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Impact of Community Factors on the Donor Quality Score in Liver Transplantation

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Abstract

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Dissertation Submitted in Partial Fulfillment

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Abstract

An increasing prevalence of metabolic syndrome and obesity has been linked to the rise in transplant indication for cryptogenic cirrhosis and nonalcoholic fatty liver disease (NAFLD), creating a growing challenge to public health. NAFLD liver transplant (LT) candidates are listed with low priority, and their waiting mortality is high. The impact of community/geographic factors on donor risk models is unknown. The purpose of this study was to develop a parsimonious donor risk-adjusted model tailored to NAFLD recipients by assessing the impact of donor, recipient, transplant, and external factors on graft survival. The theoretical framework was the social ecological model. Secondary data were collected from 3,165 consecutive recipients from the Scientific Registry of Transplant Recipients and Community Health Scores, a proxy of community health disparities derived from the Robert Wood Johnson Foundation's community health rankings. Data were examined using univariate and multivariate analyses. The donor risk-adjusted model was developed using donor-only factors and supplemented with recipient and transplant factors, classifying donors as low, medium, and high risk. NAFLD residents in high-risk counties had increased likelihood of liver graft failure. Findings may be used to allocate high-risk donors to a subset of NAFLD with excellent outcomes, increasing the donor pool and decreasing mortality on the wait list.

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Dedication

I would like to dedicate this dissertation to my beloved parents, Nicola Saracino and Maria Nicoletta Azzanese, without whom none of my success would be possible.

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The data reported here have been supplied by the Minneapolis Medical Research Foundation as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are my responsibility and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

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Chapter 1: Introduction to the Study

An increasing prevalence of metabolic syndrome and obesity has been linked to the rise in transplant indication for cryptogenic cirrhosis (CC) and nonalcoholic fatty liver disease (NAFLD) creating a growing challenge to public health (Fazel, Koenig, Sayiner, Goodman, & Younossi, 2016; Pais et al., 2016). Many NAFLD patients who develop cirrhosis or hepatocellular carcinoma (HCC) and CC patients are in need of a liver transplant (LT). Therefore, NAFLD-related end-stage liver disease including nonalcoholic steatohepatitis (NASH) cirrhosis will soon become a leading indication for LT (Mikolasevic et al., 2018).

CC is a chronic liver disease of unknown etiology, and most CC cases are attributed to advanced NASH cirrhosis (Caldwell & Marchesini, 2018). The current liver allocation system based on the model for end-stage liver disease (MELD) does not accurately capture the risk of wait-list mortality of NAFLD/CC patients (Bambha & Biggins, 2008; Patel, Berg, & Moylan, 2016). Patients with NAFLD/CC and low MELD scores have slower disease progression and low priority on the LT wait list than patients listed for other end-stage liver diseases (Kwong, Lai, Dodge, & Roberts, 2015). Although patients with NAFLD/CC cirrhosis have short-term morbidity and mortality, their mid- and long-term posttransplant outcomes are favorable, similar to other etiologies, suggesting that an LT can be an excellent treatment option for NAFLD/CC (Patel et al., 2016).

Organ shortage is a major problem that accounts for remarkable wait-list mortality (Elwir & Lake, 2016). As a result, many NAFLD/CC patients, who often have many comorbidities, are likely to drop out from the wait list or die while waiting for an LT at a higher rate compared to other etiologies (O'Leary, Landaverde, Jennings, Goldstein, & Davis, 2011; Pais et al., 2016).

Transplant centers are increasing the utilization of marginal deceased donors including older donors, extended criteria donors, and donors after cardiac death to expand the donor pool (Akkina et al., 2012; Diwan, Paterno, & Shah, 2015). The main purpose of this study was to create and validate a novel model for donor quality score tailored to NAFLD/CC recipients of LT, or the donor quality-nonalcoholic fatty liver disease (DQ-NAFLD) model, using data from the Scientific Research Transplant Registry (SRTR) as well as county-level data to incorporate the community health indicators (County Health Rankings & Roadmaps, 2018). The DQ-NAFLD model could lead to positive social change if used as a tool to quantify donor quality and assist the decision-making during an organ offer. The use of DQ-NAFLD score could be clinically relevant if used in donor-recipient matching to identify the highest DQ-NAFLD scores associated with acceptable outcomes for subsets of NAFLD/CC patients. The donor pool would increase, and more suboptimal donors would be allocated to NAFLD/CC patients on the wait list for LTs who have lower priority. Otherwise, there is a good possibility that NAFLD/CC patients could die while on the wait list because no liver will be offered to them.

In Chapter 1, I provide a brief review of the study background, the statement of

the problem, the purpose of the study, and the research questions. This chapter also provides a brief introduction to the socioecological theoretical framework, the definition of the study variables, the scope of the study, and the assumptions and limitations. Finally, I describe the significance of this study and its potential contributions in matching the right donors, including marginal donors, to NAFLD/CC recipients, and in reducing the percentage of organs wasted that could be allocated to the appropriate NAFLD/CC recipients with excellent outcomes.

Background

Liver transplant surgery has become a widely accepted, curative, and life-saving treatment for people with end-stage liver disease. Currently in the United States, about 14,000 patients are waiting for a liver donation, but only about 7,500 LTs are performed annually (United Network for Organ Sharing [UNOS], 2018). Between 2015 and 2016, LTs increased by 10.0%. Nevertheless, the proportion of liver recovered but not transplanted has reached 9.4% in 2014 (Kim et al., 2016). The disparity between liver-organ supply and demand has resulted in a remarkable organ shortage and a large number of potentially preventable deaths, which is a public health crisis (UNOS, 2018). Strategies to improve organ-recipient matching are needed (Flores & Asrani, 2017).

The U.S. Department of Health and Human Services Organ Procurement and Transplantation Network (OPTN) Final Rule contains the regulatory requirements and ethical principles for organ allocation. The organ allocation system must be fair and just and should not put any member of society in a disadvantageous position for having

access to available organs (UNOS, 2018). Liver allocation requires an appropriate balance between medical urgency and efficiency (UNOS, 2018).

Liver allocation policies have shifted from a wait-time designation to addressing more urgent cases based on the calculated MELD score (Merion et al., 2005). Nevertheless, the MELD score designed to predict short-term wait-list mortality is a weak predictor of posttransplant survival, and it is insufficient to optimize the value of each donor's liver (Asrani & Kim, 2011). In recent years, grounded in the principle of utilitarianism, investigators have developed organ allocation models seeking to maximize survival benefit of the whole population or aiming at saving more years of life, rather than more lives (Briceño, Ciria, & de la Mata, 2013). Steps taken in this direction include the development of the first donor risk index (Feng et al., 2006) and subsequent donor risk models, which seek to predict the survival of the donated liver after transplantation, enabling matching between the expected posttransplant life span of the liver with that of the recipient (Porrett, ter Horst, & Shaked, 2012; Weiss et al., 2012).

Several models have been proposed using donor factors, recipient factors, and intraoperative factors to predict posttransplant survival and facilitate transplant decision-making (Flores & Asrani, 2017). However, almost all proposed models are not widely used in clinical practice because they require inputs not readily available at the time of the evaluation of an organ offer or because they are not reliable metrics of donor characteristics that fail to consider essential predictors or include irrelevant factors (Blok et al., 2012; Braat et al., 2012; Campos-Varela, Dodge, Stock, & Terrault, 2016;

Dutkowski et al., 2011; Halldorson, Bakthavatsalam, Fix, Reyes, & Perkins, 2009; Hoyer et al., 2015; Mataya, Aronsohn, Thistlethwaite, & Friedman Ross, 2014; Northup et al., 2015; Rana et al., 2008). Additionally, some of the risk models do not reflect current clinical practice as they were developed using data before the implementation of the MELD score allocation system.

Clinical studies often focus on clinical and biological factors ignoring the importance of community conditions in risk-adjusted models. Epidemiologic factors such as socioeconomic status; access to quality health care; ecological, behavioral, and psychosocial factors; and geographic variations create disparities in posttransplant outcomes and prevent the current allocation systems from making organs available to the highest number of people (Northup et al., 2015). Understanding the epidemiologic factors that lead to inequalities in the liver allocation and posttransplant outcomes are of paramount public health importance. None of the donor risk models proposed are tailored to the NAFLD/CC population, and none of them considered unmeasured characteristics that can impact posttransplant liver allograft survival, including environmental, behavioral, and psychosocial aspects of the communities where transplant recipients reside (Nandi, Glymour, & Subramanian, 2014). Chapter 2 provides a more extensive review of the literature related to the NAFLD/CC patients, the current allocation system, and how a quantified donor quality metric can help in decision-making. This study complemented existing work and may assist researchers with donor risk models tailored to NAFLD/CC patients useful in organ allocation decision-making.

Statement of the Problem

Due to the rise in obesity and diabetes mellitus type 2, NAFLD patients listed for LT are expected to increase steadily. Nevertheless, the MELD allocation score fails to capture the actual risk of death of NAFLD candidates. As a result, many of them receive low priority and continue to die while waiting for an LT (Asrani & O'Leary, 2015). Organ shortage leads to the utilization of nonoptimal donors, and donor risk models provide a metric to quantify donor quality and help allocate nonoptimal donors to appropriate recipients. On the other hand, many organs are discarded while some of them can be utilized with excellent results if adequately selected and matched to the appropriate LT candidates. Donor risk models provide the first step to match marginal donors to the appropriate recipients. The creation and validation of a novel model for donor quality score, the DQ- NAFLD, tailored to NAFLD/CC recipients of LT can fill a gap in the current knowledge base and be a step forward in the optimal utilization of a scarce resource to achieve the ultimate goal of improving liver graft survival. None of the previously proposed liver donor risk models has considered the impact of community risk factors on the performance of donor risk models (Nandi et al., 2014).

Purpose of Study

The primary goals of this quantitative study were to develop a parsimonious risk-adjusted model, use this model to derive a donor quality score for NAFLD/CC LT recipients that will predict graft failure at 1-year post LT, and explore its relationship with transplant and recipient characteristics and with geographic and county health risk

factors. I used a quantitative method and secondary data. To be useful in clinical practice, the DQ-NAFLD will only include donor and recipient variables known at the time of the organ offer and will be built with data in the post-MELD era (see Flores & Asrani, 2017). An extended version of the model that includes transplant factors not available at the time of offer but estimable, such as cold ischemia time, will be useful for donor-recipient matching.

Recipient characteristics included age, gender, biological MELD score, and body mass index (BMI). Donor characteristics consisted of donor age, gender, height, weight, BMI, cause of death, hypertension, diabetes, donor after circulatory death (DCD), hepatitis C virus (HCV) status, Hepatitis B surface antibody (HBsAb) status, Hepatitis B surface antigen (HBsAg) status, modification of diet in renal disease (MDRD) clearance, and donor hypernatremia. Transplant variables included ABO compatibility, size compatibility, and cold ischemia time. Most importantly, the study addressed distance from the transplant center, used to identify recipients in remote communities and in geographic isolation from transplant centers, and underlying community health factors from the location of LT recipients that are significantly associated with posttransplant outcomes and can bias the performance of the novel DQ- NAFLD (see Galea, Tracy, Hoggatt, DiMaggio, & Karpati, 2011).

By finding a donor quality metric for NAFLD/CC recipients, this model will contribute to identifying NAFLD/CC LT candidates who may die while on the wait list or may be removed because they are too sick to be transplanted. Both groups would benefit

from an LT when matched appropriately. By optimizing survival benefit of NAFLD/CC LT candidates on the wait list, this model will attempt to increase the organ pool for NAFLD/CC patients, reduce wait-list mortality, improve survival outcomes, and meet the dual goal of fair allocation and optimum efficiency (Kamath et al., 2001). This study had four objectives:

1. to develop a donor risk model tailored to NASH/CC LT recipients with intrinsic donor factors to improve risk stratification for liver organs;
2. to develop an extended donor risk model tailored to NASH/CC LT recipients with donor, recipient, and transplant factors;
3. to examine the modifying effect of distance from center and its interaction with donor risk score on liver graft failure; and
4. to explore the modifying effect of community risk factors and their interaction with donor risk on liver graft failure.

Research Questions and Hypotheses

The variables used to formulate the research questions and hypotheses are defined and operationalized in the section Study Variables and Operational Definitions of Chapter 3 and in Appendix A. This retrospective cohort study was conducted to answer the following research questions through testing of corresponding hypotheses:

Research Question 1

What are the relationships between posttransplant graft survival among NAFLD/CC recipients and a number of donor characteristics (age, gender, height,

weight, BMI, the cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, and hypernatremia)?

H_{01}: There is no association between posttransplant graft survival among NAFLD/CC recipients and a number of donor characteristics (age, gender, height, weight, BMI, the cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, and hypernatremia).

H_{a1}: There is an association between posttransplant graft survival among NAFLD/CC recipients and a number of donor characteristics (age, gender, height, weight, BMI, the cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, and hypernatremia).

Research Question 2

What are the relationships between posttransplant graft survival among NAFLD/CC recipients and transplant factors (cold ischemia time, ABO matching, and size matching)?

H_{02}: There is no association between posttransplant graft survival among NAFLD/CC recipients and a number of transplant factors (cold ischemia time, ABO matching, and size matching).

H_{a2}: There is an association between posttransplant graft survival among NAFLD/CC recipients and transplant factors (cold ischemia time, ABO matching, and size matching).

Research Question 3

What are the relationships between posttransplant graft survival among NAFLD/CC recipients and a number of donor factors (age, gender, height, weight, BMI, the cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, hypernatremia) and transplant factors (cold ischemia time, ABO matching, size matching) after adjusting for characteristics of recipients of LT (age, gender, BMI, biological MELD)?

H_{03}: There is no association between posttransplant graft survival among NAFLD/CC recipients and a number of donor factors (age, gender, height, weight, BMI, the cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, hypernatremia) and transplant factors (cold ischemia time, ABO matching, size matching) after adjusting for characteristics of recipients of LT (age, gender, BMI, biological MELD).

H_{a3}: There is an association between posttransplant graft survival among NAFLD/CC recipients and a number of donor factors (age, gender, height, weight, BMI, the cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, hypernatremia) and transplant factors (cold ischemia time, ABO matching, size matching) after adjusting for characteristics of recipients of LT (age, gender, BMI, biological MELD).

Research Question 4

What are the relationships between posttransplant graft survival among NAFLD/CC recipients and the health risk status of the county where recipients reside, as measured by the community health score (CHS)?

H_{04}: There is no association between posttransplant graft survival among NAFLD/CC recipients and the health risk status of the county where recipient resides, as measured by the CHS.

H_{a4}: There is an association between posttransplant graft survival among NAFLD/CC recipients and the health risk status of the county where recipient resides, as measured by the CHS.

Research Question 5

What are the relationships between posttransplant graft survival among NAFLD/CC recipients and the distance from transplant center?

H_{05}: There is no association between posttransplant graft survival among NAFLD/CC recipients and distance from center.

H_{a5}: There is an association between posttransplant graft survival among NAFLD/CC recipients and distance from transplant center.

Research Question 6

What are the relationships between posttransplant graft survival among NAFLD/CC recipients, DQ-NAFLD risk score, and external community factors (CHS and distance from the transplant center)?

H_{06}: There is no association between posttransplant graft survival among NASH/CC recipients, DQ-NAFLD risk score, and external community factors (CHS and distance from the transplant center).

H_{a6}: There is an association between posttransplant graft survival among NAFLD/CC recipients, DQ-NAFLD risk score, and external community factors (CHS and distance from the transplant center).

Theoretical Framework for the Study

Social-ecological theory recognizes that individuals are embedded in their social structure that interacts with individual and environmental factors. Based on Bronfenbrenner's (1977) seminal work, McLeroy, Bibeau, Steckler, and Glanz (1988) proposed a five-level social-ecological system and examined the complex interplay between public policy and intrapersonal, interpersonal, institutional, and community factors. From this theory, it follows that there are complicated social determinants that increase or decrease the risk of poor posttransplant outcomes (Braveman & Gottlieb, 2014). It is necessary to act on multiple levels to improve patient and graft survival after LT.

The social-ecological model was the most appropriate framework for this study. The individual domain includes patient-level and biological factors. The family and social network levels include family members who are involved in supporting patients throughout their transplant journey. Health care system level comprises the clinical pathway to an LT, such as donor match, the transplant surgery, and quality of health care

provided. The community domain includes the contextual environment or the nature of the community where patients reside, the wait list, and organ donation policies. The social-ecological model provided the guiding framework for the literature review presented in Chapter 2.

Nature of the Study

The nature of the study was quantitative with secondary data. A retrospective cohort of consecutive NAFLD/CC adult recipients of LT who met the inclusion criteria was analyzed. To identify quantitative donor characteristics predictive of liver-graft survival after LT; the risk model associated; and the relationships with recipient, transplant, geographic, and community health indicators, Cox's proportional hazard (PH) models as well as random survival forests, a machine learning approach appropriate to analyze time-to-event outcomes, were considered. This quantitative study led to the development of a DQ- NAFLD model that quantified the donor quality associated with an LT for NAFLD/CC patients.

Definitions

The conceptual definitions of specific terms used in this study are included in this section. Some of these concepts have been further defined in Chapter 2.

Cold ischemic time (CIT): Cold ischemic time is the amount of time, usually about 12–18 hours, after a donor's liver is harvested for transplantation. CIT is defined as the time from cross clamping of the donor liver to removal from cold storage solution.

Reducing CIT improves the quality of the liver allograft. CIT can be lowered by lowering the logistical and transportation time (Pan et al., 2018).

Community Health Score (CHS): Community Health Score is a composite health index that incorporates county-level environmental and behavioral conditions, the prevalence of comorbidities, and quality of health care (a surrogate of sociodemographic characteristics). The Study Variables and Operational Definition section in Chapter 3 and Appendix A provide more details about the county health indicators used in the CHS.

Cryptogenic cirrhosis: Chronic liver disease of unknown etiology, often attributed to NASH cirrhosis (Caldwell & Marchesini, 2018).

Death drain donor (DBD): Donation after brain death (DBD) represents the majority of deceased donors and is associated with excellent liver transplant outcomes. Neurological brain death is the standard criteria for organ donation that takes place after the irreversible loss of clinical function occurs.

Donation after cardiac death (DCD): Non–heart-beating organ donation takes place after circulatory death of the donor. DCD livers are usually procured after withdrawal of life support and have a period of absence of blood flow before cold preservation, as opposed to heart beating donors who maintain organ perfusion until initiation of cold preservation (OPTN, 2018). Therefore, DCD donors are more susceptible to further ischemic injury and increased risk of graft failure than DBD donors (Halldorson et al., 2015).

Donor risk index (DRI): Donor risk index is a measurement of the donor liver quality developed from a predictive model of donor factors including donor age, race, donation after cardiac death, donor high, and use of split/partial grafts (Feng et al., 2006).

Distance from transplant center: The distance between recipient primary residence zip code and transplant center zip code.

Expanded criteria donor (ECD): Any deceased donor age 70 years or above, or age 60 years with significant medical history, or a donor with a history of hepatitis B or hepatitis C. The patient must give informed consent to accept the liver of an ECD donor (Rodrigue, Hanto, & Curry, 2011).

Modification of diet in renal disease (MDRD): Equation that utilizes four variables, including age, gender, ethnicity, and serum creatinine, to estimate glomerular filtration rate (Levey et al., 1999).

Model for end-stage liver disease (MELD) score: Model for end-stage liver disease score is used to quantify the severity of end-stage liver disease for LT and to prioritize liver allocation. The MELD score is a predictor of short-term wait-list mortality (Bernardi, Gitto, & Biselli, 2011).

Nonalcoholic fatty liver disease (NAFLD): NAFLD is a multisystem disease characterized by excess fat stored in the liver, primarily associated with other comorbid conditions such as obesity, diabetes mellitus, cardiovascular disease, hyperlipidemia, metabolic syndrome, and chronic kidney disease (Mikolasevic et al., 2018). In this study, patients with progressive NAFLD in need of a liver transplant were considered.

Nonalcoholic steatohepatitis (NASH): NASH is an advanced status of NAFLD to steatohepatitis, a progressive fibrotic liver disease indicating liver transplant is necessary (Argo & Caldwell, 2009).

Organ procurement organization (OPO): Organ procurement organization is an organization authorized by the Centers for Medicare and Medicaid Services (CMS) to procure organs for transplantation. For each OPO, CMS defines a geographic procurement territory within which the OPO concentrates its procurement efforts. No OPO is limited to or granted exclusive right to procure organs in its territory (OPTN, 2018).

Organ procurement and transplantation network (OPTN): Organ procurement and transplantation network is an organization governed by the U.S. Department of Health and Human Services and is formed by multiple committees to develop organ transplantation policies (OPTN, 2018).

Public health service (PHS) increased risk donor: The Centers for Disease Control and Prevention (CDC) developed guidelines in 1994 to designate high-risk donors based on a category of high-risk behaviors likely to increase chance of human immunodeficiency virus (HIV) transmission (Rogers, Simonds, Lawton, Moseley, & Jones, 1994). On July 2013 the PHS increased-risk criteria were introduced as an extension of the CDC high-risk criteria by adding the risk of recent hepatitis B and hepatitis C, in addition to the risk of HIV (Seem, Lee, Umscheid, & Kuehnert, 2013). More details about the two criteria are provided in Appendix B.

Scientific Registry of Transplant Recipients (SRTR): Scientific Registry of Transplant Recipients is a national database that receives transplant data from many organizations and stores data on transplant candidates, donors, transplant recipients, and posttransplant follow-up data (SRTR, 2018).

Standard criteria donor (SCD): Standard criteria donor liver comes from a deceased donor who is brain dead but still has a beating heart that may be supported by a respirator (Rodrigue et al., 2011).

Split liver donation: Split or partial liver donation refers to the split of the liver organ into two segments, the left lateral segment often transplanted to child and the right segment transplanted to an adult, although splitting the donor between two adults is also performed (Vagefi, Parekh, Ascher, Roberts, & Freise, 2011).

Transplant center: A hospital in which transplants are performed. The transplant surgeon of the transplant center receiving the organ offer for a surgeon's candidate is responsible for ensuring the medical suitability according to the candidate's blood type and subtype (OPTN, 2018).

United Network for Organ Sharing (UNOS): United Network for Organ Sharing is a private, nonprofit organization that manages the nation's organ transplant system under contract with the federal government (UNOS, 2018).

Wait list: This is a computerized list of candidates who are waiting to be matched with specific donor organs in hopes of receiving transplants. Wait list candidates are registered on the list by member transplant centers (OPTN, 2018).

