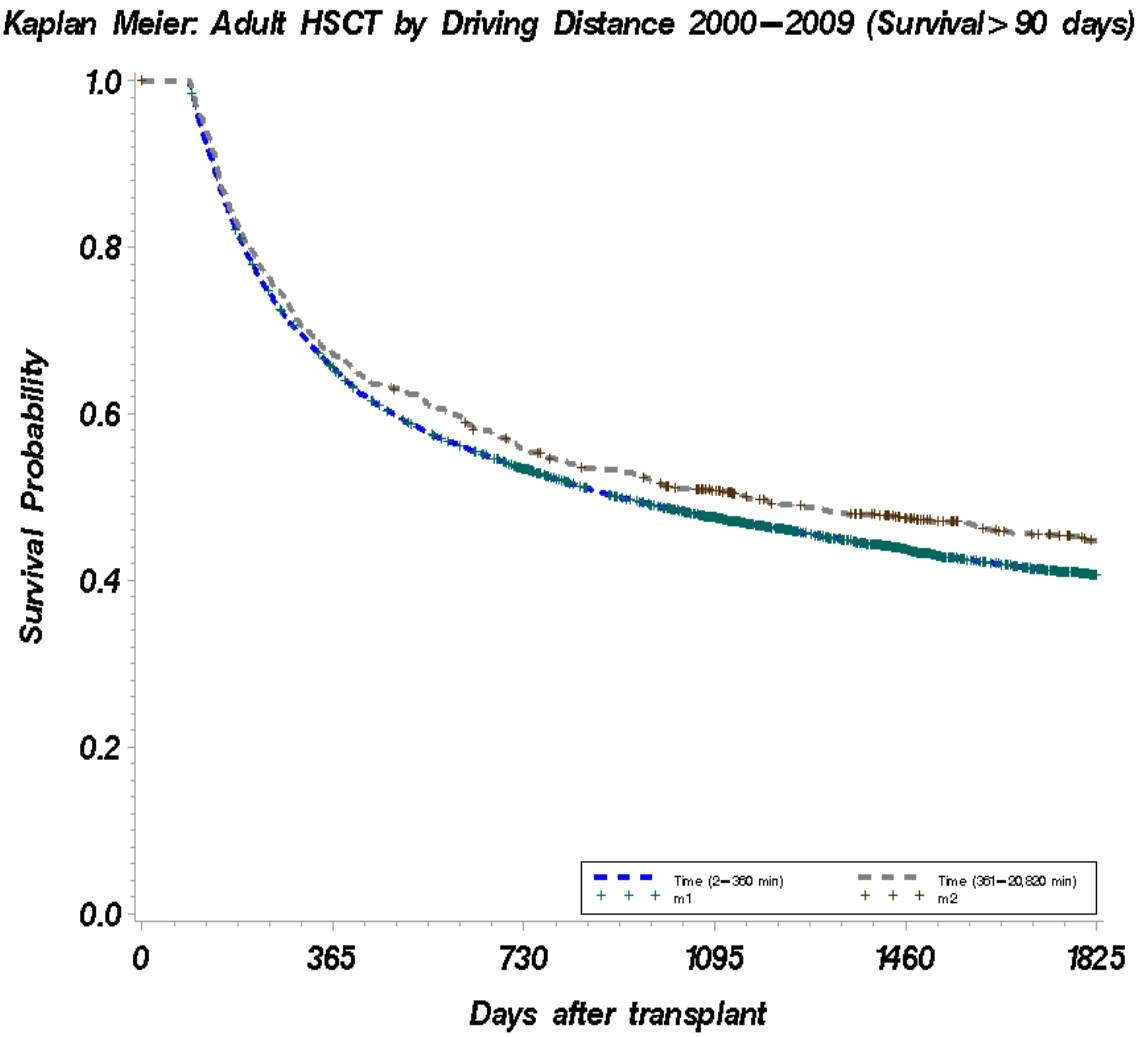
Distance Quartiles: Survival >30 Days



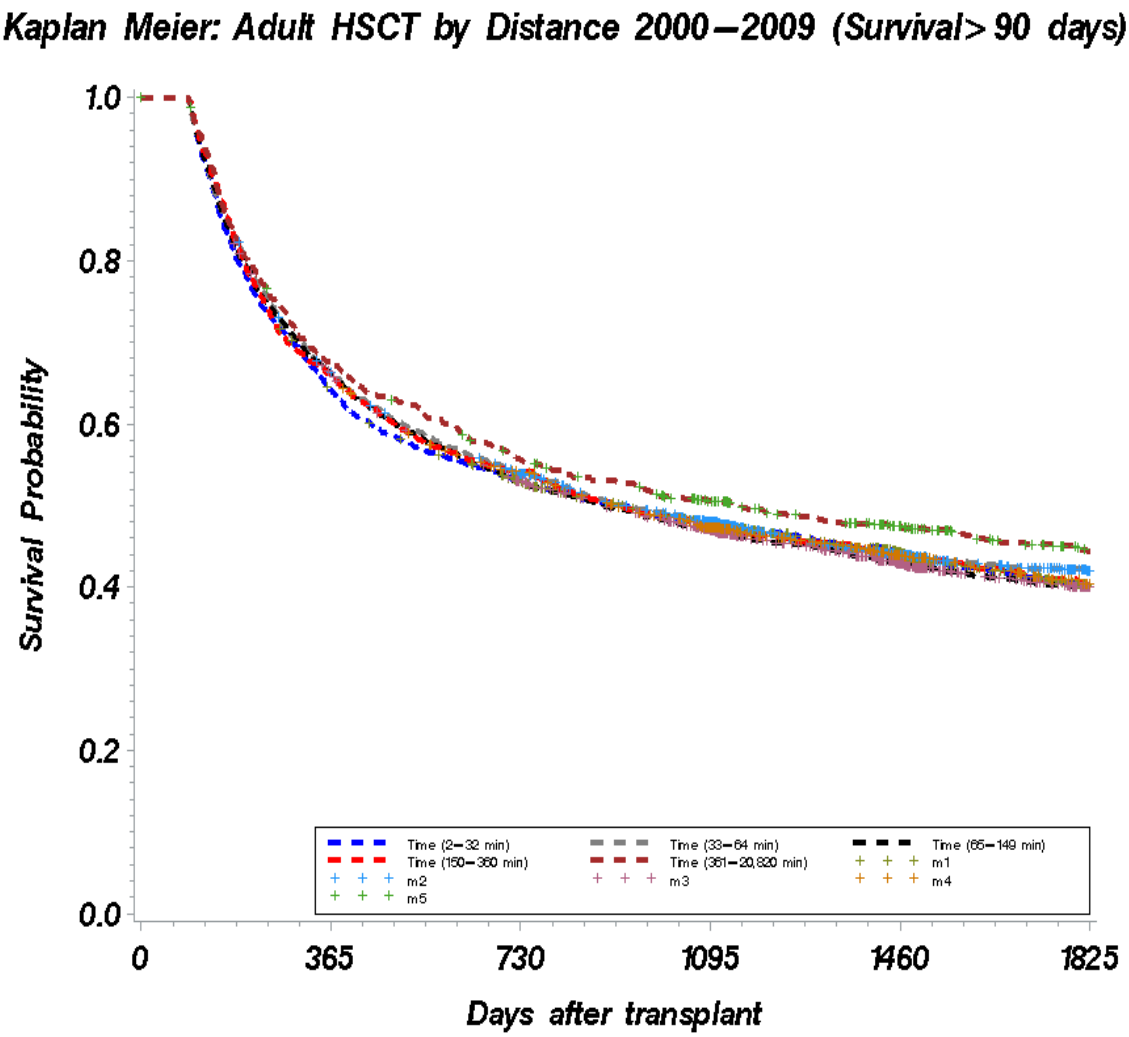

Kaplan Meier: Adult HSCT by Driving Distance 2000–2009 (Survival > 60 days)
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
365
730
1095
1460
1825
Days after transplant
Time (2–360 min)
m1
Time (361–20,820 min)
m2

