Title
Access to Liver Transplantation: Gender, Race and Geographic Disparities

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Access to Liver Transplantation: Gender, Race and Geographic Disparities

by

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DISSERTATION

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Dedication and Acknowledgements

It is with significant admiration and gratitude that I dedicate this dissertation to "my family". First to my parents, Dorothy and William Brennan for their unwavering faith that I could do whatever I set my heart to and for teaching me that with the privilege of education comes the responsibility to improve the world we live in.

Secondly, for my children Erin and Emily Fieberling, for their love and encouragement over these past several years as we sat side by side doing homework together. Thirdly, for the village of friends and colleagues for their small, and often not so small ways of supporting me when my life seemed to interrupt my graduate studies.

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For the generous support of the Moore Foundation, without whom none of this would have been possible. The forethought and generosity of this foundation has forever changed my life and the face of health care in the San Francisco Bay Area forever.

But, most importantly for my husband, Eric Fieberling, who provided unyielding support over this incredibly intense multi-year journey. For the big and little sacrifices he made on a daily basis to help me realize my dream to become qualified to enter into the health care policy debate. For his support and generosity of spirit, I am most grateful.

Abstract

Liver transplantation is the treatment of choice for End Stage Liver Failure patients. The limiting factor in providing liver transplantation is organ availability. Despite the implementation of an acuity based cadaveric liver allocation system in 2002, limited research addresses disparity in access to this scarce resource in this current era of allocation.

The primary purpose of this research project was to increase the understanding and the effect of specific predisposing, enabling and need variables in access to liver transplantation by comparing those cadaveric transplants recipients to those who continued to wait for a cadaveric liver from February 27, 2002 through November 30, 2007. The study analyzed secondary data from the federally mandated database managed by the Organ Procurement Transplant Network and the United Network of Organ Sharing that included 32,566 patients. The acuity-based model of organ allocation (MELD) adopted in 2002 was used to control for acuity at the time of transplant. Using two sets of Cox Proportional Hazard Regression analyses, time to transplant and potential disparities were evaluated. Because the analysis showed that the likelihood of receiving a cadaveric liver transplant doubled for those with MELD scores greater than or equal to 15 after the implementation of a minimum MELD score rule in 2005, the model used a dummy variable to control for the time period (after the 2005 rule adoption). The regression models found disparities in time to transplant by gender, race, and age, and geographic location controlling for acuity, time period, predisposing, enabling and need variables. Women were found to be 13 percent less likely to receive liver transplants then men. African Americans, Hispanics and Asians were found to be 11, 19 and 16

percent less likely than whites to receive a liver transplant respectively. In addition significant regional differences in hazard of transplant were discovered. There was wide variation in access time across regions with an increased likelihood of transplantation from 11 to102 percent in selected regions. Disparities in gender, race, and payer status were found across UNOS regions as well. These disparities across gender, race and geographical region suggest the need for an evaluation of the federally mandated system of allocation.

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Chapter 1

Introduction of the Problem and Purpose of the Study

Introduction

Liver transplantation is the treatment of choice for those individuals found to be in End Stage Liver Failure. The limiting factor in providing this therapeutic treatment is the availability of organs for transplant purposes. Despite the significant efforts to increase donors, including the development of living liver transplant programs, the use of segmental liver grafts and acceptance of extended criteria donors (ECD), only minimal increases in organ supply have resulted over the past decade. Consequently, the issue of access to liver transplant through allocation of this scarce resource continues to dominate the policy discussions involved in providing this life saving treatment.

There have been 87,583 liver transplants performed in the United States since 1988 (UNOS, 2008), the majority of which (84,082) have come from cadaveric donors. In calendar year 2006 alone, 6650 patients in the United States received liver transplants, 11,036 additional patients were added to the liver transplant waiting list and 1,426 were removed from the waiting list because they were deemed too ill or had died awaiting transplant (UNOS, 2008). As of February 2008, 16,952 candidates await liver transplant and approximately 10% or 1400 of those individuals will be removed from the waiting list during 2008 due to death or becoming too ill for transplant. This imbalance of supply and demand remains not only the limiting factor within the field, but also the driving force behind the need to continually evaluate and improve upon the liver transplant organ allocation system.

This imbalance between supply and demand, although currently more pronounced, has existed since the inception of liver transplantation. Consequently, an allocation system to provide for the equitable distribution of this scare resource has existed since the development of this treatment option. This system of organ allocation and distribution has been rooted in a legal and regulatory process that continues to evolve as the field of liver transplantation grapples with balancing issues of equity, justice and efficiency in the allocation and organ distribution process. Despite this evolution in the allocation process, to be described in much greater detail in Chapter 3, limited published data regarding perceived or genuine inequities during the current Era of allocation exist. It is under these circumstances and within this context that this research study is born.

This study proposes to address this policy issue through the underpinning of an expanded version of Anderson's Access to Care Model, in particular as this theory helps identify and define those predisposing, enabling and need variables that drive access to liver transplantation as a treatment modality. Through the use of a Cox regression survival model, a clearer understanding of those variables that predict transplantation as an outcome will help evaluate the effectiveness of the current Era of liver allocation. In addition, results from this analysis may provide additional insight into other areas of health policy that involve the allocation of limited resources in other clinical areas.

This introductory chapter therefore has five aims: (a) To summarize the history of the liver transplant allocation system in the United States, (b) to highlight the significance of the organ donor shortage and its associated factors, (c) to introduce the purpose and the specific aims of this research study, (d) to briefly describe the database, sample and methods used in study, (e) to articulate the significance of this study.

Historical and Logistical Aspects of Liver Allocation

The National Transplant Act of 1984 established an organ matching and procurement network which prohibits the buying and selling of organs and mandates the maintenance of an equitable system for the allocation and distribution of organs. This system of matching and allocation is known as the Organ Procurement and Transplantation Network (OPTN). The OPTN membership includes every transplant hospital program, organ procurement organization (OPO), and histocompatibility laboratory in the United States. Membership implies that these transplant programs/organizations are certified by UNOS, and that they play an active role in forming the policies that govern the transplant community.

The Transplant Act also required that the OPTN, under federal contract, be managed by a private, non-profit organization. The contract to manage the OPTN was initially awarded to the United Network for Organ Sharing (UNOS). This contract has been renewed for the past twenty years, or 5 contract renewal cycles. The main responsibility of UNOS is to provide a management system via a Board of Directors as well as committee membership to operate the OPTN.

The system of allocation employed by UNOS divides the United States into 11 geographical areas called UNOS regions (see Figure 1.1). These regions were originally established by the OPTN for administrative purposes as well as representative purposes, with each region being represented on the Board of Directors and on each of the standing committees of the OPTN.

These 11 geographical areas were never intended to provide for equal populations of potential donors or to serve equal populations of transplant centers. The division of

these 11 geographical regions was intended to recognize existing relationships within the transplant community as well the local interests of each transplant center. Over twenty years later these same geographical UNOS Regions continue to exist.

Figure 1.1: UNOS REGIONS
(source: http://www.optn.org/members/)

Within each UNOS region there are variable numbers of donation service areas (DSAs). Each DSA is served by an organ procurement organization (OPO) whose responsibility it is to identify potential donors and coordinate all the activity leading up to and including the organ procurement. Each OPO is considered the first point of contact when a potential organ donor is identified in a specific DSA. These DSAs (see Figure 1.2) are designated by the Center for Medicare Services (CMS) but vary in regard to the number of transplant centers served, square mileage of the area, state boundaries, population served, candidate/donor ratios and procurement rates and characteristics.

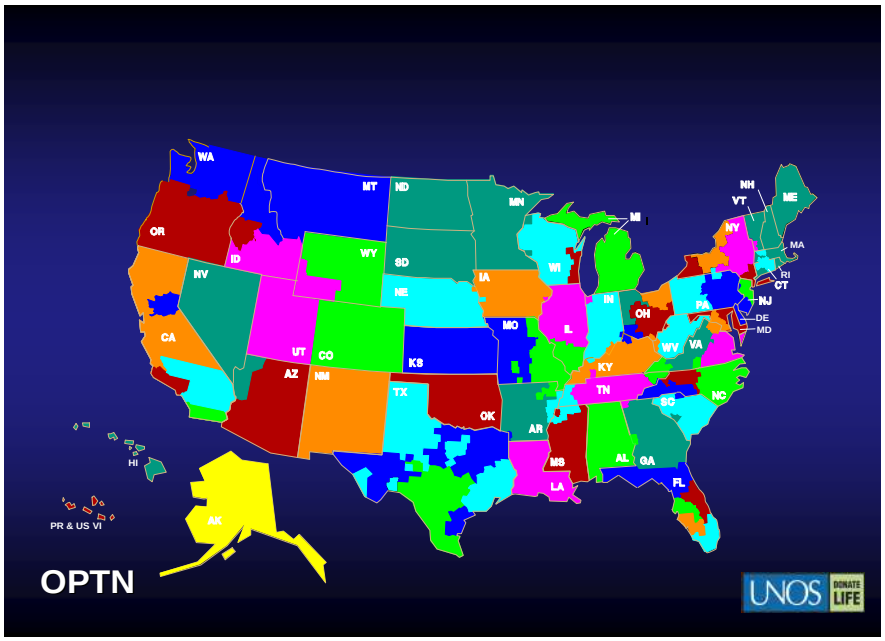


Figure 1.2: U.S. Donor Service Areas (source): http://www.optn.org/members/)

Although there are some regional variations in allocation, generally speaking, livers are offered to sicker patients within the area in which they were donated before being offered to other parts of the country. This current allocation scheme, adopted over 20 years ago, was designed to meet four objectives: to decrease organ preservation time, improve organ quality and survival outcomes, reduce cost and improve access. The National Transplant act established a system of regulation and oversight for the field, a data management system to track outcomes as well as a mandate to review and continuously provide for the equitable distribution of organs in the United States.

UNOS is viewed internationally as a regulatory entity where professional input, patient advocacy and public opinion regarding the field of transplantation are all considered. Although this contracting entity provides regulations regarding the allocation and distribution of organs, rules regarding allocation are adopted only after exhaustive dialog and consensus is reached among participating members previously described.

Given the competing interests of each one of these members, it is fairly obvious that there might, at times, be difficulty in reaching consensus within the group.

The disparity in supply and demand of cadaveric organs has driven much of the policy discussion within the life-saving liver transplantation field. Allocation of this scare resource by acuity of recipient has evolved from a system primarily based on time waiting to one of acuity level. One unintended consequence of this allocation acuity system has been an increase in transplanting patients with hepatocellular cancer as well as a disproportionate number of patients within larger organ procurement organizations (OPO) being transplanted at higher acuity levels than those patients in smaller OPO (Roberts et al, 2006).

The evolution of the liver allocation system, to be more fully described from a theoretical perspective in Chapter 2 and in regard to the research literature in Chapter 3, is currently is based on an acuity-based system utilizing the Model for End Stage Liver Disease (MELD) which has been in effect since 2002. Until January 2005 the allocation of livers by acuity remained almost an exclusive locally driven system, whereby organs were allocated to the most acutely ill patients (Status 1 patients) locally and then regionally, prior to allocation to the highest MELD score patients locally and regionally.

Implementation of the minimum-15 rule (Share 15 Rule) occurred in January 12, 2005. As illustrated below (Figure 1.3), this requires that organs be offered first to Status 1 patients locally and then regionally, then to those patients with a minimum MELD score of 15 locally and then regionally. If no such recipients are identified, offers to those patients with MELD scores less then 15 are allowed. This policy change occurred in part due to the results of a study by Merion et al (2003), in which it was determined

that undergoing a transplant with a MELD score <15 yielded a higher probability of mortality then continuing to wait for a liver transplant. In addition the minimum-15 rules was intended to begin to address inequities in organ distribution based on geographical difference in acuity of liver disease.

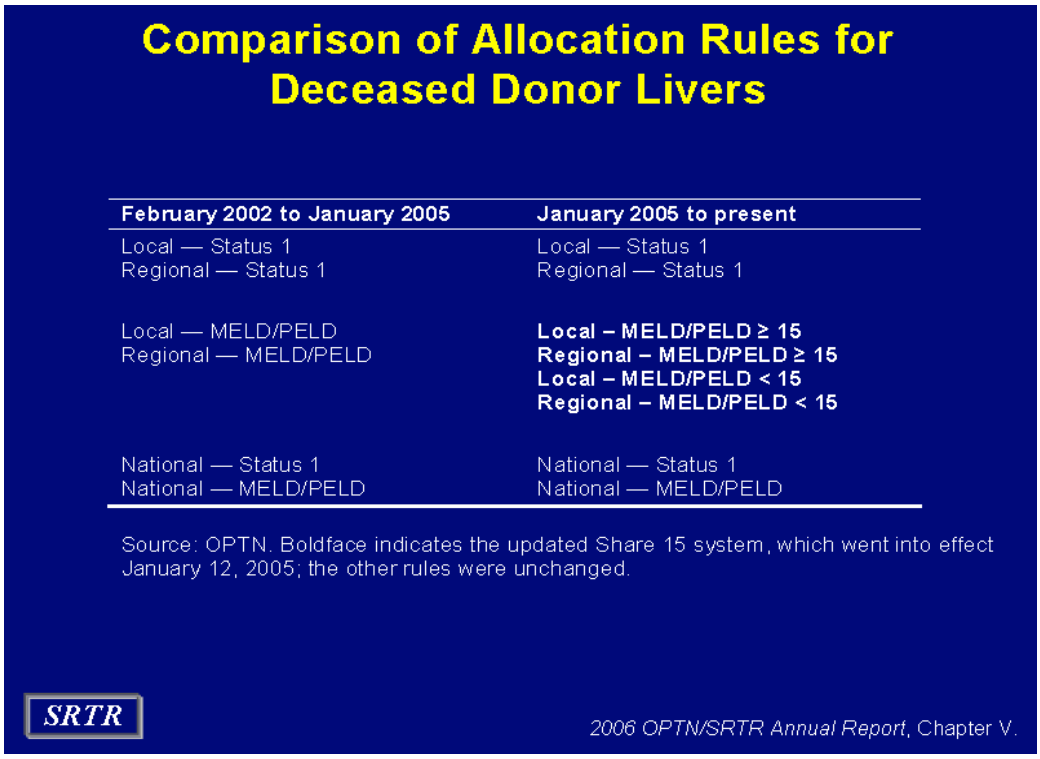


Figure 1.3: Comparison of Allocation Rules for Deceased Donor Livers (Source: UNOS, 2007)

As the allocation model has moved from a predominantly time-waiting system to a severity of illness model, many political and contextual issues have surfaced in regard to the most justifiable and equitable distribution of organs. Currently, numerous studies evaluating the MELD acuity score are underway, in particular, computer simulated modeling to determine potential consequences of geographic re-distribution. These demonstrations yield variable results, due, in part to the variable time frames used in each

study (i.e.: pre and post Meld). More consistent and replicated computer simulations are needed to assess the impact of different redistribution schemes (Roberts et al, 2006). However, prior to additional modeling of organ allocation simulations, a clear presentation of those variables that predict, and perhaps limit access to cadaveric liver transplantation must be undertaken, hence, the current study.

Purpose and Aims of this Study

The primary purpose of this study is increase the understanding and the effect of specific predisposing, enabling and need variables in access to liver transplantation by comparing those individuals who receive cadaveric transplants to those who continue to wait for a cadaveric liver.

Specific Aims

With this purpose in mind, this research study has three specific aims:

Aim 1: To describe those who received a liver transplant between 2002 and 2007 compared with those who continue to wait for a liver transplant during this same period

Aim 2: Determine how the implementation of the Share 15 Rule in January 2005 impacted time to transplantation for MELD acuity levels > or = 15.

Aim 3: Examine the factors associated with time to liver transplant, including those predisposing, enabling, need (acuity of illness measured by MELD) variables and geography while controlling for time period both before and after implementation of Share15 Rule. Examine these factors across 11 geographical UNOS regions as well.

Summary of Methods

Database

This dissertation research utilized secondary data from one large national research database. Secondary analysis provides an efficient, economical method of research that has historically been the method-of-choice in health services research. The primary database involved was the Scientific Research Transplant Registry (SRTR), with input from the federally designated Organ Procurement Transplant Network (OPTN). The primary source for the OPTN database is from transplant centers via an on-line database called the Transplant Information Electronic Data Interchange (Tiedi).

Population

The population studied was individuals who were wait-listed for a cadaveric liver transplant starting on February 27, 2002 through November 30, 2007. In this population, those that received a cadaveric liver transplant were compared with those that continued to wait for a liver transplant, excluding those that died or were removed from the list due to clinical improvement or deterioration. Patients younger than 18 years of age, in acute liver failure or who had previously received a liver transplant were excluded from the study.

Data Analysis

Kaplan Meier Survival curves were used as a basis to identify the dependent variable "time to transplant". With the ultimate goal of attempting to explain this survival curve as it relates to those variables that contribute to the hazard of liver transplant.

Descriptive statistics were used to address Aim 1 of the study: to describe those liver transplants and candidates who continue to wait during the time-frame studied. In particular, the population was described in relation to those predisposing, enabling and need variables described by Anderson (1995) that could be used to explain or predict access to liver transplantation.

Two Cox Regression Models were run to address Aim 2: to evaluate the effect of the MELD 15 Share Rule on hazard of transplantation at higher acuities within the national system and separately by region.

Multivariate Cox Regression Models were used to address Aim 3: to investigate the effects of the defined variables on hazard of transplant during the time frame (2002-2007) defined. Issues regarding differences between pre-2005 and post-2005 times were addressed by adding the dichotomous variable "period" to the final multivariate analysis in order to control for the difference in allocation that occurred with the implementation of the SHARE MELD 15 rule on January 12, 2005. In addition, individual multivariate analyses for each of the 11 UNOS Regions were run to identify significant variables predicting liver transplant by region, with identification of hazard per variable. These additional multivariate analyses included a dichotomized variable "period" to control for the implementation of the SHARE 15 rule from a regional perspective.

Significance of the Research Study

This research adds significantly to the body of knowledge regarding disparities identified in access to care for a highly resource dependent treatment modality. While this procedure (cadaveric liver transplantation) only serves an average of 6,000 individuals a year, this limitation exists only because of the limited supply of organs

available for transplant purposes. Allocation of limited organs should transcend issues of age, race, gender, educational level, economic status and geographical location. This study identified those variables that contribute significantly to the hazard of transplantation when controlling for all other predisposing, enabling and need variables. In addition, variables that provided barriers to access were also identified. From a more global perspective, this research study may serve as a model to evaluate the impact of other acuity-based systems of allocation among highly resource dependent treatment modalities.

This dissertation research project is present in five additional chapters. Chapter 2 reviews the Anderson's Behavioral Model of Access to Care, expanding upon the final model in an effort to address issues specific to the field of liver transplantation. Chapter 3 reviews the empirical literature which is the basis for this research. Chapter 4 describes the methodology used in this study. Chapter 5 presents the results of the analyses, and Chapter 6 provides a discussion of the findings and implications.

Chapter 2

Theoretical Framework

The Anderson Model is perhaps the most frequently utilized framework to evaluate health care utilization. In 1968 Ronald Anderson originally developed the Behavioral Model of Health Services to understand family health services use, measure and define equitable access and to assist in policy development (Anderson, 1968). The unit of analysis moved from the family to the individual when difficulties with heterogeneity came to light. Although debate ensued regarding whether the model predicted or explained usage (Mechanic, 1979; Rundal, 1981), Anderson contends that the model can do both (Anderson, 1995). The Model has progressed through several phases of iteration but the components and variables defining the basic structure remain. This chapter will address the first four iterations of the Model, followed by an expanded version illustrating access to liver transplantation. Models involving both vulnerable populations and safety net services are not discussed in this analysis.

Anderson Behavioral Model: Phase 1 (1960s)

Model 1 (1960s), depicted in Figure 2.1 below, suggests a linear relationship between predisposing characteristics, enabling resources and need. All of these elements work together to explain or predict health services use (Anderson, 1995).

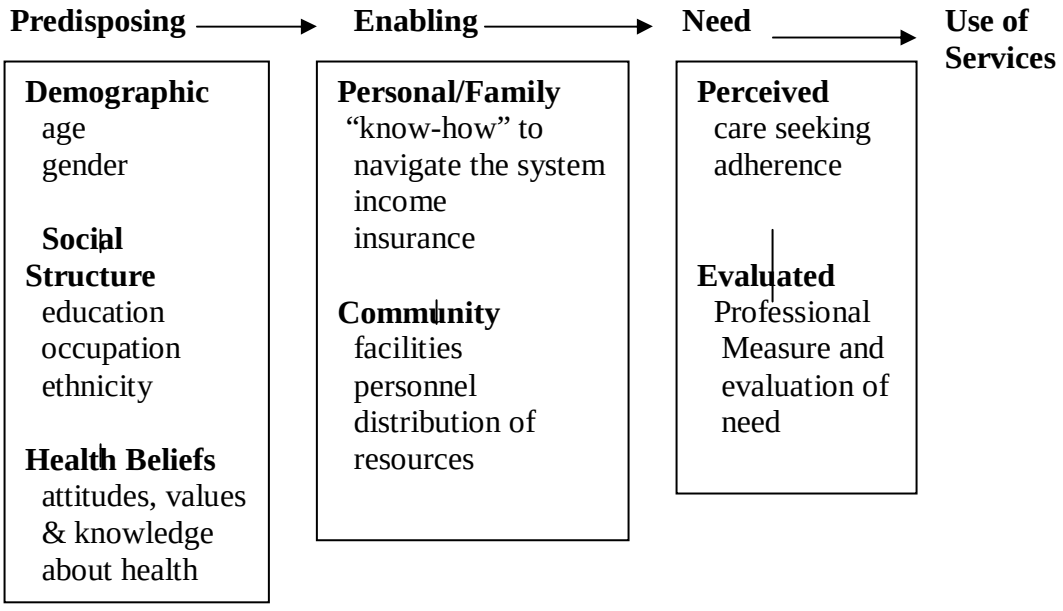
The individual predisposing characteristics make up demographic variables, social structure variables and health belief variables. Demographic variables, including age and gender, have been defined as biological imperatives predicting the need for health services (Anderson, 1995). Social structure has traditionally included education, occupation and ethnicity. Health belief variables are defined as attitudes, values and

knowledge about health. Recently genetic factors and psychological characteristics have been suggested as other major predisposing characteristics (Anderson, 1995).

The second components of the Health Belief Model are the enabling resources that can be further defined as personal/family and community. The personal or family enabling resources are best described as the "know-how" to navigate the system, income, and insurance. The community resources describe the actual facilities, personnel and distribution of this resource. Two limitations of the enabling resources described are the difficulties measuring personal resources (particularly insurance) as well as the lack of articulation of social resources that could facilitate or impede access (Anderson, 1995).

The final determinant outlined by Anderson is need; both perceived and measured (Anderson, 1995). Anderson clarifies that perceived need could best explain care seeking and adherence behavior, whereas, evaluated need reflects a professional measure and evaluation that can be quantified by measuring amount of care provided (Anderson, 1995).

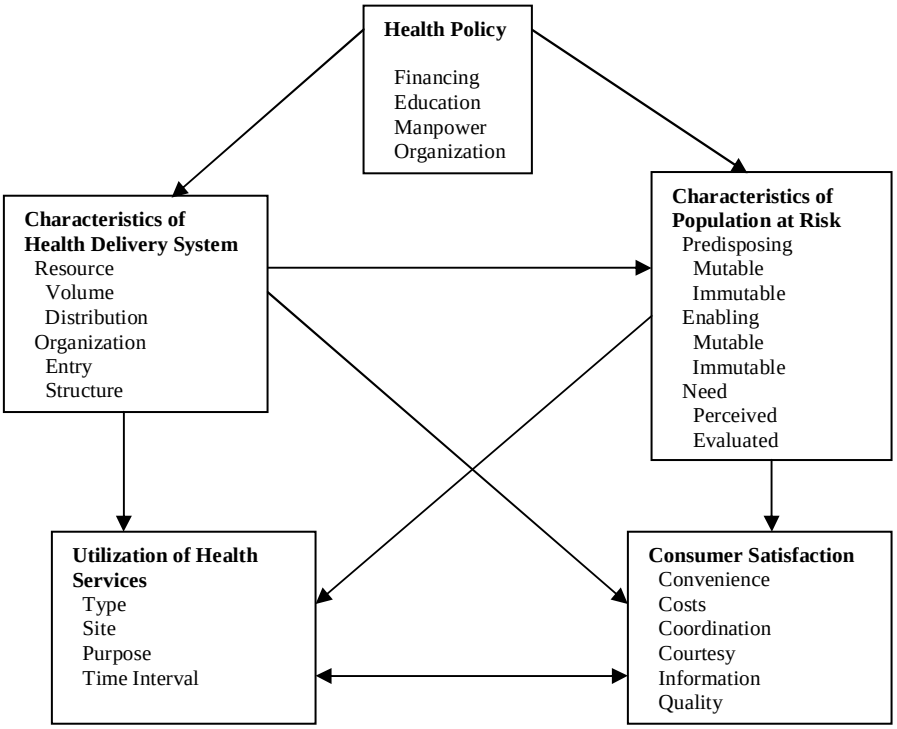
Figure 2.1: Anderson Behavioral Model Phase 1 (1960s) (Anderson, 1995)



Anderson Behavioral Model: Phase 2 (1970s)

Phase 2 of the Behavioral Model was developed in the 1970s and is depicted in Figure 5 below (Aday & Anderson, 1974). It is this depiction of the Anderson Model that introduces the health care system into the model for the first time. In doing so, Phase 2 recognizes health policy as a driving force in the field of health care utilization. In addition, a measure of use of services and an explication of outcomes through consumer satisfaction are specific areas of addition in Phase 2 (Anderson, 1995). Phase 2 further delineates those mutable or changeable characteristics affecting access. It is with this Phase 2 iteration of the Anderson Model that the components and characteristics of the liver allocation system begin to be defined and understood. Definitions of several constructs of the Anderson Model will be illustrated with respect to the liver allocation system, prior to further definition of Phase 3 and Phase 4 and the author's expanded version of the theory.

Figure 2.2: Anderson Behavioral Model: Phase 2 (1970s) from Aday & Anderson,



Understanding Access to Liver Transplantation with Anderson Model (Phase 2)

Phase 2 of the Anderson Model (Aday & Anderson, 1974) can help us begin to examine access in relation to the system of organ allocation that exists within the field of liver transplantation. A review of select transplant research literature in relation to the constructs put forward in this access framework will be used in Chapter 3 to describe the effect of the current allocation policy on the utilization of services within the liver transplant field. In addition, the measures used to operationalize the defined constructs will provide a framework that clearly articulates the organ allocation process, allowing us to better understand the real and perceived disparities and ultimately inform future research and policy development.

Health Policy Sector

Phase 2 of Anderson's framework defines the goal of the **Health Policy Sector** as improving access (Aday & Anderson, 1974). In the field of transplantation, there is a federal mandate for the fair and equal distribution of organs among those in need. This federally mandated system of organ allocation, financed and organized by federal contract, is also responsible to educate the public, professional and patient regarding the system. The contract has been awarded to the United Network for Organ Sharing (UNOS), a private non-profit entity that operates the allocation system.

Characteristics of a Health Delivery System

Phase 2 of the Anderson Model further defines the **Characteristics of a Health Delivery System** as the aggregate structural properties of the system that establishes the arrangements for the potential rendering of care to consumers. The two main elements of the delivery system are resources and the distribution of these resources. Resources are

defined in this model as the materials and equipment used in providing health services. In transplantation, the resources are the actual organs used for the surgical procedure and the system of distribution is the system known as the Organ Procurement and Transplantation Network (OPTN).

The delivery system characteristics involve volume and geography. There is a growing literature addressing perceived geographic disparities regarding the delivery of resources. Rodriguez-Luna et al (2003) describe widespread regional variations in regard to recognized exceptional diagnoses that are not uniformly categorized through the MELD system of acuity. There is a call for National Review Boards to standardize these exceptions within the national system of allocation for fair and equitable distribution.

Schaffer et al (2003) also looked at regional differences, more specifically among three specific Transplant Service Areas (TSAs). These were defined as geographic areas within OPOs that were served by certain transplant centers. This study verified the newly adopted acuity model (MELD) satisfied the IOM's recommendation to prioritize acuity over wait time but did not provide for equitable distribution of organs, outlining that acuity levels at time of transplant are vastly different among TSAs. Coombes et al (2005) in a similar descriptive analysis addressed significant geographical inequities across Organ Procurement Organizations (OPOs) nationally, an area to be further addressed.

Ellison et al (2003**)** suggests a redrawing of boundaries, which could reduce the geographic variability that exists. This study used computer-simulated modeling (CSM) to show that a redistribution of boundaries, could, in fact, reduce these geographical disparities. This analytical approach using CSM is becoming more prevalent in the literature, particularly in regard to predicting results while controlling for other variables.

Characteristics of the Population at Risk

Characteristics of the Population at Risk in the Anderson Model is the propensity of the individual to use the system. It is characterized by the classic format of predisposing, enabling and need categories. With the unit of analysis being the individual, the predisposing factors would include such properties as gender, race and age, areas of concern in regard to potential disparities. This will be explained in much greater detail in the literature review found in Chapter 3.

The enabling factor of means, as defined by money or insurance has been difficult to measure, with several proxy measures (zip code and/or average income by zip code) proving inadequate measurements. However, the ability to identify those without insurance or means of payment at all becomes almost impossible, and hence access for this group is not measured.

Geography, and the ability to access differing geographical locations, which depend on monetary resources, and "know-how" previously described by Anderson (1968) are also important enabling resources within the field of liver transplantation that will be further discussed.

The preponderance of current research literature in the field of liver transplant access has focused on need, which is further constructed as evaluated need or acuity of illness, which, in an ideal world would drive the provision of care. Individual MELD (Model for End State Renal Disease) scores operationalize need within the liver allocation system. The MELD score prioritizes those waiting for transplantation by acuity of illness. The model uses serum creatinine, total serum bilirubin, International Normalized Ratio (INR) for prothrombin time and etiology of cirrhosis to predict survival

pre-transplant. The implicit objective is to transplant the most acutely ill patient, thus decreasing mortality on the waiting list.

Implemented as an allocation tool in 2002, the MELD score has been a topic of much debate and analysis in the literature. Literature regarding the impact of MELD as a measure of perceived need shows mixed results in regard to improving access. Roberts et al (2006) confirmed the MELD score's predictive ability to prioritize the preferential allocation of livers to the most acutely ill patients. Their specific research question, however, was to look at the distribution of the probability of transplant and the average benefit of transplant across organ procurement agencies. They looked at this question through computer-simulated models of distribution and found an uneven distribution. It was this specific piece of research that frames the emerging preponderance of literature regarding reorganizing liver transplant regions (Roberts et al, 2006).

Utilization of Health Services

Stahl et al (2005) developed an analytic model that would preliminarily provide additional transplants each year with regional reorganization maximizing transplant allocation efficiency and geographic parity. These computer simulations combine the MELD score's ability to operationalize perceived need with the external validation of the effect of characteristics of the population at risk described in Anderson's Utilization of Health Services.

Phase 2 of the Anderson Model (Aday & Anderson, 1974) provides the basis of a theoretical framework to organize the empirical work outlined currently in the field of liver transplantation. The effect of policy change as evaluated by the federally mandated system of liver allocation in the United States continues to be evaluated. Computer

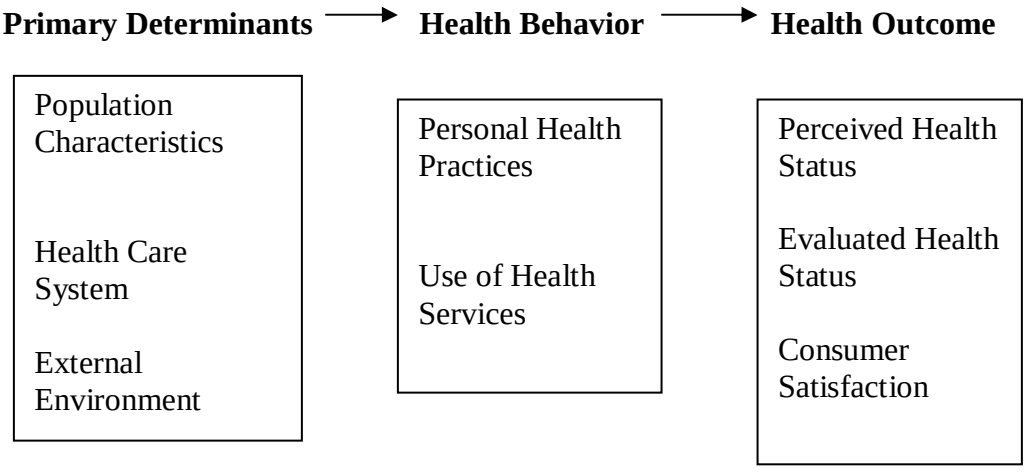
simulated models are just one tool in this evaluation process.

It is with Phase 2 of the Anderson Model, as health policy becomes identified as a factor in health care utilization that a theoretical model of access to liver transplantation emerges.

Anderson Behavioral Model: Phase 3 (1980s and 1990s)

Phase 3 of the Model (1980s and 1990s) adds health status outcomes to the framework (Figure 2.3, below) allowing measurement of access including effective access (defined as improved health status or improved satisfaction) and efficient access (when health status or satisfaction increase relative to the amount of services consumed) (Aday, 1993).

Figure 2.3: Anderson Behavioral Model: Phase 3 (1980s to 1990s) from Anderson, 1995

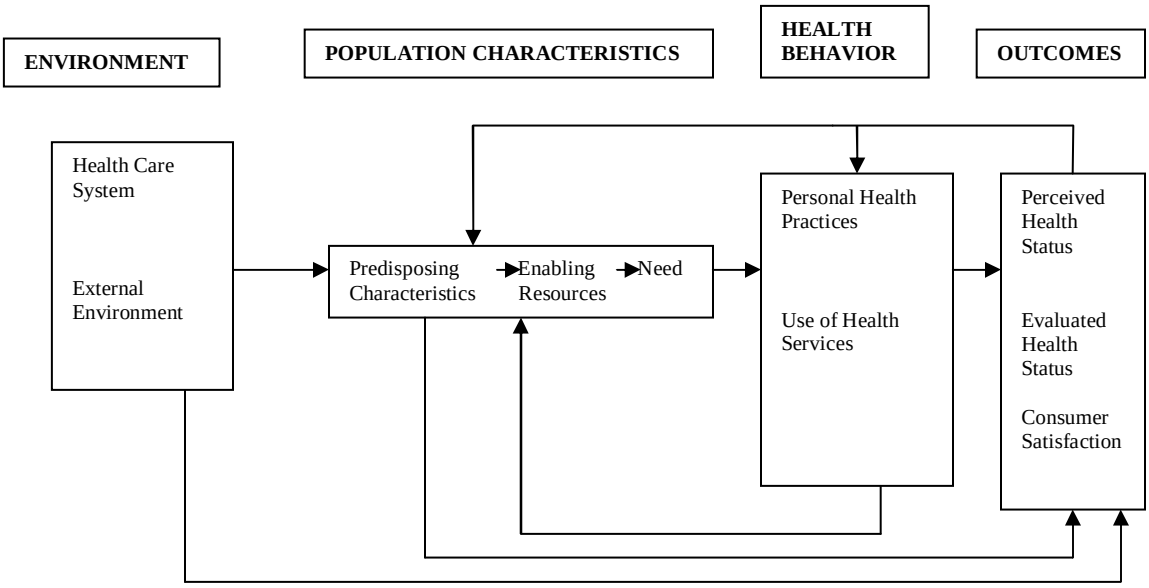


Anderson Behavioral Model: Phase 4 (1990s)

Finally, Phase 4 illustrates an emerging dynamic model (see Figure 2.4) that is recursive in nature with various feedback loops that will require creative and innovative

research and statistical analysis (Anderson, 1995). Mechanic (1993) concludes, and Anderson (1995) concurs, that continued examination of efficient and effective access need to be addressed from a systematic and comprehensive perspective, which Phase 4 of the Anderson model may allow (Anderson 1995).