Assumptions

Several basic assumptions were made during this investigation. During patient selection, environmental factors were assumed to be constant across all patients who resided in the same county. I assumed that all patients received clinical services of equivalent quality as the transplant center and center effect were not analyzed. Moreover, I assumed that data were accurately collected and correctly measured by clinical, administrative, and research staff and that lab values were not flawed. Late graft failures, which happen after 1-year posttransplant, were ignored. I assumed that an ideal donor was a standard criteria liver donor (i.e., with brain death, age less than 45 years, a whole non-split graft) and that the risk model could quantify donor risks for a heterogeneous group of nonideal donors.

Scope and Delimitation

In this study, only adult recipients (18 years or older) of cadaveric single-organ LTs were considered. Recipients of multiorgan transplants were excluded. The study population was limited to patients transplanted for NAFLD/CC; all other etiologies for LT were excluded. A cohort of patients transplanted in the most recent 5 years with at least 1-year follow-up in the post-MELD era was considered to develop models to predict graft survival within 1-year posttransplant. To develop a valid risk adjustment model, an adequate number of events (in this case graft failures or deaths) must have occurred in the development cohort to allow selection of variables for risk adjustment. A proposed

convention in multivariate prognostic modeling was to require at least 10-15 events per risk adjuster in the final model (see Harrell, Lee, & Mark, 1996).

The SRTR technical advisory committee recommends a more conservative minimum of 25 events in the development data set to attempt to build a risk adjustment model (Snyder et al., 2016). Final decisions on which variables to include for donor risk adjustment were based on published data, knowledge of subject matter, and available data. A list of potentially appropriate variables for risk adjustment was compiled based on literature review, availability in SRTR, and expert opinion about the importance and clinical relevance of proposed data elements. All transplant centers contribute to the SRTR database. The large sample size ensured that the study was powered to conduct multivariate analyses. Therefore, inferences from SRTR studies are likely to generalize across the United States. However, the model is expected to present some threats to external validity and may not generalize with data from non-U.S. transplant centers with different policies and procedures (see Massie, Kucirka, & Segev, 2014).

Limitations

SRTR database has a significant amount of data that are missing or inaccurate. The aggregate nature of the community health factors can lead to model estimates that may be subject to ecological bias. Lost to follow-up can be a threat to internal validity. The retrospective nature of SRTR data can lead to confounding attributable to unobserved variables. Transplant centers prospectively submit their data at transplant milestones, reducing recall bias. Medical and social history interviews conducted with the

deceased donor's close family members can be inaccurate if the persons interviewed have limited or inaccurate information.

A study suffers from selection bias if individuals in the study population are not representative of the target population. However, the SRTR database is a comprehensive registry of transplant recipients, which includes consecutive organ transplants that occurred in the United States since October 1, 1987. Therefore, the accurate pathology-based diagnosis paired with the inclusion of consecutive patients was likely to reduce selection bias. The designed inclusion criterion, which limited to NAFLD/CC adult recipients of LTs, optimized the external and internal validity of the study, reduced confounding, ensured the homogeneity of the sample population, and increased the likelihood of finding a true association between independent predictors, covariates, and outcomes.

Significance and Social Change

The changing patterns in patient demographics and indication for LT pointed to the development of a post-MELD era donor quality score tailored to NAFLD recipients. This study can shed some light on understanding how organ quality plays a role in posttransplant outcomes. Transplant physicians are inaccurate at predicting donor specific risks and tend to overestimate graft failure for marginal donors (Volk, Roney, & Merion, 2013). Moreover, patients prefer an active involvement in decisions about organ acceptance, and although they tend not to accept marginal donors, a closer evaluation of the competing risk of wait-list mortality can lead patients to accept higher-risk donors

(Dries, Annema, Berg, Ranchor, & Porte, 2014; Volk, 2015; Volk, Tocco, Pelletier, Zikmund-Fisher, & Lok, 2011). The results of this research have the potential to advance knowledge in clinical decision-making at the point of care during an organ offer and may provide an objective tool for physicians and patients.

The DQ-NAFLD objective donor quality metrics could lead to positive social change if used as a tool to quantify donor quality and may assist physicians and patients in the decision-making during an organ offer. The DQ-NAFLD score could be clinically relevant if used to identify high-risk donors associated with acceptable outcomes when matched to subsets of NAFLD/CC recipients. The donor pool could increase, and more suboptimal donors could be allocated to NAFLD/CC patients on the wait list who have lower priority to receive an LT. Otherwise, there is a good possibility that these patients could die while on the wait list because no liver will be offered to them.

Summary

NAFLD is becoming the leading indication for LT. Nevertheless, the wait-list mortality rate for NAFLD recipients is high compared to other indications for an LT. In this chapter, I introduced the subject matter and showed that the population of NAFLD/CC recipients could benefit from an optimized allocation of liver organs. I explained the lack of donor risk models that address NAFLD/CC patients and the need to consider community risk factors and their impact on post LT graft survival. Furthermore, the purpose of this study along with a justification of the need for this research and its theoretical framework was presented. Research questions and hypotheses were included,

and the delimitations, assumptions, and limitations of this study were given. Chapter 2 provides a comprehensive literature review of the study background and research problem.

Chapter 2: Literature Review

Mirroring obesity and type 2 diabetes prevalence, NAFLD with end-stage liver disease and NASH are projected to replace HCV as the leading indications for LT in the United States and the world (Pais et al., 2016). The number of patients with NASH listed for liver transplant in the United States has increased by 168% from 2003 to 2014, becoming the second leading etiology for liver transplantation after 2008, and still trending upward (Cholankeril et al., 2017). With the introduction of highly effective direct antiviral agents, the incidence of HCV-related decompensated cirrhosis is steadily decreasing. NASH patients on the transplant wait list have low priority, are often old with comorbidities, and have a high likelihood to die on the wait list. To fill the gap between the demand for LT and the supply of deceased donor organs, transplant centers are forced to consider using high-risk donors for transplant candidates with the longest waiting time. Factors such as donor age, donor cause of death, and donation after cardiac death can contribute to increasing the risk for graft failure that can lead to the death of the transplant recipient (SRTR, 2018).

To quantify the impact of donor factors, researchers have developed organ-specific donor risk indices to identify predictors of graft and patient survival post LT using various combinations of donor, transplant, and recipient characteristics and are actively searching to fit useful statistical risk models using objective variables that quantify the risk associated with donor organs. The concept of donor risk index (DRI) introduced by Feng et al. (2006), and the subsequent models following the development

of the DRI are important advances. However, they need to be updated to be considered in liver allocation policies and to be useful in clinical practice to guide transplant clinicians in the use of nonoptimal donors by accounting for the impact of geography and unmeasured donor characteristics. DRI could be tailored for NAFLD/CC recipients to reflect features unique to this population (Flores & Asrani, 2017). I performed a thorough literature review to gain an understanding of the current knowledge about the relationship between donor quality and patient characteristics in the NAFLD/CC population, and to identify a gap in the knowledge base about the impact of community risk factors on donor risk models. This review led to the development and validation of a novel donor quality model tailored to NAFLD/CC recipients of LT: the DQ-NAFLD. This chapter includes the following items:

- the literature review strategies;
- the theoretical framework that shaped this study and framed the research questions;
- review of literature related to the source, concept, and constructs of the theoretical framework and how the theory has been applied in similar studies;
- review of literature to describe the spectrum of NAFLD and NASH, including the donor allocation system based on the MELD score and its impact on the wait-list mortality of NAFLD patients;

- review of donor risk models previously developed, including machine learning approaches to donor-recipient matching models, the variables utilized, the similarities, the differences and the limitations of each model;
- review of the utilization of marginal donors, including older donors and donation after cardiac death; and
- review of literature that addressed the impact of community health indicators on post liver transplant outcomes.

Literature Review Strategy

A comprehensive literature review including the most recent literature and seminal studies on the study topic was conducted. This included the period 2002 through 2018 by querying the following databases: MEDLINE, Science Direct, ProQuest Central, and PubMed. Also queried were major peer-review liver transplant journals, including the American Journal of Transplantation, Liver Transplantation, Journal of Hepatology, Journal of Gastroenterology and Hepatology, and BMC Gastroenterology. Key words (in combination with *liver transplantation*) included *donor quality*, *donor risk index*, *donor allocation*, *liver transplantation*, *NASH*, *NAFLD*, *cryptogenic cirrhosis*, *wait list mortality*, *liver wait list mortality*, *donor allocation*, *MELD*, *marginal donors*, *suboptimal donors*, *DCD*, *donation after cardiac death*, *non-heart beating donors*, *Socio Ecological Model*, *SES*, and *community health indicators*. The criteria for selection of peer-reviewed articles were (a) U.S. system of allocation (although some international studies were also considered for comparison purposes), (b) English language, (c) adult subjects, (d) related

to study concept of donor quality and variables, and (e) related to the study population. Titles, abstracts, and articles were reviewed, and articles that met the inclusion criteria were selected for review.

Theoretical Foundation

The theoretical framework is the backbone of planning research. Theories shape the way research is conducted and add structure and consistency from topic selection to the literature review, development of research questions, study design, and analysis plan (Alderson, 1998). The theoretical framework that shaped this study and framed the research questions was based on the social-ecological model (SEM) (McLeroy et al., 1988). SEM is a theory-based framework that can be used to examine the complex interplay between individual, community, and social factors that increase or decrease the risk of poor posttransplant outcomes (Stilley et al., 2010). The SEM can help to understand the multifaceted and multilevel interactions between personal and environmental factors that determine behaviors and guide in identifying the social determinants of health, or those unfair conditions in the social environment that can impact access to liver donors and can increase the risk of poor post liver transplant outcomes.

Figure 1 illustrates the five nested hierarchical levels of influence of the SEM. The individual levels include biological factors and patient behaviors. The interpersonal level consists of the family and social networks. The community level includes the distance from the transplant centers, environmental health risks, and insurance. The

organization level in the current study context includes the United Network for Organ Sharing (UNOS), the Organ Procurement and Transplant Network (OPTN) and the Organ Procurement Organization (OPOs). The policy level includes the donor allocation policies.

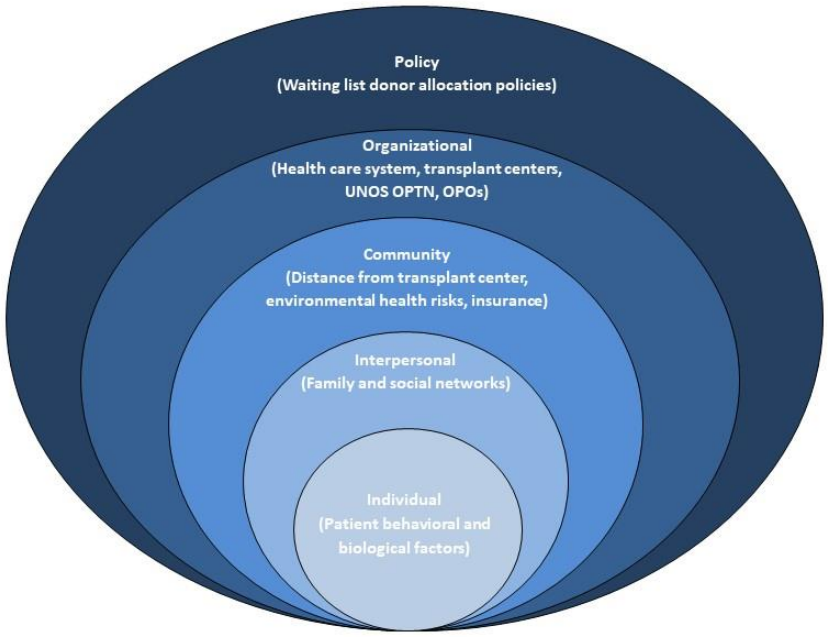

Figure 1. The social ecological model (SEM) in the context of liver transplantation.

In Figure 1, the first level identifies the patient level, including individual and biological factors, some of them modifiable through educational interventions. The family and social network level factors include family members who are involved in supporting patients throughout their transplant journey or the next of kin who provide medical and behavioral information about a donor. Health care system level comprises

the clinical pathway to a liver transplant, such as donor match, the transplant surgery, quality of health care provided, and the nature of the community where patients reside. Social level factors including listing and organ donation policies.

Researchers have studied the impact of social factors on health. Braveman and Gottlieb (2014) suggested that healthcare is responsible for only 10-15% of preventable mortality. However, individual behaviors have an impact on people's health by 40%, genetics by 30%, and social and environmental factors by 20%. Therefore, there is substantial evidence in the United States, and globally, that social determinants of health have a substantial impact on morbidity and mortality in the general population. In addition to individual factors, such as socioeconomic status, education, individual behavior, and social support, environmental factors, such as access to healthcare and healthy food options vary by region and county.

One of the implications of heterogeneity in these risks is its potential impact on risk models that predict patient outcomes. Ignoring these underlying risk factors of transplant recipients not available from medical charts can result in biased performance of transplant risk models, because social determinants of health impact the outcomes (Schold, Phelan, & Buccini, 2017). Given a socioecological conceptual framework, a donor risk model that evaluates recipient and donor match and their impact on post-transplant outcomes can be refined by adjusting for community characteristics.

The SEM framework was used in transplant studies to identify social determinant of referral for kidney transplant evaluations to plan educational intervention aimed at

improving equity in access to kidney transplant or to analyze the sociocultural pathways to organ donation among American Indian adults (Fahrenwald & Stabnow, 2005). The social-ecological theory implies that there are complex social determinants of post-liver transplant outcomes (Braveman & Gottlieb, 2014). It is necessary to act on multiple levels to improve survival after liver transplant.

Nonalcoholic Fatty Liver Disease

During the past century, the world has experienced a significant decline in mortality and a substantial increase in life expectancy. Chronic diseases have replaced acute infectious diseases becoming the predominant cause of morbidity and mortality worldwide. NAFLD is becoming the new epidemic in chronic liver disease, which mimics the worldwide epidemics of obesity and type 2 diabetes. It is projected to become the most frequent indication for LT by 2030 (Byrne & Targher, 2015).

NAFLD Spectrum

NAFLD. NAFLD is a multisystem disease in which excess fat is stored in the liver, primarily associated with other comorbid conditions such as obesity, diabetes mellitus, cardiovascular disease, hyperlipidemia, metabolic syndrome, and chronic kidney disease (Argo & Caldwell, 2009). Patients with NAFLD are often older age, with obesity and other metabolic comorbidities, and at a high risk to develop cardiovascular complications. NAFLD affects the hepatic structure and function and can lead to cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Consequently, NAFLD is a leading cause of cirrhosis, HCC, and the need for liver transplantation. However,

cardiovascular disease is the primary cause of deaths among NAFLD patients (Byrne & Targher, 2015).

NASH. The spectrum of NAFLD includes simple steatosis and steatohepatitis (NASH) which is a progressive, and fibrotic liver disease. Fatty liver accumulation or steatosis alone is classified as Type 1 NAFLD, steatosis and lobar inflammation as Type 2 NAFLD, steatosis and ballooning degeneration as Type 3 NAFLD, steatosis ballooning degeneration and fibrosis is Type 4 NAFLD. Types 3 and 4 are defined as NASH. Described for the first time by Ludwig, Viggiano, Mcgill, and Oh (1980) as "a poorly understood and hitherto unnamed liver disease" (p. 434), NASH is a progressive fibrotic liver disease that can lead to HCC and end-stage liver disease. One consequence of NASH is the appearance of liver fibrosis, measured by a score that ranges from F0 (absence of fibrosis) to F4 (liver cirrhosis) (Chalasani et al., 2018). NASH is diagnosed with a liver biopsy.

Cryptogenic cirrhosis. Cryptogenic cirrhosis (CC) is the end stage of chronic liver disease in which the underlying etiology is unknown and undentified after extensive clinical, serological, and pathological evaluations. Powell et al. (1990) observed a gradual loss of steatosis in cases that progressed from NASH to cirrhosis, and Caldwell and Marchesini (2018) noted that metabolic risk factors were common among individuals with CC. This suggests that some cases of CC can be attributed to advanced NASH, although other causes of CC do exist. Thuluvath, Kantsevoy, Thuluvath, and Savva (2018) revealed that CC should not be considered the same as NASH cirrhosis. It remains

debatable if the two entities are essentially the same. Further investigations are required to identify unknown causes of cirrhosis (Caldwell & Marchesini, 2018; Thuluvath et al., 2018). Figure 2 illustrates the NAFLD disease spectrum as revealed by biopsy results.

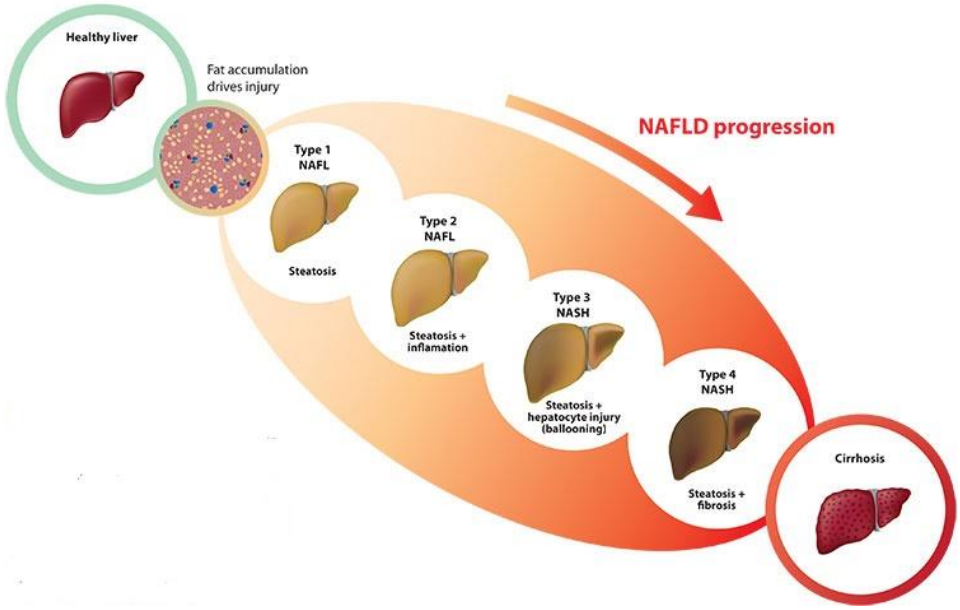

Figure 2. NAFLD spectrum.
Note. Source: NASH Biotech. Retrieved from http://www.nashbiotechs.com/newsletter.html. NAFL=Non-alcoholic fatty liver; NASH=Nonalcoholic steatohepatitis.

Epidemiology of NAFLD and NASH

The epidemiology and demographic characteristics of NAFLD usually constellate obesity and type 2 diabetes; however, a portion of NAFLD patients are lean (Younossi et al., 2016). NAFLD is increasingly prevalent in the U.S. and globally and is a major cause of advanced liver disease. Consequently, the number of liver transplants for NASH nationwide has increased over time. Many NAFLD patients are likely to progress to more

advanced liver disease. However, it is challenging to screen for NASH because invasive liver biopsy is needed.

The global prevalence of NAFLD is currently estimated to be 24% (Younossi et al., 2016). In the United States among patients with NAFLD and in the general population, the prevalence of NASH is estimated to be 21%, and 3-4%, respectively (Younossi et al., 2016). The prevalence of NAFLD in the United States varies by ethnicity: highest among American Hispanics followed by Americans of European origin and African Americans. The ethnic disparity in the prevalence of NAFLD is not fully understood. The high prevalence of obesity and hypertension and the low prevalence of NAFLD among African Americans suggest that ethnicity may influence the association of metabolic syndrome with NAFLD (Smits, Ioannou, Boyko, & Utzschneider, 2013). Moreover, even within a specific ethnic group in the United States, there may be differences in the prevalence of NAFLD associated with the country of origin, which remain unknown (Fleischman, Budoff, Ifran Zeb, & Foster, 2014). Genetic and environmental factors may explain some of these differences.

Risk Factors of NAFLD

The progression of NAFLD from steatosis to NASH fibrosis is estimated to be 14 years, and progression to each subsequent fibrosis stage is estimated to be seven years. As the stage of fibrosis increases, so does the risk of liver-related mortality. Authors of population-based and familial-aggregation studies, as well as twin-studies, have given evidence of a heritable component of NAFLD that ranges from 20 to 70 %. NAFLD

heritability differs among ethnicities, greater among Hispanics (33%), as compared to African Americans (14%) (Loomba et al., 2015; Speliotes et al., 2011).

Epigenetic factors. Various factors contribute to the development of NAFLD, including genetic predisposition, environmental exposures, and lifestyle (Gerhard & DiStefano, 2015). Major advances have uncovered the genetic basis for the heritability of NAFLD. In NAFLD, genome-wide HCV association studies have identified novel loci associated with disease severity phenotypes and approximately seven categories of genes associated with NAFLD (Anstee & Day, 2015).

Role of environmental factors. A combination of genetic predisposition and environmental factors contribute to the development of NAFLD. Dietary habits, activity, and socioeconomic factors predispose individuals to NAFLD. Patients with NAFLD tend to have easy access to fast food places and restaurants, and, therefore, more likely to have unhealthy eating habits and low physical activity levels as compared to healthy individuals. The role of socioeconomic factors is not well defined. Kallwitz et al. (2015) explored the role of environmental factors in different ethnic groups with NAFLD to investigate the effect of environmental factors on genetic predisposition. They studied the impact of dietary and lifestyle factors together with the impact of acculturation, education level, income and access to health care, and found that they were not independently associated with the risk of developing NAFLD, suggesting a joint effect between environmental and genetic factors (Younossi et al., 2016).

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 (Coombes & Trotter, 2005). The Organ Procurement and Transplantation Network (OPTN) is a system for donor matching and allocation, and its membership includes every transplant hospital program, organ procurement organization (OPO), and histocompatibility laboratory in the United States, certified by the United Network for Organ Sharing (UNOS). Each UNOS entity plays an active role in forming the policies that govern the transplant community. The Transplant Act also required that the OPTN, under federal contract, is managed by UNOS via a Board of Directors and committee members to operate the OPTN (UNOS, 2018).

UNOS Regions

The system of allocation employed by UNOS divides the United States into 11 geographical areas called UNOS regions as depicted in Figure 3.