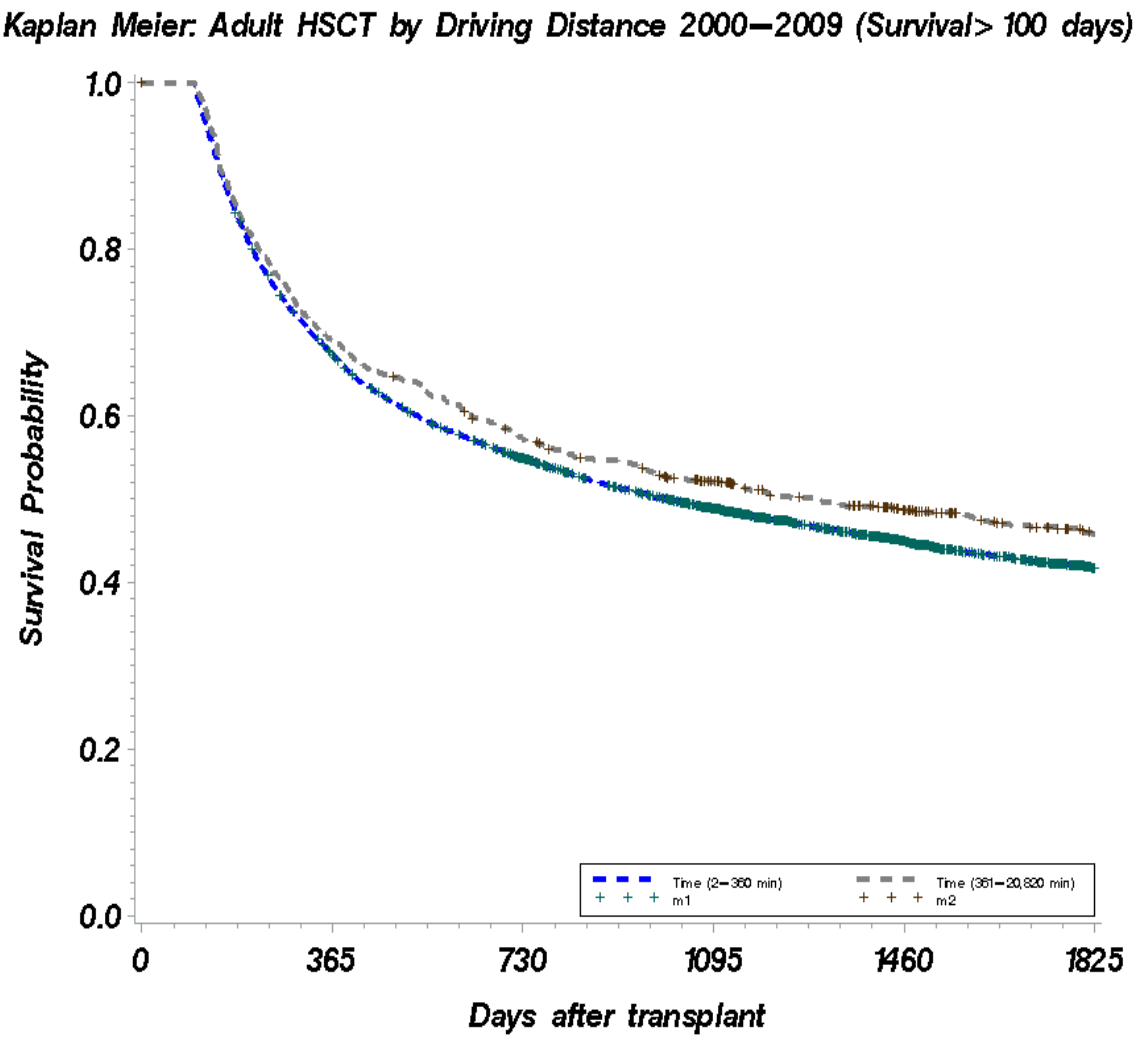
Distance Quartiles: Survival >60 Days



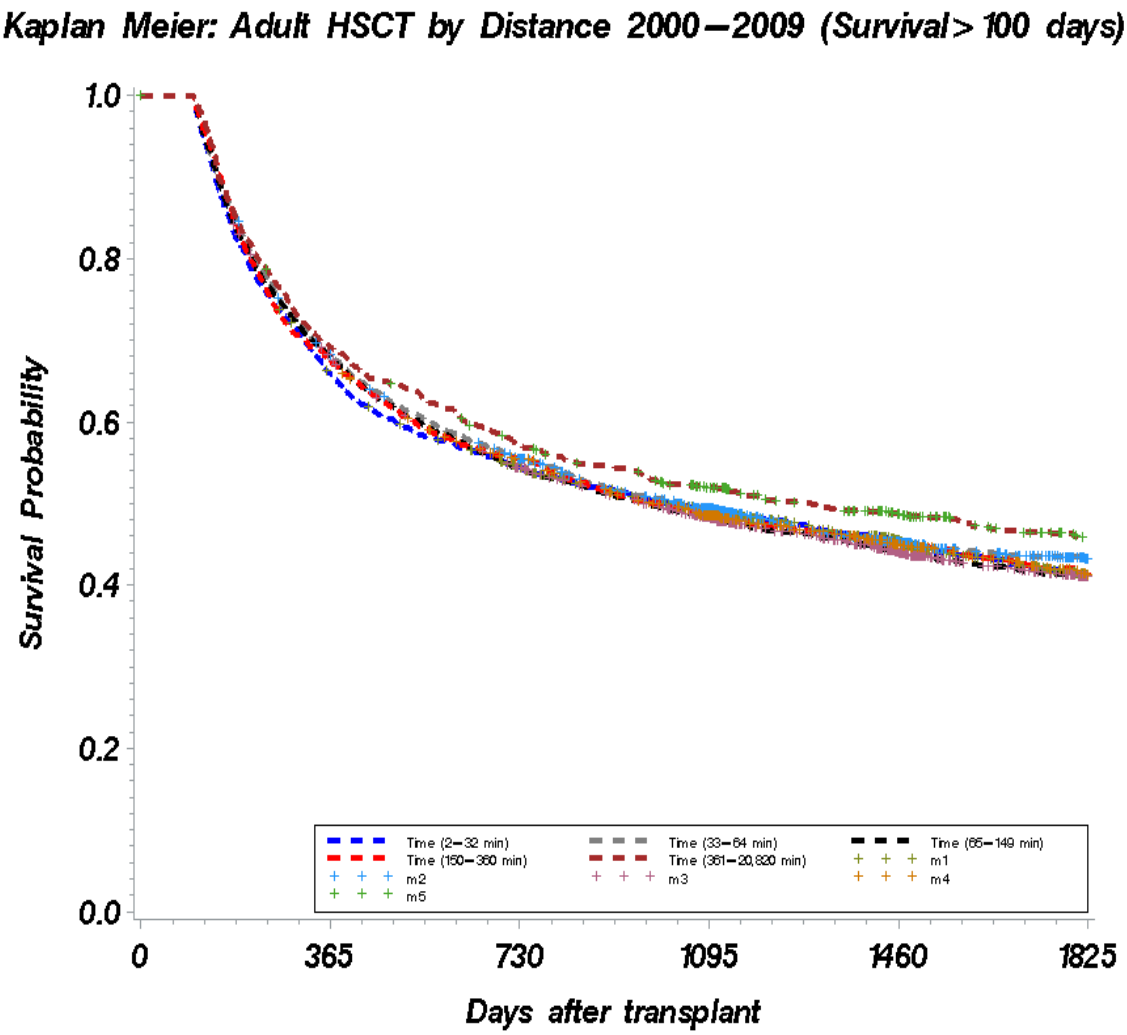

Kaplan Meier: Adult HSCT by Driving Distance 2000–2009 (Survival > 90 days)
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
365
730
1095
1460
1825
Days after transplant
Time (2–360 min)
m1
Time (361–20,820 min)
m2