Figure 2.4: Anderson Behavioral Model: Phase 4 (Anderson, 1995)



It is with the recursive nature and feedback loops from environment to outcomes and population characteristics to both health behavior and outcomes that we begin to understand the systematic nature of health care delivery. There are, however, areas that even through Phase 4, Anderson fails to identify in regard to access to care, that we will illustrate using access to liver transplantation as an example in the author's expanded version of the Anderson Model.

The Anderson Model Expanded (See Figure 2.5)

Thus far the Anderson Model in Phase 4 begins to account for the extensive and numerous levels of external environmental impact that influence access to liver transplantation. These include donation rates, the influence of public opinion in regard to cadaveric transplant, conversion rates (referring to the percentage of potential donors whose families decide to donate cadaveric organs) and referrals to transplant, among other factors.

Most importantly, the issue of resource supply, outlined in Phase 2, but obviously missing from Phase 4 is reintroduced in the expanded theoretical version presented. In regard to liver transplant, the most obvious resource is the actual liver for transplant purposes, but resources also involve transplant centers as well as surgical expertise and availability.

In terms of the population characteristics, the overriding importance of evaluated need is operationalized through the MELD score. What is not accounted for is the patient who is ill, but not yet acutely ill enough to be listed for transplant. This patient must be re-evaluated which creates an additional feedback loop as illustrated in Figure 2.5 below.

The most significant addition to the Anderson Model is the expansion of the outcome variables, in particular in regard to evaluated health status. In regard to liver transplantation there are several outcomes that may result after transplantation. These include patient and graft survival, death, primary non-function (PNF), and recurrent disease. With the exception of PNF, all outcomes require a feedback loop to the environmental characteristics of the model, this illustrates a significant addition to the established Phase 4 of the Anderson Model (see Figure 2.5).

Even when a patient dies, there is a federal mandate to provide information and data input regarding this outcome, hence a feedback loop to the environmental characteristics of the system. Patient and graft survivals also require data reporting in addition to collaborative clinical care between the transplant team and original referral community physician where the transplant patient will return for follow-up care. Successful patient and graft survivals require life-long collaboration between community physicians and transplant centers in an effort to provide clinical follow-up care and reporting of accurate survival data to the OPTN.

A third outcome following transplantation could be the recurrence of liver disease after some period of successful transplantation. Recurrent disease requires re-entering the evaluative phase of transplantation. Referral from community physicians to the transplant center initiates the process at the external environmental characteristic of the expanded version of the Anderson Model following linearly through the evaluative need phase of MELD assessment and re-listing for liver transplantation. Not only is this process recursive in nature, it is continuous, for the life of the transplant graft.

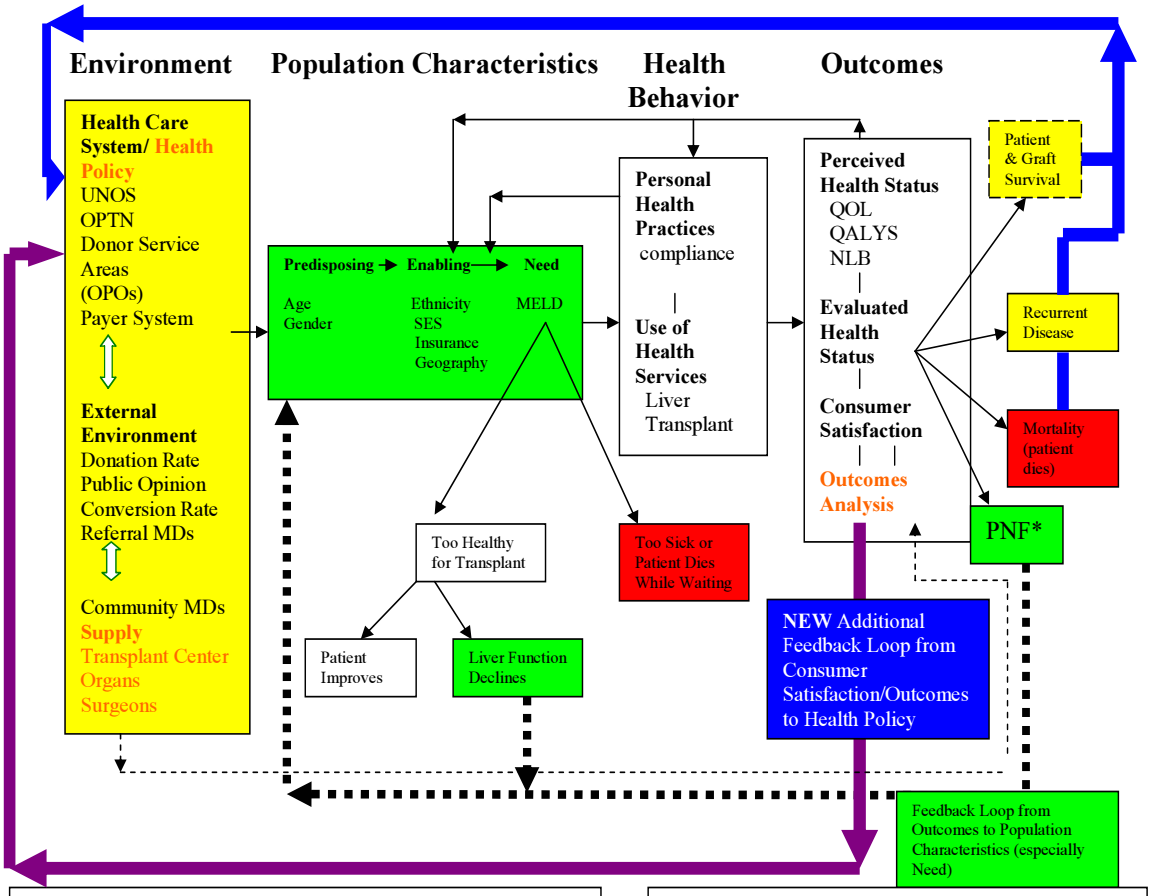
The only outcome that takes a different path is the patient experiencing primary non-function (PNF). This rare, but clinically serious outcome occurs immediately upon implantation of the cadaveric liver. PNF is defined as no liver function upon transplantation. This emergent situation requires immediate re-listing and re-transplantation, bypassing the formal listing procedures accounted for in the environmental characteristics described in Phase 4. This situation necessitates the creation of a more immediate feedback loop to the population characteristics, most importantly the need-based variable. In fact, a diagnosis of PNF provides a Status 1

acuity measure, superceding the highest acuity-based MELD score. Status 1 designation prioritizes recipients to the highest level of need, an issue to be further discussed in Chapter 3.

Transplantation is a surgical treatment modality for acute or chronic end stage liver failure. However, it is also a life-long course of treatment involving not only a surgical event but also a medical treatment across specialty areas and among a series of health care providers that make up an environment of care, much like a chronic disease model requiring interventions through the life of the patient and process. The Expanded Version of the Anderson Behavioral Model, depicted in Figure 2.5, illustrates the recursive nature of the transplant process which depends not merely on an adequate supply of organs but a collaborative effort of providers of care in the external environment through a federally mandated health care system. Theoretically, Anderson points to those population characteristics defined as predisposing, enabling and need variables as drivers of access. This dissertation attempts to confirm this thesis using liver transplantation as model while expanding this theoretical perspective as well.
While the premise is that these population characteristics provide access to care, issues of disparities in care and/or barriers to access were tested in this research study to determine if policy driving the current system of allocation currently fulfilled the mandate for a fair and equitable distribution of organs. The results of this outcome analysis should provide data, through a newly added feedback loop, to the Health Care System outlined in the Environment area of the model. This feedback loop, as illustrated below in Figure 2.5, will inform policy regarding inequities in a manner that should lead to a change effect, and confirm those parts of the allocation system that are functioning well. This expanded

version of the model, with feedback loops from Outcomes has application to many resource dependent treatments.

Figure 2.5: Expanded Version of Anderson Behavioral Model



LEGEND FOR THE EXPANSION OF THE ANDERSON MODEL

NEW Feedback Loop from Evaluated Health Outcomes to Environmental Characteristics of the Health Care System for 1) data reporting purposes and 2) communication with community MDs for follow-up care and/or referral for re-transplant

NEW Feedback Loop from consumer satisfaction to Health Care Systems and Environmental Characteristics that may influence and/or create policy change

Communication between the external environment, supply and the health care system that can influence the process

Health Policy and Outcomes Analysis were added to the Environment and Outcomes portions of the Expanded Version of the Anderson Behavioral Model. Supply was reintroduced to the Environment as well.

***primary non-function**

EXISTING FEEDBACK AND DIRECTIONAL FLOW OF PHASE IV MODEL

Original directional flow of diagrammatic model

Original Feedback Loop to Population Characteristics, from Outcomes, particularly for evaluated need assessment

Original Feedback Loop from the External Environment (referral/community MDs and transplant centers) representing collaborative and continued clinical care of the transplant patient which contributes to outcomes/satisfaction

Bold Typeface indicates original Anderson Model, Phase 4 components

Summary and Conclusion

In summary, Anderson's Health Belief Model offers an excellent theoretical basis for beginning to identify and ultimately understand those variables that contribute to providing or prohibiting access to the highly resource dependent treatment option for end stage liver disease patients known as liver transplantation. This model frames the literature review presented in Chapter 3 as we address those predisposing, enabling and need variables so aptly defined by Anderson and others.

Health Policy, the means by which access to care is directed, was introduced to the model in Phase 2 (Figure 2.2). It is conspicuously absent from the both Phases 3 and 4 models, unless it is implied that Health Policy resides in the environment as a part of the Health Care System or the External Environment. If this is the case, and Health Policy is found within the Health Care System then it would continue to influence the access and utilization of health care services, including liver transplantation.

This researcher expands Version 4 of the Anderson Model by adding an additional area to Outcomes in the model defined as **Outcomes Analysis**. In addition, feedback loops are added from Outcomes (including outcome analysis, perceived health status, evaluated health status and consumer satisfaction) back to the Environment where Health Policy would be developed to influence the Health Care System to effect change in addressing inequity within the provision of care studied.

This particular study is an illustration of an outcomes analysis based on a system of evaluated need for a highly resource dependent treatment modality. The expansion of this Anderson Model presented in Figure 2.5 suggests that the results of such an analysis could inform Health Policy and the Health Care System regarding the status of the

evaluated care. In the example of liver transplantation the feedback loop would go directly to the federally mandated system of oversight for transplantation by means of the Organ Procurement and Transplantation Network and the contracted entity, the United Network for Organ Sharing, to address inequities discovered. Similarly, a feedback loop from perceived health status, evaluated health status and consumer satisfaction should also provide data contributing toward health policy change and more equitable access and utilization for liver transplantation and other resource dependent treatment modalities, however, these new areas of theoretical expansion are not addressed within the context of this particular study.

Chapter 3

Literature Review

Research in the field of access to liver transplantation has been focused on acuity of illness measures, organ distribution areas and disparities that are encountered based on potential systematic bias. This research will be reviewed, however, more specifically; access to care will be addressed in regard to the theoretical framework provided by Ronald Anderson (Aday & Anderson, 1974, Aday, 1993, & Anderson, 1995), the theoretical underpinnings of which were discussed in greater detail in the Chapter 2.

The purpose of this current chapter is to provide a thorough literature review in regard to those variables that Anderson describes as predisposing, enabling and need variables that contribute to access to care from both a predictive and explanatory perspective (Anderson, 1995). First, an explanation of the historical context and regulatory process of liver allocation will be presented. Following this brief contextual framework, the three most current allocation schemes utilized over the past 18 years (Eras 1, 2, and 3) will be described. Brief mention of the three points of access to care in the liver transplantation process will be defined. Finally, a thorough literature review in regard to those predisposing, enabling and need variables that Anderson describes will be presented.

Historical and Regulatory Aspects of Liver Transplantation

Two specific laws frame organ transplantation in the United States. The Uniform Anatomical Gift Act of 1968 (revised in 1987) granted individuals the right to determine, prior to death, whether or not they wished to donate their organs for transplantation purposes. In addition, the National Transplant Act of 1984 established an organ

matching and procurement network which prohibits the buying and selling of organs, and mandates the maintenance of an equitable system for the allocation and distribution of organs (Coombes and Trotter, 2005).

This system of matching and allocation is known as the Organ Procurement and Transplantation Network (OPTN). The Transplant Act also required that the OPTN, under federal contract, be managed by a private, non-profit organization. The contract to manage the OPTN was initially awarded to the United Network for Organ Sharing (UNOS). This contract has been renewed for the past twenty years, or 5 contract renewal cycles. The responsibility of UNOS is to provide a management system via a Board of Directors as well as committee membership to operate the OPTN (UNOS, 2007).

These laws established a system of regulation and oversight for the field, a data management system to track outcomes as well as a mandate to review and continuously provide for the equitable distribution of organs in the United States. UNOS is viewed internationally as both a regulatory body and a forum for professional input, patient advocacy and public opinion where allocation in the field of transplantation continues to be addressed. The mission of UNOS is to advance organ availability and transplantation by uniting and supporting communities for the benefit of patients through education, technology and policy development (UNOS, 2007).

Despite clinical and scientific advances within the field, perceived inequities in regard to geographical disparity as well as increased mortality on the waiting list for those awaiting liver transplant came to light about ten years ago. In 1998 these perceived inequities were addressed by the Department of Health and Human Services in the form of a “Final Rule” to insure that the allocation of scare organs be based on medical need.

The Institute of Medicine (IOM) convened to address this issue of disparity and recommended a restructuring of the liver allocation process to deemphasize wait time and provide a more equitable distribution based on predictive prognosis (Coombes & Trotter, 2005). In addition, the "final rule" was intended to place greater emphasis on acuity and less emphasis on keeping organs within local procurement areas.

The two-fold effort this final rule recommended was (1) an expansion of the geographical area served by each organ procurement organization in order to equalize access and (2) the development of an allocation system that prioritizes based on acuity and not waiting time.

The first recommendation to expand all service areas for organ procurement to serve a population base of 9 million people was met with strong opposition by much of the transplant community and was never adopted (Ahmad, Bryce, Cacciarelli, & Roberts, 2007). Actually several states, including Louisiana, Wisconsin, Texas, Arizona, Oklahoma, Tennessee and South Carolina, even passed legislation prohibiting such expansion based on established limitations to interstate commerce (Meckler, 1998). Research regarding issues of geographical inequity, a politically contested issue, will be addressed further in this literature review.

In regard to redirecting allocation based on acuity, the Model for End Stage Liver Disease (MELD) was developed and adopted as a liver disease severity score. The premise of this new scoring system was to prioritize more acutely ill liver failure patients for transplantation. This system of allocation by acuity replaced the Child Pugh Score (CPS), which combined clinical measures of acuity with both subjective as well as wait list time to determine cadaveric liver allocation.

Because the literature reviewed spans all three liver allocation Eras, a brief review of these three Eras is necessary.

Research Studies and Allocation Eras

Three distinct eras of allocation have been in effect over the past 20 years. For purposes of critiquing the research studies reviewed, each era is described and each research study classified according to the era in which the data was collected (see Appendix A). This may appear irrelevant given that Era 3 is the current allocation system using the Model for End Stage Liver Disease (MELD) as the acuity measurement. However, the literature addresses many predisposing, enabling and need variables over various time frames, utilizing all three allocation schemes.

Given that the literature reviewed is primarily based on secondary analyses of data sets from different timeframes and employing different allocation schemes, conclusions drawn for each research study may or may not be relevant to current allocation practices. Despite this limitation, the field of transplantation often depends on and references the results and analyses from studies of prior eras to report on disparities in distribution and allocation of livers. This makes it difficult to distinguish what disparities actually exist with the current system of allocation from those that are continuing to be reported from prior allocation data sets. The results of this current study will add significantly to the current body of literature with the focus being identifying those predisposing, enabling and need variables that contribute to or provide barriers to liver transplantation in the current post-MELD allocation period.

Anderson's Theoretical Model of Access to Care will be used in this literature review to assess those predisposing, enabling and need variables that have historically

been studied in order to evaluate the status of access to liver transplantation and identify those variables that have not been focused upon and that require further research. This attention to utilization of allocation systems, although tedious, helps determine the need for additional research that is elaborated upon in the conclusion.

ERA 1: Pre-CPS Allocation Equation (prior to 1997)

Era 1 (pre-CPS), prior to 1997, prioritized patients by where they received their medical care (home, hospital or ICU), with the underlying assumption that the most acutely ill patient was being cared for in the Intensive Care Unit and the least acutely ill patient at home. Organs were allocated from most acutely ill to least acutely ill in descending order on this scale, with many ties, which were broken with time waiting. Eight of the twenty-one studies reviewed used data exclusively from Era 1.

ERA 2: CPS Allocation Equation (from 1998 to February 27, 2002)

Era 2 began in 1998 when the OPTN mandated that the Child Pugh Score (CPS) for liver disease be employed to establish medical urgency categories, which together with waiting time determined the allocation and distribution of cadaveric livers (Freeman et al, 2004).

The CPS combined both quantitative (albumin, bilirubin and prothrombin) and subjective scores (encephalopathy and ascites) to attain a total score of 5 to 15, with the greater number indicating poorer hepatic function or greater acuity level, hence priority in allocation. However, due to the limited discriminatory ability of CPS, with only 8 levels of difference between least sick transplant candidates, many ties (transplant patients with the same score) occurred. This often necessitated an emphasis on wait time to break the tie (Durand & Valla, 2005).

Although utilization of this acuity scale was perceived as somewhat of an improvement over Era 1, with clear delineation of the most acutely ill patients receiving priority for transplant, the more chronically ill patients, the much larger percentage of patients awaiting transplant, were stratified by non-standardized physician assessment, waiting time and geographical disparities between organ procurement areas.

Only 1 of the twenty-one studies reviewed used data exclusively from Era 2 (Ellison, Edwards, Edwards, & Barker, 2003). One study (Reid, Resnick, Chang, Buerstatte, & Weissman, 2004) compared data from Era 1 and Era 2.

ERA 3: MELD Allocation Equation (subsequent to February 27, 2002)

Era 3 (MELD), implemented in 2002, utilized the acuity based Model for End Stage Liver Disease (MELD) to allocate livers for transplantation (Coombes & Trotter, 2005). This system of allocation remains in effect today.

The MELD score is based on quantitative variables (serum creatinine, bilirubin, international normalized ratio) using the following equation: MELD estimate = 6.43 + 9.57*log(creatinine) + 3.78*log(bilirubin) + 11.2*log (INR). The MELD score is then rounded to the nearest integer from 6-40 (inclusive) with 40 being the maximum score and the higher number the sicker the patient, hence priority in allocation. Scores achieved over 40 are truncated into the most severe category of 40 (Kamath et al, 2001).

Additional points are added for hepatocellular cancer (HCC). MELD scores are recalculated at varying intervals based on levels achieved, to account for changes in acuity of illness. In addition, critically ill patients in fulminant liver failure (the severe impairment of hepatic functions in the absence of preexisting liver disease) and primary non-function (the non-function of a liver immediately following transplant) are allocated

livers outside the MELD system of allocation, prioritizing these two diagnoses above all other MELD scores. Only three of the twenty-one studies reviewed used data exclusively from Era 3. One of the twenty-one studies compared data from Era 2 and Era 3.

Although Era 1 and Era 2 are reflective of past practice, which informs future allocation, research studies utilizing data collected from these time periods are no longer relevant to the current allocation discussion, despite the continuation of reference to many of these studies in the current literature.

Having described the three eras of allocation used within the field of liver transplantation we turn to the three stages of access candidates face during the process of coming to transplantation.

Anderson Behavioral Model of Access to Care and Three Stages of Access

The literature review is organized in relation to the variables described by Anderson as predisposing, enabling and need variables that determine and explain access to care. This model is presented as a guide for understanding the relationships between the variables discussed and access to liver transplantation as a treatment for end stage liver disease.

Access to liver transplantation occurs at three specific time frames: referral, wait list and transplant surgery. The majority of the literature involves access to liver transplant at the time of surgery. A few studies involve wait list access, but more studies involve activity during the wait list period that affects access. Even fewer articles address referrals or referral patterns. It is particularly difficult to measure access at the referral stage. These limitations are discussed below.

Stage 1: Referral

There is very limited research regarding access to referral for liver transplantation. In fact, only two such studies were found (Julappali, Kramer, & El-Serag, 2004 & Tuttle-Newhall, Rutledge, Johnson, & Fair, 1997). There are significant limitations to performing this type of research due to the lack of databases and well-documented prevalence of liver disease to be able to measure access at this point in the process. Ozminkowski, Friedman, & Taylor (1993) raised this issue nearly 15 years ago, but the inability to measure access to referral remains today.

Tuttle and colleagues (1997), in performing a state-wide research study in North Carolina aimed to analyze those factors associated with access to liver transplant by utilizing a large population-based hospital discharge database to look at patients with diagnoses of liver disease in order to determine those variables that were associated with access to liver transplant at the point of referral.

Julapalli et al (2004) used a data system from a large VA hospital and Tuttle et al (1997) used a state-wide hospital database system. Both researchers attempted to analyze the problem of access prior to entrance into the transplant system.

Most researches have used the OPTN's transplant database of wait-listed and transplanted candidates to study access to liver transplantation. Ozinkowski, Friedman, & Taylor (1993) pointed out the following that remains true today:

> "Using the waiting list for analysis provides no information about patients with End Stage Liver Failure who do not enter the waiting list for medical, financial, geographic or other reasons" (Ozinkowski et al, 1993).

In other words, the standard practice of using the OPTN database of patients waiting for transplant only captures those patients who have gained access to the system

in the first place. Even more limiting is the ability to measure access for those who suffer from end stage liver disease who never enter the health care system and therefore cannot be referred on to specialty care to be evaluated for liver transplant as a treatment option.

Stage 2: Liver Transplant Waiting List

Once a patient is referred for liver transplant they are evaluated as a potential candidate and, if accepted with a liver transplant program, they are placed on a waiting list until their acuity is such that they receive a transplant. The current allocation system is designed so that the most acutely ill patient receives the next available liver for transplant within a particular geographical region. Significant regional variability exists in regard to acuity levels at which a patient receives a transplant (Roberts et al, 2006). This will be further discussed under geographical enabling variables.

Stage 3: Liver Transplant Surgery

The final point of access to liver transplantation is the actual surgery. The most acutely ill patients, classified as Status 1 patients, who are predicted to die within seven days, are often referred, wait listed and transplanted within expeditious fashion, appearing as though this process occurs within one and not three stages. The Status 1 patient is prioritized above the highest MELD score patient, given their extremely poor prognosis without a graft. Most research excludes Status 1 patients from the inclusion criteria used.

Non-status 1 patients are prioritized by MELD acuity score with the highest score indicating the most acutely ill and therefore the next person in line within a given organ procurement area. Most literature reviewed involves reaching this surgical phase of the

process of liver transplantation, given that the goal of the entire process is to actually receive this life saving organ.

Having described Anderson's Behavioral Model of Access to Care in Chapter 2, it was important to define the three eras of organ allocation, the historical and regulatory context of liver allocation as well as the phases of the liver transplant process. With the context and background of the transplant field described, we now turn to the actual literature review in order to understand those variables that have predicted or explained access to liver transplantation in the past, in an effort to study the current status of such access.

The Literature Review Process

The objective of the literature review is to gain an understanding of the liver allocation system in regard to those predisposing, enabling and need variables described by Anderson (1995). Databases searched included PubMed, CINAHL, PAIS, THOMAS Legislative Information, SocAbstracts and Google Scholar. Search terms (in combination with liver transplantation) included race, ethnicity, gender, sex, age, access, utilization, insurance, Anderson Behavioral Model, predictor variables, MELD, socioeconomic status, income, geography, independent variables, outcomes, UNOS and access to care.

The criteria for selection of major articles was (1) U.S. system of allocation (although some international studies were accepted for comparison purposes), (2) English language, (3) adult subjects, (4) related to study variables, (5) defined selection criteria, independent and dependent variables, (6) reported results in statistical terms, (7) research studies. Titles, abstracts and articles were reviewed and articles were selected that met the author's selection criteria of the literature search in the opinion of the author. The

articles were then categorized according to Era 1, Era 2 and Era 3 time periods. This categorization of the Era of allocation becomes important when considering actual versus historic measures of access.

This process of literature review is perceived to be extensive in regard to the variables described but by no means exhaustive in regard to all variables that could potentially contribute to access to liver transplantation.

Anderson Behavioral Model of Access to Care and Liver Transplantation

Characteristics of Population at Risk: Predisposing Variables

RACE

Historically, race has been of significant concern in regard to the equitable distribution of all solid organs. In particular, issues of referral patterns (Julapalli et al, 2005, Eckhoff et al, 1997 & Eckhoff et al 1998), time to transplant (Klassen et al, 1998, Reid et al, 2004), risk of dying on the waiting list (Klassen et al, 1998, Reid et al, 2004, Freeman & Edwards, 2000, Freeman et al, 2004), clinical outcomes (Nair, Eustace, & Thuluvath, 2002; Yoo & Thuluvath, 2004; & Eckhoff et al, 1997) and survival statistics have all been considered in regard to access to liver transplantation in the literature reviewed.

The majority of research, despite being conducted following February 27, 2002, utilized data sets from the pre-MELD era, and therefore is not reflective of current practice.

The impact of race as a predisposing population characteristic explaining or predicting access to liver transplantation has three points of analysis: referral, wait list

and transplantation. The impact of this variable needs to be analyzed at all three of these time points.

Liver Transplant Referral and Race. Referral to transplant is much more difficult to measure than the other two time points. Unlike the nationally based End Stage Renal Disease Program that is funded through Medicare and requires all patients be offered renal transplantation as a treatment option, the epidemiology of liver disease is not well defined. The true incidence and prevalence of liver disease is difficult to ascertain because there are few, if any, population-based registers of liver disease available to ensure proper case identification (Steinke, Weston, Morris, MacDonald, & Dillon, 2002).

Julapalli and colleagues (2005) were the first to attempt to characterize patterns of referral for liver transplant evaluation in the United States. Using data from Era 3 (2002-2003) these researchers from a single center study of a large VA Medical Center performed a retrospective cross-sectional analysis using the American Association for the Study of Liver Disease (AASLD) liver transplant selection criteria as a guide to determine those individuals who met criteria for referral (Julapalli et al, 2005).

The primary outcome of interest was mention of liver transplant in the medical records of those patients identified with ICD-9 codes for liver disease that met AASLD selection criteria. Of 300 encounters involving 199 patients, 21 percent met referral criteria, and 20 percent were actually referred. In this particular study, black race was determined to be an independent negative predictor of referral with an 85 percent decrease in odds of mentioning transplantation when compared to whites (Julapalli et al, 2005).

Noteworthy in this particular VA patient population is that all military veterans are eligible for transplant services, should the etiology of their disease be determined to be service related, so in these cases, access due to ability to pay is not at issue. Despite this universal coverage model, there still appears to be disparity in the referral process, the first step in gaining access to liver transplantation.

Another single-center study by Eckhoff and colleagues (1998) analyzed referral times periods during Era 1 (1989-1996) and determined that blacks were referred at a more acutely ill phase of liver disease then those in other ethnic categories, indicating that a selection bias at the point of referral may be present (Eckhoff et al, 1998). Despite this potential selection bias, the rate of transplant, as well as survival rates were not different between blacks and whites (Eckhoff et al, 1997).

Both Julapalli (2005) and Eckhoff (1997 & 1998) found similar results during Allocation Eras 3 and 1, respectively. There appears to be disparity in referral of African Americans utilizing both a hospital VA system of data as well as another single center study. This difference in acuity measures utilized does not influence actual referral patterns but is noteworthy when designing future studies addressing patterns of referral. Of additional value to add to this body of knowledge would be a large multi-center study utilizing pre versus post MELD time periods to determine if the racial disparities identified in these single center studies persist within the current system of allocation and across a larger, national database.

Liver Transplant Waiting List & Race. White candidates currently comprise about 72 percent of the liver transplant waiting list, which is a decrease of about 5 percent over the past 10 years, while the prevalence of African Americans and Asian patients on

the wait list has remained relatively constant at 5 percent and 7 percent respectively. The number of Hispanics on the waiting list has tripled over the last ten years (Pomfret, Fryer, Sima, Lake, J.R., & Merion, 2007) and comprises 15 percent of the current waiting list (UNOS, 2008).

In a study of all wait-listed patients for a two-year time frame during Era 1 (1990-1992), Klassen and colleagues (1998) determined that Hispanic Americans as well as Asian Americans waited longer for liver transplants and Asian Americans and African Americans were more likely to die while waiting. However, Hispanics did not have an increased risk of mortality in this analysis (Klassen et al, 1998).

In a more recent study, involving a more current time-frame (1994-1997) during Era 1, Reid and colleagues (2004) utilized wait list data and US Census data to determine standardized wait list and transplant ratios between blacks and whites. These standardized ratios were obtained by comparing the racial distribution of liver transplant patients with the U.S. population. Blacks were found to be younger and sicker than whites when listed. The black wait-list ratio was 69 percent versus greater then 100 percent for whites, meaning that blacks were significantly under-represented on liver waiting lists when compared with the racial distribution of the general population (Reid et al, 2004). What are missing from this, and other studies reviewed, is the prevalence of liver disease in the general population by race. This analysis by Reid and colleagues (2004) presumed equal prevalence of liver disease among all races.

Reid and colleagues (2004) found, similar to Klassen and colleagues (1998) that blacks were statistically more likely to die or become too ill while waiting for transplant. Both groups had similar wait times, however, blacks were less likely to receive a

transplant within four years, probably given their greater likelihood of dying or getting sick and becoming ineligible for transplant during that time frame.

In contrast, the Institute of Medicine's Study of 1999 analyzing a similar time frame (1995-1999) in ERAS 1 and 2, found that there were no effects of race on transplantation or wait list mortality, once patients were listed. The IOM report did concur, however, that African Americans were referred at a more severe stage of their liver disease (Gibbons et al, 2003).

Gibbons (2004) describes the reasons for such disparate results. The IOM analysis took into account changing acuity levels whereas Reid et al (2004) studied acuity only at the time of initial wait listing. In addition, Gibbons described a much more involved statistical analysis employed by the IOM versus by Reid. (Gibbons et al, 2003 & Gibbons et al, 2004).

The third, and most compelling issue related to these differing results is the lack of equal geographical distribution of African Americans across the nation's 59 organ procurement areas (Gibbons, 2004). Some organ procurement organizations (OPO) serve predominantly white populations. Inter-racial variability exists among OPOs which can confound OPO to OPO variability. All of these issues make it difficult to determine if any racial disparity truly exists. Confounding this problem is the fact that blacks are more acutely ill at referral, and therefore may actually be at even a greater disadvantage (Gibbons, 2004).

Gibbons (2004) echoing the original IOM Report, calls for an expansion of organ procurement areas to serve a population base of greater than 9 million people in addition

to expanding to regional versus local areas. This is further discussed in the geography section dealing with enabling variables.

In the research study involving wait time and mortality by Freeman and Edwards (2000), African Americans were found to have a relative risk of wait list mortality of 1.59 times that of white, Asian or Hispanic persons. This study took place during Era 1 (1997) and was aimed at determining the association between center-specific waiting time and wait list mortality. The authors verified that waiting time was not related to risk of death on the waiting list. These results contributed to the adoption of the MELD acuity score (Era 3), replacing the acuity and time waiting system of Era 2 (Freeman & Edwards, 2000).

Conflicting results in regard to racial disparities and wait list access and mortality exist. Gibbons (2004) explains these disparities by the lack of change in MELD unaccounted for in Reid et al (2004) and possibly Klassen et al (1998) studies.

There have been no research studies undertaken to address the impact of race on rate of wait listing and liver transplantation among minority populations during the current Era 3. Such a study evaluating OPO-specific differences among the current (Era 3) allocation scheme should be undertaken. Consideration of changing acuity levels, termed MELD change scores (Merion et al, 2003) are necessary along with survival analyses that incorporate competing risks of both transplantation and death, as opposed to an analysis with only one or the other outcome being evaluated (Gibbons, 2004).

Liver Transplant Surgery & Race. A comparison of both Era 2 (2001-2002) and Era 3 (2002-2003) showed fewer listings for all ethnicities, a decrease in rates of death or removal due to being too ill for transplant for Hispanics and Asians and an increase in

transplant rates for Whites, Blacks and Asians within Era 3 (Freeman et al, 2004). In addition the median wait time for blacks was shortened and blacks were still younger and included more women than other ethnic groups.

Strengths of this study include linking of the UNOS database with the Social Security Death Registry as well as the comparison of Era 2 to Era 3 allowing for the evaluation of the current acuity system with an overall finding of increased organ access for more acutely ill patients in Era 3 versus Era 2 (Freeman et al, 2004).

In this first study analyzing the impact of Era 3 as it relates to access to transplantation, Freeman (2004) verifies that MELD is successful at decreasing mortality on the waiting list, one of the priorities outlined by the Final Rule and recommended by the IOM report of 1999.

Liver Transplant Outcomes & Race. The preponderance of research related to transplantation generally involves access to the waiting list and allocation of resources for liver transplant itself; however, in balancing equity with efficiency and utility, outcomes must be measured as well. Within the field of transplantation outcomes are generally measured in terms of both patient and graft survival. Outcomes in relation to race have been an issue of significant concern, but studied to only a limited degree.

Eckhoff and colleagues (1997) found that race was not a factor in patient and graft survival outcomes in a single center study using data from Era 1 (1989-1997). A follow-up study by Eckhoff and colleagues (1998) also in Era 1 (1989-1996) found that blacks were referred later and were sicker at the time of referral but transplant rates and survivals are the same.

More recently, Nair and colleagues (2002), using the UNOS national database for transplanted patients during Era 1 (1988-1996) found conflicting results. In this study, race was found to be an independent predictor of poor survival at 2 years post-transplant. However, this research did confirm that African Americans were found to be sicker at transplantation. African Americans were also found to have lower survivals than whites or Hispanics after liver transplantation. In addition African Americans were found to have a higher rate of chronic rejection than other races (Nair. Eustace, & Thuluvath, 2002).

Criticism of this study, acknowledged by the authors, was the fact that survivals were not adjusted for socioeconomic status as a confounding variable (Nair et al, 2002). In addressing this issue a follow-up study by Yoo and colleagues (2004) was undertaken across Eras 1 and 2 (1987-2001) to determine if post-transplant outcomes were based on neighborhood income, educational status or insurance (Yoo & Thuluvath, 2004).

Utilizing UNOS data from Eras 1 and 2, (1987-2001) as well as zip codes as a surrogate marker for median income, the authors found that African Americans had a five year lower survival than whites after adjusting for SES and other confounding variables, however, neighborhood income did not influence outcome and education had only a minimal effect on outcome. Of interest, however, is that patients with Medicare and Medicaid have a lower survival than those patients with private insurance (Yoo et al, 2004).

These five studies (Freeman et al, 2004; Eckhoff et al, 1997; Eckhoff et al, 1998; Nair et al, 2002 & Yoo et al, 2004) report slightly differing outcomes among race during three eras of allocation. Despite conflicting outcomes reported in Era 1 (Eckhoof et al,

1997; Eckhoof et al, 1998 & and Nair et al, 2002) and in comparison across Eras 1 and 2 (Yoo et al, 2004), of greatest significance is the current status of the impact of race on outcomes during Era 3. During the first year's experience in Era 3, Freeman et al (2004) found an increase in overall transplant rate, a decrease in wait time as a variable and hence an increase in organ accessibility for more ill patients. In addition there was a significant decrease in deaths and removals for becoming too ill for Hispanic, Asian-Americans and Blacks in this most current study.

Summary of Liver Transplantation and Race. With the exception of research teams let by Julapalli et al (2005) and Freeman et al (2004), all studies addressing race as a potential predisposing variable involved in providing or prohibiting access to liver transplant at any stage of the process were undertaken using data from previous eras of allocation. Although of historical value in understanding biases and/or problems with access for different racial groups, these results do not necessarily reflect current practice.