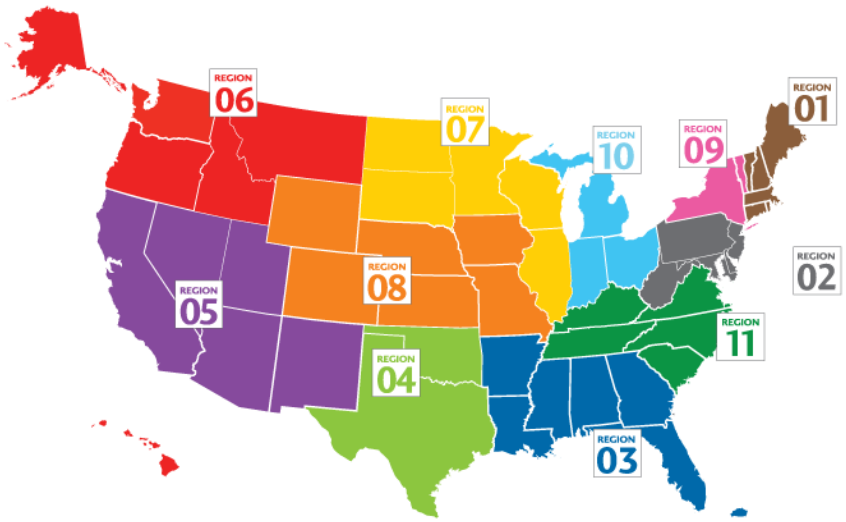

Figure 3. UNOS regions.
Note. Source: OPTN (n.d.) Retrieved from https://optn.transplant.hrsa.gov/members/regions.

The states in each region are shown in Table 1. Each of these regions, initially established by the OPTN for administrative and representative purposes, are represented on the Board of Directors and each of the standing OPTN committees. The geographic subdivisions were never established with the purpose to provide an equal distribution of organs among populations of transplant centers. The division of these 11 geographic regions was designed to recognize existing relationships within the transplant community as well as the local interests of each transplant center (OPTN, 2018).

Table 1

States in UNOS Regions

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

Note. Source: OPTN (n.d.) Retrieved from https://optn.transplant.hrsa.gov/members/regions

Donation Service Areas

Within each UNOS region, there are variable numbers of donation service areas (DSAs). Each DSA is served by one of the 58 OPOs that are responsible for identifying potential donors and coordinating 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. The Center for Medicare Services designates these DSAs (Figure 4), but they vary regarding the number of transplant centers served, square mileage of the area, state boundaries, candidate/donor ratios, and procurement rates and characteristics.

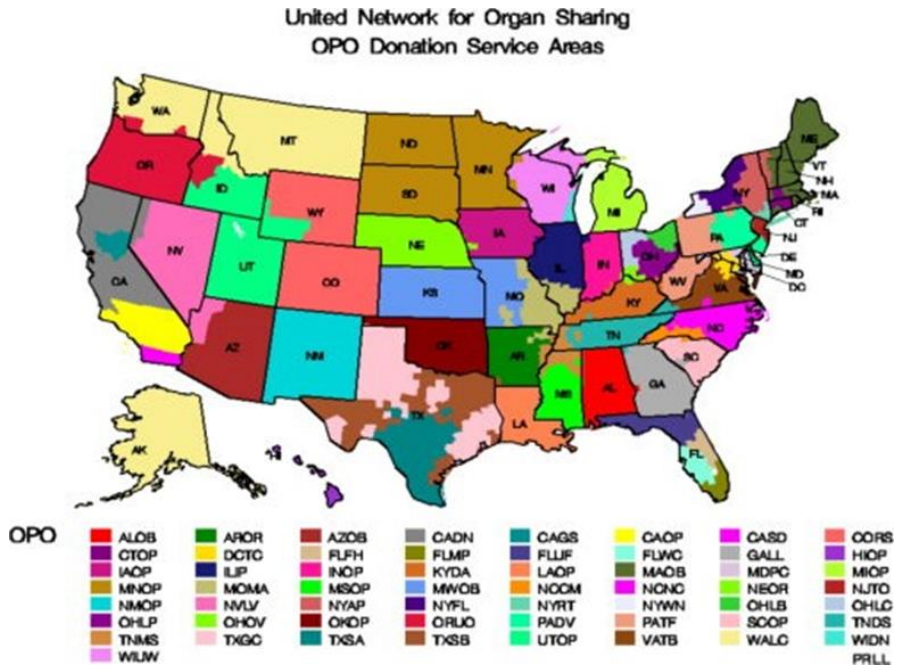

Figure 4. OPO donation service area map.
Note. Source: Wedd, Harper, and Biggins (2013)

This current allocation scheme was adopted over 20 years ago. Livers are offered to sicker patients within the donor area before being offered to other parts of the country. The variation in DSAs has raised concerns that access to deceased donors is unequal across DSAs leading to a regional variation in posttransplant outcomes. Yeh, Smoot, Schoenfeld, and Markmann (2011) analyzed organ availability in terms of transplant rate and MELD with exceptions using national data from 2002 to 2009. They found

remarkable differences across DSAs. Transplant rates varied by 20.1-fold and average MELD score ranged from 23.8 to 31.2, indicating that patients in low average MELD DSA could reach the top of the wait list faster compared to other DSAs. As a result, high average MELD DSAs, which have low organ availability, were associated with high mortality rates. Therefore, geographic inequity in access to deceased donor livers suggests that the organ distribution areas need to be restructured to guarantee equity (Yeh et al., 2011).

The National Transplant Act established a system of regulation and oversight for the field, a data management system to track outcomes and is a mandate to review and continuously provide an equitable distribution of organs in the United States. UNOS is 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 after exhaustive dialog and consensus among participating members. Given the competing interests of each member, may be difficulty to reach consensus within the group (UNOS, 2018).

The disparity in supply and demand of cadaveric organs has driven much of the policy discussion within the life-saving liver transplantation field. The method by which donor organs are allocated to individuals on the wait list for transplants is a relevant topic for research and debate, needed to meet the dual goals of fair allocation and optimum efficiency.

The Final Rule

Despite clinical and scientific advances within the field, perceived inequities exist regarding geographical disparity as well as increased mortality on the wait list for those awaiting a liver transplant. When liver transplants first initiated, the allocation policy was based on little more than total time spent on the transplant wait list. This gave decompensated patients with recent diagnoses of end-stage liver disease little hope for transplantation. Under this system, wait-list mortality and drop-out rates were high (OPTN, 2018).

In 1998, these perceived inequities were addressed by the Department of Health and Human Services in the form of a "Final Rule" to ensure that the allocation of scarce organs was based on medical need and not on wait time. The Institute of Medicine addressed 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). Moreover, the "Final Rule" was intended to place greater emphasis on acuity and less focus on keeping organs within local procurement areas. To achieve the goal of equitable distribution of a scarce resource, the Final Rule provided two recommendations to the transplant community:

1. an expansion of the geographical area served by each OPO to equalize access; and
2. The development of an allocation system that prioritizes based on acuity and deemphasizes waiting time.

Liver Allocation Based on Acuity

To address the recommendation regarding redirecting allocation based on acuity, Kamath et al. (2001) developed the MELD score in February 2002, a metric for liver allocation. The MELD score predicts short-term mortality and is calculated using three laboratory values: the total serum bilirubin, serum creatinine and the international normalized ratio (INR) according to Equation 1:

$$\text{MELD}=3.78\ ln\ [\text{serum total bilirubin (mg/dL)}] +11.2\ ln\ (\text{INR}) + 9.57\ ln\ [\text{serum creatinine (mg /dL)}] +6.43 \quad (1)$$

The MELD score is used to determine priority for LT candidates, who are placed on a national transplant list. Donor organs are allocated first regionally, then locally and regionally. The utilization of the MELD score had several advantages. Easly calculated from widely available laboratory tests, the MELD score allocation system resulted in a reduction of wait-list mortality and median waiting times (Asrani & Kim, 2011). The MELD score is intended to reflect the severity of the candidate's disease. However, for certain liver diseases, such as acutely decompensated cirrhosis, HCC, cholangiocarcinoma, hepatopulmonary syndrome, pulmonary hypertension, and familial amyloidosis, where the progressions are not weighted into the MELD scores, the calculated MELD score is inadequate to reflect the candidate's medical urgency (Bernardi et al., 2011; Martin & O'Brien, 2015). To balance their risks of tumor progression or other medical conditions, the MELD score is adjusted by adding exception points. The MELD score, with or without exception points, determines prioritization on

the transplant wait list ranked by an increased risk of death. It is applicable to a majority of chronic liver diseases (Asrani & Kim, 2011). The MELD score allocation rule is not applicable to Status 1 patients, who have acute fulminant hepatic failure at high risk of death within a week if a liver transplant is not performed.

Over the years, investigators have proposed numerous modifications to the MELD scoring system (Kalra, Wedd, & Biggins, 2016). Sharma, Schaubel, Sima, Merion, and Lok (2008) found that serum creatinine may have a high weight in the existing MELD formula and proposed a re-weighted MELD score that assigns higher weight to bilirubin and lower weight to creatinine and IRN. In liver transplant candidates, serum sodium is an independent predictor of post-transplant mortality, associated with mortality independent of MELD score, particularly for those with low serum sodium levels (Kim & Lee, 2013). Huo et al. (2007) developed the MELD to serum sodium (SNa) ratio (MESO) to combine both the predictive power of MELD and SNa. Several investigators have shown that incorporating sodium into the MELD score increases its predictive accuracy (Biggins et al., 2006; Biselli et al., 2010; Heuman et al., 2007).

Kim et al. (2008) showed that using the MELD-Na score over standard MELD score can reduce wait-list deaths by 7%. Supported by these findings, a modified MELD score with added serum sodium was implemented on January 11, 2016 (Biggins et al., 2006). The MELD-Na score is calculated through Equation 2:

$$\text{MELD-Na} = \text{MELD} + 1.32 \times (137 - \text{Na}) - [0.033 \times \text{MELD} \times (137 - \text{Na})] \quad (2)$$

Expansion of the Geographical Areas

The first recommendation to expand all service areas for organ procurement to serve a population base of nine million people was met with strong opposition from much of the transplant community and was never adopted (Ahmad, Bryce, Cacciarelli, & Roberts, 2007). Several states, including Louisiana, Wisconsin, Texas, Arizona, Oklahoma, Tennessee, and South Carolina, passed legislation prohibiting such expansion based on established limitations to interstate commerce (Meckler, 1998). Investigators are exploring new strategies to change the distribution system and reduce geographic disparities.

Regional sharing for candidates with MELD scores of 15 or greater. 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). This was done locally and then regionally, and before allocation to the highest MELD score patients locally and regionally. Merion et al. (2005) found that survival benefits from the liver transplant procedure occurred for patients with MELD score above 18, while undergoing a transplant with a MELD score below 5 yielded a probability of mortality that was higher than those continuing to wait for a liver transplant. They suggested reconsidering the liver allocation policy for low MELD candidates and adding survival benefit component in the liver allocation policy. As a result, a change in the liver allocation policy occurred when the OPTN implemented the minimum-15 rule on January 12, 2005 (Regional Share 15 Rule). This rule requires that organs be offered first

to Status 1 patients locally and then regionally, and then to patients with a minimum MELD score of 15 locally and then regionally. If no such recipients are identified, offers to patients with MELD scores less than 15 are allowed. The minimum-15 rules were intended to address inequities in organ distribution based on the geographical difference in acuity of liver disease. This organ allocation policy change resulted in a 36% decrease in the proportion of liver recipients with a MELD score less than 15 undergoing transplant but did not change the sharing outside DSAs (Bittermann, Makar, & Goldberg, 2012; Elwir & Lake, 2016).

Regional sharing for Status 1 candidates. On December 15, 2010, the OPTN implemented full regional sharing of adult donor's livers for all Status 1 candidates. Previously, livers in most regions were offered to Status 1 candidates first locally, and then regionally. Implementation of full regional sharing has promoted timely access to donor livers to Status 1 candidates and decreased wait list death rate.

Regional Share 35/National Share 15. In 2012, the Health and Human Services Advisory Committee on Transplantation recommended an evidence-based organ allocation, rather than a system based on arbitrary boundaries of OPOs or their DSAs. OPTN/UNOS acknowledged that there were unacceptable geographic disparities in access to transplantation and charged organ-specific committees to develop a policy to minimize geographic effects. In 2013 the liver allocation policy was modified with the implementation of Share 15 National and Share 35 Regional to increase regional, national access for highly urgent liver candidates with MELD score of 35 or higher (Washburn,

Pomfret, & Roberts, 2011). Regional Share 35 policy resulted in an increase in the number of transplants and a decrease in the number of discarded liver organs (Halazun et al., 2016). Additionally, the Regional Share 35 policy resulted in 30% decrease in wait-list mortality for high MELD recipients and an increase in LT patients in the intensive care unit or on life-support devices (Massie et al., 2015).

Revised Policy Exception Scores for Hepatocellular Carcinoma (HCC)

One unintended consequence of the MELD allocation system has been an increase in transplanting patients with HCC. To account for their risk of tumor progression, they were provided with MELD exception points. Subsequent studies showed that HCC priority points favored HCC candidates. Therefore, the MELD exception policy was modified several times by decreasing such exception points in 2003 and 2005 (Parikh & Singal, 2016). A recent revision of the OPTN liver allocation policy implemented in 2015 modified the maximum value and the timing of exception scores for HCC candidates. This created a better balance in transplant opportunities between candidates with HCC exceptions and those with allocation priority based on their calculated MELD score. The maximum HCC exception score was capped at 34 (Pais et al., 2016).

Currently, a national system that provides equitable access to LT for candidates whose disease severity is not accurately reflected by the calculated MELD score is not available. There are regional agreements. Each region has a review board that adopts independent criteria to evaluate requests for exceptions submitted by the liver transplant

programs. To create greater consistency in assigning exception scores for medical conditions not assessed reliably by the MELD score, the Liver Committee in January 2016 distributed a proposal to establish a national liver review board (NLRB) to replace the regional boards in each of the OPTN regions (OPTN, 2018). This step is still under evaluation.

Weaknesses of the MELD Allocation Model

In addition to favoring patients with HCC, the MELD allocation system has resulted in a disproportionate number of patients within larger OPOs who are transplanted at higher acuity levels than those patients in smaller OPO. Moreover, the MELD score is not an accurate predictor of post-transplant mortality and does not include donor characteristics (Habib et al., 2006). The MELD variables are subject to laboratory variations (Cholongitas et al., 2007; Trotter et al., 2007). Serum creatinine is inaccurate for cirrhotic patients and is influenced by gender, muscle mass, age, and ethnicity (Martin & O'Brien, 2015). The MELD score may penalize female candidates because serum creatinine, a function of muscle mass may underestimate the severity of liver disease in women who have a lower muscle mass compared to men. As a result, the MELD allocation system has resulted in a 12% decrease of the probability to receive a liver allograft, and a 15% increased mortality on the wait list (Lai et al., 2010; Myers, Shaheen, Aspinall, Quinn, & Burak, 2011). Though the MELD score has improved equity in the liver allocation process, there is still a significant mortality rate on the LT wait list. The MELD score may not be a reliable predictor of liver-related mortality for all

patients (Bambha & Biggins, 2008; Huo et al., 2007). Some candidates may have clinically significant complications not captured by the MELD, such as the NAFLD/CC patients, who may experience disproportionate rates of wait-list dropout and are thus at risk of death while on wait list (Kwong et al., 2015).

The impact of MELD allocation model on NAFLD/NASH. Patients with NASH, cryptogenic cirrhosis and low MELD score have slower disease progression and are less likely to receive an LT than patients listed for other end-stage liver diseases. Cardiovascular comorbidities, renal complications, and older age are likely to increase the risk of wait-list dropouts and unfavorable short-term outcomes. For this reason, patients with NAFLD cirrhosis have a low priority, and they often die on transplant wait list. Although patients with NAFLD cirrhosis have operative difficulties and a high rate of postoperative complications, their long-term post-transplant outcomes are not inferior to patients transplanted for other etiologies (Pais et al., 2016). Patients transplanted for NAFLD cirrhosis have short term morbidity and mortality, but high middle- and long-term post-transplant graft and patient survival rates (O'Leary et al., 2011). Proper management of NAFLD patients on the wait list can increase access to LT and decrease the risk of posttransplant complications.

High Risk Donors

Patients waiting for a liver transplant are steadily increasing. Parikh et al. (2015) conducted a study to project donor growth. They used a Monte Carlo simulation to measure the impact of several factors on population growth and liver donor utilization,

and they estimated population growth of 7.1% in 2025 but a lower 6.1% donor utilization growth. The aging of the U.S. population and the obesity epidemic indicate that potential LT candidates are growing at a faster rate than potential donors, widening the gap between donors used and waiting patients.

Organ shortage has extended the standard criteria and led to exploring innovative approaches to increase organ supply, including live donor transplants, the use of split livers, non-optimal donors, i.e., donors after circulatory death (DCD), high-risk death brain donors (DBD), and extended-risk donors (Saracino, 2018).

Donors After Circulatory Death (DCD)

Donation after cardiac death describes the retrieval of no–heart-beating organs for transplantation following confirmation of death using circulatory criteria. DCD typically have irreversible brain injuries with no chance for recovery, but they do not meet the criteria for brain death. They progress to cardiac arrest after withdrawal of life support. DCD livers are more susceptible to damage than DBD livers and can lead to posttransplant complications including ischemic-type biliary lesions complications and higher rates of primary nonfunctioning and graft failure (Blok et al., 2016; Saracino 2018).

Orman, Barritt, Wheeler, and Hayashi (2013) conducted an exploration of the association between donor characteristics and donor use. They observed a decreasing trend in donor utilization from 1988 to 2004, and then a gradual increase. The proportion of nonuse DCD livers increased from 9% in 2004 to 28% in 2010. With an aging

population, increased body mass index, and the prevalence of diabetes, the donor quality has worsened, leading to a significant decline in LT availability. The increasing proportion of discarded DCD livers indicates a reluctance to use these suboptimal allografts due to the recognition that outcomes will be worse. There is a critical need for strategies for the optimal utilization of marginal donors in subsets of LT recipients that would benefit a DCD donor without worsening post-transplant outcomes.

Public Health Service Increased Risk Donors

In 1994 CDC established criteria to define high-risk donors based on social behaviors that increase their risk for blood-borne diseases, including human immunodeficiency virus (HIV), even if these donors tested negative by serologic screening for infectious disease (Rogers et al., 1994). In July 2013 U.S. Public Health Service (PHS) published the "increased risk" guidelines that expanded the CDC "high risk" guidelines including the likelihood of recent hepatitis B virus (HBV) and HCV, in addition to HIV infection (Seem et al., 2013). The increased-risk designation refers to donor's risk behaviors including men who have had sex with other men, history of drug abuse, prostitutes, inmates, persons with hemophilia, persons who have had sex with persons who engaged in high-risk behaviors, and children born from mothers with high-risk behaviors. CDC high-risk donors before 2013 and increased-risk donors are often discarded as they are considered at risk of transmitting specific infection pathogen, and some recipients are unwilling to consider them. I have provided more details about CDC high-risk and PHS increased-risk criteria in Appendix B.

Transplant candidates should be informed if they are being offered organs from increased-risk donors to evaluate the risk of accepting a donor at risk of transmitting recent blood-born infection versus the risk of prolonging their time on the wait list (Kucirka et al., 2015). Therefore, PHS increased-risk donors are potentially underutilized and contribute to increasing wait-list time (Volk, Wilk, Wolfe, & Kaul, 2017). However, the absolute risk of transmission is very low, and many patients could utilize these organs and receive a substantial predicted survival benefit instead of prolonging their stay on the liver transplant wait list and increase their risk of mortality while waiting for a low-risk donor (Kucirka et al., 2015).

Expanded Criteria Donors (ECD)

Currently, the OPO defines Expanded Criteria Donor (ECD) as a donor at least 60-year-old or a donor between 50- and 60- year-old with at least two of the following conditions: hypertension, serum creatinine ≥1.5, or stroke as a cause of death. ECD donors are not considered ideal, but they can expand the donor pool and increase the options for some candidates to shorten their time on the wait list (Vodkin & Kuo, 2017). Based on the ECD criteria donors are either classified as ECD or as non-ECD, which does not capture all the spectrum of donor risk.

The Concept of the Donor Risk Index

The liver allocation policy based on the MELD score only includes LT candidate characteristics and estimates the short-term risk of death while waiting for an LT. However, donor-recipient matching and organ acceptance are complex decisions The

MELD score-base prioritizes sicker patients rather than prioritizing based on achieving an optimal donor-recipient match or post-transplant survival. In recent years, investigators have emphasized the need to apply the concept of utilitarianism to the organ allocation system (Briceño et al., 2013). Organ allocation models seek to maximize the survival benefit of the entire patient population rather than of an individual patient, or to save more years of life, rather than more lives (Briceño et al., 2013). Relevant steps include the development of a donor risk model, which seek to predict the survival of the donated liver after transplantation, enabling "matching" between the expected post-transplant lifespan of the liver with that of the recipient. Donor quality and recipient characteristics have an impact on graft survival after a solid organ transplant (Weiss et al., 2012).

In their seminal paper, Feng et al. (2006) developed the first donor risk index (DRI), a metrics for donor quality with emphasis on the importance of donor factors for a successful LT. The DRI has been used in multiple studies to quantify donor quality and to help understand the impact of donor factors on selected recipients, including those with a low MELD score or HCV (Flores & Asrani, 2017). In national surveys, 46% of transplant specialists felt that the availability of a reliable and practical DRI would improve shared decision making at the time of donor offer. However, unlike the MELD score, the DRI has not been translated into liver allocation policy and practice. Several risk models have been proposed using donor, recipient, and interoperative factors to predict post-transplant survival to facilitate transplant decision-making (Flores & Asrani, 2017).

With the utilization of ECD and DCD donors, the DRI may assist in decision making and in evaluating organ and patient outcomes (Akkina et al., 2012). Volk, Lok, Pelletier, Ubel, and Hayward (2008) showed that high-risk livers or livers with high DRI were more likely to be used for low disease severity recipients and less likely to be used for Status 1 or high MELD score recipients. Less urgent candidates or low MELD patients were likely to receive high-risk organs leading to unfavorable posttransplant survival. Schaubel, Sima, Goodrich, Feng, and Merion (2008) found that high DRI donors had a detrimental effect on recipients in the lowest MELD category ranging from 6 to 8, and proposed transplantation of high DRI organs for high-MELD candidates. Maluf, Edwards, and Kauffman (2006) analyzed the association between extended criteria donation and DRI>1.7 and found no interaction between DRI and MELD score, suggesting that high-DRI livers can be transplanted in high-MELD recipients with no impact. Rauchfuss et al. (2013) found that waiting time is a critical factor in high-MELD patients while DRI is less critical, suggesting that high-MELD patients would benefit from earlier transplantation with a high-DRI donor rather than waiting for an optimal organ. In decision making, it is preferable to use high-risk donors in patients with advanced MELD score rather than waiting for a low-risk donor (Amin et al., 2004).