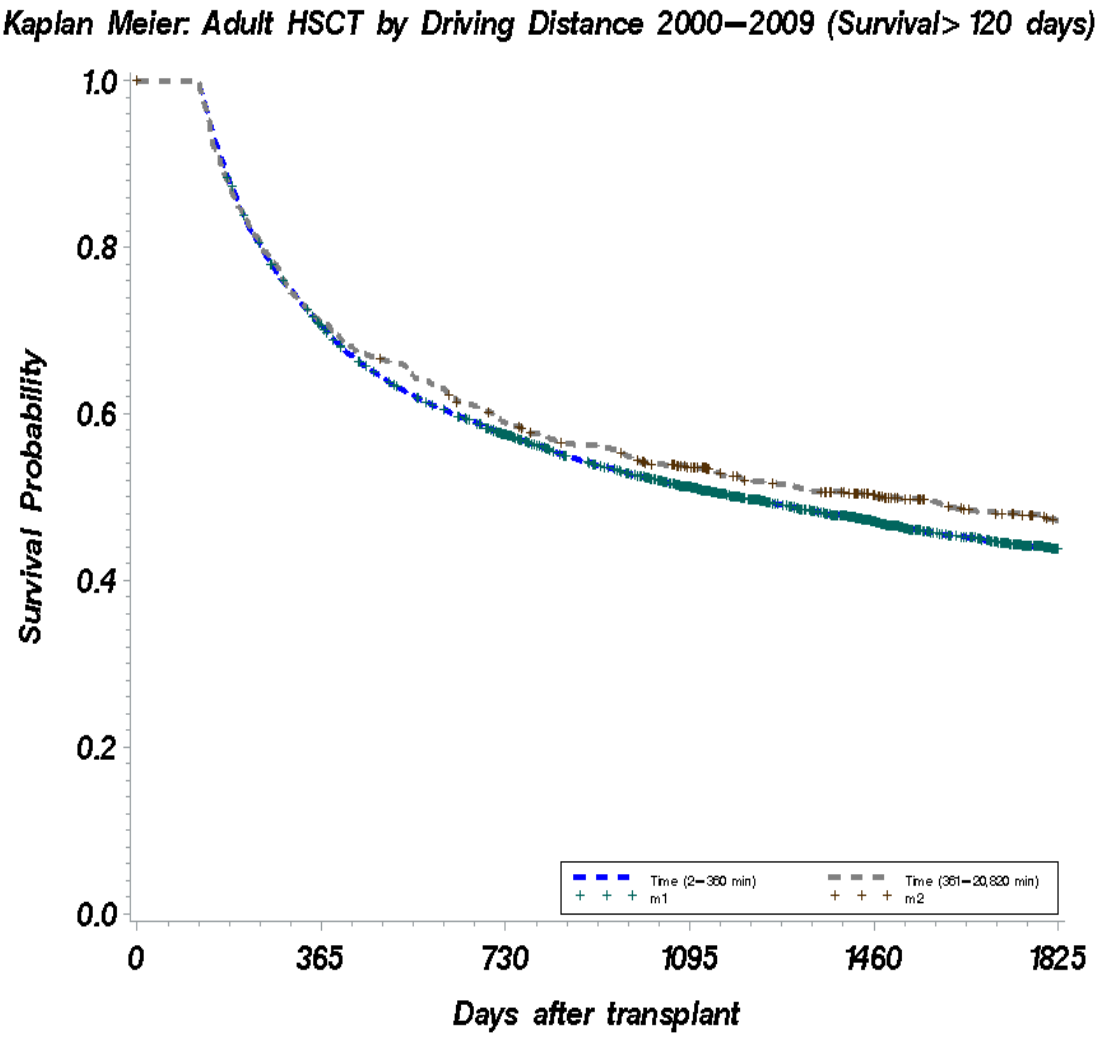
Distance Quartiles: Survival >90 Days



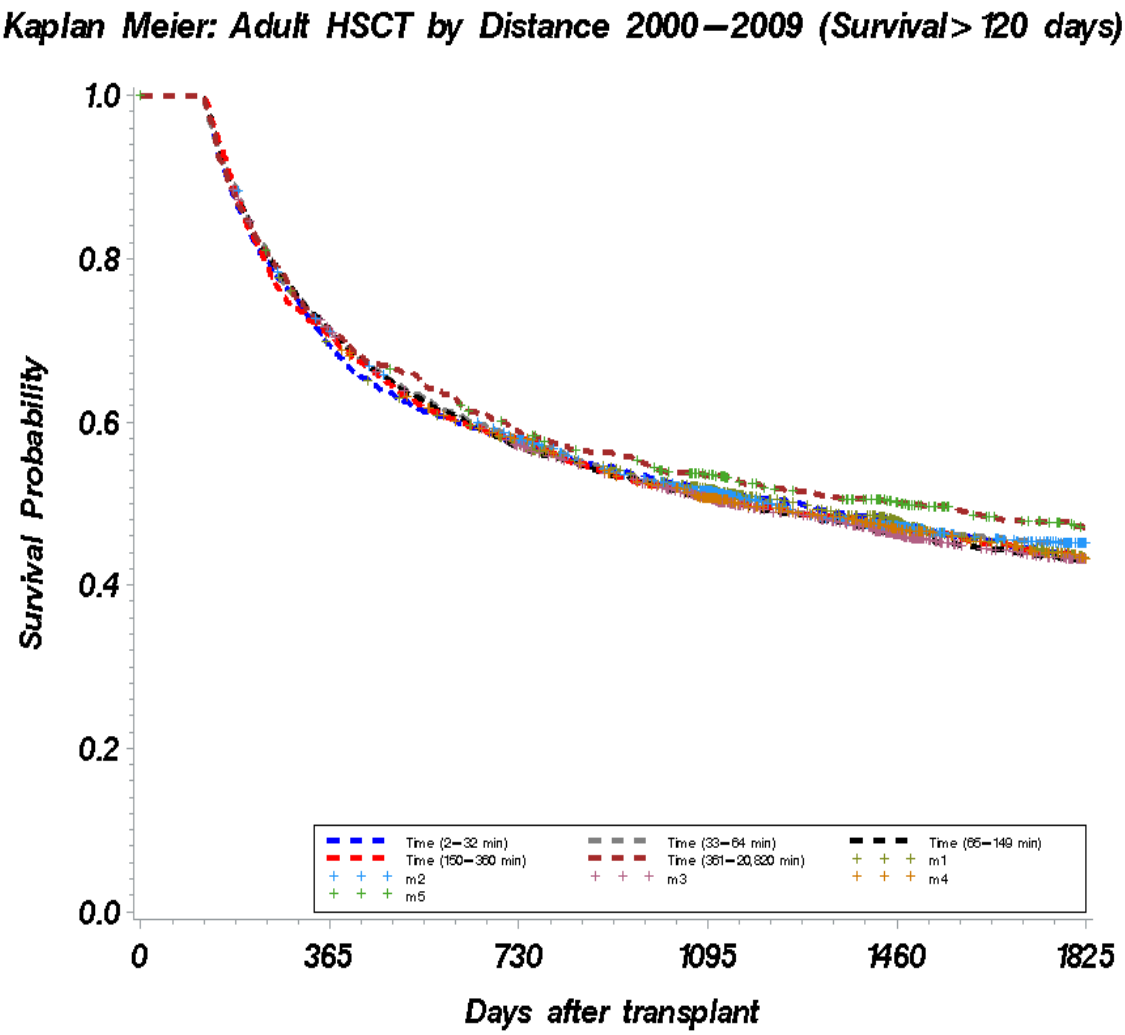

Kaplan Meier: Adult HSCT by Driving Distance 2000–2009 (Survival> 100 days)
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
365
730
1095
1460
1825
Days after transplant
Time (2–360 min)
m1
Time (361–20,820 min)
m2