Julapali and colleagues (2005) used a large regional VA system to study referral patterns, the results of which cannot be generalized to more than other VA patients hospitalized for end stage liver disease. Freeman and colleagues (2004) used UNOS data from a year prior to and following implementation of the MELD system, to determine that there has been an increase in the rate of transplantation for whites, blacks and Asian Americans.

Five years of experience have accumulated in the current allocation system, Era 3. A more comprehensive analysis at referral, wait listing and transplant surgery is necessary to determine if disparities emerge at any one of these points of care. One has to wonder if African Americans might actually have somewhat of an advantage in this

new allocation scheme, since there is a greater amount of renal insufficiency in this population and the MELD scoring system favors renal impairment (Reid et al, 2004). This current study will address race as a predisposing variable that may contribute to the knowledge regarding access to liver transplantation.

GENDER

Seven research studies were found evaluating access to liver transplantation in regard to gender. Of theses seven research studies, three involved data and analysis during Era 1 (pre 1997), two compared data between Era 1 (pre 1997) and Era 2 (1998-2002) and one compared date between Era 2 (1998-2002) and Era 3 (post 2002).

No studies addressed gender and referral to liver transplantation. Three studies addressed the waiting list and access to liver transplant (Freeman et al, 2004; Klassen et al, 1998; and Reid et al, 2004). Four studies addressed access to transplantation at the surgical phase (Cholangitis et al, 2007; Freeman et al, 2004; Ozminkoski et al, 1993; Tuttle et al, 1997).

The Waiting List and Gender. The number of females on the waiting list has decreased from 44 percent to 40 percent since 1996, but death rate on the waiting list for females is less (119 deaths/1000patient years versus 130 deaths/1000 patient years) (Pomfret, Fryer, Sima, Lake, & Merion, 2007).

Klassen and colleagues (1998) reported that during Era 1 (1990-1992) women waited longer (89 versus 68 days) for a liver transplant with a 1.24 times greater risk of death while waiting. The authors suggest that this difference of 29 days may account for the increase in death rate among women. Subsequent to this study, Reid et al (2004)

reported that when comparing Era 1 to Era 2 (1994-1998) women still waited longer then men for transplantation but death on the waiting list was not reported.

However, during this same timeframe comparing Era 1 to Era 2 (1995- 1999) Gibbons et al (2003), reporting on the IOM study, showed that there was no significant effect of gender found and that the system showed equitable distribution for women listed for transplantation. As has been noted before, the IOM report used a change in acuity levels when analyzing the results as opposed to Reid and colleagues (2004) who used acuity at time of listing which may account for these differences (Gibbons, 2004). It is unclear what data source Klassen (1998) used in analysis, so understanding the difference between these results and that of the IOM report is difficult to ascertain.

Liver Transplant Surgery and Gender. In a study utilizing the Hospital Cost and Utilization Project (HCUP) Database, Ozminkowski and colleagues (1993) reported that women were 1.52 times more likely to be transplanted during Era 1 (1986-1987). During a similar time frame in Era 1 (1988-93) Tuttle and colleagues (1997) found similar results in the State of North Carolina study. Despite a higher incidence of admissions for liver disease in males during this timeframe, woman had a 33 percent higher rate of transplantation than males. The authors attribute this result to males having a greater likelihood of liver disease secondary to alcoholism, which was negatively associated with access to liver transplantation.

Subsequent to these studies, Freeman et al (2004) reported a comparison of Era 2 to Era 3 (2001-2003) and found fewer registrations overall and a statistically significant increase in the transplant rate for males. This result reflects the initial year of experience with ERA 3 MELD scoring system.

Perhaps most informative regarding the impact of gender on access to transplantation is the study by Cholangitis and colleagues (2007) utilizing the MELD score as a means by which to determine acuity. Timing of the data collection is not explicitly stated, although it is assumed to be Era 3 since this is the era in which MELD is utilized and the entire study focuses on the variable, creatinine, which is incorporated into the MELD equation.

Durand and Valva (2005) point out that there is a problem with MELD's creatinine measurement in that an elevated level may not always indicate worsening renal function. An individual with a higher body mass index will, by virtue of their size, have a higher creatinine, and subsequently, a higher MELD score. Given that men generally have a larger body mass index then women, males may actually have an advantageously higher MELD scores due to their body size and not necessarily due to their acuity of illness. In these instances the MELD score does not reflect the measurement of acuity for which it was intended.

The study by Cholangitis and colleagues (2007) performed in a single center in England addressed this issue raised by Durand and Valva (2005). They found that women with liver disease had worse renal function, determined by measured glomerular filtration rate (GFR), then men with the same creatinine. Given that creatinine is the measurement of renal function utilized within the MELD score, this study uncovered a systematic bias against women. The authors recommend an addition of 3 points to every woman's MELD score that is >19, the point at which the disparity is present. This proposed adjustment of 3 points would be an attempt to adjust for this identified bias (Cholangitis et al, 2007).

Liver Transplant Outcome and Gender. There are no studies analyzing liver transplant outcomes in relation to gender. However, Sanfrey (2005) reviewed gender specific issues in regard to liver and kidney transplant mostly focusing on immunological differences and hormonal influences between donors and recipients, topics beyond the scope of this review.

Summary of Liver Transplantation and Gender. Access to liver transplant by gender has shown inconsistent results both prior to and following implementation of the current allocation system (Era 3). Historically using date from Era 1, there is dispute in the literature regarding the existence of gender inequity with IOM data (Gibbons et al, 2003) indicating there was no gender inequity and others maintaining a longer wait time for women (Klassen et al, 1998), greater numbers of death on the waiting list for women (Klassen et al, 1998), and yet a higher rate of transplantation among women (Tuttle et al, 1997).

In the current system however, it is not disputed that the number of females wait-listed for transplant has decreased from 44 to 40 percent (Pomfret et al, 2007) and that given the newly instituted MELD scoring system there is a systematic bias due to creatinine measurement (Cholangitis et al, 2007).

Further research replicating the single-center study in England by Cholangitis et al (2007) should be undertaken with a larger population as a multi-center study in the U.S. to determine if this bias is maintained. In addition, modeling the proposal to increase the MELD score by 3 points for every woman with a total MELD > 19 should be employed to determine the impact such a policy would have.

AGE

Age distribution for those individuals on the liver transplant waiting list has changed dramatically since 1996. In 1996 there was an equal distribution of individuals in age categories 18-49 and 50+ years. Currently, 60 percent of those listed for transplant are in the 50 - 64 age category. Pomfret and colleagues (2007) suggest that this demographic shift most likely represents the aging U.S. demographics. Of the seven studies regarding age reviewed, four used and analyzed data from ERA 1, two used and analyzed data comparing Eras 2 and 3 and one used and analyzed data from ERA 3.

Referral and Age. Julapalli and colleagues (2005) determined that older age was a statistically significantly negative determinant of liver transplant referral with a 69 percent decrease in odds of referral for every increase in 10 years of age. Although performed at a single large VA center and only generalizable to a similar sample, this is the only study addressing age and referral to liver transplantation during Era 3 (2002-2003) in the literature.

Wait List and Age. In a study undertaken by Klassen et al (1998) in Era 1 (1990-1992) there was a statistically significant risk of dying while waiting for transplant as one's age increased. Concurring with these results were Freeman and colleagues (2000) who also undertook a study of data from Era 1 (1997) that reported a relative risk of wait list mortality increasing with age. In addition, in a comparison of Eras 1 and 2, Reid and colleagues (2004) found that younger patients not only had a statistically significant shorter waiting time to transplant but the likelihood of death or being removed from the waiting list due to becoming too sick was increased by 1.5 times for each decade of life.

In another study undertaken comparing Era 2 to Era 3 (2001-2003) Freeman and colleagues (2004) found that there was a decrease in rates of removal for all ages due to becoming too sick or dying prior to transplant. This result reflects an increase in transplanting those individuals with higher acuity levels, one of the primary aims of the most current allocation scheme.

Liver Transplant Surgery and Age. Tuttle et al (1997) found that in Era 1(1988-1993) there was an increase in liver disease after age 25 and a decrease after age 65 which concurs with the rate of liver transplant that is highest in the very young, and decreased significantly with those over 65 years old. Given the currently much greater incidence of Hepatitis C in the general population, particularly the older population, these findings may not hold true in Era 3. This issue has yet to be studied.

Ozminkoski et al (1993), also studying Era 1 (1986-1987), found that those patients less than 20 years old were 4 times more likely to receive a transplant than those greater than 20 years old. In addition, individuals between 60-65 years of age were 4 percent less likely to get transplanted than others listed. Studies reporting data from Era 3 concerning age could not be found in the literature.

Summary regarding Transplantation and Age. As the population ages, demanding access to more sophisticated treatment therapies for life-saving procedures, it is no surprise that liver transplant would be among those treatments sought after. Keswani, Ahmed and Keefe (2004) recognized that the immune system is significantly less robust as one ages and therefore prevalence of organ rejection may, in fact, be lower among older transplant recipients, perhaps making an older patient a more efficient choice as a recipient. Paradoxically, older adults may be more prone to other post-

transplant complications such as malignancy and cardiovascular disease that may make them a poor choice in regard to long-term outcomes.

In terms of quality and quantity of life after transplant, younger patients may benefit from a longer lifespan and ability to return to work. However, quality of life needs to be addressed in both younger and older age groups. In an effort to fulfill mandates of justice, equity and efficiency all data needs to be considered in policy development.

As the population of end stage liver disease patients age, issues of allocation between young and old will only become more pronounced. Further attention to outcomes in the transplant population, particularly those over age 60 years will be important to research. What complicates the ability to accurately access these outcomes are the donor livers utilized for the older population. Often the organs chosen are older and even higher risk then those placed in younger recipients, making outcome comparisons difficult. Continued assessment of outcomes will be necessary to contribute to the allocation debate in regard to equitable distribution of livers for transplant, particularly since the inception of MELD and Era 3.

Characteristics of Population at Risk: Enabling Variables

EDUCATION

Access to liver transplantation in regard to educational level has been studied in regard to the impact educational level plays on socio-economic status (SES) as it relates to outcomes (Yoo et al, 2004) and the impact educational level has on multiple listing (Merion et al, 2004).

In a follow-up to Nair et al (2002), that found race to be an independent predictor of outcomes, Yoo and colleagues (2004) looked at post-transplant outcomes in a database collected during Eras 1 & 2 (1987-2001). The study looked at the impact of race by adjusting for educational level, neighborhood income and insurance. In this particular study, educational level was found to have only a minimal effect on outcomes (survival).

Merion and colleagues (2004) studied the impact of dual-listing which is the practice of listing at more than one transplant center. In this study, also performed on data from Eras 1 & 2 (1997-2000), it was found that 3.3 percent of liver candidates were multiple listed and lower educational levels were associated with significantly lower odds of multiple-listing. This will be discussed further in geography, however, important in regard to the predisposing variable of education, it appears as though candidates with a college level education or higher have 1.55 times greater odds of multiple listing than those with less than a college education.

Of significance in regard to access to liver transplant is the fact that the transplant rate for multiple-listed candidates is 195 percent higher than patients who are listed at only one center, a statistically significant finding. Although multiple-listing only accounts for 3.3 percent of all listed liver transplant candidates, this practice constitutes access to significant disparity in allocation (Merion et al, 2004).

ABILITY TO PAY

Four research studies have analyzed ability to pay and access to liver transplantation, two within Era 1, one looking at data across Eras 1 & 2, and one international study in which the U.S. Era is not relevant.

Tuttle and colleagues (1997) looked at access to liver transplant during Era 1 (1988-1993) at the time of surgery and showed that ability to pay had the strongest predictive power of the likelihood of receiving a transplant. Ozminkowski et al (1993), also during Era 1 (1986 – 1987) found the same results, with those most able to pay being 1.7 times more likely to receive a liver transplant (Ozminkowski et al, 1993). In this study insurance coverage was used as a proxy for ability to pay (Ozminkowski et al, 1993).

In regard to income affecting transplant outcomes, Yoo and colleagues (2004) in the study previously described, used zip codes as a surrogate marker of median income to determine if ability to pay impacted survivals following surgery. Findings indicated that neighborhood income did not influence outcomes, however, there was a decrease in survival for patients with Medicare and Medicaid as opposed to those with private insurance (Yoo et al, 2004).

In the study by Merion et al (2004) involving multiple-listing during Era 2 (1997-2000), it is not surprising that those with private insurance were more likely to multiple-list than those with Medicare and significantly more likely to multiple-list than those patients with Medicaid. It is inferred that those with private health insurance have a greater ability to pay than those patients with Medicare alone and/or Medicare and Medicaid.

Although an international study, McCormick and colleagues (2004) looked at liver transplant candidates in Ireland from 2000 to 2002. Of particular concern in this study was the issue of disparities with a two-tiered health care system of public and private health insurance. The findings suggest that even in a nationally based system of

health care coverage for all, candidates with additional private insurance are more likely to receive a transplant than those with only public insurance (McCormick, O'Rourke, Carey, & Laffoy, 2004). Of interest in regard to the system of allocation currently being utilized in the U.S. would be an analysis of whether there was a similar effect of private versus public funds and access to liver transplantation in the current era of allocation, an issue to be addressed in this study.

There have been no studies during the current allocation Era 3 that address the enabling variables of ability to pay or insurance coverage. Limitations to the ability to perform such research involve the lack of an integrated database linking clinical transplant data with administrative claims data. Gilmore and colleagues (2007) reported in a current study just such a linkage between the OPTN database with payer data from a large data warehouse called Health Benchmarks for the years 1995 to 2004. Future research using this linked data system will most certainly be useful in evaluating both the economic and clinical outcomes of liver transplant, particularly as this relates to access to care.

Summary of Liver Transplantation and Ability to Pay. Historically, ability to pay as measured by income or insurance coverage has been shown to be a significant enabling factor in determining access to liver transplantation. Initially, during Era 1, ability to pay was determined to be a positive predictor of transplant (Tuttle et al, 1997 & Ozminkowski et al, 1993). Era 2 showed divergent results. Median income by zip code, when utilized as a surrogate for ability to pay, was found not to be an enabling factor in providing access to care (Yoo et al, 2004). However, ability to multiple-list and the

association with this and carrying private health insurance was shown to be a significant predictor of access to care during this same time period (Merion et al, 2004).

This issue of multiple listing may have an element of "knowing the system" (Anderson, 1995) that contributes as an enabling factor in gaining access to liver transplantation as much as the issue of ability to pay. Not all patients are made aware of the potential advantages of multiple listing such as shortened waiting time and increased likelihood of transplantation (Merion et al, 2004).

Proponents of multiple listing argue that all patients should be made aware of the option to multiple list as well as detailed information regarding waiting times at various transplant centers throughout the country so that an educated decision regarding multiple listing can be made. Opponents argue that multiple listing produces an unfair advantage in terms of access and should not be encouraged or allowed (Merion et al, 2004).

Even in a country with universal coverage, more speedy access to liver transplant was found among those whose public insurance was supplemented with private insurance (McCormick et al, 2004). It will be important to study whether or not the impact of "know how" regarding multiple listing as well as the ability to pay for transplant continues to play a role in enabling access to liver transplantation during Era 3 of the organ allocation system, since acuity is presumed to be the driver of access. This will be further discussed in the need variables section of the paper.

GEOGRAPHY

Another variable that influences an individual's access to liver transplantation is geography or where someone lives. In the Anderson Model (1995) this would be an

enabling characteristic based on the way the system of organ allocation and distribution has been set up.

Historically, there was a significant limit to the number of hours from the time of procurement to transplantation of a donor liver. This is called cold ischemic time (CIT) and was originally limited to 8 to 12 hours. This limit in CIT required an organ to be recovered and transplanted within this time frame, thus limiting the distance that could be traveled for recovery. Based on these geographical limitations and other political influence, a system of allocation was developed that remains essentially the same today, decades after its inception.

As described in Chapter 1, the country is divided into 11 UNOS regions with varying numbers of organ procurement organizations (OPOs) within each UNOS region. Each OPO serves from 1 to 8 transplant centers. The population served by each OPO varies significantly. This factor, in addition to the size of the waiting list, the acuity of the patients waiting, the number of donors in an area and the ability to procure organs all contribute to access to transplantation. Given this system design, significant disparity has existed between rates of transplantation throughout the country.

Analysis of data from Era 1 (1994-1996) was undertaken by Congressional mandate in 1998 to address the geographical disparities in allocation of livers in the United States. This resulted in issuance of the "Final Rule," discussed in much greater detail in Chapter 1. In brief, the "Final Rule" called for a more equitable distribution of livers based on acuity rather than time waiting and much less emphasis on keeping organs within local procurement areas. Strong opposition, within the transplant community, to the second of these federal mandates resulted in a request that the Institute of Medicine

(IOM) review the impact of the Final Rule.

The IOM made a recommendation to establish uniform Organ Allocation Areas (OAAs), each serving a population of at least 9 million people in an attempt to equalize the number of patients each area would serve. This recommendation has never been adopted. The original eleven historically drawn regions remain with organ procurement organizations serving variable-sized populations, despite the fact that CIT has increased to 20 hours, essentially allowing travel distances spanning the country.

In order to frame the current debate regarding the geographical inequities that continue to exist, an analysis of data from the IOM report as well as subsequent studies, some utilizing computer simulated modeling will be reviewed.

Reporting on the IOM study (1999) analyzing over 33,000 records of wait list and transplant patients between 1995-1998 (Era 1) findings included a similar wait time for the most acutely ill patient but statistically significant differences in wait time for non-acutely ill patients. In addition, smaller OPOs (those serving 4 million patients or less) had a significantly larger number of transplants than those larger OPOs (serving over 9 million patients). Because of this finding the IOM recommended 9 million as a standard for patients served per OPO (Gibbons, Meltzer, & Duan, 2000; Gibbons et al, 2003).

Other recommendations included greater governmental oversight and development of an acuity based system of allocation doing away with wait time as a variable. Of these three recommendation, an acuity based system of allocation, (MELD), was adopted (Gibbons, Meltzer, & Duan, 2000; Gibbons et al, 2003).

As a follow-up to this study, the same committee studied 9,585 new listings from 1998 (Gibbons, Duan, & Meltzer, 2000). Of these new listings the excess number of less

severely ill patients that were transplanted in smaller OPOs (< 9 million) were compared to those transplanted in larger OPOs (> 9 million). Findings indicated that 298 additional patients were transplanted at a lower acuity level in smaller OPOs. The committee concluded that if broader sharing of organs were implemented, as many as 298 of the most urgently needy patients would have been transplanted. This was the first of what would become many simulation models, designed to illustrate what impact a change in the allocation system might have (Gibbons, Duan, & Meltzer, 2000).

In an effort to determine an optimal configuration of regions by a methodological approach Stahl and colleagues (2005) analyzed data from Eras 1 & 2 (1993-2000). Using an integer-program, by constraining the regions to the current number of 11, it was found that 17 additional organs could be transplanted. If the number of regions were not constrained, an additional 19 organs could be transplanted. The main purpose of this study was to establish methods and principles to develop models for future allocation schemes (Stahl, Kong, Shechter, Schaefer, & Roberts, 2005).

Ellison and colleagues (2003) analyzing data from Era 2 (1998 – 2000) used another computer-simulated model (CSM) to determine if redrawing lines of organ distribution could reduce geographical disparities. By extending the Kaplan Meier method to a competing risks model it was found that these disparities could be reduced, but not eliminated (Ellison, Edwards, Edwards, & Barker, 2003).

Following the implementation of the MELD acuity system Schaffer et al (2003) studied whether MELD insured equitable distribution within a single UNOS study region during Era 3 (2/2002 – 11/2002). Findings indicated that although MELD predicted and allocated organs to more acutely ill patients, there remained significant disparity among

centers in selection and allocation of organs, suggesting the need for a much more transparent system of regional sharing (Schaffer, Kulkarni, Harper, Millis, & Cronin, 2003).

During a similar time-frame Trotter & Osgood (2004) looked at the difference in MELD scores across different size OPOs (Era 3: 2/28/02 -3/31/03) and found that MELD scores were much higher among patients transplanted in larger OPOs versus patients transplanted in smaller OPOs, indicating that patients are transplanted at much lower acuity levels within smaller sized OPOs. Of concern in regard to this finding is the ability of those with financial means to dual list or move to an OPO of a smaller size, improving their chances of being transplanted when less acutely ill (Trotter & Osgood, 2004).

Roberts et al (2006) utilizing data from Era 3 (4/02 -4/03) employed a computer simulated model (LSAM) to determine the projected effect of a national policy of acuity of MELD > or = 15. This study looked at the current 11 UNOS Regions with 50 Donor Service Areas that serve 1-8 transplant centers each. Through this simulation a change in allocation to prioritize patients with a MELD > or = 15 was projected to decrease variability of MELD at the time of transplant (Roberts, Dykstra, Goodrich, Rush, Merion, & Port, 2006).

Similarly, Freeman et al (2002) used a specifically developed computer simulated model called ULAM to produce hypothetical distributions to determine the effect of enlarging liver distribution boundaries. None of the results of these described computer simulated models have been adopted in terms of a change in the allocation system. Significant disagreement exists within the transplant community regarding the issue of

changing the established allocation system (Freeman, Harper, & Edwards, 2002).

Summary of Geographical Disparities in regard to Transplant

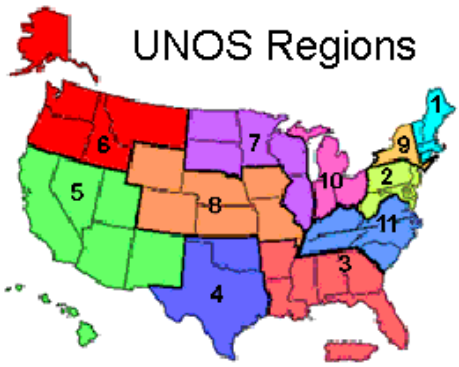


Figure 3.1: 11 UNOS Regions

As previously described in Chapter 2, over twenty years ago, a system of organ allocation and distribution was adopted in the United States based on geographical distribution within 11 UNOS Regions (Figure 3.1). Each region continues to be served by variable numbers of regional OPOs and each OPO serves 1-8 transplant centers. Organs identified for transplant purposes are offered locally first, then regionally and then nationally, based on the MELD acuity system of Era 3, previously described. This geographical allocation scheme was designed to meet four objectives: to decrease organ preservation time, improve organ quality and survival outcomes, reduce cost and improve access (Roberts et al, 2006).

The UNOS Regional system of allocation can be likened to U.S. Congressional districts, however, unlike UNOS Regions; Congressional re-districting occurs every 10 years based on population census reports. The UNOS organ allocation system, despite the adoption of an acuity-based model (MELD) in 2002, remains virtually unchanged since its adoption in 1984.

UNOS continues to serve the same 11 regions despite an increase in the number

of patients awaiting transplantation as well as an increase in liver transplant programs. The distribution of this increase in population of waiting patients has not followed any formal pattern and the ability to multiple-list or move to another area of the country to receive an organ further complicates equitable access to transplantation.

Improvements in organ preservation allowing for increased cold ischemia time (CIT), continued geographical inequities and recommendations by the IOM to address these geographical inequities have not resulted in any change in geographical distribution of livers for transplantation. This issue of geographical inequity may, in fact, be the proverbial elephant in the room, everyone recognizing its presence, but no one willing to do anything about it.

Studies reviewed confirm the original IOM report (Gibbons, Meltzer, & Duan, 2000; Gibbons et al, 2003) indicating that geographical inequities exist (Trotter & Osgood, 2004; Schaffer et al, 2003; Freeman et al, 2002; and Ellison et al, 2003). Current research suggests that the current allocation scheme may actually be providing a barrier for access to liver transplantation, especially for those individuals listed at large transplant centers (Roberts et al, 2006).

The emerging technology of computer simulation will allow us to further study geographical differences as an outcome, allowing us to better understand those factors that contribute to these geographical differences with the intent of influencing policy. Prior to further prediction through simulation modeling, a more current analysis of the impact of geographical inequities is necessary and undertaken in this study to address the context of Era 3's acuity based system and whether geographical inequities continue to exist.

Characteristics of Population at Risk: Need Variables

MELD

The Model for End Stage Liver Disease (MELD) was originally created to predict survival after transjugular intrahepatic portosystemic shunts (TIPS) but was adopted by UNOS in 2002 to prioritize the allocation of liver grafts. The model uses serum creatinine, total serum bilirubin, International Normalized Ratio (INR) for prothrombin time and etiology of cirrhosis to predict survival. Originally tested in a heterogeneous population of patients in the US undergoing TIPS for cirrhosis, the model was also analyzed with an independent data set from the Netherlands (Malinchoc et al, 2000).

The intent of the MELD score is assign a numerical value to the patient's acuity level with the goal of transplanting the most acutely ill patient under the assumption that this measure is the most objective measure of need within the population of liver failure patients.

Freeman et al. (2004) compared data pre and post MELD to determine how the application of the new severity index for allocation performed. They found a 12 percent decrease in total number of newly listed patients, probably due to the loss of advantage for patients to accumulate waiting time and thus a decrease in early referrals and subsequent listing for transplant. There was also a 3.5 percent reduction in mortality on the waiting list, likely because of the shift to transplant more acutely ill patients. There was no change in post-transplant survivals, probably related to those factors not addressed in the pre-transplant severity model such as donor age, organ condition etc. There was also a three-fold increase in transplantation for hepatoceullular carcinoma (HCC), probably due to the added priority points afforded HCC patients over and above

their MELD score (Freeman, 2004).

Other researchers have looked at additional variables that may add value to the MELD score including change in MELD measurement. In addition, research on the physiologic measurements of sodium, creatinine clearance and alpha feto-protein have been undertaken.

Liver Transplantation and Sodium Researchers at a single transplant center have studied the impact of serum sodium (Na) in predicting mortality among end stage liver disease patients in an effort to determine if inclusion of Na into the acuity based MELD model would improve its predictive ability and hence provide an improved acuity based allocation scheme (Biggins et al, 2005).

In a follow-up prospective multi-center trial, research involving the addition of serum sodium (Na) to the MELD score as a predictor of mortality in patients in end stage liver disease was undertaken with the aim of modeling inclusion of Na into the MELD score (Biggins et al, 2006).

Model developments including using serum Na as a continuous variable yielded better models than dichotomized Na (normonatremic and non-normonatremic). Once the Na variable was defined, the survival model was refit for the MELD variables with a final model named MELD-Na that is calculated using the formula: MELD-Na = MELD +1.59 (135-Na). This formula included minimum and maximum values for Na (Biggins et al, 2006).

Although tested in a small sample population, this new MELD-Na was shown to favor 27 percent of patients in this study, meaning that MELD-Na provided a higher numerical acuity value than MELD alone, therefore changing allocation for this cohort of

patients. This study requires validation and final model detail analysis through UNOS collected date, however, this first step in developing a practical guide to incorporate other potential variables into the MELD calculation is a valuable contribution to the continued optimization of the allocation model (Biggins et al, 2006).

Liver Transplantation and serum creatinine Issues regarding disparity in creatinine measurement have been reviewed with respect to gender disparities previously discussed (Cholangitis et al, 2007). This research was performed in a single center study in England. Others have alluded to the advantage an increased creatinine plays in the MELD calculation. In particular, the impact of creatinine measurement on the MELD score has contributed to an increase in the number of patients transplanted with kidney and liver disease (Gonwa et al 2006).

A more comprehensive analysis utilizing the UNOS database should be undertaken to determine the extent of the influence of creatinine and whether this impact potentiates further disparities within the allocation system. If such disparities are confirmed, another analysis should be performed to see if such disparities could be ameliorated by additional MELD points being added to those potentially disadvantaged patients (i.e.: female gender).

Liver Transplantation and Alpha-Fetoprotein Patients awaiting liver transplant with elevated serum alpha-fetoprotein (AFP) levels in the absence of radiologically confirmed hepatic tumors are given priority in the current liver allocation system. This has been accomplished through the award of extra points added onto the candidate's MELD score. In an attempt to determine if this increase in AFP correlated with the actual presence of a hepatic mass, researchers analyzed data from all patients in the

UNOS data base who were awarded extra points from 2/2002 to 3/2005 (Kemmer et al, 2006).

Hepatic tumors can be identified after the transplant surgery through pathologic testing of the ex-planted liver (diseased liver that is replaced during transplant surgery) upon its removal. Presence of hepatic tumors were confirmed in only 26 percent of those patients receiving extra points for elevated AFP levels, indicating that these extra points may have been unwarranted. The authors maintain that this poor correlation may call for a change in this policy of awarding extra points to those liver patients with elevated AFP levels. (Kemmer et al, 2006).

Liver Transplantation and Change in MELD scores When comparing results of studies involving the Era 3 allocation scheme, differences in outcome have been attributed to data analysis utilizing one-time MELD measurement at time of listing versus changing MELD scores through the wait list time period (Gibbons, 2000 and 2004). This begs the question of whether change in MELD is a more accurate measurement of acuity. Research has begun on this topic (Merion et al, 2003), but clearly needs to continue as the current allocation schemes continue to be evaluated. Kamath and Kim (2003) suggest that change in MELD may further insure that the benefits of liver transplantation will be maximized.

Analysis of MELD change will certainly be more statistically challenging and changes in MELD must also be verified to be reflective of increase acuity versus a pre-terminal event (Kamath & Kim, 2003). Should a MELD change measurement be modeled to determine usefulness and accuracy, significant effort would be required to collect, report, and calculate multiple values creating a more complicated data collection

and reporting structure requiring oversight. However, such a system may prove a more equitable way to allocate livers.

Summary of MELD as a Need Variable in Liver Allocation. Anderson (1995) describes evaluated need as the variable that reflects a professional measure and evaluation that can be quantified. The development of MELD was intended expressly for the purpose of allocating the limited supply of livers to the sickest patients listed. Since adoption as the acuity measure, several researchers have continued to evaluate its effectiveness and have even researched other variables that may strengthen MELD's predictive ability.

Further research, continued analysis of the current MELD acuity measure and study of the impact MELD has had on those previously described predisposing and enabling variables will be important. It is the responsibility of the transplant field to continue to evaluate and improve upon the liver allocation system in order to insure the most equitable system possible.

Wang and Saab (2004) point out that quality of life are not addressed in the current allocation scheme used. Although beyond the scope of this review, this issue bears mentioning as it is imperative that evaluation of quality of life be considered when considering the risks and resource allocation expended during the liver transplantation process. Despite the advantages and disadvantages of the current allocation system, issues regarding quality of life have not been analyzed in a thorough manner.

Summary and Conclusion

The intent of this chapter was to provide a thorough literature review in regard to those variables that Anderson describes as predisposing, enabling and need variables that contribute to access to care from both a predictive and explanatory perspective (Anderson, 1995).

Specific focus on the predisposing variables of race found the need for a comprehensive analysis of access to referral, the waiting list and transplant in regard to race during Era 3. Questions remain regarding the impact MELD has had with respect to African Americans, since their prevalence of renal insufficiency is greater than other races.

The literature review focus on gender called for a replication of the study by Cholangitis et al (2007) within the U.S. population to determine if MELD produces the same systematic bias against women due to the issue of serum creatinine as a measure of renal function found in the single-center in England. In addition, modeling the proposed extra 3 points for every female with a MELD score >19 would yield valuable information as well.

Given the increase in age in the current population, study regarding age and access, utilization and outcomes must be evaluated for Era 3 with donor source being taken into account as well. In addition, work regarding multiple listing in regard to educational level should be undertaken to determine if disparities exists either through this SES indicator or because of a lack of "know-how" in regard to the system.

Utilization of the new link between administrative claims data and the UNOS data base as described by Gilmore et al (2007) may prove to further clarify ability to pay and

the impact this enabling factor has on access to liver transplantation. Geographical disparities should be further studied using data from Era 3 with particular attention to further simulation modeling in order to address the original IOM mandates and the impacts these would have if implemented.

Attention spent on the need variable MELD found that this measurement appeared to decrease unnecessary additions to the waiting list and provide improved access for those more acutely ill. However, there may be additional physiologic measures that could improve upon its effectiveness.

Missing from the literature is an analysis of the impact of Era 3's allocation scheme on access using the UNOS database for this current time period. What is currently known is that the waiting list is stable, more acutely ill patients are being transplanted, and there continue to be geographical disparities in organ distribution in the United States.

There is limited data regarding the current status (Era 3) of the impact of race, gender, age, education, geography or ability to pay on access to liver transplantation. Decisions regarding improving access must be based on the current allocation Era, not data analysis on previous eras of allocation. In accessing the extensive UNOS database, this research study analyzed the impact that race, gender, education, geography, and ability to pay and MELD have on access to liver transplantation, defined as time of transplant.

Chapter 4

Research Design & Methods

Liver transplantation is the treatment of choice for those individuals found to be in End Stage Liver Failure. The incidence of liver transplantation in the United States has grown more significant over the past ten years from 15.39 to 21.73 per million population, or greater than 6,000 liver transplants annually for the past several years (OPTN/UNOS database, accessed October 12, 2007). However, the number of individuals who continue to wait for a liver transplant is almost three times those fortunate enough to receive one in any given year. The limiting factor in providing this therapeutic treatment to more individuals is the availability of organs for transplant purposes. Despite the significant efforts to increase donors previously described, only minimal increases in organ supply have resulted over the past decade. Given that demand far outstrips supply of livers for transplant purposes, the issue of access to liver transplant through allocation of this scarce resource continues to dominate the field of transplantation and is a source of scrutiny by the public, the media and ethicists alike. The issue of concern is not only who receives this limited resource, but what characteristics or variables, other then acuity of illness, provide greater access to care?

This study is designed to examine access to liver transplantation by comparing those individuals who receive cadaveric transplants to those who do not receive an organ. A national database of transplant candidates and recipients offers the opportunity to examine the factors related to time to liver transplant in regard to age, race, gender, ethnicity, socioeconomic status, geography, height, weight, blood type and diagnosis, as

well as acuity levels of illness as defined by the Model for End Stage Liver Disease (MELD). Toward this end this dissertation poses three specific aims.

Research Aim #1:

Describe those who have received a liver transplant between 2002 and 2007 compared with those that continue to wait for a transplant during this same time period.

Research Aim #2:

Determine how the implementation of the Share 15 Rule in January 2005 impacted time to transplantation for MELD acuity levels > or = 15.

Research Aim #3:

Examine the factors associated with time to liver transplant including those predisposing, enabling, need (acuity of illness measured by MELD) variables and geography while controlling for time period both before and after implementation of the Share 15 Rule. Examine these factors across 11 geographical UNOS regions as well.

Hypotheses

The following directional hypotheses will be evaluated in this study:

Ho_1: Higher rates of liver transplant will be associated with younger age, male gender, white race, higher income, higher levels of education, private insurance, and heavier weight, and taller size, while controlling for acuity.

Ho_2: There will be differences in rates of transplantation among 11 geographical UNOS regions. Specific variables contribute to these differences for each geographical region.

$H_{O3:}$ The likelihood of being transplanted at a MELD > or = 15 will increase in all 11 UNOS regions after the implementation of the MELD 15 Share rule in 1/2005 when compared to pre-MELD 15 Share implementation.

$H_{O4:}$ There will be disparity across racial, gender and socioeconomic lines in regard to access to liver transplantation among the 11 geographical UNOS regions.

Background

Liver Transplantation is a successful treatment modality for individuals in end state liver failure. There have been more than 86,000 liver transplants performed in the United States since 1988 (UNOS, 2007), about 90 percent of which have come from cadaveric donors. As of November 2007, greater than 16,000 candidates await liver transplant. Almost 15 percent or 2400 of these candidates will become too ill or die waiting for an organ and approximately 38 percent or 6500 will actually receive a transplant, after waiting from one to five years for the procedure. Annually, about 10,000 additional patients will be added to the waiting list and unless an increase in donors or other medical therapy is discovered to treat these individuals, close to 60 percent of those in medical need will go without a liver transplant, a death sentence for these patients.