Donor Risk Models to Predict Posttransplant Graft Survival

Following the development of the DRI, several risk models to predict post-transplant survival have been developed using donor, recipient, and operative factors to predict post-transplant survival. Some studies have attempted to identify the most

relevant risk factors and to develop several statistical models designed to predict graft outcomes with improved predictive ability, as compared to the DRI. Other studies have attempted to validate the DRI or to adapt it to other country populations. I summarized selected models and their relative advantages and disadvantages in Tables 2 and 3.

Table 2

Donor Risk Models to Predict Post-Liver Transplant Graft Survival

Risk model	Risk factors
DRI	Donor: age, race, height, DCD, split liver, COD. Transplant: allocation, CIT
ET-DRI	Donor: age, DCD, split liver, latest serum GGT gamma-glutamyl transpeptidase, allocation, rescue allocation. Transplant: CIT
SOFT	Donor: age, creatinine, COD. Recipient: age, BMI, previous LT, previous abdominal surgery, albumin, dialysis, UNOS status, MELD score, encephalopathy, PVT, ascites, portal bleed, life support. Transplant: allocation, CIT
BAR	Donor: age. Recipient: age, MELD score, previous LT, life support Transplant: CIT
D-MELD	Donor: age. Recipient: MELD score
DQI	Donor: age, COD, ICU stay, split liver, lowest MDRD creatinine clearance

Notes: BAR: Balance of risk; BMI: Body mass index; COD: Cause of death; CIT: Cold ischemia time; DCD: Donation after cardiac death; D-MELD: Donor age Model for End-stage Liver Disease; DQI: Donor Quality Index; DRI: Donor Risk Index; ET-DRI: Eurotransplant donor risk index; GGT: latest serum GGT gamma-glutamyl transpeptidase; ICU: Intensive Care Unit; LT: Liver transplant; PVT: Portal vein thrombosis; SOFT: Survival outcomes following liver transplantation

Table 3

Donor Risk Models. Strengths and Weaknesses

Risk model	Strengths	Weaknesses
DRI	Validated in recipient subsets. Variables available at the time of transplant.	Developed with data pre-MELD. Variables not all accountable at the time of donor offer. Race not a reliable predictor.
ET-DRI	All variables available at the time of transplant.	Not all variables available at the time of offer, poor external validation.
SOFT	Can be used to predict wasteful transplants and survival benefit.	Complex model with many variables not available at the time of offer. Predicts only short-term mortality. Similar predictions with and without donor factors.
BAR	Variables available at the time of transplant.	Predicts only short-term mortality. Lacks granularity define futility but only 3% of transplants would meet the definition.
DRI	Validated in recipient subsets. Variables available at the time of transplant.	Developed with data pre-MELD. Variables not all accountable at the time of donor offer. Race not a reliable predictor.
ET-DRI	All variables available at the time of transplant.	Not all variables available at the time of offer, poor external validation.
SOFT	Can be used to predict wasteful transplants and survival benefit.	Complex model with many variables not available at the time of offer. Predicts only short-term mortality. Similar predictions with and without donor factors.

(*table continues*)

Risk model	Strengths	Weaknesses
BAR	Variables available at the time of transplant.	Predicts only short-term mortality. Lacks granularity define futility but only 3% of transplants would meet the definition.
D-MELD	Very simple model to use.	Penalizes older donor livers with high-MELD recipients.
DQI	Use few variables available at the time of offer	Use data from French transplant registry. Not externally validated.

Notes: BAR: Balance of risk; D-MELD: Donor age Model for End-stage Liver Disease; DQI: Donor Quality Index; DRI: Donor Risk Index; ET-DRI: Eurotransplant donor risk index; SOFT: Survival outcomes following liver transplantation.

The Donor Risk Index

Feng et al. (2006) developed the first DRI using a population of adult recipients of cadaveric liver transplant in the United States from 1998 to 2002 and data from SRTR. They identified seven donor characteristics significantly associated with liver failure, three of them related to donor demographics (age, race, and height), then donor cause of death (trauma, cerebrovascular accident, anoxia, and others), the type of death (DCD or non-DCD) and whole or partial/split transplant. The model also included cold ischemia time and sharing donor service area (local, regional and national). From the Cox proportional hazard model, the derived equation to estimate the DRI is presented in Equation 3:

$$\text{DRI} = \exp[(0.154 \text{ if } 40 \leq \text{age} < 50) + (0.274 \text{ if } 50 \leq \text{age} < 60) + (0.424 \text{ if } 60 \leq \text{age} < 70) \quad (3)$$

+ (0.501 if 70 ≤ age) + (0.079 if cause of death = anoxia)

+ (0.145 if cause of death = cerebrovascular accident)

+ (0.184 if cause of death = other)

+ (0.176 if race = African American) + (0.126 if race = other)

+ (0.411 if donation after cardiac death) + (0.422 if partial/split)

+ (0.105 if regional share) + (0.24 if national share)

+ (0.010 x cold ischemia time)]

Notes: The term exp implies e raised to a value, i.e., $exp(value) = e^{(value)}$

The reference donor, or the lowest risk donor, would be a white donor with age under 40-year, who died of trauma, with height of 170 cm, with a whole local non-DCD organ with cold ischemia time of eight hours. Lowest risk donors accounted for 19% of LT recipients in the study population; their estimated one-year graft survival ranged between 87% and 89% and their estimated three-year graft survival between 80% and 83%.

Recipients with the highest-risk livers, i.e., with African-American donors of age greater than 40, who died for a cause other than trauma, with height lower than 170 cm, and a split or partial national DCD liver with cold ischemia time greater than eight hours, had an estimated 1-year graft survival between 69% and 74% and a 3-year graft survival between 57% and 63% (Feng et al., 2006).

Validation of the Donor Risk Index. Subsequent studies have validated the DRI as an independent predictor of liver graft failure in the U.S. populations as well as in

populations of other countries in the post-MELD era (Hung et al., 2015; Northup et al., 2015; Rosenberger et al., 2014). Donors with DRI of more than 1.7 have been associated with a significant increase in the risk of liver failure in each MELD category. Additionally, the DRI has also been associated with the development of post-transplant complications, such as hepatic artery thrombosis, biliary complications, end-stage renal disease (Israni et al., 2013; Stine, Argo, Pelletier, Maluf, & Northup, 2016). Some researchers have also looked at the economic impact of using high-risk livers on the cost of LT, including the cost of increasing readmissions (Axelrod, Schnitzler, Salvalaggio, Swindle, & Abecassis, 2007; Salvalaggio et al., 2011).

Donor quality quantified by the DRI score is associated with progressed fibrosis among patients with HCV, and with survival in HCC recipients of a LT as well as for those who undergo re-transplantation (Macdonald, Sewell, Harper, Roberts, & Yao, 2015; Stine et al., 2016).

Strengths and influences on transplant practices. The DRI score has been used to define organs as high or low risk and enables using this classification of donor risk in transplant practices (Feng et al., 2006). Moreover, the DRI has been instrumental in identifying disparities in organ utilization. Mathur, Schaubel, Zhang, Guidinger, and Merion (2014) showed that Hispanics were 21% more likely to get a lower-risk organ compared to Caucasians. Since the implementation of Share 35, the DRI has shown the unintended changes in practice pattern post-Share 35. Although liver acceptance offers has declined significantly after Share 35, organs discarded pre–Share 35 or post–Share 35

had no statistically different DRIs, suggesting that changes in organ acceptance could lead to increasing national discard rates and organ waste (Goldberg, Levine, Karp, Gilroy, & Abt, 2017).

An objective and effective scoring system that quantifies donor quality could be beneficial in clinical practice and risk communication. Volk et al. (2013) found that there is considerable variability among surgeons about their perception of donor risk and in their estimates of the probability of graft failure for specific clinical scenarios. A useful metric of donor quality could help physicians evaluate the donor risk and reduce surgeon bias in organ acceptance practice.

Patients prefer an active role in decision making. Volk et al. (2011) conducted a study to analyze patient decision making about donor quality in LT, and they found that patients are biased toward acceptance of high-risk donors and would rather stay on the wait list then accept a low-quality donor. They found that risk tolerance was associated with personal beliefs and not with severity of disease, suggesting that understanding how the patients think about organ quality can be used in risk communication counseling patients about the risks and benefits of accepting a low-quality organ. They demonstrated that risk communication needs to be tailored to patient understanding of organ quality. Although patients may be initially riskaverse, this tendency can be mitigated if they can understand the competing risk of dying on the wait list. Therefore, donor risk models have the potentiality to provide a useful tool to transplant clinicians to educate patients on their risks and benefits so that they can make an informed decision.

Limitations and weaknesses of the DRI. The DRI is still not accepted in clinical practice as a tool for donor-recipient matching. Mataya et al. (2014) conducted a survey among physicians to assess LT decision making and the utilization of DRI. They found that 73% of physicians perceived that the DRI did not incorporate the risk of liver failure, while 88% felt that the variables used to develop the DRI were misleading. The DRI was developed by Feng et al. (2006) using pre-MELD score data and may not reflect the current LT practice. Moreover, the DRI includes the donor variable race that not only lacks biological relevance but is also not a reliable predictor of posttransplant graft failure and should not be included in donor risk models (Asrani et al., 2010; Flores & Asrani, 2017). Unmeasured confounding factors may also have an impact on post LT graft failure.

Eurotransplant Donor Risk Index (ET-DRI)

Braat et al. (2012) developed a DRI tailored and adapted to the Eurotransplant region (ET-DRI), using cadaveric LTs from 2003 and 2007. From the Cox proportional hazard model, the derived six-factors ET-DRI is as shown in Equation 4:

$$\begin{aligned}\text{ET-DRI} = \exp[0.960\,((&0.154 \text{ if } 40 \le \text{age} < 50) + (0.274 \text{ if } 50 \le \text{age} < 60) \\ &+ (0.424 \text{ if } 60 \le \text{age} < 70) + (0.501 \text{ if } 70 \le \text{age}) + (0.079 \text{ if cause of death = anoxia}) \\ &+ (0.145\times \text{ if cause of death = cerebrovascular accident}) \\ &+ (0.184 \text{ if cause of death = other}) + (0.411 \text{ if donation after cardiac death}) \\ &+ (0.422 \text{ if partial/split}) + (0.105 \text{ if regional share}) \\ &+ (0.244 \text{ if national share})) + (0.010 \times (\text{cold ischemia time} - 8\text{ h}))\end{aligned} \tag{4}$$

+0.06((latest lab GGT (U/L) - 50)/100) + (0.180 if rescue offer)]

Notes: The term exp implies e raised to a value, i.e. $\exp(value) = e^{(value)}$

External validations of the DRI and ET-DRI when adapted to the French transplant registry led to poor calibration and discrimination, suggesting that both models need further validation and adjustment before being used for donor allocation rules (Winter et al., 2017). A refinement of the ET-DRI that combined recipient factors, or the combined donor-recipient model (DRM), showed an improved predictive ability (Blok et al., 2015)

Survival Outcomes Following Liver Transplantation (SOFT)

The Survival Outcomes Following Liver Transplantation (SOFT) score developed by Rana et al. (2008) utilized a combination of 18 recipient, donor, and operative factors to predict 3-month post-transplant survival. The most significant risk factors were previous transplants, warm ischemia time, and the need for life support. A reduced version of the SOFT score that utilized only 14 risk factors available at the time of listing, is the pre-allocation SOFT score (P-SOFT), used to evaluate a candidate prior to liver allograft allocation. The SOFT score was derived from a multivariable logistic regression model with the coefficients converted into points. The model includes multiple risk factors limiting its applicability in clinical practice. Recipient and operative factors dominate the SOFT score (Rana et al., 2008). Sensitivities analyses have shown that short-term survival models with and without donor factors have similar performance.

Therefore, the SOFT score is not an ideal tool to assess donor risk (Flores & Asrani, 2017).

Balance of Risk (BAR)

Dutkowski et al. (2011) developed a score system based on a few strong predictors of post-transplant mortality. The balance of risk (BAR) score was derived using UNOS data from 2002 to 2010 and six strong predictors of post-transplant behavior: recipient MELD score; cold ischemia time; recipient age; donor age; previous liver transplant; and life support dependence prior to transplant. A BAR score ranges from 0 to 27 points derived from a logistic regression model. The model reflects an exponential increase in 3-month mortality, and a BAR score above 18 is a marker of transplant futility (Dutkowski et al., 2011). However, only 3% of the LT had a BAR score greater than 18, or equivalently, only 3% met the definition of futile transplant indicating that the BAR score lacks granularity and has limited applicability in decision making (Flores & Asrani, 2017).

Donor Age and Recipient Model for End-Stage Liver Disease (D-MELD)

The donor age and recipient model for end-stage liver disease (D-MELD), a combination of donor age and preoperative MELD, was proposed by (Halldorson et al., 2009) to optimize donor-recipient matching. In this model, a cutoff of D-MELD score greater than 1600 predicts unfavorable outcomes. Avoiding matching organs from older donors with high-MELD recipients results in favorable patient and organ survival. However, the age of liver donors has increased in the past several years, and a few

researchers have studied the impact of donor age on LT, reaching contradictory conclusions (Lué et al., 2016).

Donor Quality Index (DQI)

After showing that the DRI and the ET-DRI were not validated in the French LT recipients, Winter et al., (2018) developed a donor quality index (DQI) using data from a French transplant registry. They utilized five donor variables: age; the cause of death; length of stay in intensive care unit; lowest MDRD creatinine clearance; and liver split. They adjusted the model for several recipient covariates, used only for adjustment. Equation 5 shows the derived DQI:

DQI=exp [0.28 (1 if donor age > 69 years, 0 otherwise) (5)

+0.06 (1 if COD is "other", 0 otherwise)

+0.30 (1 if COD is "cerebrovascular accident (CVA)", 0 otherwise)

+0.11 (1 if COD is "trauma", 0 otherwise)

+0.24 (1 if ICU stay is 4 days, 0 otherwise)

+0.22 (1 if the lowest MDRD creatinine clearance< 60 ml/min/1.73m^2, 0 otherwise)

+0.05 (1 if the lowest MDRD creatinine clearance, 60 ml/min/1.73m^2 and 90 ml/min/1.73m^2, 0 otherwise)

+0 39 (1 if split or partial liver, 0 otherwise)]

Notes: The term exp implies e raised to a value, i.e., $\exp(value) = e^{(value)}$

The authors identified three risk groups based on the DQI score; a low-risk group with 1.00 < DQI ≤ 1.58; a medium-risk group with 1.58 < DQI ≤ 2.35; and a high-risk group with DQI > 2.35. The derived DQI is yet to be externally validated in other populations.

Machine Learning Algorithms for Donor-Recipient Matching

Organ shortage has encouraged the development of donor risk models for proper allocation of donor organs using not only traditional statistical methods but also machine learning algorithms. Haydon et al. (2005) used for the first time neural network models to match donors to LT recipients and to identify potential recipients likely to benefit most from each liver offered. They used pre-MELD data and a self-organizing map, which is a form of neural network, to predict three and 12-month survival post-LT. Briceño et al. (2014) conducted a multicenter study of donor-recipient matching using data from 11 transplant centers in Spain to investigate the utilization of artificial neural networks (ANNs), as a tool to predict three and 12-month graft survival post-LT. They compared its performance with traditional donor risk models and donor-recipient matching, such as the DRI, D-MELD, BAR, and SOFT scores. Using the Spanish cohort, they developed an ANN model, the Model for Allocation of Donor and Recipient in España (MADR-E). They found that the MADR-E model was able to fit complex non-linear relationships in donor-recipient matching, better than traditional models.

Furthermore, the MADR-E model is designed to optimize both equity and efficiency by achieving the lowest rate of death on the wait list and also the optimal posttransplant outcomes. Using the same approach in a different cohort of LT recipients

from King's College Hospital, Ayllón et al. (2018) developed an ANN model (the KCH model) for donor-recipient matching to predict three and 12-month graft survival. Compared to traditional models, the KCH model resulted in a remarkable improvement in 3-month and 1-year graft failure predictions.

Lau et al. (2017) explored the use of machine learning algorithms, such as random forests and artificial neural networks, to predict graft failure after LT, based on donor-recipient characteristic known before donor allocation. They analyzed LTs from 1998 to 2013 from the Austin health database that includes the population in the states of Victoria and Tasmania and found that the performance of machine learning methods was substantially more accurate, as compared to traditional methods of matching recipients to donors.

Random survival forests (RSF), tree-based ANN methods for survival data, allow interpreting variable importance (VI) or to calculate some marginal effect of the independent variable on the dependent variable and provide an excellent tool for data exploration. RSFs use a robust computer-based algorithm that yields to an unbiased assessment of variable importance, for accurate prediction, but are still considered not suited for substantive research due to complexity.

ANN models are very flexible, and they can fit complex data. However, they are "black boxes," and it is difficult to elicit the hierarchical contribution of each factor, or to anticipate how changing a specific variable will affect the model. Moreover, they may not perform well with new data, limiting their generalization and stability. Additionally,

ANN models need to be retrained with new data periodically because they can be susceptible to changes in transplant and allocation policies, and clinical practices. An optimal dynamic ANN model for organ acceptance and allocation has the potential to guide decision making. However, before generalizing, their performance across multiple populations needs to be assessed (Kwong & Asrani, 2018).

There is a debate on weather prediction models should be developed using only classical statistical methods or if it is appropriate to use ANN methods. When more than prediction is required, i.e., relevant information about dependent and independent variables and more insights into the underlying structure of the data, traditional methods are preferred (see Harrell, 2015).

Social Determinants of Posttransplant Survival

Unmeasured recipient and donor characteristics could potentially confound the results of donor risk models. Community-level disparities remain poorly understood in existing risk models. Quillin et al. (2014) have studied the adjusted effect of socioeconomic status (SES) on access to LT and posttransplant graft and patient survival in the United States. They have found that LT candidates with lower SES appear to face barriers to LT, and low SES recipients of LT experience less favorable posttransplant outcomes. They concluded that SES is an independent predictor of access to transplant and post-transplant survival.

Schold et al. (2012), for the first time in transplant research, attempted to investigate community-level disparities. They used county health indicators publicly

available through the Robert Wood Johnson Foundation project and the University of Wisconsin Population Health Institute and evaluated the association of community health indicators with post kidney transplant outcomes. Twelve county-level health indicators were selected as proxies for community health, environmental and behavioral risks, social condition, or access to care, and developed a community health score (CHS). They found that multiple health indicators from the recipients' residence and CHS risk categories were independently associated with kidney transplant outcomes.

Ross, Patzer, Goldberg, and Lynch (2017) investigated the impact of socio-demographic considerations on the wait list and posttransplant survival for patients with end-stage liver disease. They looked at the impact of the county-level socio-demographic risk as measured by the CHS, and the distance to listing transplant centers. They found that high risk-CHS candidates and remote candidates who were more than 25 miles away from a transplant center had greater wait-list mortality but similar mortality after LT.

Critique of Methods

Feng et al. (2006) for the first time introduced the concept of donor risk index, a parsimonious risk model that may predict the survival of the donated liver after transplantation, a surrogate of donor quality. The DRI has been very useful in risk stratification and to support matching between donors and recipients. However, it has several limitations. The DRI was developed using data before the MELD era, and it does not reflect current practice patterns. Moreover, after the incorporation of Share 35 in 2013, the impact of DRI may be affected by unmeasured geographic variations (Flores &

Asrani, 2017). The DRI includes race, which is not a biologically plausible predictor of graft failure, but it is likely to be a surrogate of center performance (Flores & Asrani, 2017).

The D-MELD combines the recipient's MELD score with the donor's age to obtain a continuous variable that can identify donor-recipient matches predicted to result in significantly poorer short- and long-term outcomes (Halldorson et al., 2009). The D-MELD was designed to prevent donor-recipient matches with a high risk of unfavorable outcomes. This allocation strategy can jeopardize very sick patients in the context of low organ-donation rates.

Some studies have proposed scores to estimate graft survival, based on the combination of multiple variables. The SOFT, and BAR scores can identify subgroups of patients with poor prognoses after LT, but they use many variables, and not all of them are available at the time allocation is made (Dutkowski et al., 2011; Rana et al., 2008). The SOFT score is very complicated for clinical practice and emphasizes short term survival. The BAR score ranges from 0 to 27, with a threshold of 18 distinguishing low from high-risk LTs (Rana et al., 2008). The majority of LTs are classified as low risk according to the BAR score. Both scores are not reliable metrics of donor quality.

While hepatitis C is projected to drop with advanced in direct-acting antiviral therapy, NAFLD/NASH is projected to become the leading indication for LT due to increasing obesity rates (Pais et al., 2016). Therefore, a donor risk model needs to be tailored for recipients transplanted for NAFLD to remain relevant.

Moreover, exploration of other relevant characteristics such as community risk factors and distance from the transplant center is crucial to understand how external factors can impact a donor risk model.

Summary and Conclusion

This chapter contains a review of the NAFLD disease spectrum, of NASH, and of CC. Additionally, I conducted a literature review of the epidemiology and risk factors for NAFLD, including epigenetic and environmental factors. A review of disease trends revealed a rise in LT for NAFLD/CC, which is becoming the leading indication for LT. Furthermore, I detailed a review of historical and logistical aspects of liver allocation. Finally, I discussed a description of the UNOS regions, the DSAs, and changes in donor allocation policies from the "Final Rule." I reviewed the strengths and weaknesses of the MELD score allocation system and its impact on the NAFLD/CC patients.

From literature review has emerged a gap projected to widen between liver donor supply and LT candidates on the wait list, and the need to utilize high-risk donors. I reviewed the concept of DRI and its usage in decision making to identify optimal and suboptimal donors. Finally, I completed a thorough literature review of proposed risk score models, including traditional statistical models and machine learning-based models, along with their strengths and weaknesses. Through the extensive literature review, I revealed that current prognostic scores for donor organ quality are not reliable and robust prognostic tools that can predict short-term graft survival. Geographic variations,

unmeasured recipient and donor characteristics, and community-level disparities can play a role in predicting posttransplant graft survival.

The current study led to the creation and validation of a novel model for donor quality score tailored for NAFLD/CC recipients and evaluated the impact of county-level health indicators and geographic characteristics. The new donor risk model filled a critical gap in the current knowledge base and is a step forward in the optimal utilization of a scarce resource to achieve the ultimate goal of improving liver graft survival. In Chapter 3, I presented research methodologies used in the study, including the study design, the study population and sample, data acquisition, and statistical analyses.

Chapter 3: Research Method

The number of advanced NAFLD candidates on the liver transplants wait list is rapidly growing. Advanced NAFLD and CC candidates experience remarkably high mortality on the wait list due to persistent organ shortage and low wait-list priority. For NASH/CC patients in need of liver transplantation, the policies defining the priority of donor liver allocation are of ultimate importance. Use of marginal donors may improve donor allocation in these patients.