Distance Quartiles: Survival >100 Days



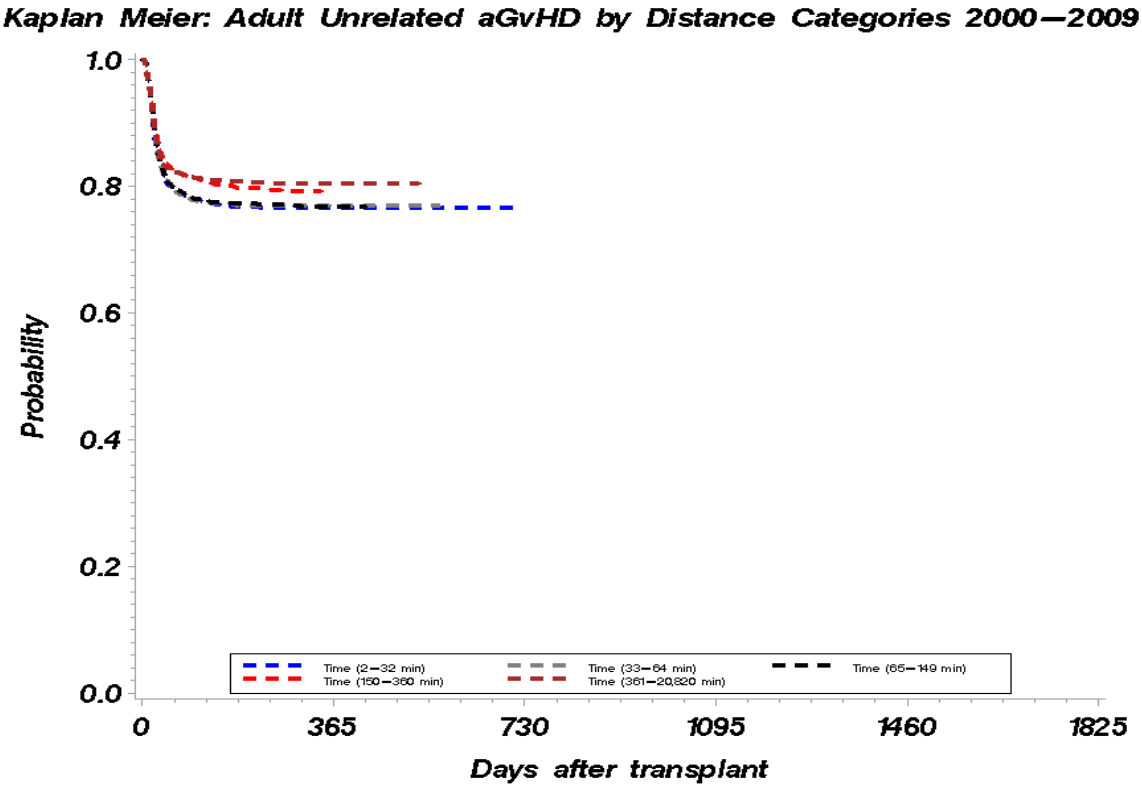

Kaplan Meier: Adult HSCT by Driving Distance 2000–2009 (Survival> 120 days)
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
365
730
1095
1460
1825
Days after transplant
Time (2–360 min)
m1
Time (361–20,820 min)
m2

Distance Quartiles: Survival >120 Days



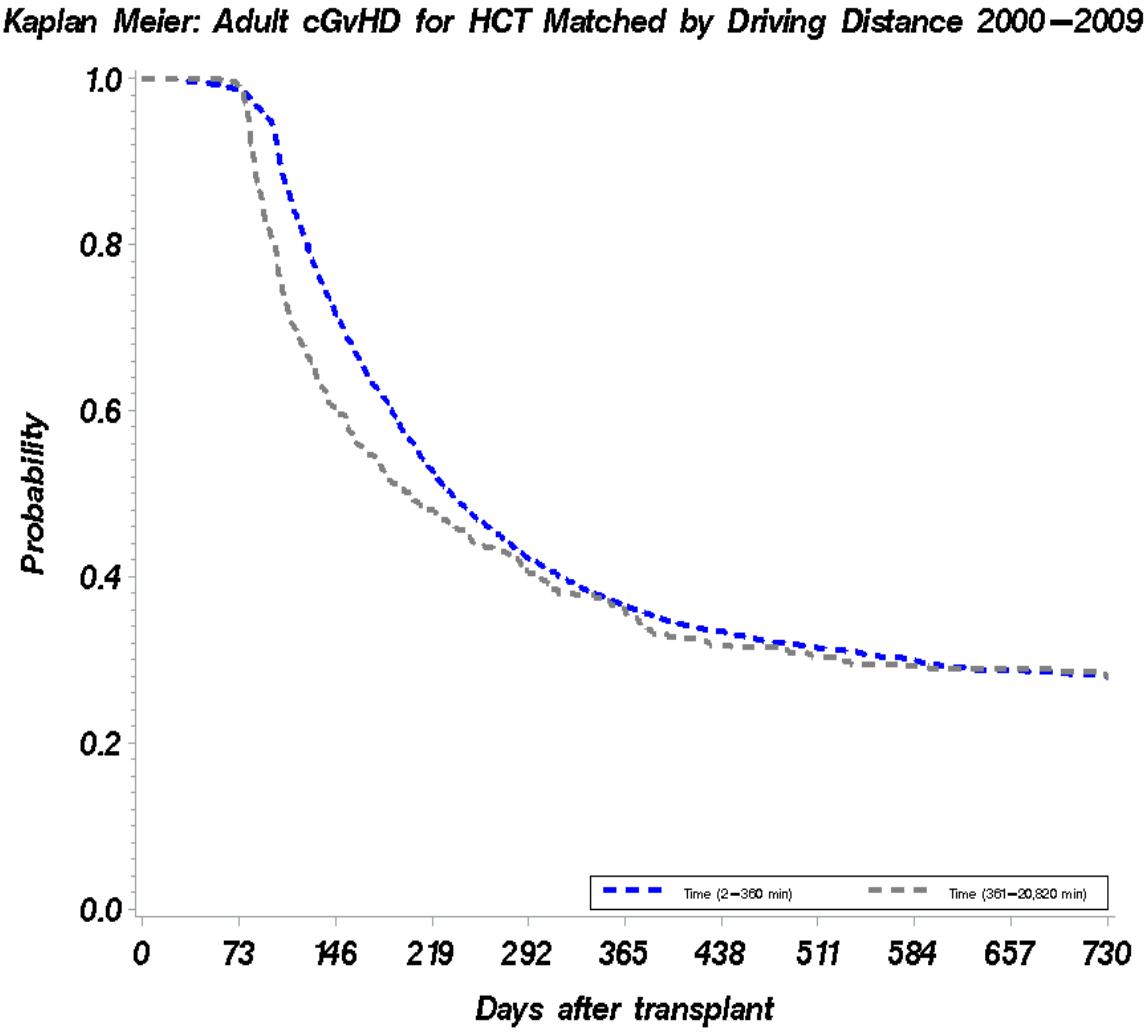
Appendix 17: Use of aGvHD to Confirm Distance Findings