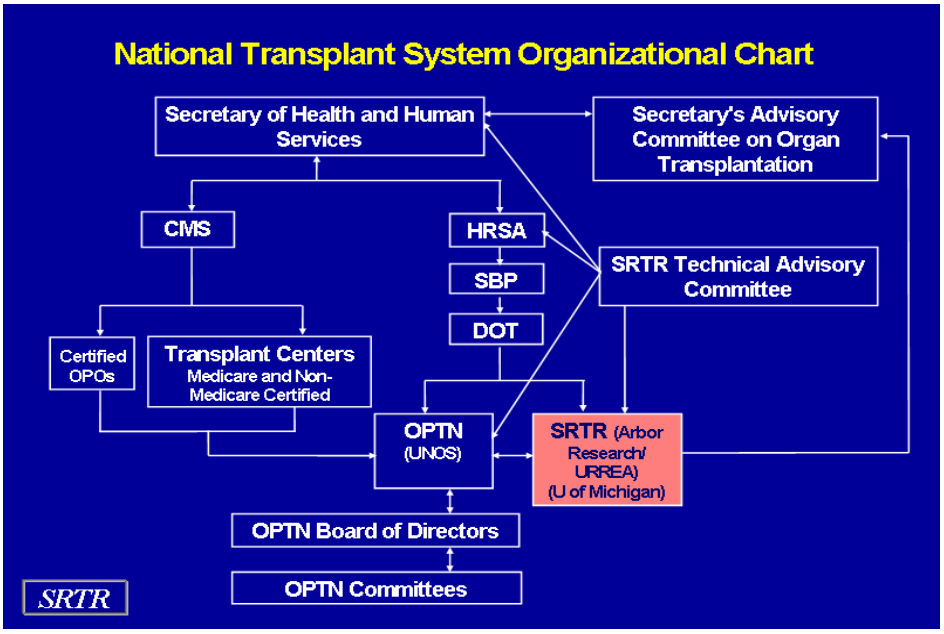
Early recognition of this imbalance in supply and demand, particularly in relation to the primarily Medicare-funded kidney transplantation, led to the development of federal legislation by means of the National Transplant Act of 1984. This mandated the establishment of an organ matching and procurement network for the development and maintenance of an equitable system for the allocation and distribution of all cadaveric organs. The system is known as the Organ Procurement and Transplantation Network

(OPTN) which is managed through federal contract by United Network for Organ Sharing (UNOS). In addition, the Scientific Research Transplant Registry (SRTR) was established as the primary database of candidate and recipient information. This is the database to be utilized in this study and described further in the Sample Section.

Organ Allocation System

Figure 4.1 below illustrates the complex nature of the systems involved in managing to organ distribution and allocation within the transplant field. Of importance in the oversight by Department of Health and Human Services as well as the continued involvement of the Centers for Medicare Reimbursement (CMS) in the allocation of all organs.

Figure 4.1
Transplant System
Organizational Chart



The Health Resources and Services Administration's (HRSA) Division of Transplantation administers and oversees two contracts to facilitate the nation's allocation

system for organ transplantation. The Organ Procurement Transplant Network (OPTN), contracted by the United Network for Organ Sharing (UNOS), is responsible for operating the national network for organ procurement and allocation, and works to promote organ donation. The Scientific Registry of Transplant Recipients (SRTR), contracted by the Arbor Research Collaborative for Health, provides analytical support for the ongoing evaluation of scientific and clinical status of solid organ transplantation. HRSA's Division of Transplantation (DOT) oversees both of these activities.

Despite the complex system of oversight involved in allocation of solid organs, inequity may continue to exist in terms of age, race, gender, educational level, payer status, ethnicity and geography. Over the years, research in the field of access to liver transplantation has focused on acuity of illness measures, organ distribution areas and disparities that are encountered based on potential systematic bias (Ahmad, Bryce, Cacciarelli & Roberts, 2007; Cholangitis et al, 2007; Ellison, Edwards, Edwards & Barker, 2003; Eckhoff et al, 1998; Freeman & Edwards, 2000; Freeman, Harper & Edwards, 2002; Gibbons, 2004; Gibbons, et al, 2003; Gibbons, Meltzer, & Duan, 2000; Gonwa, McBride, Anderson, Mai, Wadei, & Ahsan, 2006; Julapalli, Kramer, & El-Serang, 2005; Kemmer, Ahmed, & Keefe, 2004; Klassen, Klassen, Brookmeyer, Frank, & Marconi, 1998; McCormick, O'Rourke, Carey, & Laffoy, 2004; Merion, Guidinger, Newmann, Ellison, Port, & Wolfe, 2004; Nair, Eustace & Thuluvath, 2002; Ozminkowski, Friedman, & Taylor, 1993; Pomfret, Fryer, Sima, Lake, & Merion, 2007; Reid, Resnick, Chang, Buerstatte, & Weissman, 2004; Roberts, Dykstram, Goodrich, Rush, Merion, & Port, 2006; Sanfrey, 2005; Schaffer, Kulkarni, Harper, Millis, &

Cronin, 2003; Tuttle-Newhall, Rutledge, Johnson, & Fair, 1997; & Yoo & Thuluvath, 2004).

These studies, although informative, have often analyzed and compared data from different allocation periods and at different points of access or stages as described above. This heterogeneity of sampling and allocation period accounts for the inability to clearly identify barriers to access in the current liver allocation scheme and hence define current policy issues that may require re-evaluation and potential revision.

Allocation of cadaveric livers has evolved from a time-waiting to an acuity based system, the most current application of which is through the institution of the Model for End Stage Liver Disease (MELD) acuity score on February 27, 2002. Comprehensive evaluation of access since the implementation of the MELD acuity system is lacking in the literature.

In addition, access to liver transplantation occurs on a continuum, defined by three specific stages or points of access (see Figure 4.2). These are referral (stage 1), wait listing (stage 2) and surgical liver transplantation itself (stage 3). Stage 1 or the referral stage of access depends on accurate identification, diagnosis and referral to a tertiary care center with the capability of providing liver transplantation as a treatment option. Despite the importance of studying access at this stage, the absence of a comprehensive database with well-documented liver disease prevalence as well as the inability to capture those individuals not diagnosed with end stage liver disease due to lack of basic health care makes such a study difficult to embark upon. Although attempts to study this population have been undertaken, these have been limited to a state-wide study (Tuttle-

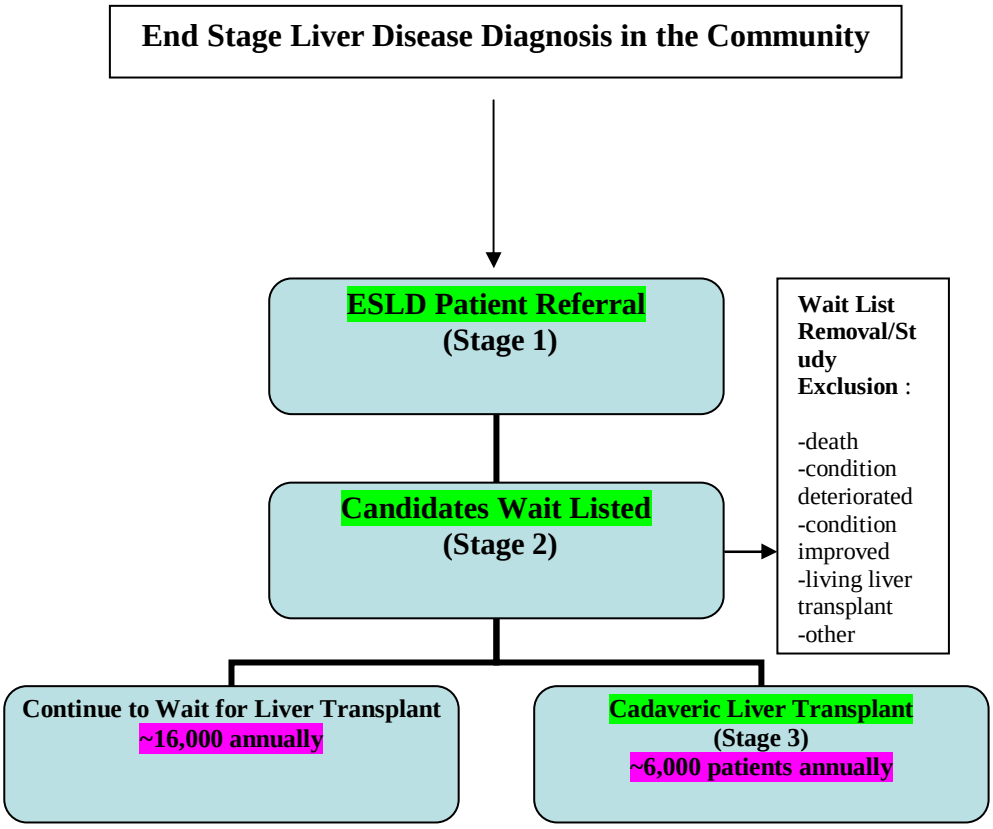
Newhall, Rutledge, Johnson, & Fair, 1997) as well as single center large VA hospital study (Julappali, Kramer, & El-Serag, 2004).

Access to liver transplant at stage 2 (wait-listing) is dependent on successfully entering stage 1 and then becomes center-driven by means of a clinical evaluation of transplant candidacy. It is difficult to evaluate access at this stage due to non-standardized acceptance criteria among centers and the lack of a comparison database of individuals denied candidacy, since data is only recorded for those chosen as candidates.

The third and final stage of access to liver transplant is at the actual time of cadaveric liver transplantation. This proposed study is designed to examine access to liver transplantation at stage 3 with an additional evaluation of those individuals who get to stage 2 but continue to wait for an organ to become available.

All of these transplant candidates have successfully been referred (stage 1) and selected (stage 2) onto a liver transplant wait list and registered with the United Network of Organ Sharing.

Figure 4.2
Stages of Access to Liver Transplantation
And
Population Studied



Once wait-listed, transplant candidates are either removed from the waiting list, transplanted, or continue to wait for a cadaveric liver transplant. Approximately 10,000 patients a year are removed from the cadaveric waiting list. Reasons for removal include transplantation, death, condition improving or deteriorating and other. In this study those removed from the list for reasons other than transplantation were excluded from the study sample.

Given that the literature is primarily based on secondary analyses of data sets from different stages in the process and employing different allocation schemes, conclusions

drawn from each research study may or may not be relevant to current allocation practices. Despite this limitation, the field of transplantation has often relied on these studies of previous allocation eras to report on disparities in distribution and allocation of livers. This makes it difficult to distinguish what disparities actually exist with the current system of allocation from those that are continuing to be reported from prior allocation data sets. Hence the need for this secondary analysis, limited to data collected since the adoption of the acuity based MELD scoring system on February 27, 2002.

The purpose of this study is to examine access to liver transplant following the adoption of the MELD system of acuity (Allocation Era 3) used for the allocation of cadaveric organs at stage 3 or the time of transplant by comparing those patients transplanted with those that continue to wait.

Contribution of this Dissertation Research

The factors that influence access to liver transplant are complex and inter-related. Given that access to liver transplant occurs at three stages on a continuum, addressing one point or stage along the continuum will only partially inform the question of access to transplantation. This being said, a study of access to care at the point of transplantation (stage 3) is clearly the most relevant question to begin with as it will define the disparities that may exist at the actual point of transplantation, given the current acuity based system of organ allocation.

This research will add significantly to the body of knowledge regarding the potential disparity in access to care for a highly resource dependent treatment modality. While this procedure (cadaveric liver transplantation) only serves an average of 6,000

individuals a year, this limitation exists only because of the limited supply of organs available for transplant purposes. Allocation of limited organs should transcend issues of age, race, gender, educational level, economic status and geographical location. This study will determine those variables most highly correlated with the probability of receiving a liver transplant as well as those that contribute to the time to transplantation, while controlling for need. In addition, variables that provide barriers to access may also be identified. From a more global perspective, this research study may serve as a model to evaluate the impact of other acuity-based systems of allocation among highly resource dependent treatment modalities.

Methods

This dissertation research utilized secondary data from one large national research database. Secondary analysis provides an efficient, economical method of research that has historically been the method-of-choice in health services research. The primary database involved is the Scientific Research Transplant Registry (SRTR), with input from the Organ Procurement Transplant Network (OPTN) and validation from the Social Security Death Master File (SSDMF) and the National Death Index (NDI).

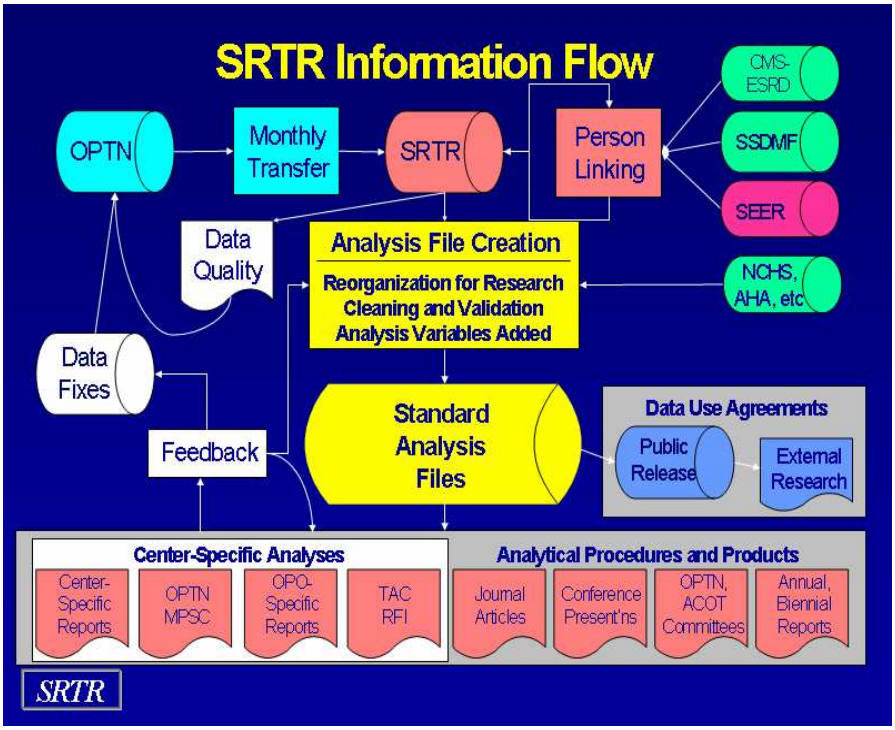
Sources of Data & Sample: SRTR / UNOS Database

The primary source of information regarding transplant candidates and recipients comes from the OPTN database which is supplied by transplant centers via an on-line database called the Transplant Information Electronic Data Interchange (Tiedi). Transplant Candidate Registration (TCR) forms and Transplant Recipient Registration

(TRR) forms (Appendix B &C) are the reports that are submitted by each transplant program where the variables studied are derived from. TCRs are generated when a patient is wait-listed for a liver transplant. TRRs are generated when a transplant has occurred. Mandatory data reporting through Tiedi began in 2003, allowing integration of patient-related data from the time of organ wait-listing until graft loss or death. The OPTN database stores information on all persons on the national waiting list. It is the responsibility of each transplant center to update this information on a continual basis, particularly in regard to severity of illness such as MELD scores for liver transplant candidates. Maintenance of the transplant waiting list is, however, dependent upon reporting of outcomes, which is center driven. Some outcomes, such as transplantation, are invariably immediate, due to the generation of a transplant record and a reporting requirement within several days. However, reporting of removal from the waiting list due to death or other reasons may occur as a lag, which can affect the accuracy of the data which will be discussed in limitations to the study (Levine, McCullough, Rodgers, Dickinson, Ashby & Schaubel, 2006).

Subsequent to the submission of data from individual transplant centers to the OPTN/UNOS database, data from the OPTN is transferred to the SRTR on a monthly basis as illustrated below in Figure 4.3. This data is then linked by person to secondary data sources such as the Social Security Master File (SSDMF) and the National Death Index (NDI) as described below. Analysis files are then created in the form of Standard Analysis Files (SAS), which are made available to the public and researcher alike for various purposes including external research, as is the case with this research study.

Figure 4.3
Transplant Data Information Flow



Sources of Data: Social Security Death Master File (SSDMF)

The Social Security Death Master File (SSDMF) is a publicly available database from the Social Security Administration containing over 70 million records of death reports from both beneficiaries and non-beneficiaries alike. The SSDMF is cross-referenced to determine death reporting when patients are lost to follow-up.

Sources of Data & Sample: National Death Index (NDI)

The National Death Index (NDI) is another secondary database that is utilized to verify the completeness of death records. It has a reporting accuracy of 95 percent and

therefore serves as an excellent secondary database to the OPTN in terms of death reports.

Population

The population studied were those individuals who were wait-listed for a cadaveric liver transplant starting on February 27, 2002 through November 30, 2007. In this population, those that received a cadaveric liver transplant were compared with those that continued to wait for a liver transplant excluding those that died or were removed from the cadaveric waiting list for reasons other than cadaveric liver transplant which were described above. This population of patients was retrieved from a de-identified data file from UNOS of all wait listed and recipients of livers from deceased donors between February 27, 2002 (MELD effect date) and November 30, 2007 (based on OPTN data as of November 30, 2007).

Exclusions

Children (age <18 years), acute liver failure patients classified as Status 1 and patients who had received a previous liver transplant were excluded from the population. Children < 18 were excluded from the analysis because liver allocation for children is based on a different acuity scale called Pediatric End-stage Liver Disease (PELD) . Acute liver failure patients (Status 1) were also excluded due to the fact that their acuity and organ allocation is based on a different allocation scheme. Patients who had received a previous transplant were also excluded because they may have been assigned additional acuity points to their MELD score when compared to the primary (or first time) liver

transplant recipients. The population totals for both wait list candidates and cadaveric liver transplant recipients can be found listed in Table 4.1 below.

After exclusions for age < 18, receipt of living donor organ, date earlier than February 27, 2002, receipt of a previous liver transplant, split liver transplant, Status 1 acuity level, or deceased donor emergency transplant, cadaveric liver transplant recipients were identified based on database removal codes in the UNOS database identifying cadaveric liver recipients. These included codes for deceased donor transplant (2, 3, & 4), transplanted at another center (14), deceased donor multi-organ transplant (19) and patient died during transplant procedure (21). The total number of transplants performed in years 2002 to 2007 were 33,825. The total number of transplant patients in this sample population were 17,118. The total number of wait-listed candidates studied during this time-frame was 15,448.

Table 4.1
Adult End Stage Liver Disease Final Sample by Year
Wait List and Transplant Patients
UNOS Data
2002-2007

Table 4.1							
End Stage Liver Disease Patients	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	
	n	**n**	**n**	**n**	**n**	**n**	**Totals**
Wait Listed Candidates (>18yo)	**1686**	**2212**	**2359**	**2504**	**2969**	**3718**	**15,448**
Cadaveric Recipients (>18yo)	**2223**	**3034**	**3444**	**3389**	**3155**	**1873**	**17,118**

Wait listed patients were followed until one of the following occurred: transplant or wait list removal for reasons previously described or the end of the study period on November 30, 2007. Multiple observations periods for each patient were included,

beginning at each MELD update. Periods of inactivity, however, were not included in the analysis.

Description of Variables - Dependent Variables

Time to Transplantation for Transplant Recipients. While the acuity based MELD allocation system was adopted to fulfill the federal mandate to decrease the death rate of those awaiting transplantation and provide a more equitable distribution of organs nationally, there remains disparity between those who receive an organ in regard to how long the recipient waits for a liver and at what measured acuity they receive a transplant (Roberts et al, 2006). Examination of time to transplantation will provide important information regarding timely and equitable access to liver transplantation. This dependent variable, measured as days to transplant, will be reported as a Kaplan Meier Survival Curve in the Results, Chapter 5. This survival analysis provides a framework to study those variables that provide a hazard or risk of transplantation. Although the dependent variable is time to transplant, the significant information from the analysis becomes the hazard or risk of transplant that individual independent variables contribute in the Model built.

End Stage Liver Disease (ESLD) patients who received a transplant between February 27, 2002 and November 30, 2007 were compared to those ESLD patients who continued to wait for a cadaveric liver transplant. Examination of this population of individuals in receipt of a liver transplant will provide important information regarding those characteristics which may provide an advantage or barrier to the provision of liver transplantation as a treatment for end stage liver disease. End stage liver disease patients receiving a transplant were measured through the SRTR database file from the original

transplant date (TRR_ID) item on the transplant recipient registration form (TRR). These patients will be compared to those ESLD patients who continue to wait for a cadaveric liver transplant through the same SRTR database file from the original listing date (TCR_ID).

Description of Variables – Predisposing Independent Variables

Age

As discussed in Chapter 3, the demographics of the aging population in the United States is reflected in the greater than 60 percent of those listed for transplantation between the age of 50 and 64 years (Pomfret et al., 2007). This is a significant departure from the almost equal distribution of those listed in the 18-49 year old category and the 50+ category.

Only three studies addressed age as in terms of cadaveric transplant recipient characteristics during the current MELD allocation era. Julapalli and colleagues (2005) determined that older age was a statistically significantly negative determinant of liver transplant referral with a 69 percent decrease in odds of referral for every increase in 10 years of age, based on a large single-center study. In addition Reid and colleagues (2004) found that younger patients not only had a statistically significant shorter waiting time to transplant but the likelihood of death or being removed from the waiting list due to becoming too sick was increased by 1.5 times for each decade of life.

On a positive note, Freeman et al (2004) reported a decreased rate of removal for all ages due to becoming to ill for transplant or dying. This may reflect a positive outcome of the MELD scoring system of which a primary goal was to decrease mortality on the waiting list

As the population of end stage liver disease patients age, issues of allocation between young and old will only become more pronounced. Further attention to outcomes in the transplant population, particularly those over age 60 years will be important to research. What complicates the ability to accurately access these outcomes are the donor livers utilized for the older population. Often the organs chosen are older and even higher risk then those placed in younger recipients, making outcome comparisons, specifically graft and patient survivals difficult to interpret.

This research study described the age distribution of both the population of transplant recipients as well as transplant candidates during the time frame studied. In addition, age as a factor in time to liver transplant was examined. Continued assessment of outcomes (patient and graft survivals as a measure of utility) will be necessary to contribute to the allocation debate in regard to equitable distribution of livers for transplant, particularly since the inception of MELD, however graft and patient survival issues post-transplant are beyond the scope of this research study. Age was measured in this study through SRTR (2007) data derived from questions on the Transplant Candidate Registration (TCR) Forms and the Transplant Recipient Registration (TRR) forms found in Appendix B and C.

Race

As reported in Chapter 3, the white population continues to predominate the liver transplant waiting list, with relative unchanged percentages of Asian and African American patients, however Hispanic candidates on the list have increased significantly. White candidates currently comprise about 72 percent of the liver transplant waiting list, which is a decrease of about 5 percent over the past 10 years, while the prevalence of

African Americans and Asian patients on the wait list has remained relatively constant at 5 and 7 percent respectively. The number of Hispanics on the waiting list has tripled over the last ten years (Pomfret, Fryer, Sima, Lake, J.R., & Merion, 2007) and comprises 15 percent of the current waiting list (UNOS, 2007).

Freeman and colleagues (2004) used UNOS data from a year prior to and following implementation of the MELD system to determine that there had been an increase in the rate of transplantation for whites, African Americans and Asian Americans. With the exception of this early study, there have been no additional research studies undertaken to address the impact of race on rate of wait listing and liver transplantation among minority populations since the implementation of the MELD system of organ allocation.

The current research study evaluated the racial distribution of both the population of transplant recipients as well as transplant candidates from the implementation of MELD through 2007. In addition, race as a factor in time to liver transplant was examined. One has to wonder if African Americans might actually have somewhat of an advantage in this new allocation scheme, since there is a greater amount of renal insufficiency in this population and the MELD scoring system favors renal impairment (Reid et al, 2004). Race was identified through SRTR (2007) data derived from questions on the Transplant Candidate Registration (TCR) Forms and the Transplant Recipient Registration (TRR) forms.

Gender

The percentage of males receiving cadaveric liver transplants has increased from 57 percent in 1995 to 66 percent in 2004. According to Alter and colleagues (1999) this

is likely due to the increased prevalence of Hepatitis C, which is twice as common in males than females. Historical differences in access to liver transplant by gender has shown inconsistent results both prior to and following implementation of the current MELD allocation system. Historically, using data from previous allocation Eras 1, there is dispute in the literature regarding the existence of gender inequity with IOM data (Gibbons et al, 2003) indicating there was no gender inequity and others maintaining a longer wait time for women (Klassen et al, 1998), greater numbers of death on the waiting list for women (Klassen et al, 1998), and yet a higher rate of transplantation among women (Tuttle et al, 1997).

In the current system however, it is not disputed that the number of females wait-listed for transplant has decreased from 44 to 40 percent (Pomfret et al, 2007) and that given the newly instituted MELD scoring system there is a systematic bias due to creatinine measurement (Cholangitis et al, 2007).

This research study describes the gender distribution of both the population of transplant recipients as well as transplant candidates during the time frame studied. In addition, gender as a factor in time to liver transplant was examined. Gender was measured through SRTR (2007) data derived from questions on the Transplant Candidate Registration (TCR) Forms and the Transplant Recipient Registration (TRR) forms.

Description of Variables – Enabling Independent Variables

Education

Level of education has been addressed in the literature in regard to its impact on socioeconomic status (Yoo et al, 2004), specifically in relation to outcomes and the ability to multiple list (Merion et al, 2004), an issue addressed in Chapter 2. However,

educational level in regard to accessing liver transplantation not related to multiple listing or the relation between race, socioeconomic status and outcomes have not been studied.

This research study evaluated educational level distribution of both the population of transplant recipients as well as transplant candidates during the time frame studied. In addition, educational level as a factor in time to liver transplant was examined. Educational Level was measured through SRTR (2007) data derived from questions on the Transplant Candidate Registration (TCR) Forms and the Transplant Recipient Registration (TRR) forms.

Ability to Pay

As reviewed previously, ability to pay over 15 years ago was shown to be a positive predictor of transplantation. More currently this result has not been replicated. In part, this has been due to the lack of an adequate measure of ability to pay.

There are no recent studies addressing ability to pay as an enabling variable in regard to access to transplantation. This variable was measured through the OPTN database and categorized as private, Medicaid (federal low income), Medicare/other (federal not low income and non-private). Ability to pay was measured through SRTR (2007) data derived from questions on the Transplant Candidate Registration (TCR) Forms and the Transplant Recipient Registration (TRR) forms in the form of primary payer status.

Geography

Issues regarding geographical distribution have been discussed in great detail in the literature review in Chapter 2. Currently many simulation models and proposals to provide a more equitably distribute scarce numbers of organs have been suggested.

However, specific clarity regarding the current state of access to transplant over time for the 11 geographical UNOS regions given the current MELD system of allocation remains unclear. One of the objectives of this study is to address these questions regarding geographical areas and access to transplantation since the adoption of the MELD acuity model on February 27, 2002.

This research study evaluated geography (as defined by the 11 designated UNOS regions) as an independent variable in regard to access to cadaveric liver transplant. In addition, geography as a factor in time to liver transplant was examined. Geography will be measured through SRTR (2007) data and designated as one of eleven UNOS geographical regions. The 11 UNOS Regions are made up of the following respective U.S. states and territories:

- Region 1: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Eastern Vermont
- Region 2: Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, West Virginia, Northern Virginia
- Region 3: Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, Puerto Rico
- Region 4: Oklahoma, Texas
- Region 5: Arizona, California, Nevada, New Mexico, Utah
- Region 6: Alaska, Hawaii, Idaho, Montana, Oregon, Washington
- Region 7: Illinois, Minnesota, North Dakota, South Dakota, Wisconsin
- Region 8: Colorado, Iowa, Kansas, Missouri, Nebraska, Wyoming
- Region 9: New York, Western Vermont
- Region 10: Indiana, Michigan, Ohio
- Region 11: Kentucky, North Carolina, South Carolina, Tennessee, Virginia

Description of Variables – Need Independent Variables

MELD

Assigning a numerical value to acuity is the intent of the MELD score and hence

an excellent example of measured acuity. The goal of MELD utilization is to transplant the most acutely ill patient under the assumption that this measure is the most objective measure of need within the population of liver failure patients.

Differences in transplant outcomes have been reported since the adoption of the MELD acuity system. These conflicting outcomes have been attributed to data analysis utilizing one-time MELD measurement at time of listing versus changing MELD scores through the wait list time period (Gibbons, 2000 and 2004). Of significance to this study of access and allocation is the MELD score at transplant, which is likely to be different than the MELD score at listing. For the purposes of this study, MELD scores for all transplanted and waitlisted patients from the time of listing until transplant outcome or end of study were analyzed, in other words MELD will be treated as a time-varying covariate or one in which the values of the covariate change over time. The MELD scores described are calculated variables derived from the OPTN database and reported by way of descriptive statistics. Analysis of other defined independent variables will be reported while controlling for MELD.

Blood Type

In calendar year 2005 approximately 45 percent of recipients were blood type O, 38 percent were blood type A, 12 percent were blood type B, and 5 percent were blood type AB. This distribution has been constant over the past several years and reflects the population distribution of blood types (UNOS database, 2007). Blood type was evaluated as a need variable measured through SRTR (2007) data derived from questions on the Transplant Candidate Registration (TCR) Form and the Transplant Recipient Registration (TRR) form in the form of blood type.

Height and Weight

The size as measured by the height and weight of an individual may influence the allocation of cadaveric livers for transplantation purposes. Durand and Valva (2005) assert that there is a problem with MELD's creatinine measurement in that an elevated level may not always indicate worsening renal function. An individual with a higher body mass index (a calculated function of an individual's height and weight) will, by virtue of their size, have a higher creatinine. Elevated creatinine, and subsequently, a higher MELD score. Since livers are allocated by acuity of illness, measured by the MELD score, those individuals with higher MELDs due to an increased creatinine because of a higher BMI may have a distinct advantage over those with a lower BMI. Patient size will be measured through SRTR (2007) data by means of a patient's height and weight which are derived from TCR and TRR Forms previously described

Etiology of Liver Disease

Etiology of chronic liver disease may also influence access time to liver transplant, especially in regard to hepatocellular cancer (HCC), given the automatic allocation of MELD scores 20 and 24 depending on specific HCC diagnostic phase. Etiology of liver disease will be measured through SRTR (2007) data derived from TCR forms in the category of etiology.

Period

In an effort to determine the impact of the implementation of the MELD 15 share rule on January 12, 2005, a dichotomized variable "period" was created to evaluate the impact this change may or may not have had on access to liver transplantation. Period

was delineated as 0 if the event being measured was prior to January 12, 2005 and period was delineated as 1 if the event being measures was on or after January 12, 2005.

RESEARCH DESIGN

Data Analysis

Data from the Organ Procurement Transplant Network (OPTN) via the Scientific Registry of Transplant Recipients (SRTR) was obtained. It was comprised of a de-identified data set of 193 variables for all listed and liver transplant recipients from 1988 through November 30, 2007. Construction of a database with variables as described above occurred. A final working database was compiled in a SAS data file in order to allow for the appropriate statistical measurements. Data was cleaned and codes were labeled as detailed in the SRTR code book provided by the OPTN. See Table 4.2 below for a complete list and definition of variables studied.

Table 4.2 ***Definition of Independent Variables***

Variables	Definitions	Code/Method of Collapse, recoding, etc
Age (Predisposing)	Chronological age at time of listing	**INIT_AGE**; continuous variable collapsed into 5 categories: 18-30(ref), 31-45, 46-60, 61-75,76+
Height (Need)	Height in cm at listing	**INIT_HGT_CM**; continuous variable collapsed to 4 categories, lowest as ref
Weight (Need)	Weight in kg at listing	**INIT_WT_KG**; continuous variable collapsed to 4 categories, lowest as ref
Gender (Predisposing)	Male or female	**Dichotomous variable** coded 1 for male and 0 for female
Race (Predisposing)	Background individual most identifies with	**8 options** collapsed into 5 categories: White (ref), Black, Hispanic, and Asian/other
Educational Level (Enabling)	Highest level of education obtained	**Edlevel**; 8 options collapsed into 4 categories: <high school, high school (ref), collage and tech school, graduate , other
Payment Source (Enabling)	Method of insurance payment	**PRIPAY**: 12 options collapsed into private (ref), Medicaid, Medicare/other public
ABO (Need)	Blood Type	**NewABO;** 8 options collapsed to A, B, AB, O (ref)
Geographical Region (Need)	US Federally designated organ allocation regions	**Regions**: 1, 2 (ref), 3,4,5,6,7,8,9,10,11
Diagnosis (Need)	Etiology of Liver Disease	**DX**; 69 options collapsed into 6 categories: Hepatitis (ref), alcohol related, biliary related, metabolic disease, hepatocellular carcinoma (HCC), cirrhosis/other
MELD (Need)	Model for End State Liver Disease quantifying acuity of illness in regard to liver disease	**MELD**; analyzed as both a continuous variable as well as a categorical variable: MELD 1 (<15), MELD 2 (16-22), MELD 3 (23-40)
Period	Pre 1/12/05 and on or after 1/12/05	**Period**; dichotomous variable coded 1 for time > or = 1/12/05 and 0 for time < 1/12/05

Data Management

Linking Data Sources

Linking of the data sources from the Social Security Death Master File (SSDMF) as well as the National Death Index (NDI) is done prior to the researcher obtaining data from UNOS.

Research Aim #1: Describe those who have received a liver transplant between 2002 and 2007 compared with those that did not receive a transplant during this time period for the entire group as well as the 11 separate UNOS Regions.

Data Analysis for Research Aim #1:

Descriptive Statistics

Descriptive statistics were utilized to describe the study cohort of individuals who received a liver transplant between 2002 and 2007 and those that did not receive a transplant during this time period (excluding those that died or were removed from the wait-list for other reasons other than transplantation) The following variables were examined with Chi square: age, gender, race, weight, height, educational level, primary payer source, geography by UNOS region, consecutive MELD scores, etiology of disease and blood type and body mass index (BMI), height and weight. All data analysis will be reported in Chapter 5 in raw numbers and percentages for this exploratory data.

Analysis began with simple univariate statistics including mean and median and ranges, evaluating frequency distribution of predictor variables. Since some of the results might be skewed, or otherwise abnormally distributed, it might have been necessary to perform log transformations in order to perform a better fit. This was not the case.

Variables of interest were chosen based on their potential to inform the research question and based on theoretical understanding and literature review.

Research Aim #2: How has the implementation of the Share 15 Rule impacted time to transplantation for MELD acuity levels > or = 15, both among the entire population of individuals studied as well as within each of the 11 UNOS regions.

Data Analysis for Research Aim #2:

Cox Regression

In an effort to address the impact of the Share 15 Rule implemented in January 2005 two models were run, one testing the impact of the Share 15 Rule on the entire population of wait listed patients/transplanted patients and a second model testing for this impact within each of the 11 UNOS regions. Model 1 used a dichotomous MELD predictor (MELD 15 =1 if MELD > or = 15 or MELD 15 = 0 if MELD <15. This was considered a time-varying covariate, a covariate whose value may vary over time. In addition, Period was a dichotomous time varying covariate with Period = 0 if the date was before 1/2005 or Period = 1 if the date is after 1/2005 (which is representative of the date of implementation of the MELD 15 rule). Model 2 addressed MELD15 by Region for all 11 UNOS Regions with determination of significant variables as well as predictors of transplant among regions.

Research Aim #3: Examine the factors associated with time to liver transplant including those predisposing, enabling, need variables and geography while controlling for time period both before and after the implementation of the Share 15 Rule. Examine these factors across 11 geographical UNOS regions as well.

Data Analysis for Research Aim #3:

Cox Regression

These variables were assessed in a multivariate model for association with time to transplant, using Cox proportional hazard analysis. Each factor as a predictor of transplant and ultimately time to transplant was compared with all other factors and then

individually compared to eliminate the influence of the specific composition of the cohort. The key advantage to the Cox Model is that there is no specific survival model assumed and therefore covariate-adjusted mortality between subgroups could be compared.

The Cox Model makes three specific assumptions. The first is that the ratio of the hazard of two individuals is the same at all times. This is called the proportional hazard assumption. The second is that the explanatory or independent variables act multiplicatively on the hazard. The third is that individual results are independent of each other.