The purpose of this study was to develop parsimonious risk adjustment models to quantify donor quality for advanced NAFLD and CC liver transplant recipients and to explore the association between derived donor quality score and distance from the transplant center, county health indicators, and communities where recipients of liver transplant reside. The donor quality score can be used to explore appropriate donor/recipient matching for risk stratification and to carefully select grafts from nonoptimal donors that can lead to satisfactory outcomes, reducing the number of donors turned down and reducing wait-list mortality. Moreover, geographic variations in liver allocation are a recurrent topic in transplant debates, reflecting concerns about health inequalities. A consideration of community-based health measures from the location where liver transplant recipients reside in risk-adjusted models and distance from the transplant center can be used to understand the interrelated causes of disparities to support policies or interventions to mitigate them.

In Chapter 2, I reviewed existing donor risk models along with their strengths and weaknesses and found that none of the donor risk models from the literature was tailored to NAFLD/CC recipients of liver transplant or adjusted for geographic or social environmental factors. The impact of community health factors on transplant risk-adjust models has been understudied. Chapter 3 includes a brief discussion of the targeted population, sampling procedures, sample size and power analysis, data collection, data cleaning, statistical analysis procedures, and techniques. Threats to internal and external validity are also presented. The chapter concludes with a discussion of ethical considerations, a summary of critical points, and a transition to the next chapter.

Research Design and Rationale

I used a quantitative correlational design (see Campbell & Stanley, 1963), more specifically a retrospective and longitudinal cohort study design of consecutive NAFLD/CC liver transplant recipients. This observational design allowed me to explore the expected relationship among variables, but it could not be used to make causal inferences. Because of the lack of randomization, there is always a possibility that the association between dependent and independent variables may be explained by other variables, the so-called unmeasured confounders that can be known or unknown.

A pivotal point in this study was that a combination of donor, recipient, transplant, geographic, and social factors explained the hazard of liver graft failure in NAFLD/CC recipients of a liver transplant. Therefore, to quantify the impact of donor factors on graft survival, the donor quality was adjusted for recipient characteristic, and

the impact of geographic and social factors was explored. The research questions addressed whether graft failure or death occurred and whether donor factors played a role. A retrospective population-based longitudinal cohort study design is appropriate when the dependent variable of interest is a time-to-event outcome. This study was quantitative and included transplant population-based registry data collected at transplant milestones and publicly available county-level data. These data sources were consistent with exploring donor risk factors of liver graft failure in the study population.

Sampling Population

The sampling population included all available adult NAFLD/CC patients on the transplant registry who underwent cadaveric liver transplant between July 1, 2013, and December 31, 2016. Multiorgan transplants were not included. Status 1 patients at risk of imminent death at listing were excluded. All recipients in the study population were transplanted after the implementation of the Share 35 allocation policy, on June 18, 2013, to minimize the impact of changes in allocation policy.

Sampling Procedures

The SRTR database included all recipients of LT since 1987 in the United States. An appropriate sampling strategy for this study was consecutive sampling, which is the best nonprobability sampling strategy because it includes all subjects who meet the inclusion criteria (Portney & Watkins, 2009). Consecutive sampling is very reliable and likely to represent the target population (Portney & Watkins, 2009).

Secondary Data Collection

Secondary data are data already available and collected for other purposes. Secondary data available from the SRTR database and the County Health Ranking & Roadmaps were used and adapted to answer the study research questions.

The SRTR Database

Every liver transplant performed in the United States since 1987 is included in the SRTR database. SRTR receives data from the OPTN database, which is managed through a federal contract by the United Network for Organ Sharing (UNOS). SRTR data comes from multiple sources, including transplant centers, organ procurement organizations, and histocompatibility laboratories.

SRTR data provide access to broad, comprehensive information on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the OPTN (SRTR, 2018). Mandated reporting of every solid organ transplant information performed in the United States allows inclusion in the study of each transplant performed in the United States that meets the inclusion criteria. SRTR data have been widely used to conduct a multitude of transplant studies (Saracino, 2017). In addition to the UNOS data, other secondary sources including the Social Security Death Master File, Centers for Medicare and Medicaid Services, National Death Index, Surveillance Epidemiology and End Results, and National Center for Health Statistics contribute to the SRTR database (Massie et al., 2014).

Data collection. Data were collected at different points in time: before the transplant, at the time of the transplant, and posttransplant. Recipients were followed longitudinally, and a large amount of information was collected at each follow-up transplant milestone until death (UNOS Transplant Pro, 2018). Donor information; candidate organ matching data; and recipient, transplant, and follow-up data were collected using standardized organ-specific data collection forms. Wait-list data were collected using the Transplant Candidate Registration. When a candidate is transplanted, the OPO recovering the organ and the transplant center complete the Transplant Recipient Registration (TRR) form, which includes information about the recipient and donor characteristics as well as information on matching donor to transplant candidates (UNOS Transplant Pro, 2018). Transplant centers complete Transplant Recipient Follow-up (TRF) forms at 6 and 12 months posttransplant and yearly after that until the recipient expires. TRR and TRF forms are submitted to the OPTN database using the UNet system (UNOS Transplant Pro, 2018). UNet is a longitudinal database in which pretransplant data are used to match waiting candidates with donated organs, and posttransplant data are used to analyze transplant outcomes (Leppke et al., 2013).

SRTR data quality. Data submission to UNOS is federally mandated. Transplant centers are required to maintain, and update transplant wait list by reporting candidate outcomes such as changes in disease severity and other events, including death and transplant (Leppke, 2013). Data used for organ allocation are generally reliable and complete. However, missing data are a limitation of SRTR data and will require careful

exploration and a strategy to address this limitation (Massie, Kucirka, & Segev, 2014; Saracino, 2018).

In the United States, federal law requires transplant center outcomes to be published. UNOS is required to publish center-specific risk-adjusted statistics to measure the performance of transplant centers. Centers are flagged for poor performance when the adjusted survival is below a threshold (SRTR, 2018). For this reason, transplant centers are required to submit timely and accurate data to UNOS so that their survival statistics can be adjusted appropriately. Therefore, transplant centers need to have processes in place to prospectively collect and submit data to UNOS, contributing to a robust national database (Leppke et al., 2013). The UNOS UNet electronic system has built-in data validation processes to increase data accuracy. UNOS conducts site visits every three years to ensure that transplant programs are following OPTN policies (UNOS, 2018). During the UNOS site visit, data submitted to UNet are audited for completeness and accuracy.

Usage of SRTR data. Data are routinely analyzed to answer research questions about the events that follow transplant candidacy, organ donation, and organ transplant, and used to publish annual trends in transplantation, outcomes, and statistics pertinent to transplant center performance. Researchers can request data from the SRTR by completing a data use agreement (DUA). Several investigators have used SRTR to answer transplant-related questions (Israni et al., 2018). Researchers have analyzed SRTR data and developed organ-specific donor risk models (Dutkowski et al., 2011;

Feng et al., 2006; Halldorson et al., 2009; Rana et al., 2008,). However, to date, this study is the only one that has used SRTR data to derive donor quality score tailored to NAFLD/CC transplant candidates.

County Health Rankings & Roadmaps

The Robert Wood Johnson Foundation and the University of Wisconsin Population Health Institute produce the County Health Rankings every year. The rankings are derived with more than 30 measures of health indicators for nearly every county in the United States, providing a snapshot of how healthy a community is. Data are collated from different sources, including the Behavioral Risk Factor Surveillance System; the National Center for Chronic Disease Prevention and Health Promotion; the Dartmouth Institute; and the U.S. Census (County Health Rankings & Roadmaps, 2018). The rankings are based on a population health model developed by the American's Health Ranking and used by the University of Wisconsin Population Health Institute to rank counties. Remington, Catlin, and Gennuso (2015) describe the methodology used to calculate the rankings. This study will utilize selected County Health Rankings.

Usage of county health rankings & roadmaps. Relationships between community health indicators and transplant outcomes were explored for the first time by Schold et al. (2012) in a kidney transplant study where the authors developed a composite index called County Health Status (CHS), which is a proxy indicator of community health disparities. They found that high-risk communities were associated with an increased risk of kidney graft failure. Ross, Patzer, Goldberg, and Lynch (2017) found

that the CHS score was a determinant of liver transplant wait-list survival. They found that LT candidates in high health risk counties were associated with increased wait-list mortality. Pointer et al. (2018) found that patients in high-risk communities had less favorable post-pancreatic surgery outcomes.

Data Access and Data Linkage

The SRTR DUA requires that data will be used solely for bona fide analysis, and not for any other purposes not indicated in the statistical analysis plan. I made no attempts to identify patients or to use data unlawfully and unethically in violation of the Health Insurance Portability and Accountability Act (HIPAA) or any federal or state laws on confidentiality of patient medical records (SRTR, 2018; OPTN, 2018). SRTR released data as SAS datasets that were linked as needed, as shown in Figure 5.

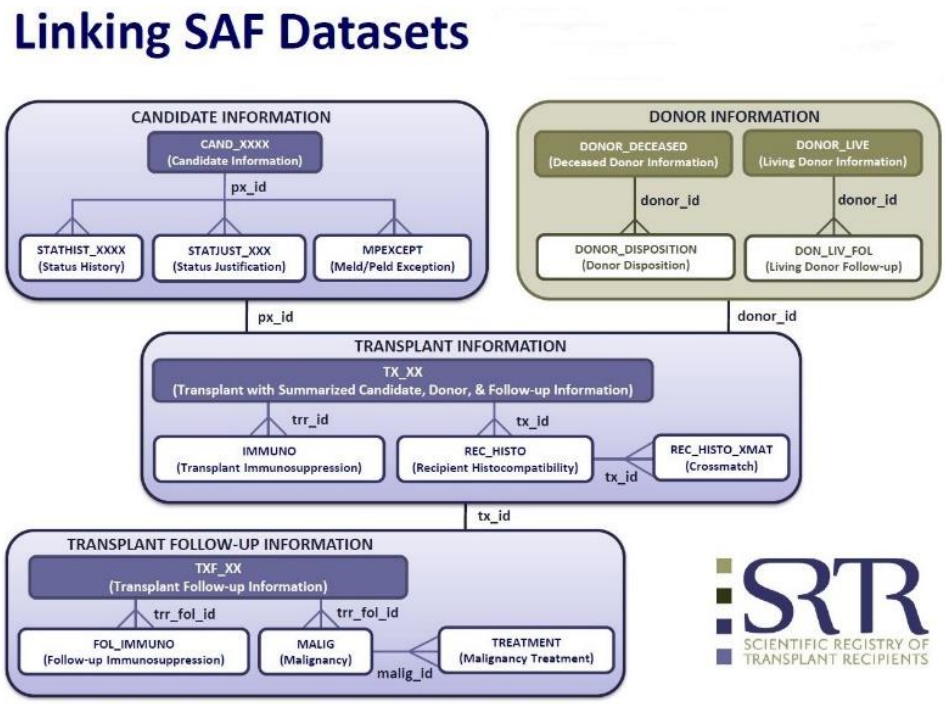

Figure 5. SRTR data linkage.
Note: Adapted from https://www.srtr.org/assets/media/docs/SAFsLinkingDiagram.pdf

I used the following SAS datasets to identify the study population and to select original or derived study variables.

1. DONOR_DECEASED: contains information on all deceased donor;
2. CAND_LIIN: includes all candidates for liver or intestine transplant and contains candidate registration and wait list information;
3. TX_LI: contains recipient and liver transplant information collected through the TRR forms; and
4. TXF_LI: post-transplant follow-up data table contains follow-up information collected at six months, one year and then annually, until the patient receives a

subsequent transplant, dies or is lost to follow-up. Follow-up information in this table is collected using the TRF forms.

I use the statistical software SAS version 9.4 (SAS Institute, Cary NC) to access the SRTR database and to prepare and combine the data in one analytical SAS dataset. The linkage diagram in Figure 5 indicates the foreign key variables needed to link the SAS datasets (SRTR, 2018). I linked the candidate SAS dataset CAND_LIIN to the donor table DONOR_DECEASED through donor_id and to the transplant table TX_LI though px_id. I linked TX_LI to the follow-up table TXF_LI through tx_id.

I downloaded county health indicators from a publicly available website, County Health Rankings & Roadmaps (2018). I used the County Federal Information Processing Standard (FIPS) code, which is the geographic identifier used in the County Health Rankings, for data linkage. I converted the county FIPS codes into zip codes and then used them to link County Health Rankings to the recipient zip code in the SRTR database.

Study Variables and Operational Definitions

I selected the research study variables based on expert opinion, literature review, and the availability in the SRTR database. Below is a list of the variables that I considered in model building; only some of these candidate predictors were included in the final parsimonious model.

Dependent Variables

I defined the outcome variable as liver allograft survival at 1-year posttransplant. Graft survival was defined considering graft status: graft failure (date of graft failure), or death (date of death), or if alive with graft functioning (date of the last follow-up). I coded a censoring variable indicating graft survival at 1-year posttransplant as "one" if liver allograft failed or if recipient expired within 1-year posttransplant, and "zero" if the patient was alive with graft functioning at the date of the last contact. The outcome variable was a time-to-event variable defined as the months from the date of LT to the date of the last contact and paired with the appropriate censoring variable (Saracino, 2017). I provide in Table 4 the name and coding of the original variables available in the SRTR database, and in Table 5, I describe the coding of the outcome variables that were used in the survival analysis.

Table 4

SRTR Variables Used to Define Outcomes and Coding

SRTR variable name	Label	Coding
TFL_PX_STAT	Patient status	A: Living; D: Death; L: Lost to follow-up; N: Not seen; R: Retransplanted
TFL_PX_STAT_DT	Patient status/date	Date
REC_TX_DT	Transplant date	Date
TFL_FAIL_PRIME_GRAFT_FAIL	Date of graft failure	Date

Table 5

Derived Outcomes and Coding: Graft Survival post-Transplant

Outcome variables	Coding
Graft survival time	Months from transplant to last contact (death, graft failure, last follow-up or date of subsequent liver transplant).
Censoring	1 = liver graft failure or recipient expired; 0 = alive or lost to follow-up at last contact or at subsequent liver transplant.

Independent Donor Variables

In the first step of the donor risk model development, I considered donor-only variables as potential independent predictors of graft survival. These factors are known at the time an offer for a liver organ is made. Some of the donor variables are related to donor demographics, some to donor behaviors that can lead to disease transmission, and some to the donor health and cause of death. Tables 6 and 7 describe donor variables as they are stored in the SRTR database, and Table 8 their operationalization that I used to develop the donor risk model.

Table 6

SRTR Donor Variables and Original Coding

SRTR variable name	Label	Coding
DON_AGE_IN_MONTHS	Donor age (months)	Numeric
DON_GENDER	Donor gender	M = Male; F = Female
DON_HGT_CM	Donor height (cm)	Numeric
DON_WGT_KG	Donor weight (kg)	Numeric
DON_CAD_DON_COD	Donor cause of death	1: Anoxia; 2: Cerebrovascular/Stroke; 3: Head Trauma; 4: CNS Tumor; 998: Unknown; 999: Other
DON_HIST_DIAB	History of diabetes	1: No; 2: Yes, 0-5 Years; 3: Yes, 6-10 Years; 4: Yes, > 10 Years; 5: Yes, Duration Unknown; 998: Unknown
DON_HIST_INSULIN_DEPND	Insulin dependent	1=Yes,0=No
DON_INSULIN	Donor insulin	N=No; Y=Yes; U=Unknown
DON_HTN	History of hypertension	1: No; 2: Yes, 0-5 Years; 3: Yes, 6-10 Years; 4: Yes, > 10 Years; 5: Yes, Duration Unknown; 998: Unknown

Table 7

SRTR Donor Labs and Infection Profile Variables and Coding

SRTR Variable Name	Label	Coding
DON_SODIUM	Last serum sodium Prior to procurement	Numeric
DON_SERUM_CREAT	Final serum creatinine	Numeric
DON_HCV_STAT	HCV antibody status	1: Positive; 2: Negative; 3: Unknown; 4: Cannot disclose; 5: Not done; 6: Indeterminate; 7: Pending.
DON_HBV_SURF _ANTIBODY	HBsAb (Hepatitis B surface antibody)	C: Cannot disclose; I: Indeterminate; N: Negative; ND: Not Done; P: Positive; PD: Pending; U: Unknown.
DON_HBV_SURF _ANTIGEN	HBsAg (Hepatitis B surface antigen)	C: Cannot disclose; I: Indeterminate; N: Negative; ND: Not done; P: Positive; PD: Pending; U: Unknown

Table 8

Derived Independent Donor Variables and Coding

Donor factors	Label	Coding
DONOR_AGE	Donor age (yrs.)	Continuous variable
DON_HGT_CM	Donor height in (cm)	Continuous variable
DON_WGT_CM	Donor weight (kg)	Continuous variable
DONOR_BMI	Body mass index (kg/m^2)	Underweight = BMI<18.5; Normal weight = 18.5≤ BMI≤ 24.9 Overweigh = 25≤ BMI≤ 29.9; Obese = BMI ≥ 30
DONOR_COD	Donor cause of death	1: Anoxia; 2: Cerebrovascular/stroke; 3: Head trauma; 4: Other
DONOR_HTN	Donor hypertension	1=yes; 0=no
DONOR_DIAB	Donor diabetes	1=yes; 0=no
DON_DCD	Donor after circulatory death	1=Yes; 0=No
HCV_POS	Donor hcv positive	1=positive; 0=negative
HBSAB_POS	Donor HBsAb	1=positive; 0=negative
HBSAG_POS	Donor HBsAg	1=positive; 0=negative
DON_HYPERN	Donor hypernatremia	1=Yes (if DON_SODIUM ≥160 µmol/L); 0=No (if DON_SODIUM <160 µmol/L
DON_MDRD	Donor MDRD ($ml/min/1.73\ m^2$)	1 = <15; 2 = 15-29; 3 = 30-44; 4 = 45-59; 5 = 60-89; 6 = >90

Below are descriptions of the donor variables that will be explored.

Donor age. The use of older donors has increased remarkably in the last two decades. Although old donors have been associated with worse graft outcomes, especially in patients with hepatitis C virus infections, there is evidence that some old donors can still lead to excellent results. The independent variable donor age is available in months and will be converted in years.

Donor height and body weight. Body height and body weights considered associated with organ volume will be considered alone or in combined measurements, such as body mass index and body surface area among the donor factor candidates for the risk model.

Body surface area (BSA). BSA will be calculated using the Mosteller's formula using Equation 6:

$$\sqrt{Height(cm)x\ \frac{Weight(kg)}{3{,}600}} \qquad (6)$$

Donor BSA together with recipient BSA will be used in donor recipient matching to estimate liver size.

Donor body mass index. The variable body mass index (BMI) of weight-for-height is an indicator of obesity. It is calculated using a person's height and weight as in Equation 7:

$$BMI = \frac{Weigh(kg)}{Height\ (m)^2} \qquad (7)$$

Chang et al. (2017) showed that the relationship between BMI and posttransplant overall survival is quadratic and U shaped. Therefore, I categorized BMI as suggested by

the CDC. A BMI of less than 18.5 kg/m² indicates underweight; a BMI of 18.5-24.9 kg/m² normal weight; a BMI of 25-29.9 kg/m² the overweight category; and a BMI of more than 30 is an indication of obesity (CDC, 2018).

Donation after cardiac death (DCD). Livers procured from DCD donors can bridge the gap between the demand for liver organs and donor supply. If properly managed, DCD donors can offer a valuable alternative to the donation after brain death (DBD), considered the standard of care which supplies the majority of LTs. DCD donors are associated with higher risk of graft failure, compared to DBD donations (Firl et al., 2015).

Donor diabetes. Donor macrovesicular steatosis is a known predictor of graft failure (Hamar & Selzner, 2017). However, macro-steatosis is only available in the SRTR database on biopsied donors. I considered donor diabetes as a surrogate of donor steatosis (Zheng et al., 2014). I combined three SRTR variables indicating the history of donor diabetes or insulin dependence to indicate the presence or absence of donor diabetes.

Donor hypertension. Donor hypertension has been identified as a strong predictor of low graft survival in kidney transplant, and I evaluated in this study as a potential independent predictor of liver graft failure (Rao et al., 2009).

Donor cause of death. Donor cause of death has been found to be an independent predictor of transplant outcomes. Stroke has been found to be associated with worse graft survival in LT and used in donor risk-adjusted models (Feng et al., 2006)**.**

Donor hypernatremia. Donor hypernatremia before procurement, which could be a surrogate of prolonged donor intensive care, is defined as donor plasma sodium level ≥160 μmol/L. Donor hypernatremia has been reported to reduce graft survival (Khosravi, Firoozifar, Ghaffaripour, Sahmeddini, & Eghbal, 2013)**.**

Disease transmission variables. Before being transplanted, donors are screened for infectious disease and tested for positive hepatitis B surface antibody (HBsAb), hepatitis B surface antigens (HBsAg) and HCV antibody status.

Modification of diet in renal disease (MDRD). Donor Glomerular Filtration Rate estimated by the 4-variable equation from the MDRD was used to estimate the renal function of potential donors using Equation 8:

$$MDRD = 175 \times SerumCr^{-1.154} \times age^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)} \quad (8)$$

Independent Transplant Variables

I considered a more extensive version of the donor risk model that included transplant variables, such as cold ischemia time, donor ABO matching, and donor size matching, to explore the impact of transplant factors and to assist in decision making about donor/recipient matching. Tables 9 and 10 describe transplant variables and their operationalization that I used in model building. I describe below the transplant variables that were considered.

Table 9

SRTR Transplant Matching Variables and Original Coding

SRTR Variable name	Label	Coding
REC_COLD_ISCH_TM	Total cold ischemic time	Numeric
REC_HGT_CM	Recipient height (cm)	Numeric
REC_WGT_KG	Recipient weight (kg)	Numeric
DON_HGT_CM	Donor height (cm)	Numeric
DON_WGT_KG	Donor weight (kg)	Numeric
DON_ABO	Donor's blood type	A; A1; A1B; A2B; AB; B, 0
REC_ABO	Recipient's blood type	A; A1; A1B; A2B; AB; B, 0

Table 10

Derived Transplant Matching Variables and Coding

Transplant Factors	Label	Coding
CIT	Cold ischemia time (hrs.)	Continuous variable
BSA_Ratio	Donor/recipient BSA ratio	Continuous variable
ABO_Match	ABO match	1: Incompatible; 2: Compatible; 3: Identical

Cold ischemia time. Geographic disparities in access to liver transplantation can lead to usage of liver organs with prolonged cold ischemia, a known risk factor for early allograft dysfunction (Sibulesky et al., 2016). Cold ischemia time is defined as the interval from the clamping of donors' vessels, loss of blood supply and infusion of cold organ preservation to the moment of removal from storage and insertion into the recipient's abdominal cavity. The in-vivo cold preservation solution maintains hypothermic conditions and minimizes ischemic injuries. Cold ischemia time is influenced by the distance between the donor and the recipient centers and increases when long distances have to be traveled (Sibulesky et al., 2016).