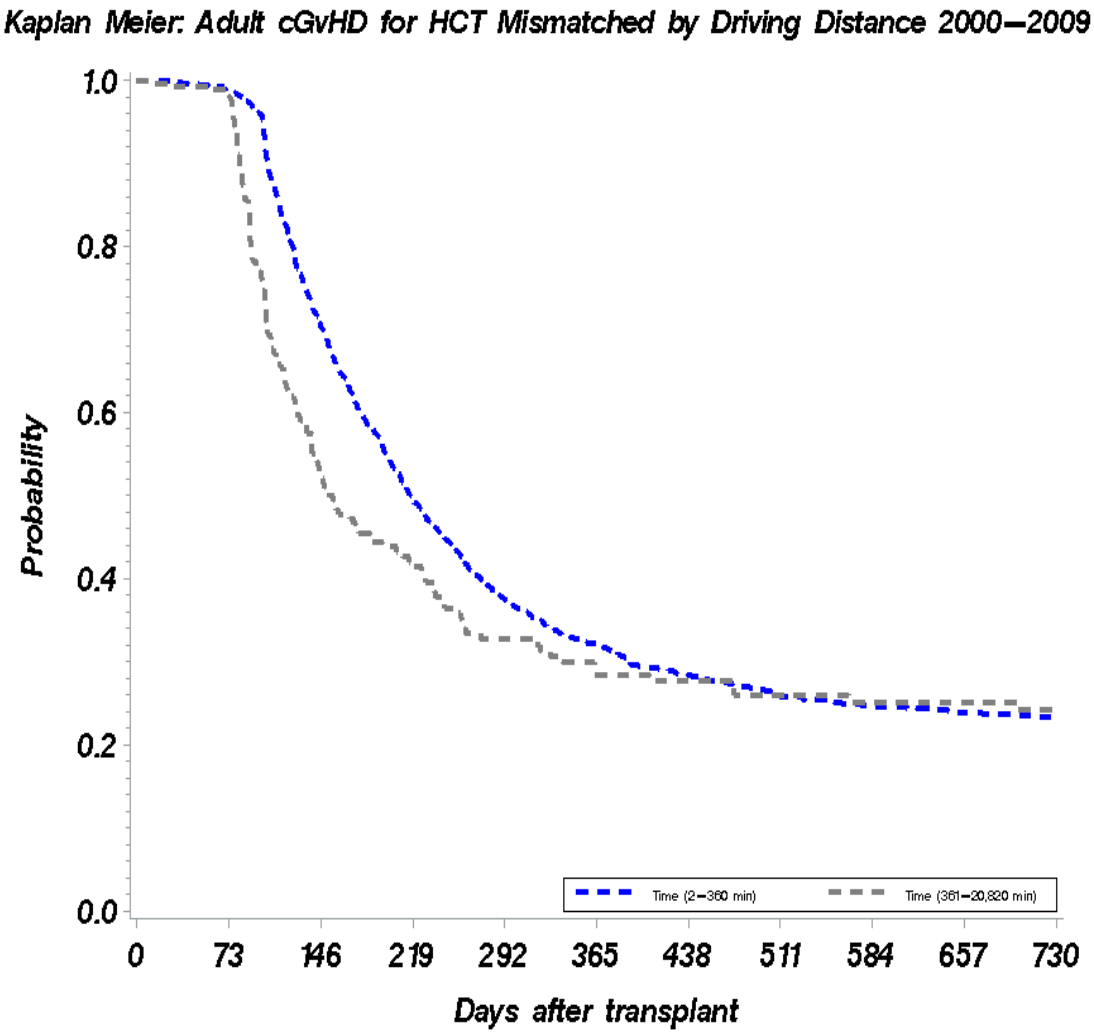
aGvHD is commonly attributed to HLA mismatch. While aGvHD is an imporatnat outcome for HCT pateints our sample did not provide sufficient N to measure differences in aGvHD by distance categories.