In this study, Cox regression was used to investigate the effect of the previously described variables upon the time to transplantation. Since the method does not assume any specific model, it is truly considered non-parametric because it assumes the effects of the predictor variables are constant over time and additive in nature.

While the Cox Regression analysis provides an excellent and superior survival analysis, errors may still occur. Therefore post-regression analysis tests were performed to examine the fit of the data. Several goodness of fit strategies for the Cox model have been developed. With consultation from a statistician, determination of the most appropriate goodness of fit tests were made. Tests described by Cox himself (1972), or Gil and Schumacher (1987) or Schoenfield (1980) were chosen and applied to the data results as appropriate.

The aim of this statistical analysis was to conduct a Cox Regression Model for the hazard of transplantation at time t (a defined starting point, in this case at the point of wait listing):

Cox Regression:

$$\lambda(t) = \lambda_o(t)\exp(\beta_1 X_1 + \beta_2 X_2 + \ldots\ldots + \beta_k T X_k)$$

$$= \lambda_o(t)\exp(\beta_1 X_{\text{period}} + \beta_2 X_{\text{predisposing}} + \beta_3 X_{\text{enabling}} + \beta_4 X_{\text{need}}$$

$$+ \beta_5 X_{\text{geography}})$$

$$= \lambda_o(t)\exp(f(X))$$

where each component X_k and the risk score function f(X) is a linear combination of X = $\{X_1, X_2 \ldots X_P\}$. In this model = $\lambda_o(t)$ is an unspecified or reference hazard function, or more formally understood as the hazard at time t (a defined starting point which for the purposes of this study will be at the time of wait listing).

The estimation of the b coefficients and the underlying hazard and Cox regression model being somewhat complex, the statistical and computational details were undertaken in consultation with a statistician utilizing the SAS statistical package.

The overall significance of the model will be illustrated by the expression of the "maximum likelihood estimates" which are the estimated parameters (the underlying hazard and the coefficients) of the Cox model. In the multivariate model period was a dichotomous time-varying covariate with period = 0 for time prior to 1/12/05 and period = 1 for time on or after 1/12/05. In addition to this overall Cox Model, individual multivariate analyses for each of the 11 UNOS regions were run as well in order to identify significant variables predicting liver transplant by region with identification of hazards per variable.

Although the system of cadaveric liver allocation is based on an acuity based model (MELD) prioritizing the sickest person first, variables such as race, gender and geographical region have not been evaluated in regard to the contribution each makes to

obtaining or limiting access to this scare resource. The Cox Model offers an excellent means by which to evaluate the effect of all of those predisposing, enabling and need variables that Anderson outlines. Two sets of regressions were run. The first Cox Model was constructed to evaluate the impact of the implementation of the MELD Share 15 rule both nationally and regionally. The second model more specifically addressed those multiple variables that may contribute to the hazard of liver transplant both from a national and regional perspective taking into account the changes in the allocation process that occurred mid-way through the study period.

Chapter 5

Results

Utilizing data from the United Network for Organ Sharing (UNOS) and survival analysis techniques, this study examines the rates of liver transplant and factors contributing to these rates of transplant. The population studied was that of all adults in the United States listed for non-urgent liver transplant as well as those who received cadaveric liver transplants between February 27, 2002 and November 20, 2007, excluding those exceptions previously noted. This analysis is framed by Anderson's Behavioral Model by exploring factors that may contribute to or explain differences in access to liver transplantation at the time of organ allocation. These factors are organized and presented as those predisposing, enabling and need variables that Anderson has defined and have been previously described in Chapter 2.

Researchers studying access to liver transplantation at the point of transplantation have found differing results in regard to influencing factors. Some of these differences can be attributed to varying data time frames, differences in organ allocation schemes and/or different statistical methods utilized. This analysis will address access to liver transplant post-MELD implementation (after February 27, 2002), extending the knowledge of the impact these factors have on liver transplantation access during the current liver allocation system.

The intent of this chapter is to present the findings from the data analyses discussed in Chapter 4. The results of Aim 1 will describe all those who received a liver transplant between 2002 and 2007 compared with those who continue to wait for a liver transplant during this same period. In addition, Aim 2 will determine how the implementation of the Share 15 Rule impacted time to transplantation for acuity levels > or = 15. And

finally, Aim 3 will present a multivariate analysis of those factors affecting hazard of transplant over the timeframe studied both from a national and regional perspective.

Following the presentation of the descriptive statistics for the entire sample population there will be a description of the dependent variable "time to transplant"/hazard of transplant and presentations of Kaplan Meier Survival Curves for time to transplant for both the entire population and again by region. The multivariate Cox regression analysis used to describe the policy effect of the MELD 15 Share Rule will be presented. Secondly, results from Cox's Proportional Hazard Model analyzing the factors affecting liver transplantation access by the study population are presented. A second set of Cox regression multivariate models for each of the 11 UNOS regions is presented. The chapter will be completed by a summary of the study findings. Discussion of the findings and limitations to the study will be presented in Chapter 6.

Baseline Characteristics of the Study Population

Baseline characteristics of the entire study population followed by specific characteristics by region will be presented for those individuals who received a liver transplant between February 27, 2002 and November 30, 2007 as well as those who did not receive a transplant during this same timeframe. Table 5.1 presents the basic descriptive characteristics of those categorical variables of this entire population of patients and Table 5.2 represents the descriptive statistics for the continuous variables for the same group.

Demographics will be presented in terms of those predisposing, enabling and need variables described by Anderson (1995) as either predicting or explaining usage of health services. In this particular study the intent is to identify and determine the impact these

variables have on access to liver transplantation.

Research Aim 1

The first aim of the study was to describe the study cohort of individuals who received a liver transplant between February 27, 2002 and November 30, 2007 as well as those who did not receive a transplant during this same timeframe. Table 5.1 presents the basic descriptive characteristics of those categorical variables of this population for the entire group of patients and Table 5.2 presents the descriptive statistics for the continuous variables of this same group.

In terms of the entire group's demographics, males comprised 69 percent of the transplanted group which was predominantly white (76 percent), between the ages of 46-60 (62 percent), high school educated (37 percent) and covered by private insurance (61 percent). The greatest percentage of those transplanted came from UNOS Region 3 (18 percent) and the most common etiology of disease was cirrhosis/other (54 percent), with the most common blood type being O (43 percent) and most frequently transplanted with a MELD score >23 (48 percent).

Comparing these transplanted patients with those that continued to wait for a liver during this same timeframe, the descriptive statistics are all statistically different at a *p value <.0001* with the exception of primary payment which still had a statistically significant *p value of .0009*. Those that continued to wait for a liver were predominantly white (72 percent), male (62 percent), between the ages of 46-60 (64 percent), predominantly high school educated (34 percent) with private insurance (62 percent). The highest percentage were from UNOS Region 5 (25 percent), diagnosed with cirrhosis/other (59 percent) of blood type O (49 percent) with a MELD score between 6 and 14 (58 percent).

Table 5.1
Characteristics by Transplant Outcome
for Categorical Variables
UNOS Data
2002-2007
(N = 32,566)

Characteristics	**Transplanted N=17,118 n (%)**	**Not Transplanted N=15,448 n (%)**	***p value***
Predisposing			
Gender			<.0001
Male	11,748 (69)	9,548 (62)	
Female	5,370 (31)	5,900 (38)	
	17,118	15,448	
Race			<.0001
White	13,029 (76)	11,052 (72)	
African American	1,479 (9)	974 (6)	
Hispanic	2,001 (12)	2,654 (17)	
Asian/Other	609 (3)	767 (5)	
	17,118	15,447	
AgeGroup			<.0001
18-30	518 (3)	404 (3)	
31-45	2,874 (17)	2298 (15)	
46-60	10,598 (62)	9850 (64)	
61-75	3,115 (18)	2880 (18)	
76+	13 (<1)	16 (<1)	
	17,118	15,448	
Enabling			
Education			<.0001
<High school	605 (4)	731 (5)	
High school	6,390 (37)	5,236 (34)	
College or Tech	4,514 (26)	4,182 (27)	
Graduate School	795 (5)	664 (4)	
Not Reported	4,814 (28)	4,635 (30)	
	17,118	15,448	
Primary Payer			.0014
Private	9,779 (61)	9,346 (62)	
Medicaid	2,498 (16)	2,393 (16)	
Medicaid/public	3,744 (23)	3,244 (22)	
	16,021	14,983	

Characteristics	**Transplanted N=17,118 n (%)**	**Not Transplanted N=15,448 n (%)**	***p value***
Region			<.0001
1	440 (3)	616 (4)	
2	2,227 (13)	2,370 (15)	
3	3,031 (18)	1,190 (8)	
4	1,745 (10)	1,679 (11)	
5	2,003 (12)	3,823 (25)	
6	587 (3)	361 (2)	
7	1,542 (9)	1,373 (9)	
8	1,081 (6)	725 (5)	
9	1,248 (7)	1,710 (11)	
10	1,660 (10)	664 (4)	
11	1,554 (9)	937 (6)	
	17,118	15,448	
Need Variables			
Diagnoses			<.0001
Hepatitis	648 (4)	536 (3)	
Alcohol	4,271 (28)	3,698 (26)	
Biliary	1,709 (11)	1,297 (9)	
Metabolic	379 (2)	195 (2)	
HCC	207 (1)	176 (1)	
Cirrhosis/Other	8,571 (54)	8,297 (59)	
	15,785	14,199	
MELD			<.0001
6-14	2,138 (13)	8,942 (58)	
16-23	6,718 (9)	3,840 (25)	
>23	8,229 (48)	2,666 (17)	
	17,085	15,448	
Blood Type			<.0001
A	6,522 (38)	5,813 (38)	
AB	982 (6)	349 (2)	
B	2,236 (13)	1,673 (11)	
O	7,378 (43)	7,613 (49)	
	17,118	15,448	

N=sample size, n=number of observations

Table 5.2 illustrates the descriptive statistics of the continuous predictors studied. The average age for the transplanted group was 52.12 versus 52.76 for the non-transplanted group. The mean height for the transplanted group was 172.77cm versus 170.96cm in the non-transplanted group. The mean MELD score for the transplanted group 19.98 and for the non-transplant group was 14.20.

Table 5.2
Characteristics by Transplant Outcome
for Continuous Variables
UNOS Data
2002-2007
(N = 32,566)

Variable	Censor	N	Mean	SD	Median	Min-	Max	Mann-Whitney p value
Age	Transplanted Non-transplant	17118 15448	52.12 52.76	9.51 9.25	52.00 53.00	18.00 18.00	83.00 80.00	<.0001
Height	Transplanted Non-transplant	17039 15357	172.77 170.96	10.07 10.38	172.72 170.18	142.20 142.24	225.00 223.52	<.0001
Weight	Transplanted Non-transplant	17072 15394	85.67 83.88	19.47 19.67	83.92 81.65	41.00 41.19	200.00 199.58	<.0001

Descriptive statistics were also obtained for each of the 11 UNOS Regions and showed wide variation by region with statistically significant differences among all measured variables. See Appendix D for complete descriptions of these categorical and continuous variables.

Evaluation of the MELD Share 15 Rule:

As described in Chapter 3, the current policy regarding the allocation of livers for transplant purposes evolved from a more subjective measure of need in conjunction with time-waiting to the current MELD acuity based system. Early on in the MELD Era of

allocation, it was recognized that this acuity scale was, in fact, being used to list patients but that many regions were still utilizing organs for patients with much lower MELD scores in areas adjacent to centers with patients waiting who had much higher MELD scores. Hence the evaluation and development of the MELD 15 Share Rule in January 2005 that required regional distribution of organs to those with an MELD Score of > or =15 prior to the allocation of organs to patients locally, with MELD scores <15. Although it was perceived that this would certainly provide a more equitable distribution of organs, documentation of the impact of this policy change on a regional basis was found to be missing from the literature. Therefore, aim 2 below and the evaluation of the MELD 15 rule was undertaken in order to determine the impact of this policy change on the allocation of livers, particularly for those with higher acuity levels, both nationally and by region.

Research Aim #2:

Determine how the implementation of the MELD Share 15 Rule in January 2005 impacted the hazard of transplantation for MELD acuity levels > or = 15. Descriptive statistics were reviewed for MELD levels pre and post policy implementation. The transplant group studied included 17,085 patients and the non-transplant group included 15,448 patients. The mean MELD score for transplant recipients pre-2005 was 19.80 with a standard deviation of 8.15 and a median of 18.00. The mean MELD score for recipients post-2005 was 20.10 with a standard deviation of 8.14 . These values were not statistically different with a *p* value of .0064. (See Table 5.3 below).

The mean MELD score for non-transplant recipients pre-2005 was 18.84 with a

standard deviation of 9.59 and a median of 16.00. The mean MELD score for non-transplant recipients post-2005 was 13.41 with a standard deviation of 5.99 . Unlike the transplant group, these descriptive statistics from the non-transplant group were statistically significantly different with a *p* value of <.0001. (See Table 5.4 below).

Table 5.3
MELD Descriptive Statistics
Periods Pre-2005 and Post-2005
Transplant Group
(N =17,085)

Variable	Censor	N	Mean	SD	Median (CI)	Min	Max	Mann-Whitney p value
MELD	Pre-2005 2005 on	6,927 10,158	19.80 20.10	8.15 8.14	18.00 (18.00-18.00) 18.00 (18.00-18.00)	6.00 6.00	60.00 61.00	.0064

Table 5.4
MELD Descriptive Statistics
Periods Pre-2005 and Post-2005
Non-Transplant Group
(N =15,448)

Variable	Censor	N	Mean	SD	Median (CI)	Min	Max	Mann-Whitney p value
MELD	Pre-2005 2005 on	2,247 15,448	18.84 13.41	9.59 5.99	16.00(16.00-17.00) 12.00 (12.00-1200)	6.00 6.00	55.00 61.00	<.0001

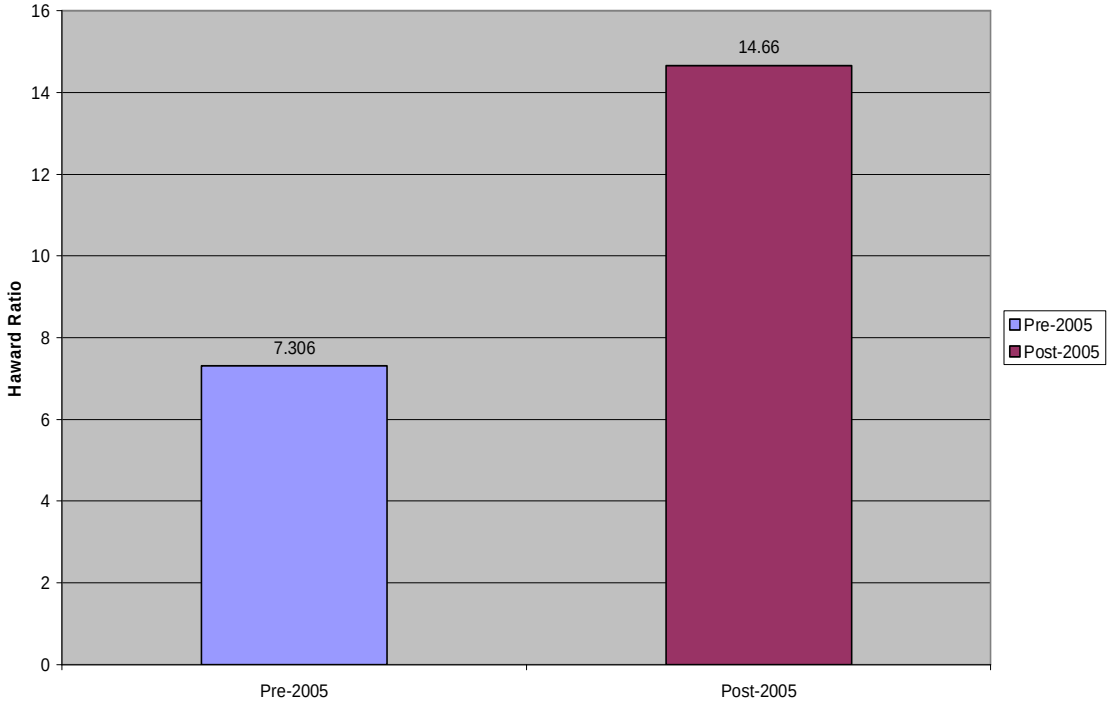
In an effort to address the impact of the Share 15 Rule implemented in January 2005 two Cox Models were run; one testing the impact of the Share 15 Rule on the entire population of wait listed patients/transplanted patients; and a second model testing for this impact within each of the 11 UNOS regions.

Model 1 used a dichotomous MELD predictor (MELD 15 =1 if MELD > or = 15 or MELD 15 = 0 if MELD <15). This was considered a time-varying covariate. A time-varying covariate is a covariate that will change over time. In this case MELD, which changes over the course of patients listing time is considered a time-varying covariate, also referred to as a time-dependent covariate.

In addition, Period was a dichotomous covariate with Period = 0 if the date was before 1/2005 or Period = 1 if the date is after 1/2005 (which is representative of the date of implementation of the MELD 15 rule). Model 2 addressed MELD15 by Region for all 11 UNOS Regions in the same way as Model 1, testing for the hazard ratio of MELD > or = 15 both pre and post MELD 15 implementation.

The overall hazard indicated that the likelihood of being transplanted with MELD >=15 doubled after January 2005 with a risk of transplant with MELD >= 15 at a hazard of 7.306 pre MELD 15 Rule implementation increasing to a hazard of 14.66 after January 2005. In other words the risk of transplant with a MELD > or = almost doubled from prior to the implementation of the MELD Share 15 rule on January 12, 2005 when compared to the period beginning on January 12, 2005. This is illustrated in Figure 5.1 below.

Figure 5.1
Transplant Hazard Ratio with MELD >= 15
UNOS Data 2002-2007

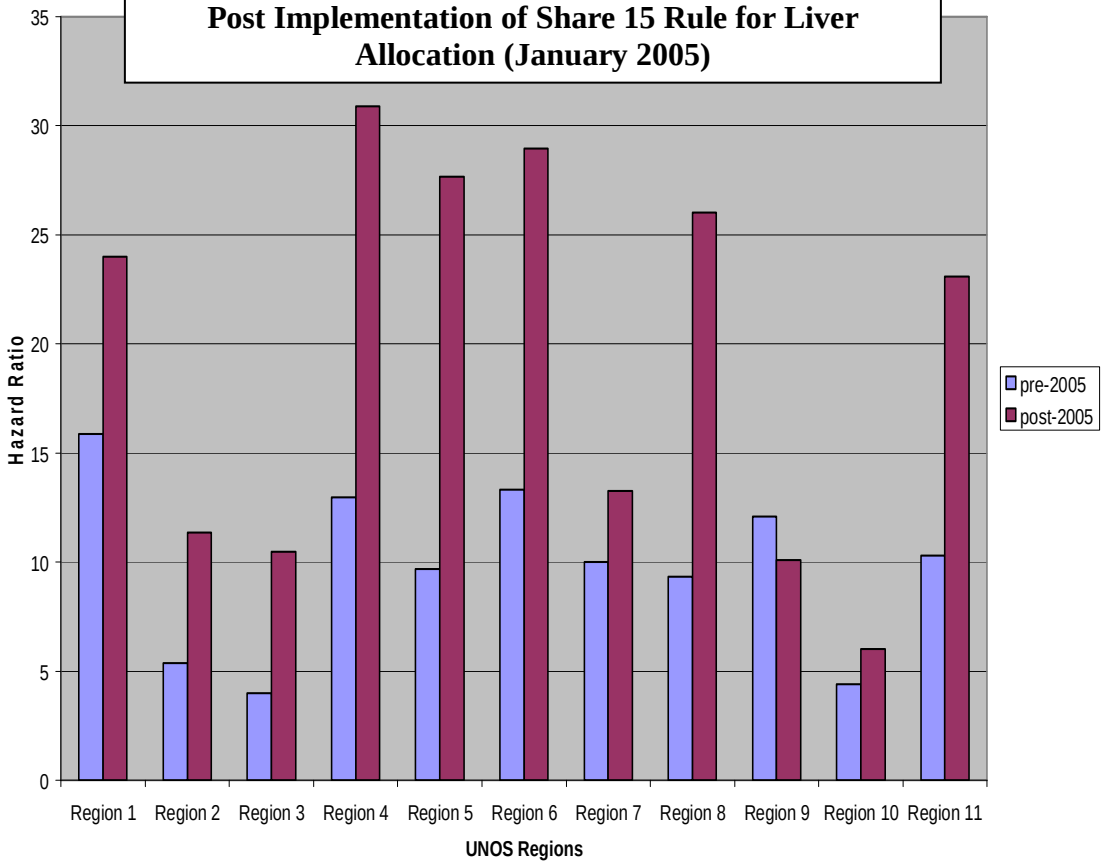


Model 2, testing for a difference in effect of the MELD 15 Share Rule in all 11 UNOS regions also showed statistical significance. This data is listed in Table 5.5 below and illustrated in Figure 5.2 as well. It appears that the greatest effects of change in MELD 15 policy is for regions 2, 3, 4, 5, 6, 8 and 11 compared to 1, 7 and 10 where the hazard ratio was stable after the Meld 15 rule implementation. This data illustrates significant impact of policy implementation that will be further discussed in Chapter 6.

Table 5.5
Hazard Rates by Region for MELD >= 15 both Pre and Post Implementation of Share 15 Rule for Liver Allocation (January 2005)

Region	**Hazard Ratio MELD > or =15 Pre-2005**	**Hazard Ratio MELD >or=15 Post-2005**	*p value*
Region 1	15.86	24	.2470
Region 2	5.38	11.36	<.0001
Region 3	4.01	10.47	<.0001
Region 4	12.97	30.87	<.0001
Region 5	9.68	27.67	<.0001
Region 6	13.32	28.94	0.0098
Region 7	10.01	13.26	0.0868
Region 8	9.32	26.02	<.0001
Region 9	12.09	10.10	0.2733
Region 10	4.40	6.02	0.0041
Region 11	10.31	23.08	<.0001

Figure 5.2
Hazard Rates by Region for MELD >= 15 both Pre and Post Implementation of Share 15 Rule for Liver Allocation (January 2005)



There was a significant difference in hazard of transplant both nationally and regionally with the implementation of the MELD 15 Share rule on January 12, 2005 with a significant increase in MELD score in most regions for those transplanted. Therefore, in order to address Aim 3 it is important to control for period to take into account these differences. Introduction of the dichotomous variable period into the multivariate analysis will be utilized to accomplish this and is described further below.

Time to Transplant for the Study Population

Research Aim 3:

The third aim of the study was to examine the factors associated with time to liver transplant/hazard of transplant between 2002 and 2007, including those predisposing, enabling, and need variables defined by Anderson (1995). In order to do this we used a survival analysis as the statistical technique to analyze time to transplantation, the study's dependent variable. Time to transplant is of interest from both a national as well as a region perspective, not merely to define the time-waiting period for those that receive a transplant but to understand the factors that contribute to the risk of receiving a transplant as well as those factors that prolong or perhaps provide barriers to the transplant event occurring.

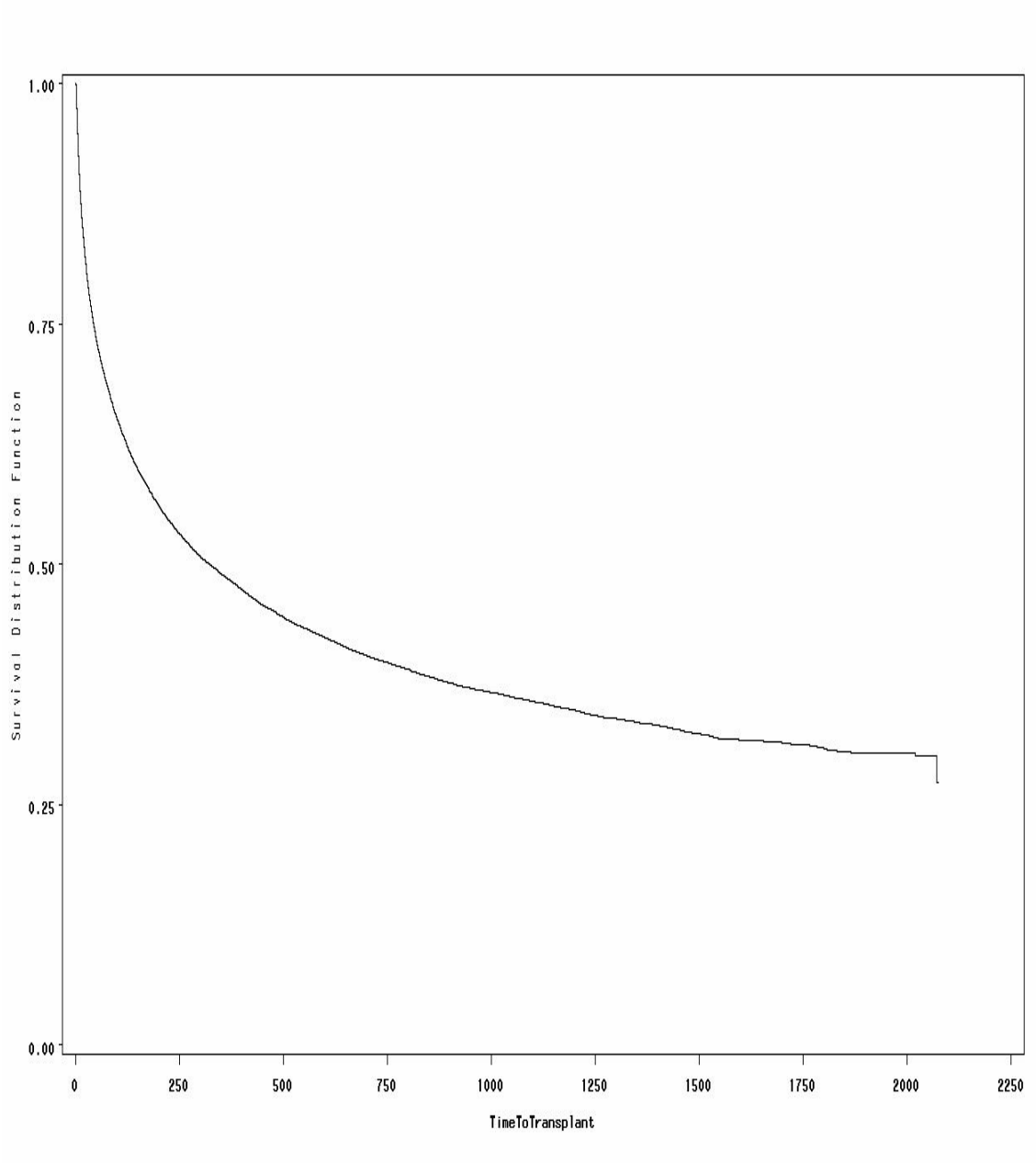
Survival Analysis.

The first step in the process of addressing Aim 3 was to run a survival analysis of time to transplant for the entire group. Table 5.6 depicts the data illustrating the patients at risk of transplant at 60 day intervals. This is included in these results, in part, to verify that the right end of the survival curve is not based on only a handful of observations. In addition, Figure 5.3 depicts the survival probability of receiving a liver transplant by Kaplan Meier Method.

Table 5.6
Patients at Risk of Transplant at 60 Day Intervals
UNOS Data
2002-2007

Day	Number at Risk	Day	Number at Risk	Day	Number at Risk	Day	Number at Risk	Day	Number at Risk
0	32,566	420	9,128	840	4,570	1260	2,210	1680	770
60	21,094	480	8,259	900	4,155	1320	1,954	1740	621
120	17,267	540	7,457	960	3,785	1380	1,717	1800	511
180	14,757	600	6,730	1020	3,418	1440	1,523	1860	380
240	12,881	660	6,095	1080	3,106	1500	1,310	1920	275
300	11,364	720	5,581	1140	2,772	1560	1,102	1980	187
360	10,205	780	5,073	1200	2,511	1620	929	2040	68

Figure 5.3
Survival Curve of Dependent Variable,
Time to Liver Transplant, by Kaplan Meier Method for all
UNOS Wait-Listed Candidates (2002-2007)



The median waiting time by Kaplan Meier is 324 days with a 95 percent confidence interval of 307 to 342 days.

Time to Transplant for the Study Population by Region

Survival Analysis by Region

Kaplan Meier survival analyses were also performed separately for all 11 UNOS Regions. Descriptive statistics for the time to transplant for all Regions can be seen below in Table 5.7. Mean time to transplant by region ranged from 103.03 days in Region 3 to 209.73 days in Region 1. Figure 5.4 below illustrates the Kaplan Meier survival curves of the probability of receiving a liver transplant in each of the 11 UNOS Regions.

Table 5.7
Descriptive Statistics on Time to Transplant by Region
UNOS Data
2002-2007

Region	N	Mean	SD	Median	CI (Lower/Upper)	Min	Max	P-Value
1	440	209.73	283.38	103.50	80.00/126.00	2.00	1850.00	<.0001
2	2227	150.36	234.36	58.00	53.00/63.00	1.00	1832.00	
3	3031	103.03	180.53	37.00	34.00/40.00	1.00	2020.00	
4	1745	164.34	245.65	59.00	50.00/70.00	1.00	1695.00	
5	2003	207.50	291.24	83.00	73.00/93.00	1.00	1869.00	
6	587	194.04	281.20	73.00	63.00/94.00	1.00	1640.00	
7	1542	158.65	257.05	53.00	46.00/61.00	1.00	2071.00	
8	1081	172.57	255.66	70.00	62.00/81.00	1.00	1581.00	
9	1248	163.75	266.48	47.50	42.00/55.00	1.00	1802.00	
10	1660	126.31	203.07	44.00	39.00/51.00	1.00	1740.00	
11	1554	180.12	277.89	65.00	57.00/73.00	2.00	1823.00	

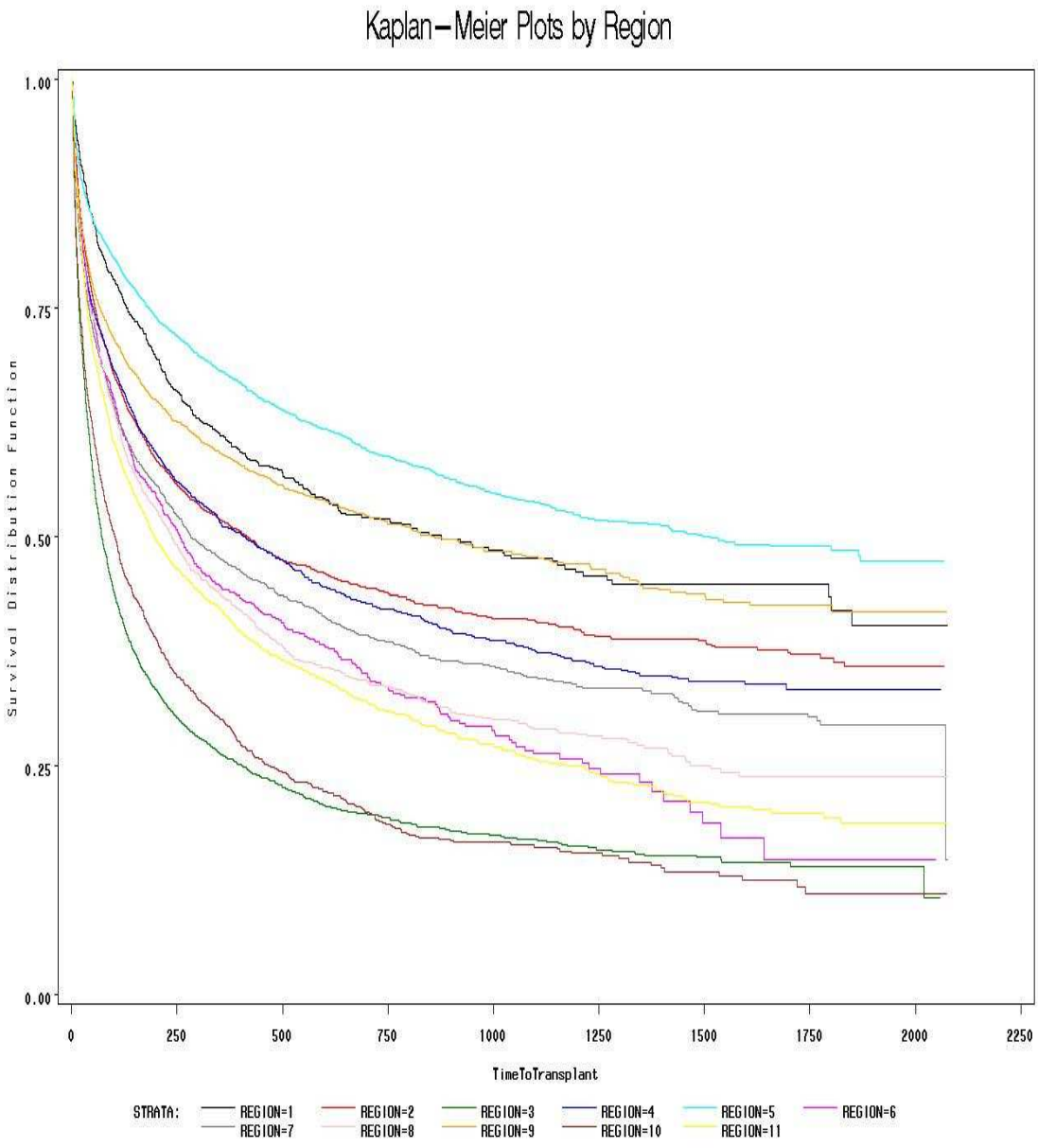


Figure 5.4
Survival Curves of UNOS Data
Dependent Variable, Time to Liver Transplant
by Kaplan Meier for all UNOS Regions (2002-2007)

Factors Affecting Time to Transplant

The third aim of this research study was to examine the factors associated with time to transplant, which, in actuality, is an explanation of these survival curves. Proceeding to address these factors that contribute to transplant occurring, the conceptual framework of Anderson's Behavioral Model will be used. Factors hypothesized to affect transplant are organized into three categories: 1) predisposing, 2) enabling and 3) need. The results of analyzing the influence of these factors on the hazard rate of transplantation by the study population will be presented in this order as well.

In evaluating these potential predictor variables it is important to evaluate the dataset for missing data within each measured variable. The program utilized to run the multivariate analysis used list-wise deletion to insure that those variables with missing data be eliminated from the analysis. This means that those entries with missing data for a variable will be eliminated from the analysis resulting in an analysis with complete data for all variables. This effectively decreased the number in the dataset to 28,651 including 14,707 for the transplant group and 13,944 for the individuals who continued to wait for a liver transplant. Table 5.8 below shows the descriptive statistics for the categorical variables to be used in the Multivariate Analysis addressing Aim 3. Table 5.9 below shows the descriptive statistics for the continuous variables in this same sample.