BSA donor recipient ratio. Many factors affect liver size, such as weight, height, BMI and BSA. Fukazawa et al., (2013) proposed using the ratio of donor to recipient BSA index to predict size match. They found that both small-for-size and large-for-size liver grafts had an adverse effect on liver graft survival.

Donor-to-recipient ABO match. Livers are usually matched by ABO. Mismatched donors may either be ABO compatible or ABO incompatible. The usage of ABO-mismatched organs has been controversial in liver transplantation in the past because of the high risk of antibody-mediated rejection. However, due to improvements in immune-suppressant regimen and improved graft survival, ABO incompatible organs can be considered a viable option to increase donor availability and reach the goal of full potential in organ utilization (Goss & Rana, 2017). Often, an ABO incompatible graft can

represent the only option in case of urgency when an ABO compatible organ is not readily available.

Recipient Covariates

Graft survival is affected not only by donor factors and transplant factors but also by recipient factors. Moreover, the transplant center has an impact on graft outcomes. Recipient factors will be used as covariates for risk adjustment. Table 11 presents known recipient characteristics associated with graft survival after LT, and Table 12 indicates grouped or calculated variables.

Table 11

SRTR Recipient Covariates and Original Coding.

SRTR variable name	Label	Coding
REC_AGE_IN_MONTHS_AT_TX	Calculated recipient age in months at TX	Numeric
CAN_GENDER	Candidate gender	M = male; F = female
REC_HGT_CM	Recipient height (cm)	Number
REC_WGT_KG	Recipient weight (kg)	Number
CAN_LAST_SERUM_SODIUM	Last SRTR MELD	Numeric

Table 12

Derived Recipient Covariates and Coding.

SRTR variable name	Label	Coding
REC_AGE_AT_TX	Age at transplant	Continuous Variable
CAN_GENDER	Candidate gender	1 = Male; 2 = Female
REC_BMI	Body mass index (kg/m²)	underweight = BMI<18.5; normal weight = 18.5≤ BMI≤ 24.9 overweigh = 25≤ BMI≤ 29.9; obese = BMI ≥ 30
MELD	MELD score	1=<15; 2=15-20; 3=26-30; 4=>30
REC_DIAB	Recipient diabetes	1=Yes; 0=No

Recipient age and gender. I used recipient age and gender for demographic adjustments.

Recipient BMI. BMI, an indicator of obesity in recipients of LT, was categorized as suggested by CDC. Recipient BMI has been associated with graft and patient survival.

Model for end-stage liver disease score (MELD). The MELD score, a reliable measure of disease severity, and known mortality risk after LT ranges from 6 to 40, with low scores indicating healthier recipients. It is calculated using pre-transplant labs serum creatinine, serum bilirubin, International Normalized Ratio for prothrombin time, as well as ascites and hepatic encephalopathy, available in SRTR database (Kamath et al., 2001). The MELD score is used to prioritize patients on the liver wait list. It represents the recipient risk of wait-list mortality.

Recipient diabetes. Recipientdiabetes, is a known risk factors of patient post-transplant survival (Northup et al., 2010). I recoded the SRTR variable that indicates the type of diabetes to reflect the presence of non-insulin dependent, insulin dependent, or absence of recipient diabetes.

Modifying External Variables

Modifying variables are associated with the outcome but not with the independent predictors. The effect of the donor risk score can change among different subgroups. I explored two external variables: distance from the transplant center and community health status, as described in Table 13.

Table 13

Mediating External and Coding

Mediating variable	Label	Coding/measurement
DIST_FROM_CTR	Distance from center (miles)	Numeric
CHS_GRP	Community health status group	0–10; 11–20; 21–30; 31-40

Community health status (CHS). The CHS is a composite index that combines ranks of 10 selected county health indicators likely to be related to transplant outcomes. I provided detailed information on county health indicators in Appendix A. CHS ranges from 0 (indicating that a county is in the first quintile or the lowest risk for each of the 10 health indicators) to 40 (indicating that a county is in fifth quintile or higher risk for each

of the 10 health indicators). Table 14 illustrates the data sources and contributing community health indicators that make up the CHS.

Other Variables

Expanded criteria donor. The SRTR database has a variable that indicates whether or not a donor meets the expanded criteria. I did not include this variable in the model because I explored the variables included in the ECD definition (donor age, hypertension, and serum creatinine), individually in model building.

PHS increased-risk donors. Information about PHS increased-risk donors (previously known as CDC high-risk donors) was available in SRTR. Increased-risk donors are often discarded and not considered by LT candidates because at high risk of blood-borne disease transmission. I explored the impact of increased-risk donors on liver graft survival in the study population to determine if these donors increased the risk of graft failure in NAFLD/CC recipients. The concept of increased risk donors was created to identify a donor population potentially at risk of a recent acquisition of HIV or viral hepatitis. These recently infected donors could inadvertently transmit the virus to recipients yet would appear negative on serologic testing. Importantly, most increased risk donors will be truly negative for each of these infections, and the chance that they will transmit the infection is very low. So increased risk is not necessarily related to the donor quality. Therefore, I did not consider the denomination PHS increased risk in the model. Appendix B provides more details about CDC high-risk and PHS increased-risk criteria.

Table 14

Community Health Score and Contributing Health Indicators

Community Health Indicator	Source	Value
Premature death (years)	National Center for Health Statistics - Mortality files	Quintiles: $1^{st} = 0$; $2^{nd} = 1$; $3^{rd} = 2$; $4^{th} = 3$; $5^{th} = 4$
Low birth weight (%)	National Center for Health Statistics - Natality files	Quintiles: $1^{st} = 0$; $2^{nd} = 1$; $3^{rd} = 2$; $4^{th} = 3$; $5^{th} = 4$
Poor physical health (days)	Behavioral Risk Factor Surveillance System	Quintiles: $1^{st} = 0$; $2^{nd} = 1$; $3^{rd} = 2$; $4^{th} = 3$; $5^{th} = 4$
Poor mental health (days)	Behavioral Risk Factor Surveillance System	Quintiles: $1^{st} = 0$; $2^{nd} = 1$; $3^{rd} = 2$; $4^{th} = 3$; $5^{th} = 4$
Fair or poor health (%)	Behavioral Risk Factor Surveillance System	Quintiles: $1^{st} = 0$; $2^{nd} = 1$; $3^{rd} = 2$; $4^{th} = 3$; $5^{th} = 4$
Income inequality	American Community Survey	Quintiles: $1^{st} = 0$; $2^{nd} = 1$; $3^{rd} = 2$; $4^{th} = 3$; $5^{th} = 4$
Preventable hospital stays (%)	Dartmouth Atlas of Health Care	Quintiles: $1^{st} = 0$; $2^{nd} = 1$; $3^{rd} = 2$; $4^{th} = 3$; $5^{th} = 4$
Adult smoking (%)	Behavioral Risk Factor Surveillance System	Quintiles: $1^{st} = 0$; $2^{nd} = 1$; $3^{rd} = 2$; $4^{th} = 3$; $5^{th} = 4$
Adult obesity (%)	CDC Diabetes Interactive Atlas	Quintiles: $1^{st} = 0$; $2^{nd} = 1$; $3^{rd} = 2$; $4^{th} = 3$; $5^{th} = 4$
Physical inactivity (%)	CDC Interactive Atlas	Quintiles: $1^{st} = 0$; $2^{nd} = 1$; $3^{rd} = 2$; $4^{th} = 3$; $5^{th} = 5$

Study Validity

Observational studies are not experimental as they involve the direct observation of study subjects in their natural setting. Therefore, they are assessed for potential selection or information biases that may influence the validity and reliability of study findings. There are a few critical issues to consider in evaluating observational transplant studies where the outcome is a time-to-event, such as patient and graft survival, including a potential differential loss to follow-up and misclassification bias.

Information Biases

Transplant registry data are collected longitudinally. Therefore, it is possible to analyze long-term outcomes, but at the same time, differential loss to follow-up can lead to bias. In SRTR data, transplant recipients are followed until death occurs. However, incomplete follow-up is often present for many reasons. Statistical methods used to analyze cohort studies assume that censoring is non-informative, i.e., not related to the study outcome, graft survival. Informative censoring occurs when subjects are lost to follow-up for reasons related to this study, that may only lead to biased estimates in the regression models and also reverse the effect of a risk factor that can appear as a protective factor. Sensitivity analyses can be used to analyze data under the informative censoring assumption using considering the best and worst-case scenarios and use of the drop-out event as a study endpoint (Steyerberg, 2008, Saracino, 2017). Moreover, it is likely that various recipient and donor factors were measured with error. Centers may use different data collection approach or systematic errors in data collection.

Selection Biases

Marginal or non-optimal donors are considered non-ideal for multiple reasons. However, improvements in surgery strategies and medical management of these organs have led to improved post-transplant graft and patient survival in the last decade. Marginal donors are considered a plausible option to offset donor shortage, and, their utilization has increased. Studies still provide conflicting results impeding the creation of accepted guidelines, and transplant programs have center-specific decision-making rules to determine which patients should receive marginal donors (Pezzati, Ghinolfi, De Simone, Balzano, & Filipponi, 2015). Unobserved heterogeneity in center practice variation can lead to selection bias. Heterogeneity between centers can be addressed by incorporating the transplant center as a random effect. Survival models with random effect, called frailty models, can be used to account for the center effect on graft survival. I did not address center variation in this study.

Threats to Internal and External Validity

I did not include all possible donor factors associated with liver graft survival in thefinal donor risk model. When relevant variables are omitted, the model functional form is misspecified, or data are missing not at random. Therefore, in these cases, the statistical model does not capture adequately the variation in the dependent variables for the population being studied and can be a threat to internal validity. I used bootstrapping to assess internal model validation (Harrell, 2015). I considered several steps to address the threat of internal validity including the use of restricted cubic splines to fit nonlinear

patterns and, appropriate coding of predictors, including combining variables (Harrell, 2015). Internal validation addressed the stability of the selection of predictors, and the quality of predictions, and helped in selection among candidate models.

Inferences from SRTR studies are likely to generalize across the United States, but unlikely to be extrapolated to other countries. External validation outside the United States can be questionable due to differences in policies and procedures or because not all variables available in SRTR are collected in foreign transplant registries (Massie, Kucirka, & Segev, 2014). The donor risk models only apply to adult NAFLD/CC LT recipients are invalid in a pediatric setting.

Data Analysis Plan

I described the data cleaning procedures in this section, and also the power analysis and the statistical analysis approach used to answer the research questions.

Sample Size and Power Analysis

The study was not underpowered because SRTR data included all NAFLD/CC LT performed in the United States that met the inclusion criteria. Therefore, the sample size was sufficient for bootstrapping validation (Harrell, 2015). I used the Cox PH regression to analyze the primary research question. The model tested whether or not the independent variables predicted graft failure at 1-year post-transplant. Because I included the total population of NASH/CC LT in the study, a priori power analysis was not required but was useful to indicate the minimum sample size that was necessary to get the desired power and effect size.

I conducted Cox PH model-based power calculations using the R statistical package powerSurvEpi (Qiu et al., 2015). Assumptions for sample size calculation included: a power of .80, a type I error rate α=.005, and a postulated hazard ratio of 1.6 (i.e., the DCD donors having 1.6 times an expected risk of graft failure, compared to non-DCD donors). Previous studies assumed 15 percent of recipient transplanted with DCD donors, and 16 percent of NAFD/CC recipients experiencing liver graft failure within 3-year post-transplant. The required sample size was 1,742 (Qiu et al., 2015). Observational studies need covariate adjustment, and the sample size calculation requires an additional assumption regarding the correlation between the covariate of interest and the other covariates. The sample size required increased to 2,178 under the assumption of covariate correlation, ρ^2= 0.20 and to 2,489 for ρ^2= 0.30 (Qiu et al., 2015).

Data Cleaning and Screening Procedures

The SRTR database package provided Standard Analysis Files (SAF), datasets and SAS formats along with information about data linkage and the data dictionary, primary and foreign key variables that allowed linkage between candidate information; donor information; transplant information; and post-transplant follow-up information (SRTR, 2012). The first data management step I undertook was to identify the study variables to include in the analysis either directly or as derived variables. In this preliminary data preparation phase, I merged different datasets and processed to obtain a final dataset that contains both original variables and composite variables, restricted to NASH/CC recipients of LT that meet the inclusion criteria. I prepared the variables to

perform survival analyses. I merged the SRTR data with the Community Health Indicators.

I used summary statistics to describe the study population. I summarized quantitative variables using mean, standard deviations, minimum, maximum, median and other quantiles. I summarized categorical variables using frequencies. I used descriptive statistics to describe the distribution, central tendency, and dispersion to screen for outliers, inconsistencies, and missing values. I set outliers to missing if there were obvious mistakes. When necessary, I combined discrete variables in collapsed categories. Different transplant centers collect SRTR data, and some variables are collected for purposes other than research. Therefore, missing data and measurement errors were possible. Exploratory data analysis of key variables helped identify quality issues (Massie, Kucirka, & Segev, 2014).

Statistical Analysis

I summarized the characteristics of the study population through descriptive statistics. I assessed group comparisons for continuous variables using independent t-tests or when the assumption of normality is not met by Wilcoxon rank sum rank tests. I used Fisher exact tests or the likelihood ratio chi-square tests to compare categorical variables. I used the Cox PH regression model to assess the effect of independent donor, transplant, recipient and external variables on the risk of the occurrence of graft failure for all causes. I performed Wald tests to determine whether or not individual coefficients of the Cox PH models were equal to zero.

I selected the initial set of potential predictors and covariates to consider in the model based on previous studies and expert knowledge. After restricting the list, I reviewed variable distribution and missing data. I discarded variables with a large number of missing data that were known to be powerful predictors of graft failure. I removed variables with narrow distribution not expected to be important predictors of graft failure. I used Kaplan-Meier curves to depict the univariate relationships of categorical predictors at the initial stage of the analysis, as well as at the end of the study to present the prediction characteristics of the model. I used the log-rank tests to compare survival curves.

I performed preliminary univariate Cox PH regressions as a screening tool to evaluate the association of each candidate predictor with graft survival, to assess the functional form and to explore the non-linear effect of continuous predictors. I categorized continuous variables when possible, based on clinically accepted thresholds. When not possible, and when non-linear relationships exist, I transformed continuous predictors using restricted cubic splines functions and modeled them as non-linear predictors.

Restricted cubic splines are piecewise polynomial joined together at knots which are constrained to be liner at the tails. Harrell (2015) suggests modeling continuous predictors using restricted cubic splines with no more than five knots as they shape well the non-linear predictors and provides a useful tool to investigate the relationships

between dependent and independent variables. Restricted cubic splines are very flexible and with a robust behavior at the tails of the predictor distributions (see Harrell, 2015).

I used augmented backward variable elimination using 1000 bootstrap samples for model building and to select the final variables. I examined the proportional hazard assumption, verifying the pattern of the scaled Schoenfeld residuals against time. To evaluate the Cox PH model's discriminative ability, I used Harrell's C-statistics. Model performance on the data used to fit it is optimistic, better than the performance with new data from the same population. Overfitting causes optimism, a threat to model validity. I used bootstrap resampling to correct overfitting or optimism in model performance (see Harrell, 2015).

Most studies on identifying risk factors for graft failure risk have employed the Cox PH model. Traditional models are unable to address the complexities of the donor, transplant, recipient, and external factors. In this study, I explored the potential of random survival forest (RSF), a statistical learning method adapted to right-censored survival data. RSFs grow many trees using bootstrap samples from the original data and use aggregate results of many trees for prediction and to rank variables by their predictive importance. RSFs are non-parametric alternatives to the Cox PH model that can capture complex and non-linear relationships and, high order interactions, and do not rely on distributional assumptions. However, they are "black boxes," and their inferential procedures are not understood. In this study, I used machine learning approaches to complement traditional models, not to replace them.

I performed all statistical analyses using SAS version 9.4 (SAS Institute) and R version R3.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Research Questions and Hypotheses

The purpose of this retrospective cohort study was to investigate donor, transplant, recipient and community factor that impact graft survival in the study population. I answered the following research questions and hypotheses:

Research Question 1

What are the relationships between post-transplant graft survival among NAFLD/CC recipients and a number of donor characteristics (age, gender, height, weight, BMI, the cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, hypernatremia)?

H_{01}: There is no association between post-transplant graft survival among NAFLD/CC recipients and a number of donor characteristics (age, gender, height, weight, BMI, the cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, hypernatremia).

H_{a1}: There is an association between post-transplant graft survival among NAFLD/CC recipients and a number of donor characteristics (age, gender, height, weight, BMI, the cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, hypernatremia).

The analytic objective of this research question was to develop a donor risk model that evaluated the intrinsic qualities of the liver allograft and predicted graft failure risk

capturing donor only characteristics, and that summarizes into a single continuous graft failure risk score the quality of the deceased liver donor, the DQ-NAFLD score. Therefore, I included only variables known at the time of the donor offer and evaluation in the development of a donor-only score. I fit a Cox PH model to estimate the relative risk of graft failure independently associated with each donor variable. I generated graphical displays of how each donor predictor is related to the log hazard of graft failure. The Cox PH model expressed a relationship between the hazard rate and a set of predictors or covariates. I derived the DQ-NASH score from the coefficient of the Cox proportional hazard model.

Research Question 2

What are the relationships between post-transplant graft survival among NAFLD/CC recipients and transplant factors (cold ischemia time, ABO matching, and size matching)?

H_{02}: There is no association between post-transplant graft survival among NAFLD/CC recipients and a number of transplant factors (cold ischemia time, ABO matching, and size matching).

H_{a2}: There is an association between post-transplant graft survival rate among NAFLD/CC recipients and transplant factors (cold ischemia time, ABO matching, and size matching).

This research question explored the impact of transplant factors on graft survival. I fit a Cox PH model to estimate the relative risk of graft failure independently associated

with transplant factor. I generated graphical displays of how each transplant predictor is related to the log hazard of graft failure.

Research Question 3

What are the relationships between post-transplant graft survival among NAFLD/CC recipients and a number of donor characteristics (age, gender, height, weight, BMI, the cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, hypernatremia) and transplant factors (cold ischemia time, ABO matching, size matching,) after adjusting for characteristics of recipients of liver transplant (age, gender, BMI, biological MELD).

H_{03}: There is no association between post-transplant graft survival among NASH/CC recipients and a number of donor characteristics (age, gender, height, weight, BMI, cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, donor hypernatremia) and transplant factors (cold ischemia time, ABO matching, size matching) after adjusting for characteristics of recipients of liver transplant (age, gender, BMI, biological MELD).

H_{a3}: There is an association between post-transplant graft survival rate among NASH/CC recipients and a and a number of donor characteristics (age, gender, height, weight, BMI, cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, hypernatremia) and transplant factors (cold ischemia time, ABO matching, size matching) after adjusting for characteristics of recipients of liver transplant (age, gender, BMI, biological MELD).

Adding additional factors to the DQ-NAFLD donor-only model to account for these other sources of variation resulted in a higher predictive ability of the model, or a slightly higher C-statistic. However, the initial goal of the donor-only DQ-NAFLD was to summarize the risk of graft failure based on deceased donor factors only, and not to explain all sources of variation that contribute to liver graft outcomes. To address this question, I adjusted the Cox PH model for recipient characteristics to evaluate how the strength of the association between the donor risk score and graft failure changes after the adjustment. I developed a more extended version of the DQ-NASH risk score that included donor, transplant, and recipient factors useful in decision making for matching individual candidates to donors.

Transplant clinicians are interested in exploring how donor age, brain versus cardiac death, and cold ischemia time changed in subgroups of biochemical MELD scores (S. Asrani, personal communication, September 3, 2018). To assess these factors, I tested pre-specified interactions within strata of biochemical MELD score. I considered a model containing a second-order interaction for the triplet of factors, as well as all first-order interactions. All interaction effects were not significant.

Research Question 4

What are the relationships between post-transplant graft survival among NAFLD/CC recipients and the health risk status of the county were recipients reside measured by the community health score (CHS)?

H_{04}: There is no association between post-transplant graft survival among NAFLD/CC recipients and the health risk status of the county were recipient resides, measured by the CHS.

H_{a4}: There is an association between post-transplant graft survival among NAFLD/CC recipients and the health risk status of the county were recipient resides, measured by the CHS.

I used univariate Cox PH model to explore the effect of graft failure across counties grouped by risk category to assess if high-risk counties were associated with increased patient and graft survival.

Research Question 5

What are the relationships between post-transplant graft survival among NAFLD/CC recipients and the distance from the transplant center?

H_{05}: There is no association between post-transplant graft failure among NAFLD/CC recipients and distance from the transplant center.

H_{a5}: There is an association between post-transplant graft failure among NAFLD/CC recipients and distance from the transplant center.

This question explored the associations of distance from center and liver graft failure, to study if living in a high community health risk is associated with worse post-transplant outcomes. To address this question, I developed a univariate Cox PH model to explore the effect of increased distance from the transplant center on the risk of patient

and graft survival. I used choropleths maps to visualize patterns in patient and graft survival outcomes in relation to their geographic distance from the transplant center.

Research Question 6

What are the relationships between post-transplant graft survival among NAFLD/CC recipients, DQ-NAFLD risk score and external community factors (CHS and distance from the transplant center)?

H_{06}: There is no association between post-transplant graft survival among NASH/CC recipients, DQ-NAFLD risk score and external community factors (CHS and distance from the transplant center).

H_{a6}: There is an association between post-transplant graft survival among NAFLD/CC recipients, DQ-NAFLD risk score and external community factors (CHS and distance from the transplant center).

I used Kaplan Meier curves to explore the graft survival curves by quintiles of DQ- NAFLD risk score, by quintiles of community health risk score, and by quintiles of distance from the transplant center. I tested differences in survival curves using the log-rank test.

Moreover, I tested the interaction effect between DQ- NAFLD score and Community Health Risk score as well as the interaction between DQ- NAFLD score and distance from the transplant center. More specifically, I tested the hypothesis that recipients who reside in high-risk communities, or who are very distant from the

transplant center, are more likely to fail their high-risk graft compared to recipients in low-risk communities.