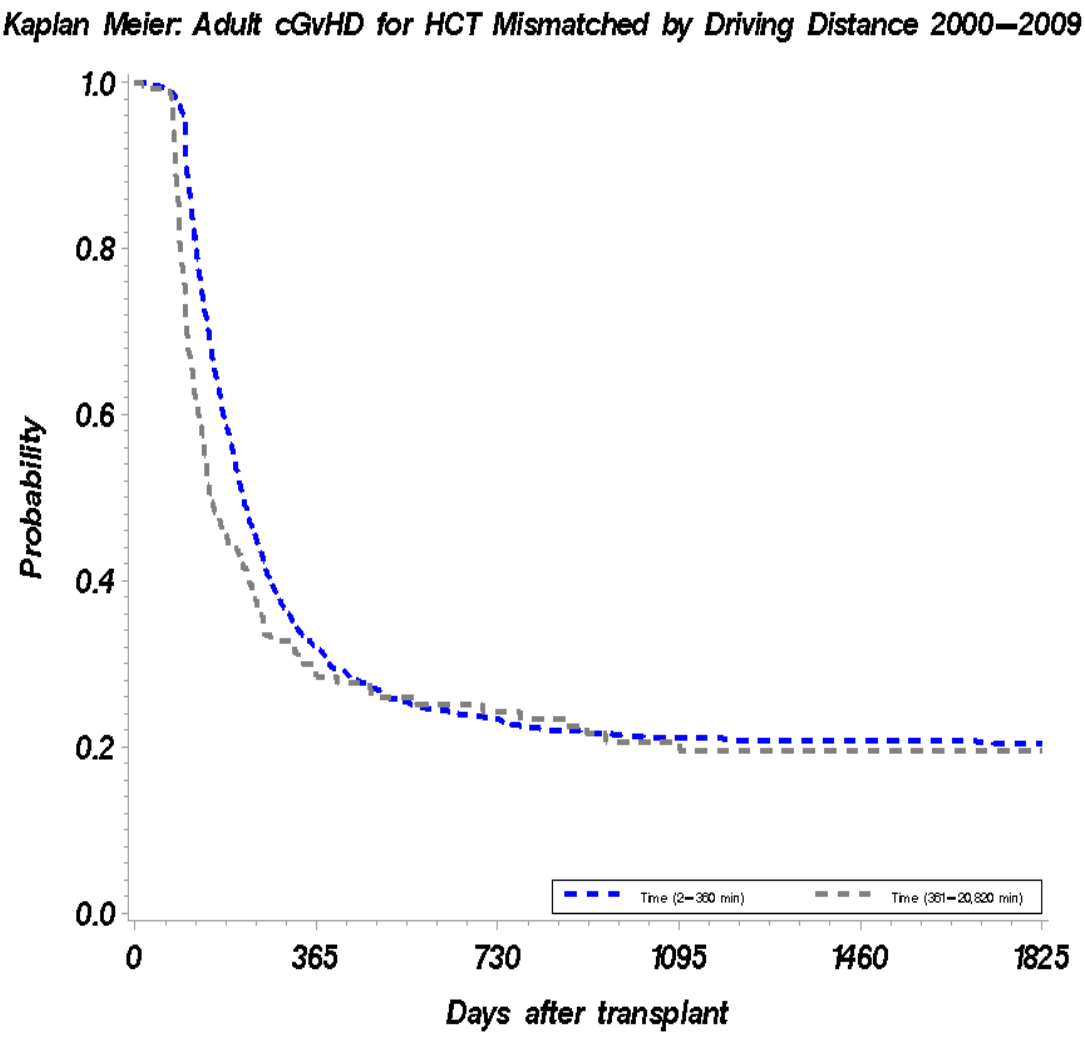


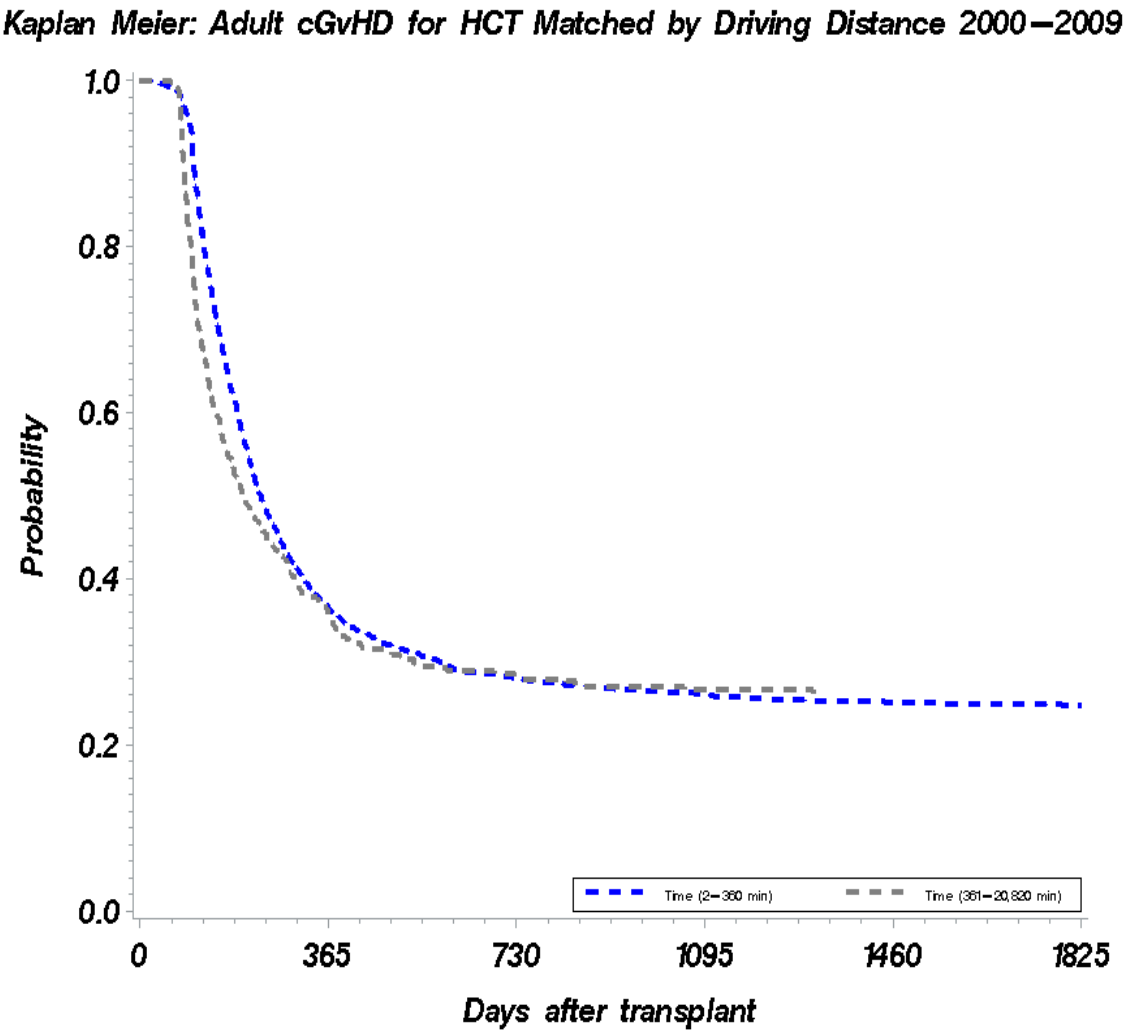
Appendix 18: Use of cGvHD to Confirm Distance Findings for HLA Mismatched Patinets

cGvHD is commonly attributed to HLA mismatch. In order to ensure that our distance trends that illustrated that the unadjusted probablity of cGvHD was less commmon for pateints travelling >6 hours for HCT, we used Kaplan Meier curves for driving distance by HLA match/mismateched status. As the risk of cGvHD tails off after 2 years we used 730 days as the end of our observation period. Below we include Kaplan Meier curves for both the 730 days and the full 9 year observation period. Our sensitvity analysis inicated that the unadjusted probablity of cGvHD was less commmon for both HLA matcehd/mismatched pateints travelling >6 hours for HCT.