Table 5.8
Descriptive Statistics for Categorical Variables
Final Multivariate Cox Regression Model
UNOS Data: 2002-2007
N=28,651

Characteristics ***Predisposing***	**Transplanted N=14,707 n (%)**	**Not Transplanted N=13,944 n (%)**	***p value***
Gender			<.0001
Male	10,161 (69.1)	8,686 (62.3)	
Female	4,546 (30.9)	5,258 (37.7)	
	14,707	13,944	
Race			<.0001
White	11,144 (75.8)	9,993 (71.7)	
African American	1,282 (8.7)	841 (6.0)	
Hispanic	1,770 (12)	2,446 (17.5)	
Asian/Other	511 (3.5)	664 (4.8)	
	14,707	13,944	
Enabling			
Primary Payer			.0027
Private	8,976 (61)	8,715 (62.5)	
Medicaid	2,321 (15.8)	2,221 (15.9)	
Medicaid/public	3,410 (23.2)	3,008 (21.6)	
	14,707	13,944	
Region			<.0001
1	383 (2.6)	574 (4.1)	
2	1,647 (11.2)	2,010 (14.4)	
3	2,757 (18.7)	1,104 (7.9)	
4	1,434 (9.8)	1,544 (11.1)	
5	1,771 (12.0)	3,593 (25.8)	
6	561 (3.8)	351 (2.5)	
7	1,351 (9.2)	1,199 (8.6)	
8	1,018 (6.9)	706 (5.1)	
9	945 (6.4)	1,391 (10.0)	
10	1,480 (10.1)	620 (4.4)	
11	1,360 (9.2)	852 (6.1)	
	14,707	13,944	
Need Variables			
Diagnoses			<.0001
Hepatitis	615 (4.2)	528 (3.8)	
Alcohol	4,057 (27.6)	3,652 (26.2)	
Biliary	1,541 (10.5)	1,257 (9.0)	
Metabolic	356 (2.4)	189 (1.4)	
HCC	188 (1.3)	172 (1.2)	
Cirrhosis +Other	7,950 (54.1)	8,146 (58.4)	
	14,707	13,944	
Blood Type			<.0001
A	5,609 (38.1)	5,216 (37.4)	
AB	1,967 (13.4)	1,493 (10.7)	
B	851 (5.8)	308 (2.2)	
O	6,280 (42.7)	6,927 (49.7)	
	14,707	13,944	

N=sample size, n=number of observations

Table 5.9
Descriptive Statistics for Continuous Variables
Final Multivariate Cox Regression Model
UNOS Data: 2002-2007
N=28,651

Variable	Censor	N	Mean	SD	Median	Min-	Max	Mann-Whitney p value
Age	Transplanted Non-transplant	14707 13944	52.14 52.77	9.39 9.08	52.00 53.00	18.00 18.00	83.00 80.00	<.0001
Height	Transplanted Non-transplant	14707 13944	172.85 171.04	10.05 10.38	172.72 170.18	142.20 142.24	225.00 223.52	<.0001
Weight	Transplanted Non-transplant	14707 13944	85.68 84.03	19.39 19.60	83.92 81.65	41.00 41.19	200.00 199.58	<.0001

In order to examine the factors associated with liver transplant access a widely used multivariate statistical model for survival data was used called the Cox Proportional Hazards Model. This model is based on a hazard function that is closely related to the survival curve and can therefore explain the Kaplan Meier survival curves previously presented. The dependent variable is the hazard of transplant at a given time, in this case the hazard of liver transplant. And the independent variables are the variables thought to explain the variation in hazard.

There are two important assumptions of the Cox Proportional Hazards Model. The first is the proportional hazards assumption which is that the effects of different variables on survival (or hazard) are constant over time. The second assumption is that the effects of different variables are additive (Crichton, 2002). Generally a univariate analysis is performed initially to determine which potential variables, drawn from theoretical knowledge and the literature, have significance in and of themselves. The

proportional hazards assumption can be testing in the univariate analysis and if violated, further diagnostics can be utilized to correct for this.

A univariate Cox regression analysis of the predisposing, enabling and need variables described was run. The univariate model showed that all predictors were statistically significant. Significant predictors of liver transplant in the univariate model were the predisposing variables: gender, race, and age; the enabling variables: educational level, primary payer and region; and the need variables: height, weight, diagnosis, blood type and MELD.

Problematic, however, were that the variables race, weight, educational level, primary payer, region and diagnosis all showed violations of the proportional hazard assumption. As a precautionary measure and to address the proportional hazard assumption violations found in the univariate analysis, a multivariate model was run to test for the proportional hazard assumption by looking at interactions between region and time (RegionTime), race and time (RaceTime), primary payer and time (PriPaymentTime), educational level and time (EdLevelTime), weight and time (WtTime) and diagnosis and time (DxTime). Results for these proportional hazard time trend tests can be seen below in Table 5.10 below.

Those variables that failed the time trend test, indicating a continued proportional hazard violation, include region, educational level and weight. Race, primary payer and diagnosis did not violate the time trend test of the proportional hazard assumption in this multivariate model. Educational level was excluded from the final analysis due to the fact that 29% of responses were categorized as unknown and could not, by an reasonable

assumptions be assigned to another category. Weight was retained as a variable as well as region, since these variables were considered essential to the research question at hand.

Table 5.10
Multivariate Model Results of Time Trend Test for Proportional Hazard Assumption Violation

Effect (Variable Name)	DF	Wald Chi-Square	Pr > ChiSq
Region and Time (RegionTime)	1	15.4269	<.0001*
Race and Time (RaceTime)	1	2.0735	0.1499
Primary Payer and Time (PriPaymentTime)	1	1.6544	0.1984
Educational Level and Time (EdLevelTime)	1	78.8506	<.0001*
Weight and Time (WeightTime)	1	11.3770	0.0007*
Diagnosis and Time (DXTime)	1	0.7572	0.3842
Region and Time (RegionTime)	1	3.8787	0.0489

*denotes Proportional Hazard Assumption Violation

With diagnostics complete for testing the proportional hazards assumption and variables chosen, the final multivariate Cox regression analysis was run. Given the effect of the implementation of the MELD 15 Share rule seen in Aim 2, a dichotomous period variable was also added to the MV analysis. Variables included the predisposing variables: gender, race, and age; enabling variables: primary payer and region; and need variables: diagnosis, height, weight, blood type and MELD score.

The results of the Multivariate Cox regression for Access to Liver Transplant can be seen below in Table 5.11.

Table 5.11
Multivariate Cox Model of Access to Liver Transplant
UNOS Data: 2002-2007

Variable	Parameter Estimates	Standard Error	Hazard Ratio(CI)
Predisposing Factors			
Gender[1]			
Female	-0.13015	0.02258	0.878** (.840-.918)
Race[2]			
African American	-0.11255	0.02833	0.894** (0.845-0.945)
Hispanic	-0.20651	0.02639	0.813** (0.772-0.857)
Asian/Other	0.17214	0.04352	0.842** (0.773-0.917)
Age			
	0.00428	0.0008541	1.004** (1.003-1.006)
Enabling Factors			
Primary Payer[3]			
Medicaid	0.02673	0.02306	1.027 (0.982-1.075)
Medicare/Public	-0.02572	0.01956	0.975 (0.938-1.013)
Region[4]			
1	-0.48055	0.05256	0.618**(0.554-0.679)
3	0.71035	0.02826	2.035**(1.924-2.138)
4	0.11870	0.03276	1.126** (1.052-1.191)
5	-0.55892	0.03178	0.572**(0.523-0.589)
6	0.35157	0.04691	1.421**(1.280-1.534)
7	-0.11020	0.03364	0.896** (0.830-0.943)
8	0.14549	0.03751	1.157**(1.086-1.253)
9	-0.16874	0.03598	0.845**(0.741-0.846)
10	0.70353	0.03295	2.021**(1.904-2.155)
11	0.35616	0.03338	1.428**(1.300-1.432)
Need Factors			
Diagnosis[5]			
Alcohol	-0.01525	0.04295	0.985 (0.905-1.071)
Biliary	0.11631	0.04722	1.123* (1.024-1.232)
HCC	0.57202	0.08058	1.772**(1.513-2.075)
Metabolic	0.20708	0.06538	1.230**(1.082-1.398)
Cirrhosis/Other	0.03152	0.04118	1.032 (0.952-1.119)
Height			
	0.00454	0.00112	1.005**(1.002-1.007)
Weight			
	- 0.00159	0.0004553	0.998* (0.998-0.999)
ABO[6]			
A	0.11560	0.01719	1.123**(1.085-1.161)
AB	0.34211	0.02450	1.408**(1.317-1.449)
B	0.91989	0.03444	2.509**(2.345-2.684)
MELD			
	0.14079	0.0007569	1.151**(1.149-1.153)
Period	**0.06477**	**0.01579**	**1.067****

Likelihood RatioChi Square=26793.1654 (p<.0001)

Comparison Groups: 1. Gender: Male 2. Race: White 3. Primary Payer: Private 4. Region: 2 5. Diagnoses: Hepatitis 6. ABO Blood Group: O (**p<.05; **p<.0001);*

Multivariate Cox Regression Results by Variable

Predisposing

Gender

In multivariate analysis of those listed for cadaveric liver transplant between 2002 and 2007 while controlling for other predisposing, enabling and need variables females had a lower hazard (risk) of transplant than males. The estimated hazard ratio was .88, indicating that females had 12 percent lower hazard (risk) of transplant than males. Accounting for sampling variability, the decrease in risk for females could be as large as 16 percent or as small as 8 percent (95 percent CI for the hazard ratio 0.84-0.92). This result was very significant with a *p* value <.0001.

Race

In terms of racial disparity, African Americans were 11 percent less likely to receive a cadaveric liver transplants than whites as evidenced by the estimated hazard ratio of .89 for this racial group. Accounting for sampling variability, the decrease in risk for African Americans could be as large as 15 percent and as small 5 percent (95 percent CI for the hazard ration 0.85-0.95). This result was very significant with a *p* value <.0001.

Hispanics were found to be 19 percent less likely than whites to receive a cadaveric liver transplant as evidenced by the estimated hazard ratio of .81 for this racial group. This decreased in risk for Hispanics could be as high as 23 percent and as low as 14 percent (95 percent CI for hazard ratio 0.77-0.86). This result was very significant with a *p* value <.0001. Finally, the Asian/other population of liver candidates has a 16

percent decreased likelihood of receiving a liver transplant as compared to whites as seen in the estimated hazard ratio of .84 for Asian/other population. This decreased risk for Asians could be as high as 23 percent or as low as 8 percent (95 percent CI for hazard ratio 0.773-0.917). This result was very significant with a *p* value <.0001.

Age

In this multivariate analysis, when age was studied continuously, there is a .04 percent increase in hazard of transplant for every year of age. In addition, age was analyzed categorically and there was an increase in likelihood of transplant until after age 75 at which time hazard of transplant is stable. When studied as a categorical variable the reference age was 18-30 years. Those in the age category 31-45 were 14 percent more likely to receive a cadaveric liver transplants than those 30 years old and less as evidenced by the estimated hazard ratio of 1.14. Accounting for sampling variability, the increase in risk for those aged 31-45 could be as large as 25 percent and as small 4 percent (95 percent CI for the hazard ration 1.041-1.257). This result was significant with a *p* value <.05.

Those aged 46-60 years old were found to be 12 percent more likely to receive a liver transplant than those 30 years or less as evidenced by the estimated hazard ratio of 1.12 for this age group. This increased risk for ages 46-60 could be as high as 29 percent and as low as 7 percent (95 percent CI for hazard ratio 1.079-1.291). This result was significant with a *p* value <.05.

The highest hazard of transplant by age group controlling for all other predisposing, enabling and need variables were those 61-75 years of age. This age group

had an estimated hazard ratio of 1.27 indicating that those 61-75 years of age had a 27 percent increased likelihood of receiving a liver transplant than those 30 years of age or less. This increased risk could be as high as 39 percent or as low as 15 percent (95 percent CI for hazard ratio 1.153-1.393). This result was very significant with a *p* value <.0001.

Enabling

Primary Payer

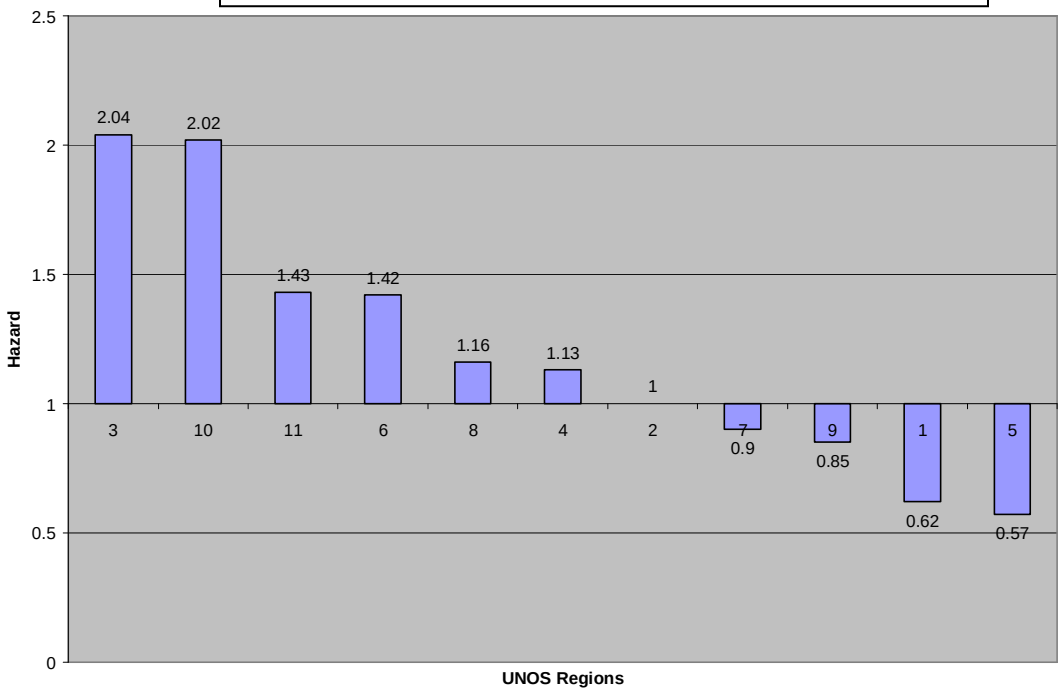
Although the univariate analysis, showed an increased likelihood of liver transplantation among Medicaid and Medicare versus private payers, 5 percent and 8 percent higher respectively, in the multivariate analysis primary payer status was not significant.

Region

There are significant regional differences in hazard of transplant in this multivariate analysis when controlling for all other predisposing, enabling and need variables. Regions 1, 5, 7 and 9 showed a 39 percent, 45 percent, 10 percent, and 16 percent decreased likelihood of liver transplant, respectively, when compared to Region 2. As opposed to the increased likelihood of being transplanted in Regions 3, 4, 6, 8, 10 and 11 which showed a 104 percent, 12 percent, 42 percent, 15 percent, 102 percent and 43 percent increased likelihood of liver transplant, respectively, when compared to Region 2. Results for all Regions 1, 3, 5, 6, 9, 10 and 11 were very significant with *p* values of <.0001. Results for Regions 4, 7, & 8 were significant with *p* values <.05.

Figure 5.3 presents the results of these hazards by UNOS region. This issue of differences in Regional Hazard will be further explored in the chapter through additional multivariate analyses of each of the 11 separate UNOS regions.

Figure 5.5
Multivariate Cox Regression Results
Hazard of Liver Transplant by Region
UNOS Data



Regions 4, 7 and 8 ($p<.05$) and Regions 1, 3, 5, 6, 9, 10, and 11 ($p<.0001$)

Need

Diagnosis

As was previously discussed in Chapter 3, the MELD acuity based system was designed and implemented to allocate organs based on clinical status at a certain point in time. Given the speed with which hepatocelluar cancer (HCC) can spread, when the MELD system of allocation was implemented, it was determined that those with an HCC

diagnosis would receive extra points to be added to their calculated MELD scores based on number and size of tumors identified. Not surprisingly, this multivariate analysis showed that patients with a diagnosis of HCC have a 77 percent increased likelihood of liver transplant when compared to cirrhotic/other patients as evidenced by the Hazard Ratio of 1.772 which was very significant at a *p* value of <.0001. This increased risk of liver transplant could be as high as 107 percent or as low as 51 percent (95 percent CI for hazard ratio 1.513-2.075). The author chose to include this diagnosis in the original population in order to evaluate the effect of HCC in the post-MELD era of allocation. Pair wise comparisons of HCC to other diagnoses (alcohol, biliary related and other) proved to be statistically significant as well.

Height

While holding all other variables constant, for every one centimeter increase in height there is a greater risk of transplant. Specifically, for every 1 cm increase in height there is a .04 percent increased likelihood of being transplanted. This was a very significant result with a *p* value of <.0001. The variable height was also evaluated as a categorical variable. As height of the recipient increases, the hazard for transplant increases with the greatest hazard seen in the tallest patient. Those individuals 180.6cm or taller had a 13 percent increased likelihood of being transplanted when compared to patients less than 165.5cm. This is evidenced by the hazard ratio of 1.137 which was very significant at a p value of <.0001. This increased likelihood of transplant at this height could be as high as 20 percent and as low as 7 percent (95 percent CI for hazard ratio 1.073-1.204).

Weight

As with the height variable, while holding all other variables constant, for every one kilogram increase in height there is a greater risk of transplant. Specifically, for every 1 kg increase in height there is a 1 percent decreased likelihood of being transplanted. This was a significant result with a *p* value of <.0001. When weight was used as a categorical variable these results are more clearly understood.

Except for weight of 83.1-96.6 kg, which showed a 7 percent increase in likelihood of transplantation when compared with those weighing < 71kg, which was significant with a p value of <.05, weight was not a significant variable in determining likelihood of transplantation.

Blood Type

Blood types A, AB and B all showed increased likelihood of liver transplantation when compared with blood type O at 12 percent, 40 percent and 150 percent, respectively. These results were all very significant with *p* values <.0001.

MELD

While holding all other variables constant, for every one point increase in MELD score there is a significantly greater risk of transplant. Specifically, for every 1 point increase in MELD there is a 15 percent increased likelihood of being transplanted, a result that is congruent with the intent of the MELD system to provide organs based on acuity level of liver disease. This was a very significant result with a *p* value of <.0001.

What will be discussed further in Chapter 6 is whether this sufficiently fulfills the objective set forth by the Institute of Medicine.

Period

In order to control for the impact of the implementation of the MELD 15 Share policy, implementation half way through our study period in January of 2005, a dichotomous variable, period, was added to the multivariate model to first assess the effect of period on hazard of transplant and secondly control for this change in allocation when evaluating these predisposing, enabling and need variables of interest. It was found that there is a statistically significant 7% increased risk of transplant in Period 2 (post MELD share 15 rule in 2005) when compared to Period 1 (pre MELD Share 15 in January, 2005).

Summary of Multivariate Model

This multivariate analysis provided data to support the hypotheses that despite the implementation of an acuity based model of liver allocation, disparities in gender, race, age, geographical region, height, weight and ABO blood type exist. In addition, there appears to be a 7% increased likelihood of transplantation after January 2005 compared to the risk of transplantation prior to that time. The implications and discussion of these disparities will follow in Chapter 6. All results of this Multivariate Cox Regression can be seen on page 129 in Table 5.10.

Multivariate Model for Transplantation by Region

In an effort to continue to address Aim 3, to identify factors that contribute to the hazard of liver transplantation by region , 11 separate multivariate Cox regression models were run for each of the 11 UNOS regions. Rather than initially running univariate analyses on all 11 Regions to determine those variables of significance to include in each multivariate model, the best overall multivariate model was used for each of the 11 regressions. While controlling for the predisposing, enabling and need variables utilized in the overall multivariate model, 11 distinct models emerged with unique combinations of significant predictive factors influencing hazard of transplant by region. In addition, as in the overall MV model the variable period was included to determine if the hazard of transplant by region was different pre and post MELD 15 implementation. Results of those factors significant to each region are reported below.

Region 1 (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island & Eastern Vermont)

Region 1 showed a mean time to transplant of 209.73 days, 53.12 days longer than the entire nation. In terms of the enabling variable primary payer Medicaid patient had a 26 percent decreased likelihood of cadaver transplant compared to those with private pay and Medicare patients had a 31 percent decreased likelihood of cadaveric transplant when compared to those with private pay. In addition, the average MELD at transplant for Region 1 was 27.20 (SD: 9.23) and for every 1 point increase in MELD there was a 21 percent increase in likelihood of transplantation in Region 1. There was no period effect found in Region 1.

Region 2 (Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, West Virginia, Northern Virginia)

Region 2 showed a mean time to transplant of 150.36 days, 6.25 days less than the entire nation. In terms of the predisposing variable gender; women had a 14 percent decreased likelihood of cadaveric liver transplant compared to men. In terms of race; African Americans in Region 2 had a 23 percent decreased likelihood of cadaveric liver transplant while Asians had a 30 percent decreased likelihood of liver transplant in Region 2 when compared to whites. In terms of enabling characteristics, patients with Medicaid as their primary payer in Region 2 had a 30 percent increased likelihood of undergoing liver transplant than those with private insurance. And in terms of need variables, patients with hepatocellular carcinoma (HCC) had a 95 percent increased likelihood of liver transplant compared to those with hepatitis. The average MELD at transplant for Region 2 was 22.48 (SD: 8.96) and for every 1 point increase in MELD there was a 15 percent increase in likelihood of liver transplant. There was no effect of period in Region 2.

Region 3 (Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi, Puerto Rico)

Region 3 showed a mean time to transplant of 103.03 days, 53.58 days less than the entire nation. In terms of the predisposing variable gender, women had 20 percent less likelihood of being transplanted then men and African Americans in Region 3 had a 20 percent decreased likelihood of cadaveric liver transplant than whites. In terms of need variables, HCC patients had a 68 percent increased likelihood of transplantation than those with hepatitis. In addition, the average MELD at transplant for Region 3 was 21.73 (SD: 7.73) and for every 1 point increase in MELD there was a 13 percent increase in likelihood of liver transplant. There was no effect of period in Region 3.

Region 4 (Oklahoma and Texas)

Region 4 showed a mean time to transplant of 164.34 days, 7.73 days longer than the entire nation. In terms of the predisposing variable gender, women had a 19 percent decreased likelihood of being transplanted then men and Hispanics had a 33 percent decreased likelihood of being transplanted than whites. Those with Medicaid as a primary payer were 20 percent less likely to be transplanted than those with a private insurance and those with HCC as a diagnosis had a 143 percent increased likelihood transplant were compared to those with hepatitis. In addition, the average MELD at transplant for Region 4 was 23.27 (SD: 8.09) and for every 1 point increase in MELD there was a 15 percent increase in liver transplant. Period showed a 20 percent decreased likelihood of transplantation after January 2005 compared to prior when controlling for all other variables.

Region 5 (Arizona, California, Nevada, New Mexico, Utah)

Region 5 showed a mean time to transplant of 207.50 days, 50.89 days longer than the entire nation. In terms of the predisposing variable race, Hispanics had a 17 percent decreased likelihood of cadaveric liver transplant compared to whites. In terms of need variables, HCC patients had a 75 percent increased likelihood of transplantation than those with hepatitis. In addition, the average MELD at transplant for Region 5 was 28.94 (SD: 10.04) and for every 1 point increase in MELD there was a 19 percent increase in likelihood of liver transplant. There was a period effect found in Region 5 with a 33 percent increased likelihood of transplantation was found following January 2005 when compared to prior when controlling for all other variables.

Region 6 (Alaska, Hawaii, Idaho, Montana, Oregon, Washington)

Region 6 showed a mean time to transplant of 194.04 days, 37.43 days longer than the entire nation. In terms of the predisposing variable race, Hispanics in region 6 had a 37 percent decreased likelihood of cadaveric liver transplants than whites. In terms of need variables, HCC patients had a 188 percent increased likelihood of transplantation than those with hepatitis. In addition, the average MELD at transplant for Region 6 was 21.48 (SD: 6.95) and for every 1 point increase in MELD there was an 18 percent increase in likelihood of liver transplant. There was no period effect found in Region 6.

Region 7 (Illinois, Minnesota, North Dakota, South Dakota, Wisconsin)

Region 7 showed a mean time to transplant of 158.65 days, 2.04 days longer than the entire nation. In terms of the enabling variable Primary Payer, patients with Medicaid had a 28 percent increased likelihood of liver transplant while Medicare patients had an 15 percent increased likelihood of liver transplant when compared to private payers. In terms of need variables, HCC patient have a 125 percent increased likelihood of transplantation than those with hepatitis. In addition, the average MELD at transplant for Region 7 was 25.73 (SD: 9.68) and for every 1 point increase in MELD there was a 14 percent increase in likelihood of liver transplant. No period effect was found in Region 7.

Region 8 (Colorado, Iowa, Kansas, Missouri, Nebraska, Wyoming)

Region 8 showed a mean time to transplant of 172.57 days, 15.96 days longer than the entire nation. In terms of the predisposing variable race; Hispanics had a 47 percent decreased likelihood of transplant when compared to whites. In terms of the enabling variable primary payer; Medicaid patients had a 23 percent increased likelihood

of transplant compared to those with private pay. In terms of need variables, HCC patients had a 43 percent increased likelihood of transplant when compared to hepatitis patients. In addition, the average MELD at transplant for Region 8 was 23.61 (SD: 8.16) and for every 1 point increase in MELD there was a 16 percent increase in likelihood of liver transplant. There was a 27 percent increased likelihood of transplantation after January 2005 than before.

Region 9 (New York and Western Vermont)

Region 9 showed a mean time to transplant of 163.75 days, 7.14 days longer than the entire nation. In terms of the predisposing variable race, Hispanics had a 24 percent decreased likelihood of transplant when compared to whites. In addition, the average MELD at transplant for Region 9 was 24.99 (SD: 10.92) and for every 1 point increase in MELD there was a 16 percent increase in likelihood of liver transplant. There was a period effect found in Region 9 with a 67 percent increased likelihood of transplantation after January 2005 compared to prior.

Region 10 (Indiana, Michigan and Ohio)

Region 10 showed a mean time to transplant of 126.31 days, 30.30 days less than the entire nation. In terms of the predisposing variable race, Asians had a 68 percent decreased likelihood of liver transplant in Region 10 compared to whites. In addition, the average MELD at transplant for Region 10 was 20.03 (SD: 7.62) and for every 1 point increase in MELD there was a 12 percent increase in likelihood of liver transplant. There was a period effect seen in Region 10 with a 28 percent decreased likelihood of transplantation after January 2005 when compared to prior.

Region 11 (Kentucky, North Carolina, South Carolina, Tennessee, and Virginia)

Region 11 showed a mean time to transplant of 180.12 days, 23.51 days longer than the entire nation. In terms of the enabling variable payer status, Medicare patients were 12 percent less likely to be transplanted than private payer patients. In addition, the average MELD at transplant for Region 11 was 22.46 (SD: 7.41) and for every 1 point increase in MELD there was a 17 percent increase in likelihood of liver transplant. There was also a significant period effect in Region 11 where there was a 47 percent increased likelihood of transplantation after January 2005 when compared to prior.

Summary of Regional Analysis:

These regional findings indicate that each and every Region has a very specific set of predictor variables. In addition, factors affecting hazard of transplantation across specific variables by region are discussed below. The predisposing variables gender and race, the enabling variable primary payer and the need variable hepatocellular cancer diagnosis will be described below in an effort to show the regional differences that are present in the current system of acuity-based liver allocation. Although comparisons can't be made between regions in regard to these specific hazards of transplant for each specific variable, the presentation of the data allows the reader to appreciate the significant impact each factor has in a particular UNOS Region. For instance, although gender had a significant negative impact on hazard of transplant in Regions 2, 3 and 4, gender had no significance in risk of transplant for any of the other 8 UNOS Regions. Likewise, the category of primary payer designated as Medicare provided an 15 percent increased hazard of transplant in Region 7 and provided a 31 percent decreased hazard of

transplant in Region 1.

Regional Multivariate Cox Regression Results by Variable

Predisposing

Gender

In UNOS regions 2, 3, and 4 female gender provided a 14 percent, 20 percent, 19 percent decreased likelihood of liver transplantation respectively compared to male gender in each of these respective regions. Although there were 11 separate multivariate analyses performed, these hazards cannot be compared to each other but do provide for a better understanding of gender disparities among UNOS regions. It was only these 3 regions that showed a statistically significant difference between males and females in terms of hazard of transplant.

Race

When controlling for all other predisposing, enabling and need variables in each of the 11 UNOS Regions, there were significant differences across racial categories. In Regions 2 and 3 African Americans showed a decreased likelihood of liver transplant compared to whites by 23 percent and 20 percent respectively. Hispanics, when compared to whites had a 33 percent, 17 percent, 37 percent, 47 percent, and 24 percent decreased likelihood of liver transplantation in Regions 4, 5, 6, 8 and 9 respectively. Finally, Asians/other had a 30 percent decreased likelihood of transplantation in Region 2 and a 68 percent decreased likelihood of transplantation in Region 10 compared to whites. These findings will be discussed in Chapter 6.

Enabling

Primary Payer

Medicaid as a primary payer source appears have provided an increased likelihood of liver transplant in Regions 2, 7, and 8 at 30 percent, 28 percent and 23 percent respectively when compared to private payer as a primary payer source and controlling for all predisposing, enabling and need variables. Medicaid also appears to provide a 26 percent decreased likelihood of transplant in Region 1 when compared to private payer. In addition, Medicare appears to have provided a 15 percent increased risk of transplant in Region 7 while providing a 31 percent, 20 percent, and 12 percent decreased risk of transplant in Regions 1, 4 and 12 respectively, when compared to private payer sources.

Need

Hepatocellular Carcinoma (HCC) Diagnosis

Seven of the eleven UNOS Regions showed an increased likelihood of liver transplantation with the diagnosis of HCC as the etiology of their disease when compared to hepatitis as a diagnosis, when controlling for all other predisposing, enabling and need variables including acuity level (MELD). Region 2 patients with HCC were found to be 95 percent more likely than hepatitis patients to receive a cadaveric liver transplant as evidenced by the estimated hazard ratio of 1.95 for this diagnosis. This increased risk for HCC patients could be as high as 241 percent and as low as 95 percent (95 percent CI for hazard ratio 1.954-3.416). This result was significant with a p value <.05.

Region 3 patients with HCC were found to be 68 percent more likely than

hepatitis patients to receive a cadaveric liver transplant as evidenced by the estimated hazard ratio of 1.68 for this diagnosis. This increased risk for HCC patients could be as high as 159 percent and as low as 9 percent (95 percent CI for hazard ratio 1.091-2.597). This result was significant with a *p* value <.05.

Region 4 patients with HCC were found to be 143 percent more likely than hepatitis patients to receive a cadaveric liver transplant as evidenced by the estimated hazard ratio of 2.43 for this diagnosis. This increased risk for HCC patients could be as high as 234 percent and as low as 36 percent (95 percent CI for hazard ratio 1.36-4.34). This result was significant with a *p* value <.05.

Region 5 patients with HCC were found to be 75 percent more likely than hepatitis patients to receive a cadaveric liver transplant as evidenced by the estimated hazard ratio of 1.75 for this diagnosis. This increased risk for HCC patients could be as high as 165 percent and as low as 16 percent (95 percent CI for hazard ratio 1.158-2.65). This result was significant with a *p* value <.05.

Region 6 patients with HCC were found to be 188 percent more likely than hepatitis patients to receive a cadaveric liver transplant as evidenced by the estimated hazard ratio of 2.88 for this diagnosis. This increased risk for HCC patients could be as high as 640 percent and as low as 12 percent (95 percent CI for hazard ratio 1.12-7.399). This result was significant with a *p* value <.05.

Region 7 patients with HCC were found to be 125 percent more likely than hepatitis patients to receive a cadaveric liver transplant as evidenced by the estimated hazard ratio of 2.246 for this diagnosis. This increased risk for HCC patients could be as high as 272 percent and as low as 35 percent (95 percent CI for hazard ratio 1.355-3.721).

This result was significant with a *p* value <.05.

Region 8 patients with HCC were found to be 167 percent more likely than hepatitis patients to receive a cadaveric liver transplant as evidenced by the estimated hazard ratio of 2.672 for this diagnosis. This increased risk for HCC patients could be as high as 400 percent and as low as 43 percent (95 percent CI for hazard ratio 1.429-4.996). This result was significant with a *p* value <.05.

Hepatocellular carcinoma was a significant predictor variable when compared to hepatitis in Regions 2,3,4,5,6,7 and 8. Discussion of these rates of increased likelihood of liver transplant will be discussed in Chapter 6.

Summary of Multivariate Models by Region

These 11 Multivariate Cox Models for Transplantation by Region are presented in an effort to begin to explain Regional differences in access to liver transplantation. The significant variables within each multivariate model were presented followed by presentation of data specific to each region for time to transplant as well as those significant variables contributing to hazard of transplant in each region. In addition, data specific to the predisposing variables gender and race, enabling variable primary payer and need variable hepatocellular carcinoma diagnosis were also presented. Further discussion of this data will be presented in Chapter 6.

Chapter Summary and Conclusions

Utilizing a national database of all patients listed for cadaveric liver transplant between 2002 and 2007, time to transplant and those variables Anderson (2005) describes

as predisposing, enabling and need variables were studied. Following reporting of descriptive statistics for those having received a liver transplant as well as those who continue to wait, the evaluation of the implementation of the MELD 15 policy change was reported both for the entire population of listed/transplant patients as well as at a regional level.

Following the evaluation of the MELD 15 policy implementation results of several Cox regression analyses were reported. Initially, a univariate analysis identifying those variables that were statistically significant contributors to time to transplant were identified. Diagnostic tests evaluating the proportional hazard assumption were undergone and a final multivariate Cox regression with all significant variables was run while controlling for the differences in time period with the MELD 15 rule change by including an additional variable period in the final multivariate model. In addition, separate multivariate analyses for each of the 11 UNOS Regions were run in order to determine the impact of each variable at a regional level.

In summary, this study finds that there are differences in gender, race and region in the current era of liver allocation. Despite increased transplantation rates for those of greater acuity (MELD>15) since the implementation of the MELD 15 rule, disparities still exist nationally overall and within the 11 UNOS regions. A discussion of the meaning of these findings will be presented in the following chapter.

Chapter 6

Discussion

The overall intent of this research was to evaluate access to liver transplantation given the current system of organ allocation, implemented in 2002. This is the first population-based study using Anderson's Behavioral Model of Access to Care to examine those predisposing, enabling and need variables that influence the likelihood of liver transplantation in the current acuity based allocation system (MELD). This study evaluated transplant access from national and regional perspectives. The policy implications of the MELD 15 Share Rule, implemented in January 2005 will be discussed first, followed by the discussion of the results of the Cox Multivariate Model for the national data. In addition, a discussion of the findings from 11 additional Cox Multivariate Models examining regional results will be explored. Both the national and regional discussions will be organized around two topics: (1) the meaning of the findings presented in Chapter 5 and their congruence or lack of congruence with previous research on access to liver transplantation; (2) the significance and policy implications of these findings. The other topics to be addressed in this discussion: (3) the limitations of the study, (4) the implications for future research and (5) a reiteration of the expanded Anderson model will be addressed at the conclusion of the chapter. A summary of study conclusions completes this chapter.

Aim 1

The first aim of this study was to describe those who have received a liver transplant between 2002 and 2007 compared to those who continue to wait for a transplant during

the same time period. The study population was drawn from the federally mandated United Network of Organ Sharing (UNOS) database. Included were those individuals who were wait-listed for a cadaveric liver transplant starting on February 17, 2002 through November 30, 2007. In this population, those that received a cadaveric liver transplant were compared with those that continued to wait, excluding those that died or were removed from the list due to their condition improving, deteriorating or receiving a living donor liver. In addition, patients less than 18 years old, in acute liver failure, or having previously received a liver transplant were excluded from the sample. The total number of transplants performed during the study time-frame was 33,825. With the exclusions discussed above, the total number of subjects in the study was 32,566 including 17,118 who received cadaveric liver transplants and 15,448 who remained candidates and continued to wait during the study time-frame.

Findings for Aim I showed that males comprised 69 percent of the sample, had a mean age of 52.12 years, a mean height of 172.77 cm and a mean weight of 85.67 kg. Mean MELD score for the transplant group was 19.98. Transplant recipients were primarily high school educated (37 percent), with private insurance (61 percent), the majority of which came from Region 3 (eighteen percent). Blood type O was most prevalent (forty- three percent) and cirrhosis was the primary etiology of disease (fifty-three percent). These descriptive statistics for transplant recipients, when compared to those who continued to wait, were all statistically different with *p values* <.0001 with the exception of primary payer type, which was still significant with *p* at .0014. Those who continued to wait for a liver transplant during this same time frame were also predominantly males (62 percent), with a mean age of 52.76 years, a mean height of

170.96cm and a mean weight of 83.88cm. Mean MELD score for the transplant group was 14.20. Those who continued to wait for a liver were primarily high school educated (thirty-four percent) with private insurance (sixty-two percent). The majority of the transplant recipients came from Region 5 (twenty-five percent), had cirrhosis as a primary etiology of disease (fifty-seven percent) and were of blood type O (forty-nine percent). These findings were consistent with data published on by the United Network for Organ Sharing (UNOS, 2008). These descriptive statistics regarding both wait-listed and transplanted patients have not differed significantly over the past 6 years, since MELD implementation (UNOS, 2008).