Ethical Considerations

In general, the usage of existing secondary data does not require IRB approval if it does not involve human subjects. The Walden Institutional Review Board reviewed the study to determine if the study met the ethics. Data requests to SRTR required completing a DUA which included a research plan and a security plan, describing how data would be stored and who would have access to data (Leppke et al., 2013). Data were password protected, available only to authorized researchers.

Researchers required using the data solely for bona fide analysis, and not for any other purposes. Researchers did not attempt to identify patients and use the information unlawfully and unethically in violation of the Health Insurance Portability and Accountability Act (HIPAA) or any federal or state laws regarding confidentiality of patient medical records (Gliklich, Dreyer, & Leavy, 2014; OPTN, 2018). The final analysis was reviewed by SRTR to ensure compliance with the terms of the DUA regarding confidentiality (OPTN, 2018).

Summary

I proposed a population-based longitudinal cohort study that used SRTR data between 2013 and 2016 and Community Health data to develop the DQ-NAFLD/CC a donor quality index score. I achieved this by assessing multiple donor characteristics estimates for the quality of a liver allograft. This study provides a useful metric for risk

evaluation and stratification. Through additional analyses, I explored how donor quality can predict liver graft survival independently or additively with recipient characteristics, transplant, and external community factors. The analysis of how external factors impact the transplant risk models shed important light on the understudied effect of environmental factors on post-liver transplant outcomes. Chapter 4 presents the results of the statistical analyses performed to answer the study hypotheses according to the statistical analysis plan. Chapter 5 provides an interpretation of the results and the potential implications and contributions of study findings, as well as suggestions for future research.

Chapter 4: Results

The purpose of this retrospective observational quantitative study was to analyze data from the SRTR registry to develop a donor quality score tailored to NAFLD/CC candidates on the wait list for a liver transplant (the DQ-NAFLD risk score) and to explore the impact of external factors including community health indicators and geographic factors related to the counties where recipients of LT reside. Both a donor intrinsic factor DQ-NAFLD risk score, as well as an extended DQ-NAFLD risk score, were developed. The study population included consecutive adult recipients of LT between July 1, 2013, and December 31, 2016, whose indication for LT was NAFLD/CC. During the study period, 24,497 patients received an LT, but only 3,165 met the inclusion criteria. Moreover, the purpose of the study was to analyze the external impact on graft survival within 1 year post LT, and of community health factors and distance from recipient residence to transplant center on liver graft survival within 1 year post LT. SRTR data were merged with data from the County Health Rankings & Roadmaps database to link patients to their community health risk based on their county of residence.

Cox PH models were used to predict liver graft failure at 1-year post LT. The fourth chapter outlines the selection of the study cohort and contains the results of the statistical analysis conducted to answer six research questions. This chapter contains a summary of the baseline and demographic characteristics of the study cohort of NAFLD/CC recipients of LT and a comparison of these characteristics to a control cohort

of recipients transplanted for etiologies other than NAFLD/CC and HIV. The statistical analysis methods used were checked to ensure the assumptions were met, and study findings were summarized for each research question.

Data Collection

This study included retrospective secondary observational data from the SRTR registry, a transplant population-based database that contains nationwide information on recipients of solid organs transplant. SRTR combines data from different sources including transplant centers. All recipients in the SRTR database remained anonymized, and no attempt was made to identify patients. For this study, SRTR database tables were merged with county health indicators downloaded from a publicly available website, the County Health Rankings and Roadmaps (2018). The FIPS code was converted into zip code and used to link county health indicators and rankings to the recipient zip code in the SRTR database.

Data Access and Acquisition

Data were requested from SRTR. Walden University's IRB approval number for the study is 12-10-18-0296616. The SRTR database was queried to identify subjects that met the inclusion criteria. Furthermore, all of the prespecified variables listed in Chapter 3 were reviewed. Donor steatosis, an important predictor of graft failure, was available only when donor biopsy was performed. Not all donors were biopsied. Because a large number of missing biopsies was expected, donor steatosis was not included on the original list of the study variables. However, donor biopsy data were reviewed to assess

the sample size availability and to evaluate the feasibility of a subset analysis that included donor steatosis. The response variable, graft survival post LT, was censored at 1 year while graft failure or death for any causes were considered events as described in the study protocol outlined in Chapter 3. Some variables were not used because insufficient information was available or because they had poor distributions.

Inclusion Criteria and Cohort Selection

There were 24,997 liver-only transplants performed between July 1, 2013, and December 31, 2016. Figure 6 depicts the selection process steps along with the patients excluded at each step. By applying the exclusion criteria in sequence, I excluded recipients younger than 18-year old (1,953), recipients with a previous transplant (1,161), multiorgan transplant recipients (2,079), live donor transplant recipients (884), Status 1 recipients (540), and recipients transplanted for indication other than NAFLD and CC (15,220). As showed in Figure 6, the final study population consisted of 3,165 adult NASH/CC recipients of a primary, deceased donor, liver-only transplant during the study period. Patient follow-up for graft failure started on the day of the transplant. The outcome of interest in the current analysis was graft failure or death for any causes. Patients were followed from the time of transplant until the earliest of graft failure, death, loss to follow-up, or the conclusion of the observation period. In total, there were 419 graft failure events of which 294 died within 1-year post LT, whereas 2,746 patients had a functioning graft at the end of follow-up. All consecutive patients who met the inclusion criteria were considered.

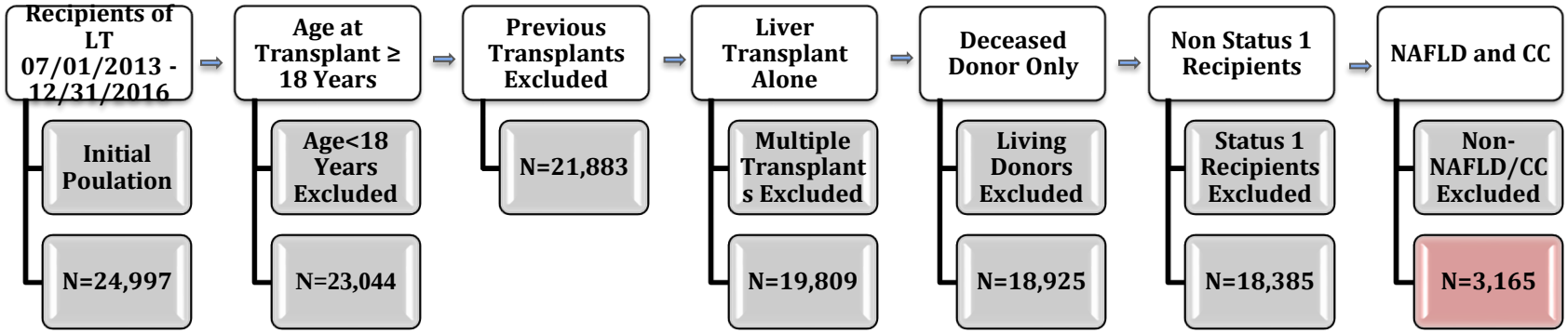

Figure 6. Flow chart of study population including exclusion criteria.

Exploratory Data Analysis

Data were initially explored to get a good first glimpse before formal modeling using summary statistics and graphical representations to spot potential outliers, to investigate patterns of missing variables, to assess correlations among variables, and to explore the distributional shape of continuous variables and the frequency distribution of categorical variables. Graphical analysis of study variables is provided in Appendix C.

Before modeling, I analyzed the mechanism of missingness to quantify the extent of missing data and to examine combinations of predictors with missing data on the same subjects. Most of the donor variables, including donor demographics, height and weight, donor sodium, donor diabetes, and donor cause of death, had no or very few missing values. Only 0.06% of patients in the study cohort had missing HIV data, while 0.09% had missing cold ischemia time. Donor diabetes was missing in 1.14% of subjects, while donor hypertension was missing in 0.76% of subjects, and they tended to be missing in the same patients. Donor steatosis was missing in 38% of cases and was not included in multivariate analyses. Data on HBsAb was missing in 79.3% of subjects; therefore, these data were excluded from subsequent analyses.

Outliers are values outside a typical range. Boxplots were used to detect outliers, or values at least 3 times the interquartile range, and those were checked for biological plausibility. Exploratory data analysis did not indicate implausible values for most of the study variables. Four extreme outliers for MDRD were found and removed.

Descriptive Statistics

I compared the baseline characteristics of the study cohort to a control group of recipients transplanted for other etiologies to identify differences. Since the advent of DAAs, the number of LTs due to HCV has dramatically decreased. Therefore, patients transplanted with HCV were excluded from the comparison because no longer relevant in transplant practice. I compared and summarized baseline characteristics of LT recipients for both NAFLD/CC and other indications for LT in Table 15, confirming literature finding that NAFLD/CC patients are older and have more comorbidities (O'Leary et al., 2011), and supporting the decision to develop risk models tailored to NAFLD/CC. I assessed group differences using the non-parametric Wilcoxon rank sum test for continuous variables and the chi-squared test or Fisher's exact test to compare proportions of categorical variables. I presented continuous data as median and interquartile range (IQR), and categorical data as percentages as reported in Table 15.

Table 15

Characteristics of Study and Control Cohorts

	Non-NAFLD/CC N=10534	NAFLD/CC N=3165	p-value
Recipient characteristics			
Recipient age	58.0 (50.0, 64.0)	60.0 (54.0, 66.0)	<.001
Recipient sex:			<.001
Female	31.8%	43.2%	
Male	68.2%	56.8%	
Recipient BMI (kg/m^2)	28.0 (24.0, 32.0)	31.0 (27.0, 35.0)	<.001
Recipient BSA (m^2)	1.99 (1.81, 2.17)	2.08 (1.88, 2.27)	<.001
Biological MELD score	19.0 (12.0, 30.0)	23.0 (17.0, 32.0)	<.001

(table continues)

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	Non-NAFLD/CC N=10534	NAFLD/CC N=3165	p-value
Donor characteristics			
Donor age	43.0 (28.0, 56.0)	45.0 (29.0;57.0)	.003
Donor sex:			.850
Female	41.1%	41.3%	
Male	58.9%	58.7%	
Donor height (cm)	170 (165, 178)	172 (163, 180)	.264
Donor weight (kg)	80.0 (68.0, 94.0)	81.0 (68.9, 97.5)	<.001
Donor BMI (kg/M^2)	27.0 (23.0, 31.0)	28.0 (24.0, 32.0)	<.001
Donor BSA (M^2)	1.95 (1.77, 2.14)	1.97 (1.79, 2.18)	<.001
Donor diabetes			.224
No diabetes	87.5%	86.3%	
No insulin dependent	6.52%	7.03%	
Insulin dependent	6.00%	6.65%	
Donor HTN	38.3%	40.1%	.083
Donor hypernatremia	7.15%	7.74%	.278
Donor cause of death:			.243
Trauma	29.6%	28.8%	
Anoxia	34.0%	32.8%	
Cva	33.9%	35.8%	
Other	2.54%	2.65%	
Donor DCD	6.89%	6.96%	.942
Donor MDRD:	70.0 (40.0, 103)	69.0 (39.0, 102)	.405
Whole/split:			.073
Whole	98.6%	99.0%	
Reduced/split	1.41%	0.98%	
Increased risk	21.5%	19.2%	.006

(table continues)

	Non-NAFLD/CC N=10534	NAFLD/CC N=3165	p-value
Transplant/matching			
Cold ischemia time (hrs.)	5.96 (4.65;7.42)	5.90 (4.60;7.33)	.360
ABO compatibility:			1.000
ABO identical/compatible	98.9%	98.2%	
ABO incompatible	1.11%	1.80%	
Donor/recipient size match:			<.001
Small for size	7.82%	10.2%	
Normal for size	83.1%	81.7%	
Large for size	9.12%	8.06%	
Geography and community			
Distance to transplant center	36.0 (14.0, 104)	51.0 (18.0, 117)	<.001
Distance to transplant center:			<.001
0-8	15.2%	10.2%	
9-51	43.1%	40.5%	
52-218	31.1%	39.3%	
219+	10.5%	10.0%	
Community health score	15.0 (10.0, 21.0)	17.0 (12.0, 25.0)	<.001
Community health score:			<.001
<=10	28.6%	21.6%	
11-20	45.2%	41.4%	
21-30	20.8%	26.2%	
>30	5.32%	10.8%	
1-year graft survival (%)	86.1 (84.3, 87.9)	87.4 (85.8, 89.1)	.310

Note. In the non-NAFLD/CC group, HCV patients (N=7,850) were excluded because they were no longer relevant in transplant practice.

NAFLD/CC recipients were statistically significantly older (*Mdn*=60; *IQR*=54-66) than the control group (*Mdn*=58, IQR=50-64) with a higher BMI (*Mdn*=31; *IQR*=27-35), as compared the other etiologies (*Mdn*=28; *IQR*=24-32). There were statistically

significantly more females (43%) than males (32%), with $p<.001$. NAFLD/CC recipients were transplanted at significantly higher median MELD score at 23 (*IQR*=17-32), as compared to the control group (*Mdn*=19; *IQR*=12-33) and received statistically significantly more donor livers small for size, 10.2% versus 7.8%, $p<.001$). The overall liver graft survival curves for the two groups were compared through the Kaplan-Meier curves, as depicted in Figure 7. NAFLD/CC recipients were significantly less likely to survive without losing the liver allograft within 1-year post LT, with an overall liver graft survival at 1-year of 86.7% versus 89.0% ($p<.001$). The median CHS for the study cohort was 15. Subjects were grouped by CHS, as shown in Table 16.

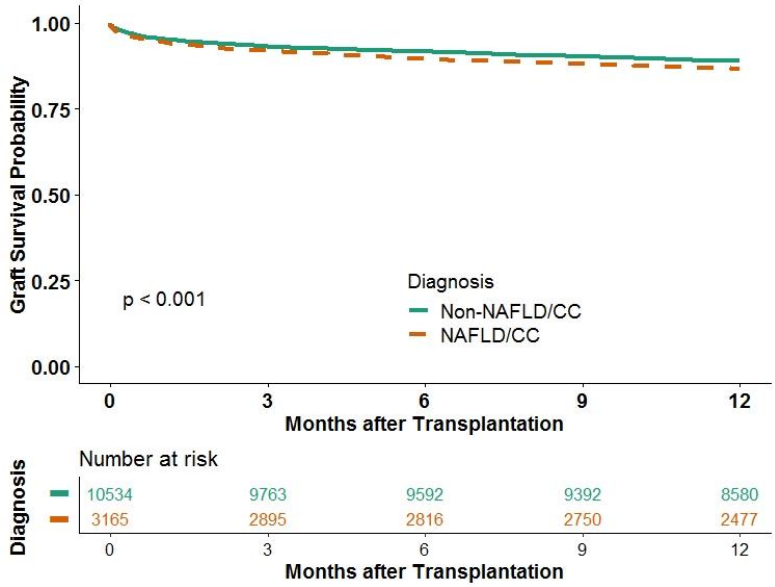

Figure 7. Kaplan-Meier survival curves by liver etiology.

Table 16

Characteristics of Study Cohort by Community Health Score

	Low CHS risk N=1,463	High CHS risk N=1,554	p-value
Recipient characteristics			
Recipient age	61.0 (54.0, 66.0)	60.0 (54.0, 65.0)	.056
Recipient sex:			.496
Female	42.7%	44.0%	
Male	57.3%	56.0%	
Recipient BMI (kg/M^2)	31.0 (26.0, 35.0)	32.0 (27.0, 36.0)	.001
Recipient BSA (M^2)	2.05 (1.85, 2.26)	2.10 (1.91, 2.29)	<.001
Meld	24.0 (18.0, 34.0)	22.0 (17.0, 29.0)	<.001
Donor characteristics			
Donor age	44.0 (29.0;57.0)	45.0 (30.0, 57.0)	.791
Donor sex:			.303
Female	39.9%	41.8%	
Male	60.1%	58.2%	
Donor height (cm)	173 (164,180)	172 (165,180)	.876
Donor weight (kg)	81.0 (69.1;96.4)	81.6 (69.4,98.9)	.131
Donor BMI (kg/M^2)	27.0 (24.0;32.0)	28.0 (24.0, 2.0)	.155
Donor BSA (M^2)	1.97 (1.79;2.17)	1.98 (1.80, 2.19)	.156
Donor diabetes:			.565
No diabetes	86.7%	86.1%	
No insulin dependent	7.16%	6.87%	
Insulin dependent	6.12%	7.06%	
Donor HTN	39.5%	40.1%	.778
Donor hypernatremia	6.70%	8.88%	.031

(table continues)

	Low CHS risk N=1,463	High CHS risk N=1,554	p-value
Donor cause of death:			.337
Trauma	29.8%	27.9%	
Anoxia	33.6%	32.3%	
Cva	34.2%	37.1%	
Other	2.46%	2.77%	
Donor DCD:			.084
DBD	91.9%	93.6%	
DCD	8.07%	6.37%	
Donor MDRD	70.0 (41.0, 101)	68.0 (37.2, 103)	.389
Transplant/matching			
CIT (hr)	6.06 (4.95, 7.76)	5.70 (4.43, 7.10)	<.001
Abo compatibility:			.221
Identical/compatible	98.6%	99.2%	
Incompatible	1.37%	0.84%	
Donor/recipient size match:			.001
Normal for size	80.0%	83.5%	
Small for size	10.0%	10.2%	
Large for size	9.98%	6.25%	
Distance to Tx Ctr	31.0 (14.0, 97.0)	70.0 (29.2;132.0)	<.001
1-year graft survival (%)	86.1 (84.3, 87.9)	87.4 (85.8, 89.1)	.310

Demographic characteristics of recipients in low and high-health risk communities were comparable. Recipients resident in low health risk communities had a statistically significantly lower BMI (*Mdn*=31.0; *IQR*=26.0-35.0) compared to residents in high-risk communities (*Mdn*=32.0; *IQR*=27.0-36.0). NAFLD/CC recipients in low health risk communities were transplanted at a statistically significantly higher median MELD score at the time of transplant at 24 (*IQR*=18.0-34.0) compared to the high health

risk counterpart at 22 (*IQR*=17.0-29.0). Recipients from low health risk counties were more likely to receive donors who were large for size (9.98% versus 6.25%, *p*<.001). Recipients resident in low health risk counties had a much longer median distance from the transplant center (31 miles, *IQR*=14.0-97.0) than those who resided in high health risk counties (70 miles, *IQR*=29.2-132.0). The Kaplan-Meier survival analysis in Figure 8 showed that 1-year graft survival did not differ significantly between recipients in low and high health-risk communities.

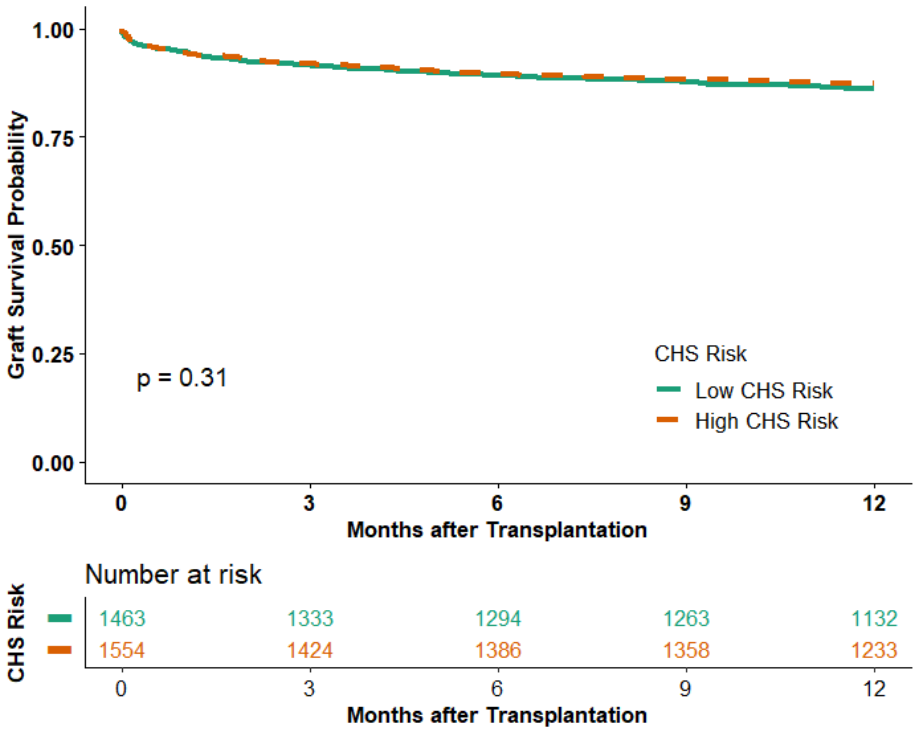

Figure 8. Kaplan-Meier survival curves by community health score.

Univariate Preliminary Analysis

I conducted univariate analyses to learn about candidate predictors and their relation to 1-year graft survival post LT as a prelude to subsequent multivariate analyses. The variables included in the univariate screening were donor's gender, age, height, BMI, BSA, donor cause of death, hypertension, diabetes, hypernatremia, microsteatosis, macrosteatosis, MDRD, DCD, recipient's age, gender, BMI, BSA, cold ischemia time, ABO compatibility, donor and recipient size match.

Univariate Analysis of Continuous Predictors`

I conducted univariate analyses to explore the association between categorical and continuous variables with 1-year graft survival post LT. Continuous predictors included in a Cox PH model must meet the underlying assumption of linear relationship with the log hazard of the time to event outcome. I transformed continuous variables using RCS transformations, which are flexible functions with robust behavior at the tails of predictor distributions. I used the linearity Wald tests via RCS transformations to test the assumptions of linear relationships between continuous predictors and the risk of graft failure for NAFLD/CC recipients of LT. I also used splines to model the effects of nonlinear predictors in subsequent analyses, and I placed the knots on the spline curve defining the end of one segment and the start of the next so that the overall curve was smooth and continuous.

The fit depends more on the number of knots, and the exact location of knots is not critical (see Harrell, 2015). So, I placed the knots at fixed percentiles of predictor's

marginal distribution as recommended by Harrell (2015), who also suggested that five knots are sufficient to provide a good fit of nonlinear patterns that are likely to occur in practice. Therefore, I selected the number of knots for each continuous predictor between three and five to balance the best fit and overfitting, resulting in a parsimony model with the lowest Akaike Information Criteria and maximum likelihood. In a univariate Cox PH model, the relative hazard, which is the ratio of the hazard at time t to the hazard at baseline is a function of the exponentiated continuous predictor x, as shown in Equation 9:

$$\frac{h(t)}{h(0)} = e^{x} \tag{9}$$

If the natural logarithm is taken in both size of the Cox PH model, the log relative hazed is a linear function of the predictors:

$$ln(\frac{h(t)}{h(0)}) = x$$

Figures 9-11 depict univariate display plots of the estimated relationship between continuous independent predictors modeled as RCSs and log hazard ratio for graft failure from a sample of 3,165 NAFLD/CC recipients and 419 graft failures, including deaths.