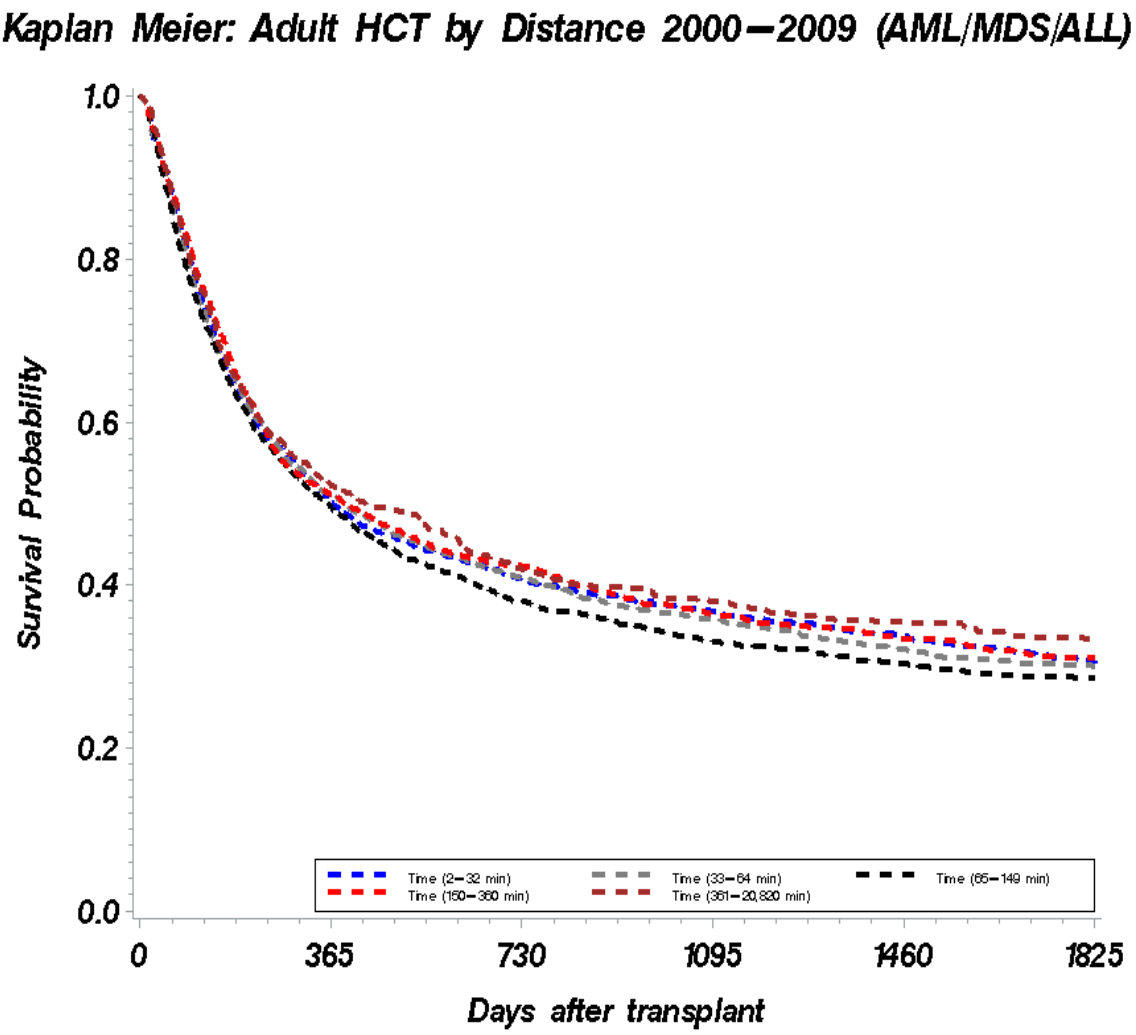

Kaplan Meier: Adult cGvHD for HCT Mismatched by Driving Distance 2000–2009
Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
73
146
219
292
365
438
511
584
657
730
Days after transplant
Time (2–360 min)
Time (361–20,820 min)

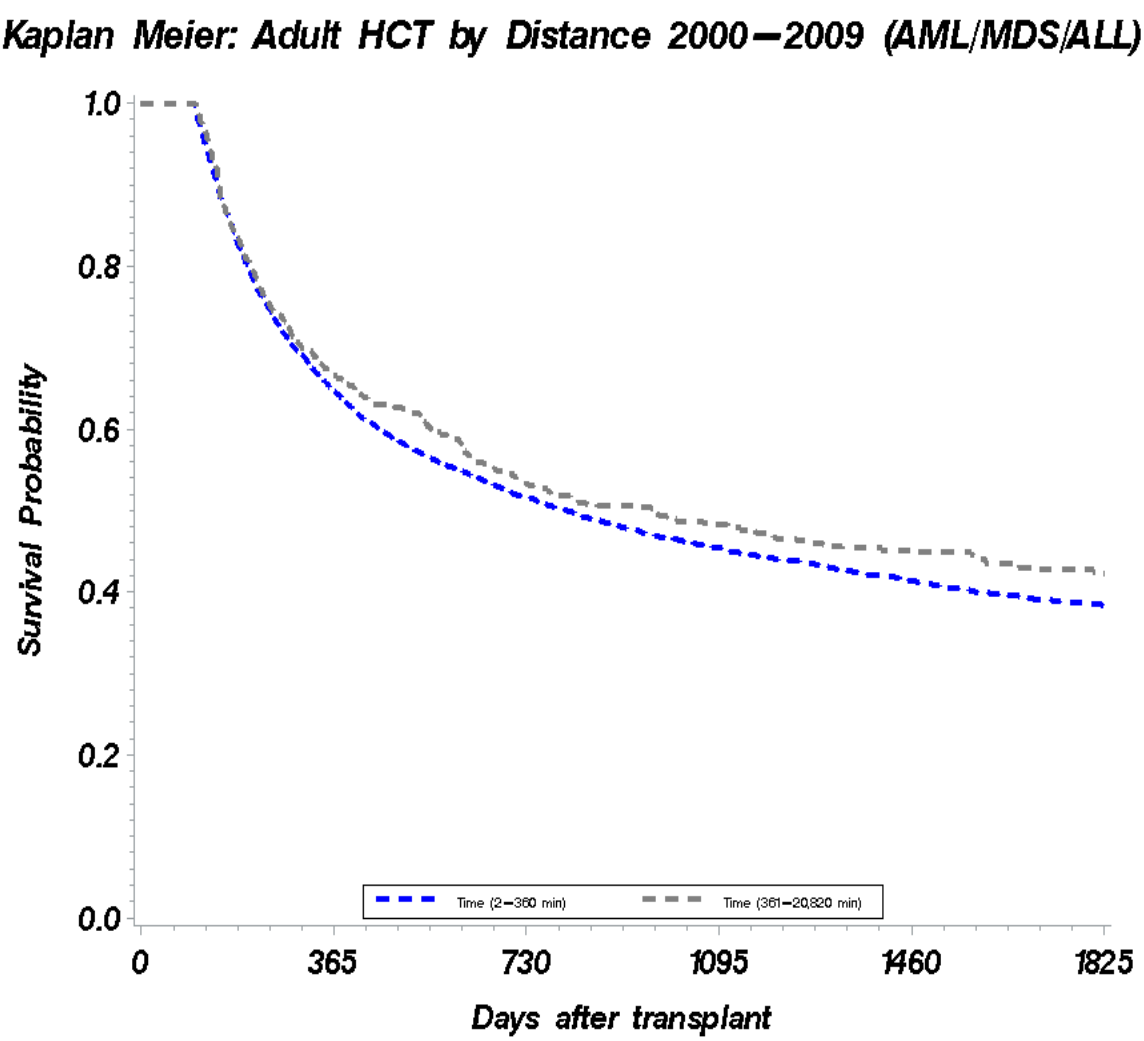

Kaplan Meier: Adult cGvHD for HCT Mismatched by Driving Distance 2000–2009
1.0
0.8
0.6
0.4
0.2
0.0
Probability
0
365
730
1095
1460
1825
Days after transplant
Time (2–360 min)
Time (361–20,820 min)


Kaplan Meier: Adult cGvHD for HCT Matched by Driving Distance 2000–2009
1.0
0.8
0.6
0.4
0.2
0.0
Probability
0
365
730
1095
1460
1825
Days after transplant
Time (2–360 min)
Time (361–20,820 min)

Appendix 19: Disease specific (AML MDS and ALL) Distance Results

In order to ensure that disease categories were not driving our distance results we prefromed a subset anlysis of 3 major diease categoreis, AML, MDS and ALL. Our Kaplan Meier curves did not produce results of different magnitude or direction.




Kaplan Meier: Adult HCT by Distance 2000–2009 (AML/MDS/ALL)
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
365
730
1095
1460
1825
Days after transplant
Time (2–360 min)
Time (361–20,820 min)