The original hypothesis that higher rates of transplant would occur with Caucasian men of a larger body size were correct, however, it appears as though older, as opposed to younger age may be a more positive predictor of transplant. Perhaps this is due to aging demographics in general, an increasing demand by those of all ages for the latest advances in health care, when before such advances were limited to younger, and presumably healthier patients. Private insurance, as a proxy for higher economic status is also not surprising, given the significant cost of and likely higher reimbursement rates for liver transplant surgery. Higher MELD scores, suggesting compliance with the federal mandate to transplant those with higher acuity levels is also expected however, differences in rates of transplantation and continued wait listing by geographic location are not explained by this simple descriptive analysis. Overall these descriptive results suggest disparities across gender, racial, socioeconomic and, perhaps, geographical location. These implications provided support to pursue questions of inequity in hazard of liver transplantation by controlling for all of the predisposing, enabling and need

variables described by Anderson (1995) in his Behavioral Model of Health Services through the use of survival statistics and Multivariate Cox Regression Analyses to be further discussed.

Aim 2

MELD Share 15 Rule. The second aim of the study was to determine how the implementation of the Share 15 Rule in January 2005 impacted time to transplant for MELD acuity levels > or = 15. This was addressed from both a national perspective as well as on a regional basis evaluating the impact on the 11 separate UNOS regions.

In an effort to address the impact of the Share 15 Rule implemented in January 2005 two additional models were run, one testing the impact of the Share 15 Rule on the entire population of wait listed patients/transplanted patients and a second model testing the impact within each of the 11 UNOS regions. Model 1 used a dichotomous MELD predictor (MELD 15 =1 if MELD > or = 15 or MELD 15 = 0 if MELD <15). This was considered a time-varying covariate. In addition, Period was a dichotomous time varying covariate with Period = 0 if the date was before 1/2005 or Period = 1 if the date is after 1/2005 (which is representative of the date of implementation of the MELD 15 rule).

The results of Model 1 showed an increase in likelihood of transplantation for those with MELD > or equal to 15 doubled after the initiation of Share 15 which verifies success of the policy to increase transplants among more acutely ill patients.

Model 2 used the same MELD predictor and period covariates but addressed MELD15 by Region for all 11 UNOS Regions. Slightly different results were found. Unlike the overall doubling of likelihood of transplant for a MELD greater than 15, there

was regional variation with the MELD 15 policy implementation. Statistically significant changes were seen in Regions 2, 3, 4, 5, 6 and 8 where likelihood of transplant increased by 2 to 3 times pre-MELD 15 implementation, whereas, hazard ratio was stable after the MELD 15 rule implementation for regions 1, 7 and 10. These findings suggest that the MELD 15 rule has made a significant impact on access to transplant for greater acuity patients, but again, with regional variation.

The regional differences found when evaluating the MELD 15 Share rule further support the need for continued evaluation of the current regional system of organ allocation as well as the 11 Regions that make up the system. This is a clear example of the measured impact of a policy change in the allocation system. The outcome, hazard of transplant with a higher level of acuity (MELD >= 15), clearly has different affects among the 11 separate regions. If the acuity-based model of organ allocation was solely based on acuity measures, the hazard of transplant in one region based on acuity measure or MELD score should be the same as in another region, and this is not the case. Further evaluation of regional differences in allocation of organs is necessary.

Aim 3

The third aim of this study was to examine the factors associated with time to transplant/hazard of liver transplant between 2002 and 2007, including those predisposing, enabling and need variables Anderson describes (2005) from both a national and a regional basis. Time to transplant was evaluated with the Kaplan Meir method both for the entire population and again for all 11 Regions. Variables were chosen to be studied in an effort to explain these survival curves for the entire population

as well as the 11 individual UNOS regions. These variables were assessed in univariate and multivariate models for association with hazard of transplant, using the Cox Proportional Hazard Model. This is an extensively used multivariate statistical model for survival data. The model provides a means by which to explain survival while allowing, or controlling, for the effects of multiple variables (Crichton, 2002).

Using Anderson's theoretical framework, with guidance from literature reviewing previous liver allocation eras the following variables were chosen. Predisposing variables gender, race and age; enabling factors primary payer and geographical location and need variables diagnosis, MELD score, weight, height and blood type were chosen for study in univariate and multivariate analysis.

In addition, the variable period was added to test for the influence of the implementation of the MELD Share 15 rule in January 2005 since the time period tested ranged from 2002 through 2007 clearly a change in allocation could, in fact, impact the results. Period was = 0 if time was prior to January 12, 2005 and = 1 if on or after January 12, 2005. There was a statistically significant 7 percent increased risk of transplant after 2005 when compared to pre-2005 in the multivariate analysis completed.

An additional benefit of including period as a variable in the multivariate analysis is that we controlled for any changes occurring over the course of the study period and could be confident that hazards derived from other measured variables were indeed accurate over the entire time frame studied.

This same model was used for additional multivariate analyses to address differences across all 11 UNOS regions. A discussion of the results of the multivariate results will be presented below, organized according to those predisposing, enabling and

need variables previously described.

Predisposing Variables

Gender

Access to liver transplantation by gender has shown inconsistent results in previous allocation eras. Historically, the IOM data (Gibbons et al, 2003) did not report gender inequity in regard to liver transplant listing or transplantation, however, others reported longer waiting times, and higher rates of transplants among women (Tuttle et al, 1997). These studies were all performed on data collected prior to MELD implementation.

Studies of the current era of allocation reported a statistically significant increase in transplant rates for males (Freeman et al, 2004) that some researchers have attributed to a systematic bias against women, given the logarithmic weight placed on creatinine in the MELD scoring system (Durand and Valva, 2005) and the inherent bias against women due to their decreased body mass index. In an effort to address this issue, the current study evaluated gender as a predictor, while controlling for acuity level and size (height and weight) and still found an 11% decreased likelihood of liver transplant for females. Although this confirmed the study hypothesis that males would be more likely to be transplanted, size and acuity level did not explain this disparity. Gender, in and of itself, when controlling for all predisposing, enabling and need variables showed an 11% decreased likelihood of transplantation and hence a gender disparity within the current MELD acuity based allocation system.

This gender disparity is significant because it is the first time such a disparity has been identified in the current system of liver allocation when controlling for all

predisposing, enabling and need variables. Body size differences do not contribute to this disparity as these were controlled for with the weight and height variables. However, renal function, as defined by the clinical measure of creatinine in the MELD score, may still contribute to this hazard disparity. In order to address this, calculated glomerular filtration rate (GFR) by Cockcroft-Gault or MDRD estimation should be added as a variable to the model and a new multivariate model should be run to determine if a higher GFR increases the likelihood of transplantation and if there is an interaction with GFR and gender.

There are certainly policy implications for this current gender disparity finding. Clearly further investigation into whether an interaction with GFR and gender contributes to this identified disparity must first be determined. If this is the case, using computer simulated modeling techniques (ULAM) to test for the effectiveness of mitigating these disparities through the use of specific models should be undertaken. Durand and Valva (2005), suggest such a model that would provide an increase in points for every female with a MELD score >19. Determining whether such a model could mitigate the identified gender disparity is essential.

Alternatively, if there is no effect of GFR level on likelihood of transplant by gender then additional research regarding causes for this finding of gender disparity must be explored. Perhaps the influence of educational level, referral issues and/or physician decision-making processes, factors not addressed in the context of this research study, should be explored.

In conclusion, the gender disparity identified by this research study is an issue that needs to be further researched. In addition, these findings, when communicated back to

the federally mandated organizations (UNOS, OPTN) responsible for the equitable distribution of organs, should contribute to a continued process of re-evaluation of the current system of allocation, the ultimate goal of which is to eliminate or, minimally, mitigate the effects of this gender disparity. The author's contribution to the theoretical models used to address access to care in regard to this disparity will be further addressed in the conclusions.

Race

The current study uncovered issues of racial disparity with regard to Hispanics, African Americans and the Asian/other group. Hispanics were found to be 20 percent less likely than whites to receive a cadaveric liver transplant when controlling for the MELD score and other variables. . This disparity has not been reported to date, in the current acuity based system of organ allocation. There are certainly many reasons that this disparity may exist, some of which were addressed in this particular study, others of which were unable to be evaluated. Educational level, could certainly play a role in this disparity, but was not able to be evaluated due to missing data for this variable. Cultural issues such as language barriers and attitudes regarding trust and belief in the health care system may play a role as well as socioeconomic issues addressed below.

In the univariate analysis African Americans were actually found to be 27 percent more likely to receive a cadaveric liver transplants than whites. However, when considered in the multivariate model, while controlling for all previously defined variables, including need, any apparent advantage for blacks disappeared and they were found to 11 percent less likely than whites to receive a cadaveric liver transplant. The

univariate result of an advantage for the African American supports the author's premise that the MELD system of acuity may actually advantage the African American patient given the increased incidence of renal disease in this population. However, when MELD was controlled for, this advantage disappears. It would be important to evaluate an interaction between race and MELD to determine if this might add more to the understanding of this racial inequity.

Finally, controlling for need and all other variables, the Asian population of liver candidates had a 16 percent decreased likelihood of transplantation than the white candidate. This finding is consistent with that for other races studied and may be due to reasons previously addressed.

Previous research evaluating race as a predisposing variable at the time of transplant during the current era of transplantation is limited. Only Freeman and colleagues (2004) evaluated race at the time of transplantation and found increasing rates of liver transplants among whites, African Americans, and Asians on descriptive statistics, but did not address the overall likelihood of transplantation based on race. Although increasing rates of transplantation were found among these groups, disparity among African Americans and Asians, when compared to whites, could still have been present, and not identified.

Interestingly, El-Serag et al (2006), reported a greater likelihood of Asians receiving local (ablation) and surgical (resection) therapy for hepatocellular carcinoma (HCC). Ablation therapy and surgical resection are approaches to remove tumors from the liver as a primary treatment for HCC and/or initiated as a precursor to future liver transplantation therapy. Access to this treatment may, in certain instances, preclude the

need for future liver transplantation and partially explain decreasing likelihood of liver transplant. However, HCC only accounts for about 3% of the total population of liver recipients on an annual basis. So, if there were a relationship between access to other treatment modalities and liver transplant for the Asian population this would certainly not explain the 16% decreased likelihood of transplant found in this population.

Siegel and colleagues (2007) found a lower percentage of Asians with HCC were reported to have received liver transplants than their white counterparts. The study period predominantly involved the pre-MELD era (1998-2002) so it is not possible to compare these divergent results for the Asian population. Given the increased incidence of HCC in the Asian population, evaluation of an interaction between Race and Diagnosis in the post-MELD era of organ allocation would be important to perform to further clarify these identified disparities.

The significance of these racial disparities is difficult to explain. For African American and Hispanic and Asian recipients, issues of educational level and physician decisions at time of selection may play a role. Since education was not able to be added in the multivariate model to determine if there is an education effect, this should be considered in future research. In addition, given that there are decision-making processes that occur among the transplant team at the point of an organ offer in the allocation process, a qualitative research study would also add to the body of knowledge in terms of identifying those additional areas that may contribute to this defined disparity.

An educational effect may help explain several alternative outcomes. A decreased likelihood of transplant in the Hispanic population may be due to an unmeasured educational effect related to language literacy and/or knowledge about liver

transplant as a treatment modality in general. In addition, socioeconomic class, including income and social class were not measured in this study. These variables may contribute to this disparity. Means of defining income level should be identified and tested as an influencing factor in this analysis, in particular in regard to the impact income plays on this racial disparity. Perhaps there is an interaction between income and/or other measures of socioeconomic level or status that need to be considered.

Despite the absence of a significant impact on payer status and hazard of transplant there may be a relationship with primary payer and race that was not explored in this study. Given the high costs of liver transplant as a therapy for end stage liver disease, potential recipients are required to provide proof of ability to pay to be listed for transplantation. This data should then be entered in the UNOS system. Provided it is entered, there is question as to the accuracy of this data going forward, as changing payer sources are not accounted for in the system of reporting in the database used. In addition, if there is a relationship between race and payer status, particularly if minorities of lower income have coverage from Medicaid, for instance, that likely pays at a lower rate than other payment sources, will this influence recipient selection and/or access to liver transplantation? There is much to be studied in regard to these racial disparities. A more accurate measure of socioeconomic status (including income) as well as payer status over time and the influence of educational level are just several variables to be studied that may provide additional understanding of these identified racial disparities.

Age

The current study illustrates an increased likelihood of transplantation of .04 percent for every year of age when controlling for MELD and all other factors. This result, other

than explaining an increased risk of transplant with increasing age has little practical implications. When age was studied as a categorical variable more usable information was obtained. Prior research regarding age as a predictor of transplant using the MELD system of allocation was not found, however, discussion regarding the aging population of liver disease patients abounds in the literature. Age distribution for those awaiting liver transplantation has changed dramatically over the past 20 years. Currently, greater than 60% of those listed for transplant are between 50 and 64 years of age, a statistic that Pomfret and colleagues (2007) suggested was due to the aging U.S.demographics. As the demographics of the country shift to an older cohort of patients, a greater incidence of hepatitis and hepatocellular cancers would likely predominate and subsequently require therapy. It appears, from the results of this current analysis, that this shift in demographics may already be influencing those who are receiving transplants. An issue not addressed or controlled for in this study, however, was whether or not the use of less than optimal donors could be contributing to this statistically significant likelihood of older patients receiving liver transplants.

In addition, in prior years, a relative rate of wait list mortality was reported with increasing age (Freeman et al, 2000) and although those that died while waiting were excluded from this study, improved treatment therapies for liver disease and decreased rates of wait list mortality may have also contributed to increasing numbers of aging patients being transplanted for end stage liver disease (Freeman et al, 2004). The combination of decreased mortality on the waiting list, increasing numbers of older individuals waiting for transplant and willingness to utilize extended criteria donors in older recipients may all contribute to the explanation of increasing age as a predictor of

liver transplantation.

The increasing likelihood of liver transplant by age has significance related to economics, quality of life and survivals in general. As diagnostic measures are extended to the rapidly growing aging population the disparity between supply and demand will also grow. Decisions regarding who will actually receive this increasingly scare resource of donor livers will most assuredly be based on measures of quality of life and survival unless alternative increasing donor sources can be identified (i.e.: older donors for older recipients).

Enabling Variables

Education

Liver transplantation access has been studied in the past in regard to the impact educational level plays on socio-economic status and, in turn, how economic status relates to transplant outcomes (Yoo et al, 2004). There has also been research on the influence educational level has on multiple listing for transplantation (Merion et al, 2004). But no research was identified that addressed educational level as a predictor of liver transplantation. Unfortunately, data on educational level for the population studied showed missing data for 29% of patients and therefore this variable was omitted from the final multivariate model. Perhaps looking at the data for which there is level of education data and running another multivariate analysis would begin to address this question of the potential impact of education would be useful. Certainly, the role education plays in access to liver transplant must be determined and understood to improve upon the current allocation system and potentially mitigate some of the disparities found.

Primary Payer

There have been no studies to date that address ability to pay as a predictor variable in regard to liver transplantation during the current allocation era. Limitations in performing such important research involve the lack of an integrated database to perform such research. In the current study, no significant results were found when comparing private payer to Medicaid and Medicare as primary payers in the national dataset used. There are potential future opportunities available utilizing a linkage with a claims database studied by Gilmore and colleagues (2007) that may prove to be valuable in looking at other payer issues in the future.

Region

Regional disparity has been an identified as issue in all areas of solid organ transplantation from prior to the passage of the Final Rule in 1998. The intent of this Congressional mandate was to put much less emphasis on wait time and keeping organs local and much greater emphasis on the Institute of Medicine's ultimate recommendation to establish an acuity-based model as well as a means by which to establish Organ Allocation Areas (OAAs) serving at least 9 million people to more fairly distribute organs across the United States. Obviously, the latter IOM recommendation to expand Organ Allocation Areas was never adopted and other then computer simulated modeling of different allocation schemes, little data exists that address which areas of the country may, in fact provide either a decreased or increased likelihood of liver transplantation, when holding all other variables constant.

This question was explored in the first multivariate analysis using all 11 UNOS regions as categories of the enabling variable, region. Significant disparities were

identified by region. In addition, a second multivariate analysis by region was run with the same set of predisposing, enabling and predictor variables as this original multivariate model to determine which variables contributed to the increased or decreased likelihood of transplant by region. The former question will be addressed here.

Regions 3, 4, 6, 8, 10, and 11 showed a 12 to 103 percent increased likelihood of being transplanted when compared to reference Region 2. Whereas, Regions 1, 5, 7 and 9 showed a 10 to 43 percent decreased likelihood of being transplanted when compared to reference Region 2. Other pair-wise comparisons showed similar and significant results. Previous research provided very little in terms of explanation of these most recent findings.

Prior research has focused on size of organ procurement organizations (OPOs), indicating that transplants provided at larger OPOs are performed at much higher acuity levels (Trotter and Osgood, 2004). There has also been research on organ allocation disparities among a single UNOS region (Barshes et al, 2007) suggesting that there are disparities across various donor service areas within the same OPO, in one particular region. The questions of disparity across all 11 Regions, when looking for differences in variable effects have not been addressed in the current era of organ allocation.

Since there was no prior research to explain why this disparity across regions exists, a decision to perform further multivariate analysis by region with those predisposing, enabling and need variables utilized in this current analysis was undertaken.

Significance of the Study

In terms of the significance of this multivariate analysis of all regions together, it is clear that the regional disparities identified by the Department of Health and Human Services in 1991 (DHHS, 1991), and again in 1998 through the Institute of Medicine Report (Gibbons et al, 2004) continues to exist. A system of allocation of livers that has changed only minimally since 1991 provides a likely reason for this continued disparity. Although a national governing and oversight body (UNOS) responsible for the equitable distribution of organs exists on a national basis, essentially 11 separate and distinct areas of allocation are present that may have the greatest influence on who receives a transplant.

Allocation has changed only minimally since 1991, with the implementation of an acuity based model of allocation in 2002 and the MELD 15 Share rule in 2005. Clearly, the acuity-based MELD system has contributed to fewer deaths on the waiting list and decreased numbers of patient listings given that accrual of time on the waiting list no longer holds a value. In addition, the MELD 15 Share rule significantly influenced allocation policy, as has been previously discussed in this chapter.

However, the same 11 regions, designated over 20 years ago, exist today with increasing populations of end stage liver disease patients served. Each region has a unique make-up and number of donor service areas, organ procurement agencies, transplant centers, clinical expertise and donors per million population. Although, beyond the scope of this research study, qualitative and quantitative analysis of each region will be necessary to inform future research to help explain the disparity identified within the context of this study.

The policy implications for these findings of regional differences are varied. Although only 3% of patients are multiple-list for a liver transplants (UNOS, 2007), perhaps this will increase with the knowledge that differences in regional access may be influenced by certain identifiable variables. Decisions regarding whether multiple listing should continue to be allowed, and regulations regarding multiple listing will need to be established with implementation of systems of oversight. Of course the opportunity for such multiple-listing would only be possible for those with the financial resources to do so, which may lead to further inequities across socioeconomic lines. It will be necessary to monitor this regional disparity.

In addition, regional disparities identified must come to the attention of the governing bodies responsible, under federal mandate, to provide an equitable system of allocation (UNOS and the OPTN). In addition, this information should be shared with the general public in an effort to put additional pressures on the system to address this identified inequity, which, most likely crosses over to other organ systems since the same 11 geographical regions are utilized in the process of all solid organ allocation.

What this study did not do is take into consideration organ procurement size, number of OPOs within each region, ratio of OPOs to transplant programs per region, number of transplant programs per region as well as characterization of each (i.e.: surgical expertise, tertiary care center versus community hospital setting, for profit versus non-for profit medical centers), percentage of donors per million population etc. These issues of provider supply and organization may contribute to the inequities identified. Consideration of these issues is essential. However, bringing these disparities to light prior to being able to explain all of the reasons why they exist is also essential in order to

determine what possible policy solutions might contribute to improved equity.

Need Variables

Diagnosis

As discussed previously, the MELD acuity-based system was designed and implemented to allocate organs based on clinical status at the time of transplant. No additional points were assigned based on diagnosis, with the exception of hepatoceullular cancer (HCC). In the national system of allocation, given the speed with which HCC can spread, it was determined that those with a diagnosis of HCC would receive extra points to be added to their calculated MELD scores based on the number and size of tumors identified. Not surprisingly, this multivariate analysis showed that patients with a diagnosis of HCC have a 77 percent increased likelihood of liver transplant when compared to hepatitis patients when controlling for MELD an all other factors. The author chose to include this diagnosis in the original population in order to evaluate the effect of HCC in the post-MELD era of allocation. Pair-wise comparisons of HCC to other diagnoses (alcohol, biliary related and other) proved to be statistically significant as well, meaning that it was not just when HCC was compared with hepatitis (the reference diagnosis in the analysis) was a significant difference found, but when HCC was compared with all alcohol, biliary related and diagnosis "other" as well.

This result is significant in that the original intent of providing more immediate transplant to someone with what might be a rapidly growing tumor, contributing to accelerated clinical deterioration is important. What is equally important to understand is whether or not this disadvantages those with other types of liver disease. What is needed

in terms of additional analysis are outcome studies addressing survival and quality of life following transplantation for HCC to address whether or not this policy to provide extra points to those with HCC is a prudent and use of resources.

Height

As the height of the recipient increases, the hazard for transplant increases, by 04% with every 1 centimeter increase in height when controlling for MELD and all other variables. Given the inability to implant a large liver into a smaller body habitus, with the exception of implanting partial grafts, an issue not addressed in this current study, this disparity appears unavoidable.

Weight

Every 1 kilogram increase in weight showed a decreased hazard of transplant by 1 percent when controlling for MELD and all other factors. It is unclear what this result means. It would be logical to theorize that very low weight individuals and those of much greater heights would be much less likely to receive a liver transplant due to organ/body size match issues. Issues for the smaller weight individual could be due to size mismatch between donor liver and recipient habitus. Issues for the larger weight individual, especially if obese, could be due to concerns from the surgeon regarding longer anesthesia time, concern about fat embolism and wound healing issues once immunosuppresed. All these concerns could result in a surgeon's decision not to transplant patients on both ends of the weight continuum, another issue not addressed in this particular study. Despite all these valid concerns, none of these issues were substantiated in the model.

Blood Type

Like the size-mismatch issue described above, blood type requires a compatible match between liver and recipient. With blood-type O as a reference, blood types A, AB and B all showed increased likelihood of liver transplantation at 12%, 38%, and 142% respectively when controlling for MELD and all other factors. There really are no solutions that could mitigate this blood-type mismatch issue, with the exception of technological advances related to organ/ABO mismatch, which is beyond the scope of this research.

MELD

Since the intent of the MELD acuity scale is to provide those with the greatest acuity the needed organs for transplant, if the score were working as designed, the higher the MELD the greater the likelihood of transplant. In this multivariate model this is indeed the case. While holding all other variables constant, for every one point increase in MELD there is a 15 percent increased likelihood of being transplanted, a result that is congruent with the intent of the MELD system, to provide organs based on acuity level of liver disease.

Summary of Multivariate Model

This multivariate analysis provided data to support the hypotheses that despite the implementation of an acuity based model of liver allocation, significant disparities in gender, race, and, geographical region can be found when controlling for all predisposing, enabling and need variables including time period of transplant pre and post MELD 15 implementation. In particular, the regional disparities identified in this

first multivariate analysis led to the construction of separate multivariate analyses for each of the 11 UNOS regions. While controlling for the same predisposing, enabling and need variables utilized in the overall multivariate model, 11 additional multivariate analyses by UNOS region were run. Focus for these analyses will be on differences in time to transplant and the impact gender, race, primary payer status and acuity have on these differences.

Regional Time to Transplant Statistics

This study appears to be the first to evaluate those predisposing, enabling and need variables that explain time to transplant and ultimately access to liver transplant by region in the current acuity-based allocation era. Time to transplant has disparate results among the 11 UNOS Regions of liver allocation. This can be explained by those predisposing, enabling and need variables that Anderson (1995) describes. However, no consistent predictors exist, with the exception of the acuity measure, MELD.

These regional findings indicate that each and every Region has a very specific set of predictor variables. Regional disparities proved distinct for each of the 11 UNOS Regions, however, issues of gender disparity were identified in Regions 2, 3, and 4. Issues of racial disparity were identified in all but Regions 1, 7 and 11. Issues of primary payer disparity were identified in Regions 1, 2, 4, 7, 8 and 11. And finally, issues of differences in transplantation by diagnosis of HCC were significant in 7 of the 11 UNOS regions. These regional findings require further clarification and understanding, however, identification of these disparities is the first step in understanding that there are problems with the current acuity-based allocation system. The significance of the

identified disparities by region creates a basis for discussion and further research related to determining why these disparities exist. In addition, there was a period effect in regions 4,5,8,9,10 and 11, indicating that the MELD Share 15 rule had and impact on hazard of transplant within these regions.

Distinct subsets of predisposing, enabling and need variables appear to determine the likelihood of liver transplant in each of the 11 specific UNOS regions. This makes it difficult to prioritize the many areas of further research in regional disparity. Why do certain variables matter in one region and not in another? What has not been evaluated in the context of allocation is that each and every region has their own variances (meaning exceptions to the general allocation rules) and selection methods that are not standardized, not to mention the impact of center selection criteria, clinical expertise of the transplant team, other available therapies to treat end stage liver disease etc. Some or all of these issues may contribute to the regional disparities identified. Further qualitative as well as quantitative work to evaluate many of these system-based issues is essential.

These identified regional disparities imply that despite the success of the current acuity-based allocation system, in terms of decreased mortality on the waiting list, there are identified disparities across predisposing, enabling and need characteristics requiring further study and analysis. Although the federal mandate to decrease mortality on the wait list and develop an acuity-based model of organ allocation was met, disparity across gender, racial, payer status and diagnosis had not been identified either before MELD implementation or after, to any significant degree.

Geographic regional disparity, on the other hand, dates back to the original IOM report from 1998. Similar results were found when studying Era 1 of the organ allocation

system (1995-1998). Analyzing over 33,000 records of wait list and transplant patients, statistical differences in wait time for non-acutely ill patients was found. In addition, based on differences in volume of patients served by varying-sized OPOs, recommendations to standardize the number of patients served to 9 million people was recommended but never adopted (Gibbons, Meltzer, & Duan, 2000; Gibbons et al, 2003).

Now, ten years later, we have an acuity based model that has decreased mortality on the waiting list but continues to provide a geographic disparity. It is not surprising that this geographic disparity still exists given there have been no policy changes to a system where similar disparities were reported years ago. However, now additional disparities across gender and race among the entire population and varying combinations of disparity by region in terms of gender, race, payer status and diagnosis exist.

What was not evaluated in the current study were the characteristics of each Donor Service Area (DSA), Organ Procurement Organization (OPO) and Transplant Center that would most assuredly help inform these issues of disparity that have been brought to light. In addition, local and regional variances regarding allocation exist and need to be considered when trying to understand these disparities.

Important to note, however, is that these disparities exist, whether or not additional variables contribute to this disparity. It is imperative that there be acknowledgement of this issue of health disparity and continued study and policy development to address these disparities occur.

Limitations of the Study

There were limitations to this study, primarily related to data availability and analysis and competing risks. These limitations will be discussed below.

Data. Data utilized for this study was extracted from a large federally funded dataset, making it a secondary analysis of previously collected data. Each element of data reported is self-reported by either an organ procurement agency or a transplant program, which, although verified by the United Network for Organ Sharing, makes this data dependent on systems and mechanisms of collection that could be problematic. In addition, although data entry for all data points are requested and required, reports can be submitted that are not 100% complete.

This issue was problematic in the current study in regard to the variable educational level. Even though educational level was a variable of significant interest in the study and included in the database, it was not able to be included in the final multivariate model because the percent of missing observations for this variable were too high. Unfortunately, there was not a mechanism by which to follow-up on the missing values for this item.

In addition to missing data, given the size and complexity of this data, significant interface with an expert statistician was necessary throughout the course of the study. Although invaluable, this type of required support could limit future research in this area due to what may become prohibitive financial costs. Unless one is a statistical expert, utilizing a Cox regression analysis, especially on such an extensive database, could prove untenable.

The lack of education as a variable to be measured severely limited the potential strength of the study given the significance this enabling characteristic may play in the allocation process.

Analysis. Given the complexity and significant variables to be analyzed from both a national and regional perspective, additional multivariate analyses using interactions between specific variables were not undertaken. In particular, interactions between MELD and region as well as region and race and region and gender would have strengthened the results of this study, regardless of the findings.

An additional multivariate analysis was run following the completion of the study with the interaction term gender*Race. This interaction was significant with a *p value* of .0137 in the large model but only significant in one of the eleven regional analyses (Region 4). Further study of this and other interactions should be undertaken in future studies.

Competing Risks. A study design decision made early on to exclude those who died while waiting for liver transplant was made. Although this was an appropriate decision given the aims of the research, this decision could be criticized for several reasons. Those patients that died or became too sick to transplant may, in fact, look very different than those who were ultimately included in the study, hence providing further data to evaluate in terms of potential or perceived inequities. Including these patients would have added an additional statistical challenge to the research but may have also been able to inform the researcher regarding potential differences in regional acuities that were not accounted for in the research study performed.

Implication for Future Research

There are many implications for future research. These will be presented in terms of Anderson's predisposing, enabling and need variables.

Predisposing

Gender. Calculated glomerular filtration rate, either by Cockcroft-Gault or MDRD method should be added as a variable to the multivariate model to determine if a higher GFR increases the likelihood of transplantation. If this is the case, an interaction between GFR and gender should also be added to the model to determine if GFR mediates the gender disparity seen in this original study. If there is such an interaction replication of the single center study by Cholangitis and colleagues (2007) to further evaluate renal dysfunction in males versus females by studying glomerular filtration rate by "gold standard" of inulin secretion should be considered.

Race. In terms of the racial disparities identified in this study, several areas need further research. First, qualitative work in regard to the decision making process of the surgeon upon accepting an organ for transplant is a body of knowledge that would prove invaluable to understanding the subjective nature of the organ allocation system. The means by which decisions are made when accepting an organ for a particular patient is an area that has never been addressed. Issues of racial bias are not the only potential considerations. There has been literature to support the increased incidence of rejection in solid organ transplants among different racial groups and this knowledge may certainly contribute to decisions made during acceptance of an organ for transplant purposes. Although there exist a very objective measure of acuity and many algorithms specific to the inner workings of every transplant center, it remains a fact that when the call comes

in to offer an organ to a program it is most often the surgeon who decides if that organ is suitable for the specific person it is being offered to. Although substantiation is required explaining why an organ is declined for a specific patient, there may be yet unmeasured reasons for decline, such as concern over immunologic interaction and/or gender or racial bias based on a physiologic or socioeconomic basis. Evaluating these potential impacts, although difficult to study, will be important to add to the current body of knowledge regarding disparity.

In addition, the measurement of language literacy, especially for the Hispanic patient population may prove valuable in understanding disparities in likelihood of transplant previously discussed under significance of racial disparity in this chapter.

Enabling

Age. There is significant additional research to be done with age and the issue of the increasing age demographic in the transplant population. As suggested in the discussion, determining quality of life and survivals post-transplant may provide insight into the value of the current system for the aging population. In addition, determining if higher risk donors and/or older aged donors prove to be an acceptable solution to the growing need for organs among all aged populations, but in particular for the older patient, could prove valuable as well. A qualitative analysis regarding physician attitude and selection for this group, as discussed previously, would also be an important area to explore.

Education. Given that fact that education was not utilized due to missing data, future researchers must look for and identify ways to include educational level in a future studies. Perhaps using a smaller sample of those transplanted patients for whom

educational level from the UNOS database is available would result in acceptable data to measure educational level. Important to do once educational level were identified and if found to be significant would be to interact educational level with race, region and gender to determine if there is an impact on these resultant disparities.

Region. Additional analysis of regional disparities in relation to OPO size, percentage of donors per million population served, the number of transplant centers served, the clinical expertise of the transplant team, center specific selection criteria and the availability of other therapies to treat end stage liver disease along with regional differences in allocation and consideration of the granting of exception points to the MELD score by region should be undertaken.

Need

Diagnosis. Diagnosis, in particular the study of HCC, should involve survival and quality of life following transplant to determine if the advantage the allocation system now provides the HCC patient in terms of likelihood of transplantation is appropriate.

Size. As discussed earlier with race and socioeconomic considerations, an analysis of physician decision-making will inform the process of organ acceptance and differences across centers.

Summary

This research study, undertaken to evaluate access to liver transplant in the current system of acuity-based organ allocation is merely a jumping off place to begin to understand a federally-mandated system of resource allocation, how it operates and the variables that explain or help define the access or disparity that exists. Although the results proved not only statistically significant in terms of disparities across gender, race

and geographical lines, the possibilities of future work within this policy laden arena are limitless. Continued evaluation of the identified disparities through further quantitative and qualitative research regarding regional variability and other decision making processes involved with allocation will be important to explore.

Should this model of evaluating health care delivery systems prove valuable and informative, similar models to study allocation across other organ systems could be applied. In addition, evaluation of other treatment regimes for chronic and acute disease processes could be pursued with a similar model as well.

In summary, this research of the acuity based system of liver transplantation has identified both disparities in the predisposing variables of gender and race as well as the enabling variable, geography while controlling for all other predisposing, enabling and need variables. The first multivariate analysis provided an evaluation of the MELD 15 rule that illustrated the increased incidence of transplantation for those with MELDS > or = 15 in 9 of the 11 UNOS Regions, a clear example of a successful policy implementation.

The second model helped explain the survival analysis identified by the Kaplan Meier Method. Model 3 involved 11 additional Multivariate Analyses each explaining separate UNOS regions and identified similar disparities in addition to differences in primary payer source and diagnosis by region. The methods used proved successful in the ability to fulfill the aims set forth by the study. Continued work will be required to further understand this complicated system of resource allocation and access to care. Perhaps this research contribution will help provide guidance to future researchers in

their quest to understand the role of health policy in providing for or evaluating a framework for access.

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Appendices

Appendix A
Research Studies by Study Era and Variables

Researcher (Date)	Data Analysis Collection Dates	Data Source	Era 1 Pre-CPS (before 1997)	Era 2 CPS (1998-2002)	Era 3 MELD (since 2/28/02)	Variables Studied
Ahmed	2/27/02-4/30/06	UNOS			X	Geography
Cholangitis (2007)	?suspect current	England single center			?X	Gender
Eckhoff (1997)	10/89 – 1/97	UNOS	X			Race
Eckhoff (1998)	10/89 – 12/96	UNOS	X			Race
Ellison (2003)	1/20/98-12/31/00	UNOS		X		Geography
Freeman (2000)	1/1/97 – 12/31/97	UNOS	X			Race, age, Geography
Freeman (2004) Results of 1st YR of New Allocation System	2/27/01 – 2/27/02 2/27/02 – 2/27/03	UNOS & SS Death Registry		X	X	Race, gender, geography
Gibbons (1/2000) Report of IOM review 7/99	1995 – 1999	UNOS	X	X (some Era 2)		Race, gender, geography, acuity
Gibbons (7/2000)	1998	UNOS		X		Acuity, geography

Appendix A
Research Studies by Study Era and Variables

Researcher (Date)	Data Analysis Collection Dates	Data Source	Era 1 Pre-CPS (before 1997)	Era 2 CPS (1998-2002)	Era 3 MELD (since 2/28/02)	Variables Studied
Gibbons (2003) Report of IOM review 7/99	1995 - 1999	UNOS	X	X		Race, gender, geography, acuity
Julapalli (2005)	10/2002 – 9/2003	Single VA Center			X	Race, age
Kemmer	2/02-10/05	UNOS			X	Geography
Klassen (1998)	10/1/90-12/31/92	?	X			Race, age, gender
Merion (2004)	7/97 – 6/00	UNOS	X	X		Education, Dual-Listing
Nair (2002)	1988 - 1996	UNOS	X			Race, outcomes
Ozminkoski (1993)	1986-1987	HCUP	X			Gender, age, $, geography, race
Reid (2004)	1994 - 1998	Census & UNOS	X	X		Gender, race, age
Roberts (2006)	4/1/02 – 4/1/03	UNOS			X	Geography
Schaffer (2003)	2/02 – 11/02	UNOS			X	Geography
Stahl (2005)	1993-2000	UNOS	X	X		Geography
Trotter-Osgood (2004)	2/02 – 3/03	UNOS			X	Geography
Tuttle-Newhall (1997)	1988-1993	NC State discharge data	X			Age, gender, $, geography
Yoo (2004)	1987-2001	UNOS	X	X		Race, $, outcomes, &, SES

Appendix B
UNOS Transplant Candidate Registration Form (TCR)

Provider Information
Recipient Center:
Candidate Information
Organ Registered: Date of Listing or Add:
Last Name: First Name: MI:
Previous Surname:
SSN: Gender: ○ ○ ● Male ○ ○ ● Female
HIC: DOB:
State of Permanent Residence:
Permanent ZIP Code: -
Is Patient waiting in permanent ZIP code: ○ ○ ● YES ○ ○ ● NO ○ ○ ● UNK
Ethnicity/Race:
(select all origins that apply)
American Indian or Alaska Native
American Indian
Eskimo
Aleutian
Alaska Indian
American Indian or Alaska Native: Other
American Indian or Alaska Native: Not Specified/Unknown
☐ ☐
☐ ☐
☐ ☐
☐ ☐
☐ ☐
☐ ☐
Asian
Asian Indian/Indian Sub-Continent
Chinese
Filipino
Japanese
Korean
Vietnamese
Asian: Other
Asian: Not Specified/Unknown
☐ ☐
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Black or African American
African American
African (Continental)
West Indian
Haitian
Black or African American: Other
Black or African American: Not Specified/Unknown
☐ ☐
☐ ☐
☐ ☐
☐ ☐
☐ ☐
☐ ☐
Hispanic/Latino

Mexican
Puerto Rican (Mainland)
Puerto Rican (Island)
Cuban
Hispanic/Latino: Other
Hispanic/Latino: Not Specified/Unknown

Native Hawaiian or Other Pacific Islander
Native Hawaiian
Guamanian or Chamorro
Samoan
Native Hawaiian or Other Pacific Islander: Other
Native Hawaiian or Other Pacific Islander: Not Specified/Unknown

White
European Descent
Arab or Middle Eastern
North African (non-Black)
White: Other
White: Not Specified/Unknown

Citizenship:
U.S. CITIZEN
RESIDENT ALIEN
NON-RESIDENT ALIEN, Year Entered US
Year of Entry to the U.S.
Highest Education Level:
NONE
GRADE SCHOOL (0-8)
HIGH SCHOOL (9-12)
ATTENDED COLLEGE/TECHNICAL SCHOOL
ASSOCIATE/BACHELOR DEGREE
POST-COLLEGE GRADUATE DEGREE
N/A (< 5 YRS OLD)
UNKNOWN
Medical Condition at time of listing:
IN INTENSIVE CARE UNIT
HOSPITALIZED NOT IN ICU
NOT HOSPITALIZED
Patient on Life Support: YES NO
Ventilator
Artificial Liver
Other Mechanism, Specify
Specify:
Functional Status:
Physical Capacity:
No Limitations
Limited Mobility
Wheelchair bound or more limited

Not Applicable (< 1 year old or hospitalized)
Unknown

Working for income: YES NO UNK

If No, Not Working Due To:

If Yes:

Working Full Time
Working Part Time due to Demands of Treatment
Working Part Time due to Disability
Working Part Time due to Insurance Conflict
Working Part Time due to Inability to Find Full Time Work
Working Part Time due to Patient Choice
Working Part Time Reason Unknown
Working, Part Time vs. Full Time Unknown

Academic Progress:

Within One Grade Level of Peers
Delayed Grade Level
Special Education
Not Applicable < 5 years old
Status Unknown

Academic Activity Level:

Full academic load
Reduced academic load
Unable to participate in academics due to disease or condition
Not Applicable < 5 years old/ High School graduate
Status Unknown

Previous Transplants:

Organ Date Graft Fail Date

If there are any prior transplants that are not listed here, please contact the UNet Help Desk to have the transplant event added to the database by calling 800-978-4334 or by emailing unethelpdesk@unos.org.

Previous Pancreas Islet Infusion: YES NO UNK

Source of Payment:

Primary:

Specify:

Secondary:

Clinical Information: AT LISTING

Height: ft. in. cm **%ile ST=**

Weight: lbs kg **%ile ST=**

BMI: %ile

ABO Blood Group:

Primary Diagnosis:

Specify:

Secondary Diagnosis:

Specify:

General Medical Factors:

Diabetes:

No
Type I
Type II
Type Other
Type Unknown
Diabetes Status Unknown

Dialysis:

No dialysis
Hemodialysis
Peritoneal Dialysis
CAVH: Continuous Arteriovenous Hemofiltration
CV VH: Continuous Venous/Venous Hemofiltration
Dialysis Status Unknown
Dialysis-Unknown Type was performed

Peptic Ulcer:
- No
- Yes, active within the last year
- Yes, not active within the last year
- Unknown

Angina:
- No
- Yes, and documented Coronary Artery Disease
- Yes, with no documented Coronary Artery Disease
- Yes, but Coronary Artery Disease unknown
- Status Unknown

Drug Treated Systemic Hypertension: YES NO UNK

Symptomatic Cerebrovascular Disease:
YES NO UNK

Symptomatic Peripheral Vascular Disease: YES NO UNK

Drug Treated COPD: YES NO UNK

Pulmonary Embolism: YES NO UNK

Any previous Malignancy: YES NO UNK

Specify Type:
- Skin Melanoma
- Skin Non-Melanoma
- CNS Tumor
- Genitourinary
- Breast
- Thyroid
- Tongue/Throat/Larynx
- Lung
- Leukemia/Lymphoma
- Liver
- Other, specify

Specify:

Most Recent Serum Creatinine: mg/dl **Name:**

Liver Medical Factors

Name: YES NO UNK

Previous Upper Abdominal Surgery: YES NO UNK

Spontaneous Bacterial Peritonitis: YES NO UNK

History of Portal Vein Thrombosis: YES NO UNK

History of TIPSS: YES NO UNK

Appendix C
UNOS Transplant Recipient Registration Form (TRR)

Name: DOB:
SSN: Gender:
HIC: Tx Date:
State of Permanent Residence:
Permanent Zip: -

Provider Information

Recipient Center:
Surgeon Name:
UPIN#:

Donor Information

UNOS Donor ID #:
Donor Type:

Patient Status

Primary Diagnosis:
Specify:
Date of: Report or Death:
Patient Status:

- LIVING
- DEAD
- RETRANSPLANTED

Primary Cause of Death:
Specify:
Contributory Cause of Death:
Specify:
Contributory Cause of Death:
Specify:

Transplant Hospitalization:

Date of Admission to Tx Center:
Date of Discharge from Tx Center:
Was patient hospitalized during the last 90 days prior to the transplant admission: YES NO UNK
Medical Condition at time of transplant:

- IN INTENSIVE CARE UNIT
- HOSPITALIZED NOT IN ICU
- NOT HOSPITALIZED

Patient on Life Support: YES NO

- Ventilator
- Artificial Liver
- Other Mechanism, Specify

Specify:
Functional Status:
Physical Capacity:

- No Limitations
- Limited Mobility
- Wheelchair bound or more limited
- Not Applicable (< 1 year old or hospitalized)
- Unknown

Working for income: YES NO UNK
If No, Not Working Due To:
If Yes:

- Working Full Time
- Working Part Time due to Demands of Treatment
- Working Part Time due to Disability
- Working Part Time due to Insurance Conflict

Working Part Time due to Inability to Find Full Time Work
Working Part Time due to Patient Choice
Working Part Time Reason Unknown
Working, Part Time vs. Full Time Unknown

Academic Progress:

Within One Grade Level of Peers
Delayed Grade Level
Special Education
Not Applicable < 5 years old
Status Unknown

Academic Activity Level:

Full academic load
Reduced academic load
Unable to participate in academics due to disease or condition
Not Applicable < 5 years old/ High School graduate
Status Unknown

Source of Payment:

Primary:

Specify:

Secondary:

Clinical Information : PRETRANSPLANT

Height: ft. in. cm **%ile ST=**
Weight: lbs kg **%ile ST=**
BMI: %ile
Previous Transplants:
Previous Transplant Organ Previous Transplant Date Previous Transplant Graft Fail Date
If there are any prior transplants that are not listed here, please contact the UNet Help Desk to have the transplant event added to the database by calling 800-978-4334 or by emailing unethelpdesk@unos.org.

Viral Detection:

Have any of the following viruses ever been tested for:
(HIV, CMV, HBV, HCV, EBV)

YES NO

HIV: YES NO

Test Result

Was there clinical disease (ARC, AIDS): YES NO UNK

Antibody:

Positive
Negative
Not Done
UNK/Cannot Disclose

RNA:

Positive
Negative
Not Done
UNK/Cannot Disclose

CMV: YES NO

Test Result

Was there clinical disease: YES NO UNK

IgG:

Positive
Negative
Not Done
UNK/Cannot Disclose

IgM:

Positive
Negative
Not Done
UNK/Cannot Disclose

Nucleic Acid Testing:
Positive
Negative
Not Done
UNK/Cannot Disclose
Culture:
Positive
Negative
Not Done
UNK/Cannot Disclose
HBV: YES NO
Test Result
Was there clinical disease: YES NO UNK
Liver Histology:
Positive
Negative
Not Done
UNK/Cannot Disclose
Core Antibody:
Positive
Negative
Not Done
UNK/Cannot Disclose
Surface Antigen:
Positive
Negative
Not Done
UNK/Cannot Disclose
Surface Antibody:
Positive
Negative
Not Done
UNK/Cannot Disclose
E Antigen:
Positive
Negative
Not Done
UNK/Cannot Disclose
HBV DNA:
Positive
Negative
Not Done
UNK/Cannot Disclose
HDV (Delta Virus):
Positive
Negative
Not Done
UNK/Cannot Disclose
HCV: YES NO
Test Result
Was there clinical disease: YES NO UNK
Liver Histology:
Positive
Negative
Not Done
UNK/Cannot Disclose
Antibody:
Positive

Negative
Not Done
UNK/Cannot Disclose

RIBA:
Positive
Negative
Not Done
UNK/Cannot Disclose

HCV RNA:
Positive
Negative
Not Done
UNK/Cannot Disclose

EBV: YES NO

Test Result

Was there clinical disease: YES NO UNK

IgG:
Positive
Negative
Not Done
UNK/Cannot Disclose

IgM:
Positive
Negative
Not Done
UNK/Cannot Disclose

EBV DNA:
Positive
Negative
Not Done
UNK/Cannot Disclose

Any tolerance induction technique used: YES NO UNK

Pretransplant Lab Date:

SGPT/ALT: U/L **ST=**

Specify:

Clinical Information : TRANSPLANT PROCEDURE

Multiple Organ Recipient

Were extra vessels used in the transplant procedure:

Surgical Procedure:
ORTHOTOPIC
HETEROTOPIC

Procedure Type:
Whole Liver
Partial Liver, remainder not Tx or Living Transplant
Split Liver
Whole Liver with Pancreas (Technical Reasons)
Partial Liver with Pancreas (Technical Reasons)
Split Liver with Pancreas (Technical Reasons)

Split Type:

Preservation Information:

Warm Ischemia Time (include anastomotic time): min **ST=**

Total Cold Ischemia Time (if pumped, include pump time): hrs **ST=**

Risk Factors:

Did Patient receive 5 or more units of packed red blood cells within 48 hours prior to transplantation due to spontaneous portal hypertensive bleeding:
YES NO UNK

Spontaneous Bacterial Peritonitis: YES NO UNK

Previous Abdominal Surgery: YES NO UNK
Portal Vein Thrombosis: YES NO UNK
Transjugular Intrahepatic Portacaval Stint Shunt: YES NO UNK
Incidental Tumor found at time of Transplant: YES NO UNK
If yes, specify tumor type:
- Hepatocellular Adenoma
- Hemangioma
- Hemangioendothelioma
- Angiomyolipoma
- Bile Duct Cystadenocarcinoma
- Cholangiocarcinoma
- Hepatocellular Carcinoma
- Hepatoblastoma
- Angiosarcoma
- Other Primary Liver Tumor, Specify

Specify:

Clinical Information : POST TRANSPLANT

Pathology Conf. Liver Diag. of Hospital Discharge:

Specify:

Graft Status: Functioning Failed

If death is indicated for the recipient, and the death was a result of some other factor unrelated to graft failure, select Functioning.

Date of Graft Failure:

Causes of graft failure:

Primary Graft Failure YES NO UNK
Vascular Thrombosis YES NO UNK
Biliary Tract Complication YES NO UNK
Hepatitis: DeNovo YES NO UNK
Hepatitis: Recurrent YES NO UNK
Recurrent Disease (non-Hepatitis) YES NO UNK
Acute Rejection YES NO UNK
Infection YES NO UNK

Other, Specify:

Discharge Lab Date:

Total Bilirubin: mg/dl **ST=**

SGPT/ALT: U/L **ST=**

Serum Albumin: g/dl **ST=**

Serum Creatinine: mg/dl **ST=**

INR: ST=

Did patient have any acute rejection episodes between transplant and discharge:

- Yes, at least one episode treated with anti-rejection agent
- Yes, none treated with additional anti-rejection agent
- No

Was biopsy done to confirm acute rejection:

- Biopsy not done
- Yes, rejection confirmed
- Yes, rejection not confirmed

Treatment

Biological or Anti-viral Therapy: YES NO Unknown/Cannot disclose

If Yes, check all that apply:

- [ ] Acyclovir (Zovirax)
- [ ] Cytogam (CMV)
- [ ] Gamimune
- [ ] Gammagard
- [ ] Ganciclovir (Cytovene)
- [ ] Valgancyclovir (Valcyte)
- [ ] HBIG (Hepatitis B Immune Globulin)
- [ ] Flu Vaccine (Influenza Virus)

Lamivudine (Epivir) (for treatment of Hepatitis B)
Other, Specify
Valacyclovir (Valtrex)

Specify:
Specify:

Other therapies:

YES NO

If Yes, check all that apply:

Photopheresis
Plasmapheresis
Total Lymphoid Irradiation (TLI)

Immunosuppressive Information

Are any medications given currently for maintenance or anti-rejection: YES NO

Did the patient participate in any clinical research protocol for immunosuppressive medications: YES NO

If Yes, Specify:

Immunosuppressive Medications

View Immunosuppressive Medications

Definitions Of Immunosuppressive Medications

For each of the immunosuppressive medications listed, select **Ind** (Induction), **Maint** (Maintenance) or **AR** (Anti-rejection) to indicate all medications that were prescribed for the recipient during the initial transplant hospitalization period, and for what reason. If a medication was not given, leave the associated box(es) blank.

Induction (Ind) immunosuppression includes all medications given for a short finite period in the perioperative period for the purpose of preventing acute rejection. Though the drugs may be continued after discharge for the first 30 days after transplant, it will not be used long-term for immunosuppressive maintenance. Induction agents are usually polyclonal, monoclonal, or IL-2 receptor antibodies (example: Methylprednisolone, Atgam, Thymoglobulin, OKT3, Simulect, or Zenapax). Some of these drugs might be used for another finite period for rejection therapy and would be recorded as rejection therapy if used for this reason. For each induction medication indicated, write the total number of days the drug was actually administered in the space provided. For example, if Simulect or Zenapax was given in 2 doses a week apart, then the total number of days would be 2, even if the second dose was given after the patient was discharged.

Maintenance (Maint) includes all immunosuppressive medications given before, during or after transplant *for varying periods of time which may be either long-term or intermediate term with a tapering of the dosage until the drug is either eliminated or replaced by another long-term maintenance drug* (example: Prednisone, Cyclosporine, Tacrolimus, Mycophenolate Mofetil, Azathioprine, or Rapamycin). This does not include any immunosuppressive medications given to treat rejection episodes, or for induction.

Anti-rejection (AR) immunosuppression includes all immunosuppressive medications given for the purpose of treating an acute rejection episode during the initial post-transplant period or during a specific follow-up period, usually up to 30 days after the diagnosis of acute rejection (example: Methylprednisolone, Atgam, OKT3, or Thymoglobulin). When switching maintenance drugs (example: from Tacrolimus to Cyclosporine; or from Mycophenolate Mofetil to Azathioprine) because of rejection, the drugs should not be listed under AR immunosuppression, but should be listed under maintenance immunosuppression.

If an immunosuppressive medication other than those listed is being administered (e.g., new monoclonal antibodies), select Ind, Maint, or AR next to Other Immunosuppressive Medication field, and enter the full name of the medication in the space provided. **Do not list non-immunosuppressive medications.**

Ind. Days ST

Steroids (Prednisone,Methylprednisolone,Solumedrol,Medrol,Decadron)
Atgam (ATG)
OKT3 (Orthoclone, Muromonab)

Thymoglobulin
Simulect - Basiliximab
Zenapax - Daclizumab
Azathioprine (AZA, Imuran)
EON (Generic Cyclosporine)
Gengraf (Abbott Cyclosporine)
Other generic Cyclosporine, specify brand:
Neoral (CyA-NOF)
Sandimmune (Cyclosporine A)
Mycophenolate Mofetil (MMF, Cellcept, RS61443)
Tacrolimus (Prograf, FK506)
Sirolimus (RAPA, Rapamycin, Rapamune)
Myfortic (Mycophenolate Sodium)

Other Immunosuppressive Medications

Ind. Days ST Maint AR

Campath - Alemtuzumab (anti-CD52)
Cyclophosphamide (Cytoxan)
Leflunomide (LFL)
Methotrexate (Folex, PFS, Mexate-AQ, Rheumatrex)
Rituximab
Other Immunosuppressive Medication, Specify
Other Immunosuppressive Medication, Specify

Investigational Immunosuppressive Medications

Ind. Days ST Maint AR

Everolimus (RAD, Certican)
FTY 720

Appendix D
Descriptive Statistics for UNOS Regions

Region 1. In Region 1 (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Eastern Vermont) males comprised 74.8 percent of the transplanted group which was predominantly white (86.4 percent) between the ages of 46-60 (66.6 percent) with a mean age of 51.26 years, high school educated (41.6 percent), with private insurance (66.4 percent), blood type O (43.4 percent), mean height 171.99cm, mean weight 84.69kg and a mean MELD score of 21.60. The most common diagnosis of transplant recipients in Region 1 was cirrhosis/other (42.76 percent). Non-transplants in Region 1 were also predominantly male (67.5 percent), white (84.6 percent), between the ages of 46-60 (67.7 percent) with a mean age of 51.44 years, educational level not disclosed, with private insurance (62.1 percent), blood type O (49.8 percent), mean height 171.64cm, mean weight 82.66kg and a mean MELD score of 14.61. The most common diagnosis in Region 1 for those not transplanted was cirrhosis/other (51.12 percent). Comparing these transplanted patients with those that continued to wait for a liver during this same timeframe, the descriptive statistics were all statistically different at a *p value <.0001*.

Region 2. In Region 2 (Delaware, District of Columbia, Maryland, New Jersey, Pennsylvania, West Virginia, Northern Virginia) males comprised 72.2 percent of the transplanted group which was predominantly white (79.3 percent), between the ages of 46-60 (62.1 percent) with a mean age of 52.54 years, non-reported educational level (45.2 percent), with private insurance (58.1 percent), blood type O (40.2 percent), mean height 173.3cm, mean weight 85.76kg and a mean MELD score of 19.25. The most common diagnosis of transplant recipients in Region 2 was cirrhosis/other (52.87 percent). Non

transplants in Region 1 were also predominantly male (65.5 percent), white (79.4 percent), between the ages of 46-60 (61.2 percent) with a mean age of 52.54 years, high school educated (41.1 percent), with private insurance (61.3 percent), blood type O (47.1 percent), mean height 172.03cm, mean weight 84.95kg and a mean MELD score of 14.27. The most common diagnosis in Region 2 for those not transplanted was cirrhosis/other (55.41 percent). Comparing these transplanted patients with those that continued to wait for a liver during this same timeframe, the descriptive statistics were all statistically different at a *p value <.0001*.

Region 3. In Region 3 (Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi's, Puerto Rico), males comprised 67.88 percent of the transplanted group, which was predominantly white (76.0 percent), between the ages of 46-60 (59.6 percent) with a mean age of 52.46 years, high school educated (33.1 percent), with private insurance (63.9 percent), blood type O (44.8 percent), mean height 172.66cm, mean weight 85.12kg and a mean MELD score of 19.69. The most common diagnosis of transplant recipients in Region 3 was cirrhosis/other (56.52 percent). Non-transplants in Region 3 were also predominantly male (57.6 percent), white (77.8 percent), between the ages of 46-60 (61 percent) with a mean age of 53.27 years, educational level not disclosed (38.5 percent), with private insurance (58.7 percent), blood type O (48.2 percent), mean height 170.97cm, mean weight 83.68kg and a mean MELD score of 15.21. The most common diagnosis in Region 3 for those not transplanted was cirrhosis/other (60.75 percent). Comparing these transplanted patients with those that continued to wait for a liver during this same timeframe, the descriptive statistics were all statistically different at a *p value <.0001*.

Region 4. In Region 4 (Oklahoma, Texas), males comprised 64.8 percent of the transplanted group which was predominantly white (67.4 percent), between the ages of 46-60 (64.3 percent) with a mean age of 51.27 years, educational level not reported (43.2 percent), with private insurance (62.8 percent), blood type O (49.3 percent), mean height 172.18cm, mean weight 85.53kg and a mean MELD score of 19.77. The most common diagnosis of transplant recipients in Region 4 was cirrhosis/other (58.81 percent). Non transplants in Region 4 were also predominantly male (56.8 percent), white (64.6 percent), between the ages of 46-60 (64.6 percent) with a mean age of 52.61 years, educational level not disclosed (38.3 percent), with private insurance (65.7 percent), blood type O (52.1 percent), mean height 170.27cm, mean weight 84.50kg and a mean MELD score of 12.83. The most common diagnosis in Region 4 for those not transplanted was cirrhosis/other (61.39 percent). Comparing these transplanted patients with those that continued to wait for a liver during this same timeframe, the descriptive statistics were all statistically different at a *p value <.0001.*

Region 5. In Region 5 (Arizona, California, Nevada, New Mexico, Utah), males comprised 69 percent of the transplanted group which was predominantly white (60 percent), between the ages of 46-60 (62.7 percent) with a mean age of 51.89 years, high school educated (33 percent), with private insurance (59.3 percent), blood type O (42.5 percent), mean height 172.18cm, mean weight 84.65kg and a mean MELD score of 22.18. The most common diagnosis of transplant recipients in Region 5 was cirrhosis/other (55.93 percent). Non-transplants in Region 5 were also predominantly male (61.8 percent), white (55.4 percent), between the ages of 46-60 (63.7 percent) with a mean age of 52.86 years, high school educated (34.2 percent), with private insurance (60

percent), blood type O (52.1 percent), mean height 170.02cm, mean weight 82.18kg and a mean MELD score of 14.43. The most common diagnosis in Region 5 for those not transplanted was cirrhosis/other (58.74 percent). Comparing these transplanted patients with those that continued to wait for a liver during this same timeframe, the descriptive statistics were all statistically different at a *p value <.0001.*

Region 6. In Region 6 (Alaska, Hawaii, Idaho, Montana, Oregon, Washington), males comprised 69 percent of the transplanted group which was predominantly white (80.7 percent), between the ages of 46-60 (66.8 percent) with a mean age of 51.43 years, college educated (47.5 percent), with private insurance (57 percent), blood type O (45.7 percent), mean height 172.97cm, mean weight 85.61kg and a mean MELD score of 18.80. The most common diagnosis of transplant recipients in Region 6 was cirrhosis/other (53.83 percent). Non transplants in Region 6 were also predominantly male (64.5 percent), white (83.7 percent), between the ages of 46-60 (68.4 percent) with a mean age of 52.77 years, college educated (46 percent), with private insurance (55.1 percent), blood type O (46.3 percent), mean height 171.77cm, mean weight 84.43kg and a mean MELD score of 12.84. The most common diagnosis in Region 6 for those not transplanted was cirrhosis/other (56.41 percent). Comparing these transplanted patients with those that continued to wait for a liver during this same timeframe, the descriptive statistics were all statistically different at a *p value <.0001.*

Region 7. In Region 7 (Illinois, Minnesota, North Dakota, South Dakota, Wisconsin), males comprised 65 percent of the transplanted group which was predominantly white (76.5 percent), between the ages of 46-60 (58.2 percent) with a mean age of 52.52 years, high school educated (37.5 percent), with private insurance

(57.5 percent), blood type O (41 percent), mean height 172.28cm, mean weight 85.97kg and a mean MELD score of 21.33. The most common diagnosis of transplant recipients in Region 7 was cirrhosis/other (41.37 percent). Non-transplants in Region 7 were also predominantly male (59 percent), white (80.8 percent), between the ages of 46-60 (66.6 percent) with a mean age of 52.71 years, high school educated (39.6 percent), with private insurance (64.7 percent), blood type O (48.1 percent), mean height 171.48cm, mean weight 86.18kg and a mean MELD score of 15.78. The most common diagnosis in Region 7 for those not transplanted was cirrhosis/other (47.49 percent). Comparing these transplanted patients with those that continued to wait for a liver during this same timeframe, the descriptive statistics were all statistically different at a *p value <.0001*.

Region 8. In Region 8 (Colorado, Iowa, Kansas, Missouri, Nebraska, Wyoming), males comprised 66.6 percent of the transplanted group which was predominantly white (84.3 percent), between the ages of 46-60 (64.7 percent) with a mean age of 51.31 years, high school educated (48 percent), with private insurance (63 percent), blood type O (42.7 percent), mean height 173.90cm, mean weight 86.12kg and a mean MELD score of 20.08. The most common diagnosis of transplant recipients in Region 8 was cirrhosis/other (52.03 percent). Non-transplants in Region 8 were also predominantly male (64 percent), white (78.8 percent), between the ages of 46-60 (66.6 percent) with a mean age of 50.79 years, high school educated (48 percent), with private insurance (68.2 percent), blood type O (48.4 percent), mean height 171.81cm, mean weight 82.69kg and a mean MELD score of 13.99. The most common diagnosis in Region 8 for those not transplanted was cirrhosis/other (46.83 percent). Comparing these transplanted patients with those that continued to wait for a liver during this same timeframe, the descriptive

statistics were all statistically different at a *p value <.0001.*

Region 9. In Region 9 (New York, Western Vermont), males comprised 70.4 percent of the transplanted group which was predominantly white (69.2 percent), between the ages of 46-60 (57.5 percent) with a mean age of 53.74 years, educational level not disclosed (40.1 percent), with private insurance (62.1 percent), blood type O (39.8 percent), mean height 171.43cm, mean weight 84.45kg and a mean MELD score of 20.78. The most common diagnosis of transplant recipients in Region 9 was cirrhosis/other (56.62 percent). Non-transplants in Region 9 were also predominantly male (62.9 percent), white (68.2 percent), between the ages of 46-60 (63.9 percent) with a mean age of 53.88 years, educational level not disclosed (56 percent), with private insurance (66 percent), blood type O (46.5 percent), mean height 169.78cm, mean weight 83.13kg and a mean MELD score of 13.43. The most common diagnosis in Region 9 for those not transplanted was cirrhosis/other (62.33 percent). Comparing these transplanted patients with those that continued to wait for a liver during this same timeframe, the descriptive statistics were all statistically different at a *p value <.0001.*

Region 10. In Region 10 (Indiana, Michigan, Ohio), males comprised 67 percent of the transplanted group which was predominantly white (87 percent), between the ages of 46-60 (62.5 percent) with a mean age of 52.28 years, high school educated (64.1 percent), with private insurance (67.6 percent), blood type O (41.3 percent), mean height 173.25cm, mean weight 86.96kg and a mean MELD score of 17.68. The most common diagnosis of transplant recipients in Region 10 was cirrhosis/other (46.57 percent). Non transplants in Region 10 were also predominantly male (58.7 percent), white (86.7 percent), between the ages of 46-60 (68.4 percent) with a mean age of 53.39 years, high

school educated (45 percent), with private insurance (68.7 percent), blood type O (47.1 percent), mean height 171.68cm, mean weight 84.58kg and a mean MELD score of 13.89. The most common diagnosis in Region 10 for those not transplanted was cirrhosis/other (52.39 percent). Comparing these transplanted patients with those that continued to wait for a liver during this same timeframe, the descriptive statistics were all statistically different at a *p value <.0001*.

Region 11. In Region 11 (Kentucky, North Carolina, South Carolina, Tennessee, Virginia), males comprised 72.3 percent of the transplanted group which was predominantly white (85.6 percent), between the ages of 46-60 (64 percent) with a mean age of 51.73 years, high school educated (38.2 percent), with private insurance (54.2 percent), blood type O (43.6 percent), mean height 174.06cm, mean weight 87.33kg and a mean MELD score of 19.36. The most common diagnosis of transplant recipients in Region 11 was cirrhosis/other (54.48 percent). Non-transplants in Region 11 were also predominantly male (64.4 percent), white (85.1 percent), between the ages of 46-60 (67.4 percent) with a mean age of 52.47 years, high school educated (39 percent), with private insurance (57.8 percent), blood type O (49.5 percent), mean height 172.73cm, mean weight 86.31kg and a mean MELD score of 14.04. The most common diagnosis in Region 11 for those not transplanted was cirrhosis/other (60.98 percent). Descriptive statistics for transplant and non-transplant patients during this same time frame are statistically different at a *p value <.0001*.

Appendix E
Characteristics of UNOS Data of Transplanted Patients for Continuous Variables by Region 2002-2007 (N = 17,118)

Variable	Region	N	Mean	SD	Median	CI	P-Value
Age	1	440	51.26	9.17	52.00	50.00-52.00	<.0001
	2	2227	52.24	9.53	52.00	52.00-53.00	
	3	3031	52.46	10.07	53.00	52.00-53.00	
	4	1745	51.27	9.24	52.00	51.00-52.00	
	5	2003	51.89	9.03	52.00	52.00-53.00	
	6	587	51.43	9.11	52.00	52.00-53.00	
	7	1542	52.52	9.74	53.00	52.00-53.00	
	8	1081	51.31	9.37	52.00	51.00-53.00	
	9	1248	53.74	9.76	54.00	53.00-55.00	
	10	1660	52.28	9.29	53.00	52.00-53.00	
	11	1554	51.73	9.18	52.00	52.00-53.00	
Height	1	438	171.99	9.91	172.72	170.18-172.72	<.0001
	2	2212	173.35	9.76	172.72	172.72-175.26	
	3	3017	172.66	10.16	172.72	172.72-172.72	
	4	1741	172.18	10.28	172.72	172.72-172.72	
	5	1990	172.10	10.12	172.72	172.72-172.72	
	6	586	172.97	9.86	173.00	172.72-175.00	
	7	1538	172.28	10.26	172.72	172.72-172.72	
	8	1079	173.90	10.37	175.26	172.72-175.26	
	9	1231	171.43	9.81	172.72	170.18-172.72	
	10	1657	173.25	9.91	175.26	172.72-175.26	
	11	1550	174.06	9.80	175.26	175.26-175.26	
Weight	1	440	84.69	18.57	83.92	82.10-86.18	<.0001
	2	2218	85.76	19.84	83.46	82.10-84.15	
	3	3023	85.12	20.35	83.46	82.55-83.92	
	4	1742	85.53	18.76	83.96	83.46-85.28	
	5	1997	84.65	19.34	83.46	82.10-84.00	
	6	587	85.61	18.11	85.00	83.01-86.18	
	7	1539	85.97	21.27	83.92	82.55-85.20	
	8	1081	86.12	17.77	84.82	83.92-86.32	
	9	1245	84.45	19.60	82.10	81.65-83.91	
	10	1651	86.96	19.08	85.73	84.37-86.18	
	11	1549	87.33	18.34	85.28	84.37-86.64	
MELD	1	440	21.60	8.31	20.00	19.00-20.00	<.0001
	2	2225	19.25	7.83	18.00	17.00-18.00	
	3	3024	19.69	7.26	18.00	18.00-19.00	
	4	1743	19.77	7.78	18.00	18.00-18.00	
	5	2000	22.18	9.59	20.00	19.00-20.00	
	6	584	18.80	6.98	17.00	17.00-18.00	
	7	1541	21.33	8.90	19.00	19.00-20.00	
	8	1079	20.08	7.75	18.00	18.00-19.00	
	9	1246	20.78	9.78	19.00	18.00-19.00	
	10	1649	17.68	6.99	16.00	16.00-17.00	
	11	1554	19.36	7.04	18.00	18.00-18.00	

Appendix F
Characteristics of UNOS Data of Non-Transplanted Patients for Continuous Variables by Region 2002-2007 (N = 15,448)

Variable	Region	N	Mean	SD	Median	CI	P-Value
Age	1	616	51.44	8.61	52.00	51.00-53.00	<.0001
	2	2370	52.54	9.71	53.00	53.00-54.00	
	3	1190	53.27	9.73	53.00	53.00-54.00	
	4	1679	52.61	8.97	53.00	53.00-53.00	
	5	3823	52.86	8.92	53.00	53.00-53.00	
	6	361	52.77	8.93	54.00	53.00-55.00	
	7	1373	52.71	9.76	53.00	53.00-54.00	
	8	725	50.79	9.11	52.00	51.00-53.00	
	9	1710	53.88	9.37	54.00	54.00-55.00	
	10	664	53.39	8.87	54.00	53.00 54.00	
	11	937	52.47	8.82	54.00	53.00-54.00	
Height	1	614	171.64	10.23	172.72	170.18-172.72	<.0001
	2	2358	172.03	10.29	172.72	172.72-172.72	
	3	1181	170.97	10.39	170.18	170.18-172.72	
	4	1673	170.27	10.68	170.18	170.18-170.18	
	5	3796	170.02	10.63	170.18	170.18-170.18	
	6	361	171.77	10.34	172.72	170.18-173.00	
	7	1366	171.48	10.00	172.00	170.18-172.72	
	8	724	171.81	10.54	172.72	172.70-172.72	
	9	1685	169.78	9.78	170.18	170.18-170.18	
	10	664	171.68	10.16	172.72	170.18-172.72	
	11	935	172.73	10.08	172.72	172.72-175.26	
Weight	1	611	82.66	19.11	80.74	78.93-82.10	<.0001
	2	2361	84.95	20.29	82.10	81.65-83.01	
	3	1187	83.68	19.98	82.55	81.00-83.92	
	4	1672	84.50	19.36	82.53	81.19-83.92	
	5	3802	82.18	19.47	80.10	79.38-81.00	
	6	361	84.43	18.46	83.92	82.55-86.40	
	7	1368	86.18	21.77	83.46	82.00-84.90	
	8	723	82.69	18.09	81.65	79.83-83.46	
	9	1709	83.13	18.90	81.19	79.83-81.65	
	10	663	84.58	19.67	83.46	81.65-86.00	
	11	937	86.31	18.50	85.28	83.91-86.64	
MELD	1	616	14.61	6.57	13.00	13.00-14.00	<.0001
	2	2370	14.27	7.07	13.00	12.00-13.00	
	3	1190	15.21	6.73	14.00	13.00-14.00	
	4	1679	12.83	5.29	12.00	12.00-12.00	
	5	3823	14.43	6.89	13.00	13.00-13.00	
	6	361	12.84	5.15	12.00	11.00-12.00	
	7	1373	15.78	8.49	14.00	13.00-14.00	
	8	725	13.99	6.00	13.00	13.00-13.00	
	9	1710	13.43	7.54	11.00	11.00-12.00	
	10	664	13.89	6.55	12.00	12.00-13.00	
	11	937	14.04	6.46	13.00	12.00-13.00	

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Patricia Dunne — 9/8/08

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