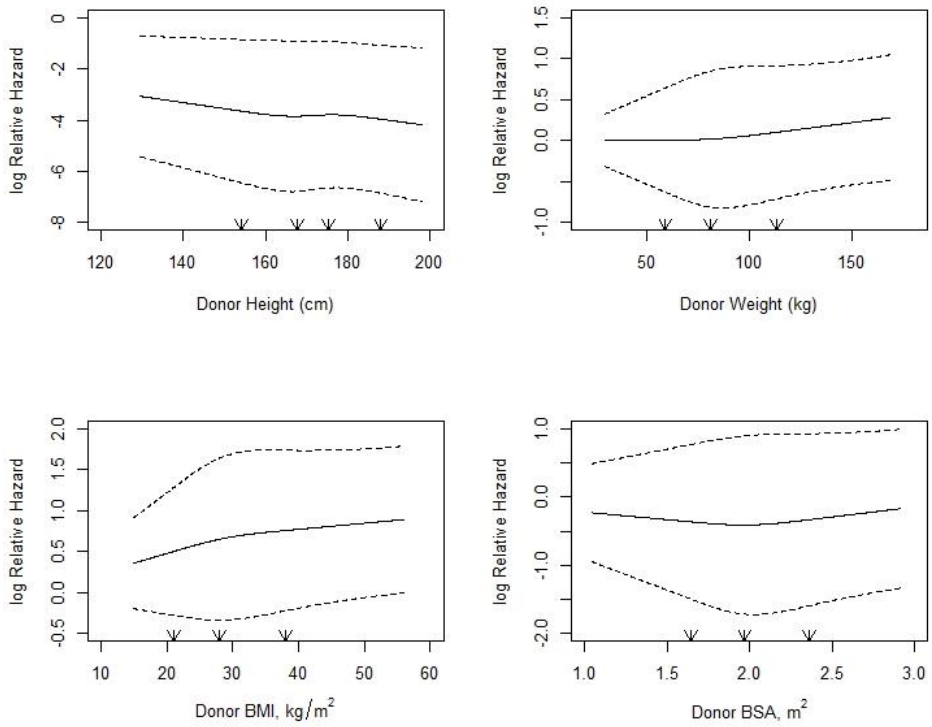

Figure 9. Functional relationships between donor height, donor weight, donor BMI and donor BSA, and log relative hazard of graft failure at one-year post LT.
Note. Number of knots and location, respectively: donor height (3 knots at 157, 172 and 185 cm), donor weight (3 knots at 59, 81 and 113 kg), donor BMI (3 knots at 21, 28, and 23kg/m^2), donor BSA (knots at 1.6, 2.0, and 2.4m^2).

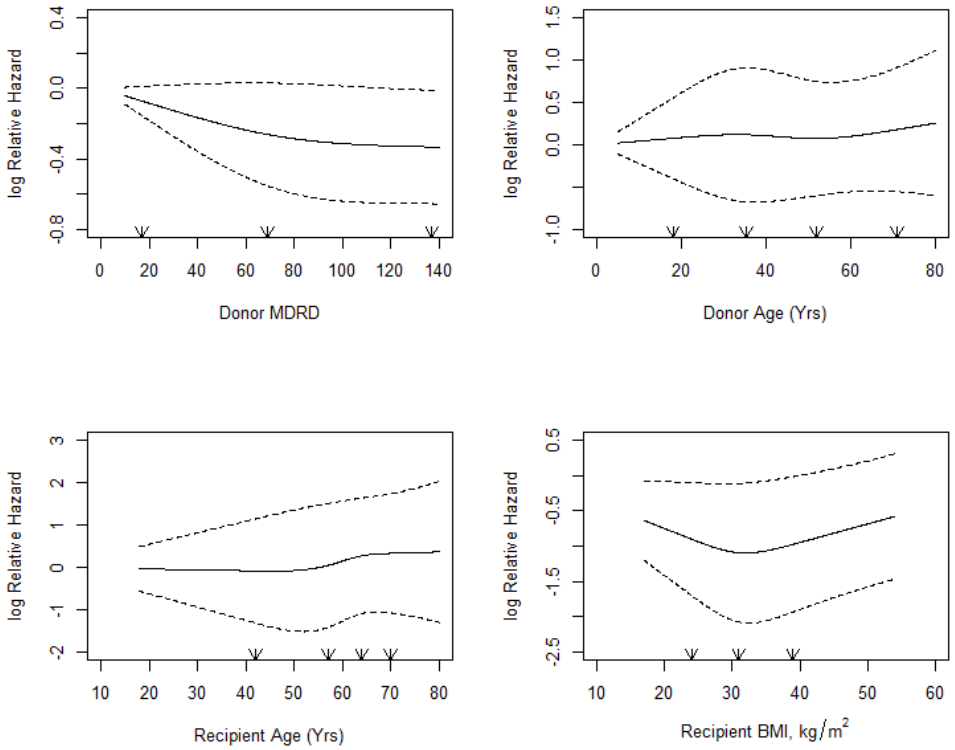

Figure 10. Functional relationships between donor MDRD, donor age, recipient age and recipient BMI, and log relative hazard of graft failure at 1-year post LT.
Note. Number of knots and location, respectively: donor MDRD (3 knots at 17, 69, and 137), donor age (4 knots at 18, 35, 52, and 71 years), recipient age (4 knots at 42, 57, 64, and 70 years), and recipient BMI (3 knots at 24, 31 and 39 kg/m^2).

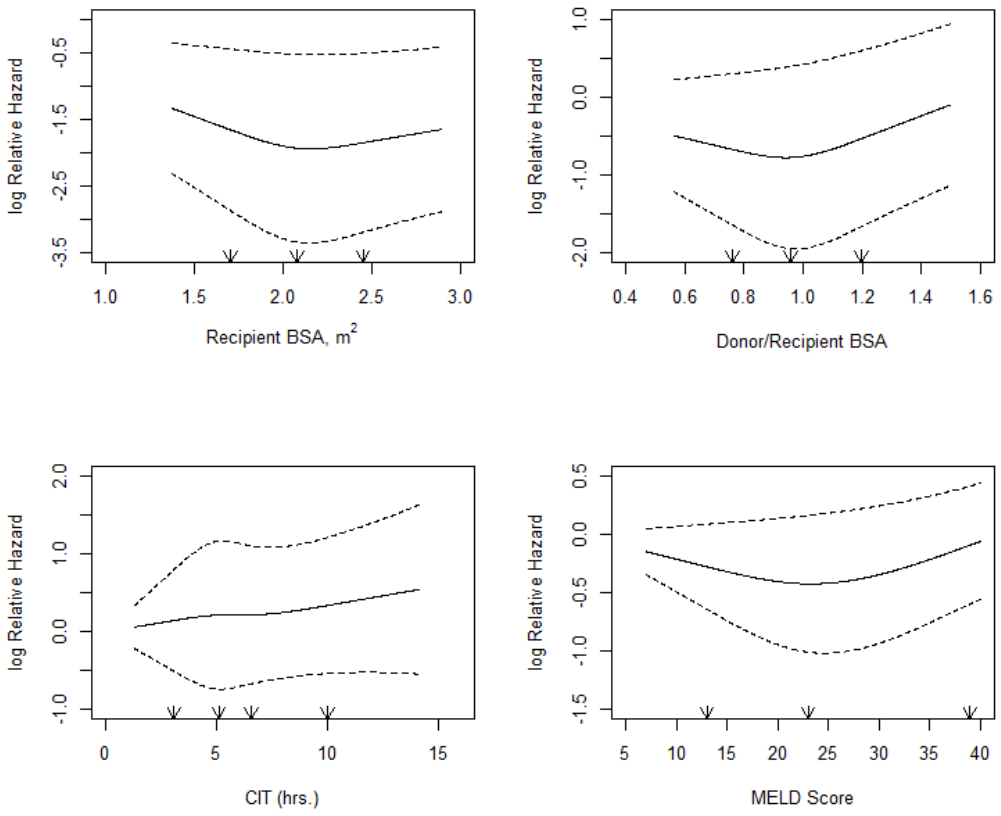

Figure 11. Functional relationships between recipient BSA, donor/recipient BSA, CIT, and MELD score, and log relative hazard of graft failure at 1-year post LT.
Note. Number of knots and location, respectively: recipient BSA (3 knots at 1.7, 2.1 and 2.4m^2), donor/recipient BSA (3 knots at 0.8, 1.0 and 1.2), CIT (4 knots at 3.1, 5.1, 6.6 and 10.0 hours) MELD score (3 knots at 13, 23 and 39).

Table 17 summarizes the results of the univariate association of each continuous predictor modeled through RCS with the time-to-event outcome and formal tests of the linearity using, respectively the Wald χ^2 test for association and the Wald χ^2 test for linearity (Harrell, 2015). Donor height was significantly associated with the log hazard for graft failure post LT ($\chi^2(3) = 8.23, p = .035$), and the association was not

significantly different from linear $\chi^2(2) = 2.97$, *p*=.226). The donor's factors, weight, BMI, BSA, MDRD, and age were not significantly associated with liver graft survival.

Recipient's age ($\chi^2(3) = 10.12$, *p*=.016), BMI ($\chi^2(2) = 6.12$, *p*=.047), BSA ($\chi^2(2) = 7.32$, p = .025) and MELD score ($\chi^2(2) = 6.02$, *p*=.044), were significantly associated with graft failure, with significant nonlinearity, respectively, ($\chi^2(1) = 6.10$, *p*=.013) for BMI, ($\chi^2(1) = 5.13$, *p*=.024) for BSA, and ($\chi^2(1) = 4.37$, *p*=.037) for MELD score. Donor/Recipient BSA was significantly associated with the outcome ($\chi^2(2) = 8.27$, *p* = .016), and with significant nonlinearity ($\chi^2(1) = 5.12$, *p*=.024), while CIT was not significantly associated with the outcome.

Table 17

Univariate Association and Linearity Tests for Continuous Variables Predicting Liver Graft Failure

Variable	Association Wald $\chi^2(d.f.)$	Linearity Wald. $\chi^2(d.f.)$
Donor height (cm)	8.23 (3)*	2.97 (2)
Donor weight (kg)	1.02 (2)	0.14 (1)
Donor BMI (kg/M^2)	4.18 (2)	0.37 (1)
Donor BSA (M^2)	0.81 (2)	0.74 (1)
Donor MDRD	4.18 (2)	1.42 (1)
Donor age (yrs.)	0.52 (3)	0.39 (2)
Recipient age (yrs.)	10.12 (3)*	1.73 (2)
Recipient BMI (kg/M^2)	6.12 (2)*	6.10 (1)*
Recipient BSA (M^2)	7.34 (2)*	5.13 (1)*
Donor/recipient BSA	8.27 (2)*	5.12 (1)*
CIT (hrs.)	1.62 (2)	0.07 (1)
MELD score	6.02(2)*	4.37 (1)*

Note. NAFLD/CC Recipients (n=3165).* *p*<.05. Each predictor modeled as RCS.

Univariate Analysis of Categorical Predictors

I conducted univariate Kaplan-Meier survival analyses to examine independent predictors and their effect on graft survival by comparing the survival experiences across each predictor categories. I performed log-rank tests to determine if there were differences in the survival distribution for the different categories of each independent variable. Pairwise log-rank comparisons were conducted to determine which categories had different survival distributions. Compared to recipients of DBD donors, DCD donor recipients experienced a significantly worse graft survival at 1-year post LT, χ^2 (1) = 18, p = <.0001 (Figure 12).

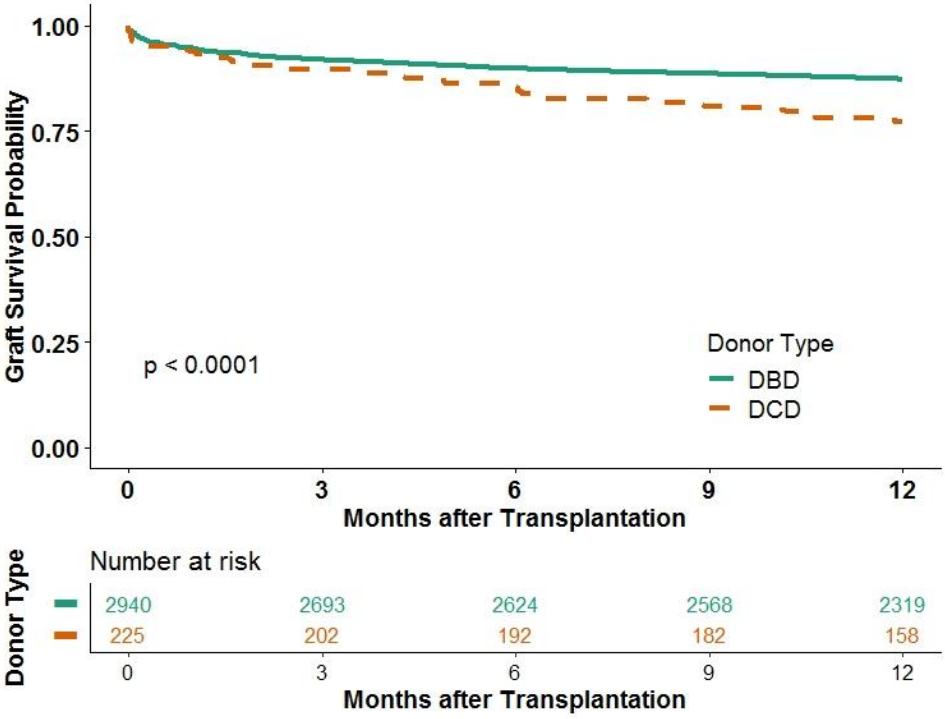

Figure 12. Kaplan-Meier survival curves by donor type.

The survival distributions for the three categories of donor diabetes were statistically significantly different, χ^2 (2) = 17.6, p < .0001 (Figure 13). The Bonferroni corrected pairwise comparisons found that recipients who received a diabetes insulin dependent donor had a statistically significant worse graft survival at one year, as compared to recipients who received donors without diabetes (p=.004) or donors with non-insulin dependent diabetes (p=.001) (Figure 13).

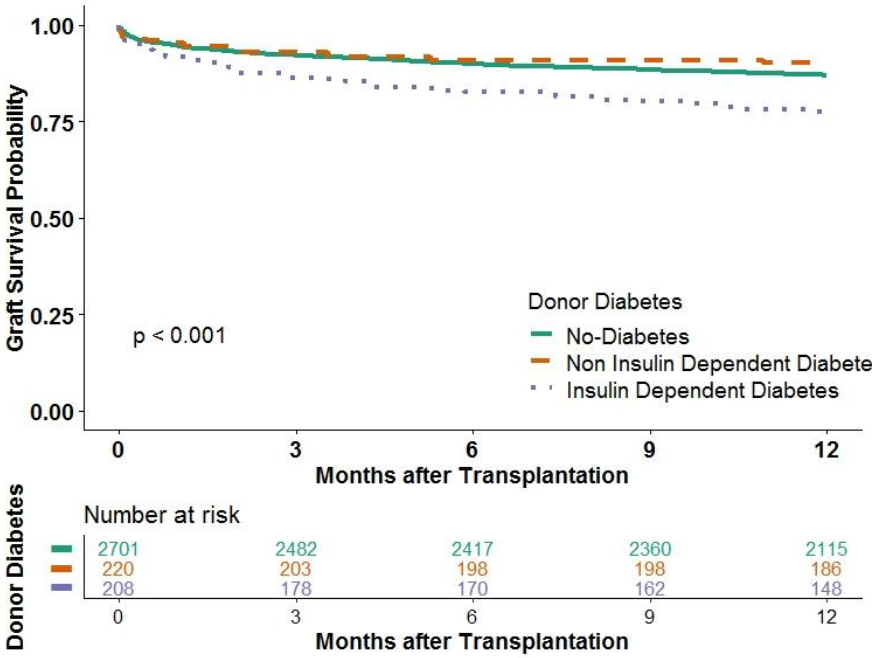

Figure 13. Kaplan-Meier survival curves by donor diabetes.

Donor/recipient liver size was associated with graft survival at 1-year post LT, χ^2(2) = 10.7, p = .005 (Figure 14). Bonferroni corrected post-hoc comparisons revealed that compared to normal for size donors, large for size donors was associated with an unfavorable graft survival experience (p = .003).

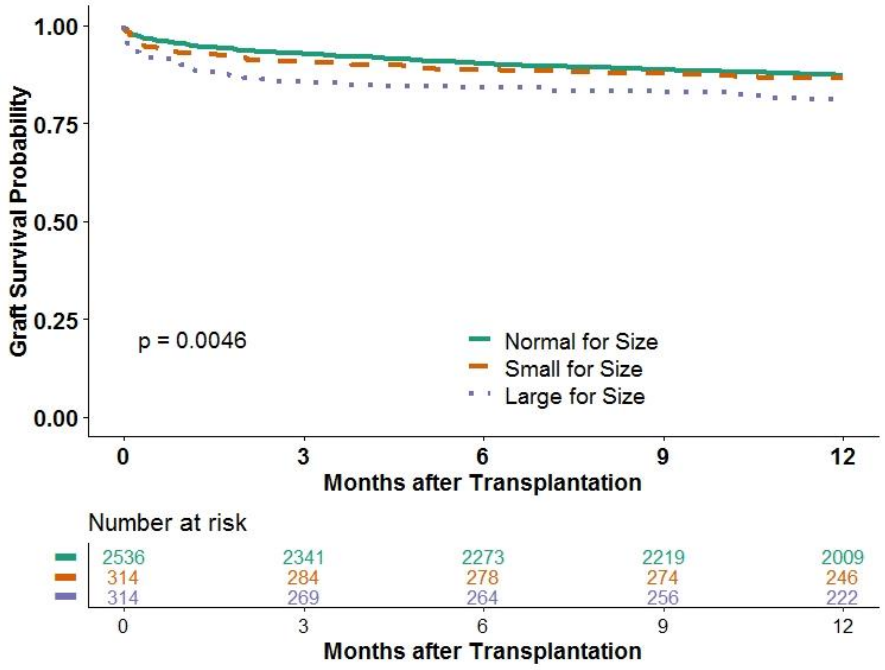

Figure 14. Kaplan-Meier survival curves by donor/recipient size match.

Donor gender ($\chi^2(1) = .4$, $p = .51$), hypertension ($\chi^2(1) = .3$, $p = .58$), donor cause of death ($\chi^2(3) = 3.8$, $p = .28$), micro steatosis ($\chi^2(2) = 4.2$, $p = .12$), macro steatosis ($\chi^2(3) = 5.1$, $p = .079$), ABO compatibility ($\chi^2(1) = 0.1$, $p = .74$), and hypernatremia ($\chi^2(1) = 0.1$, $p = .72$), were not associated with 1-year post LT graft survival in Kaplan-Meier analyses (Figures 15, 16, 17, 18, 19, 20, 21).

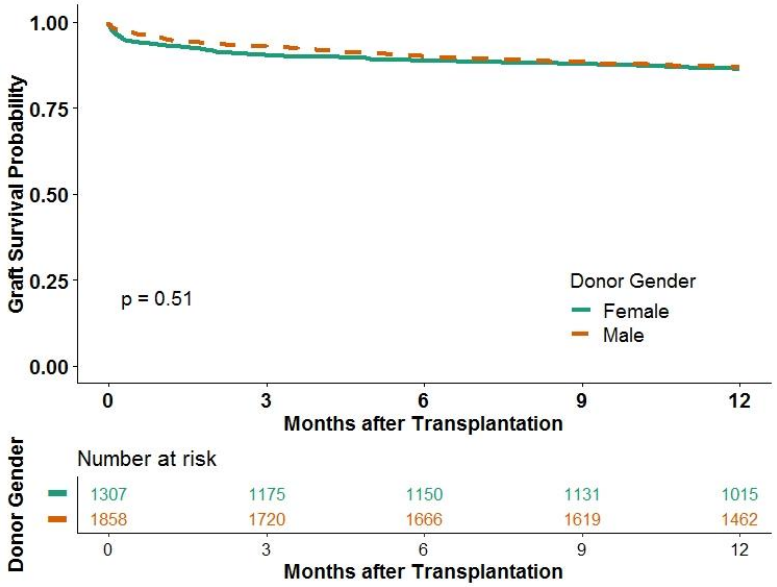

Figure 15. Kaplan-Meier survival curves by donor gender.

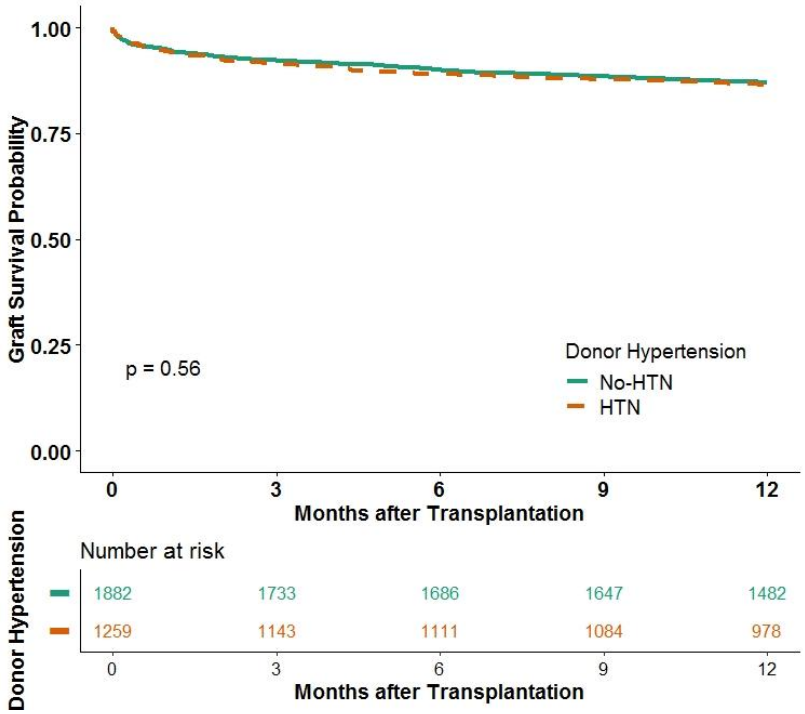

Figure 16. Kaplan-Meier survival curves by hypertension.

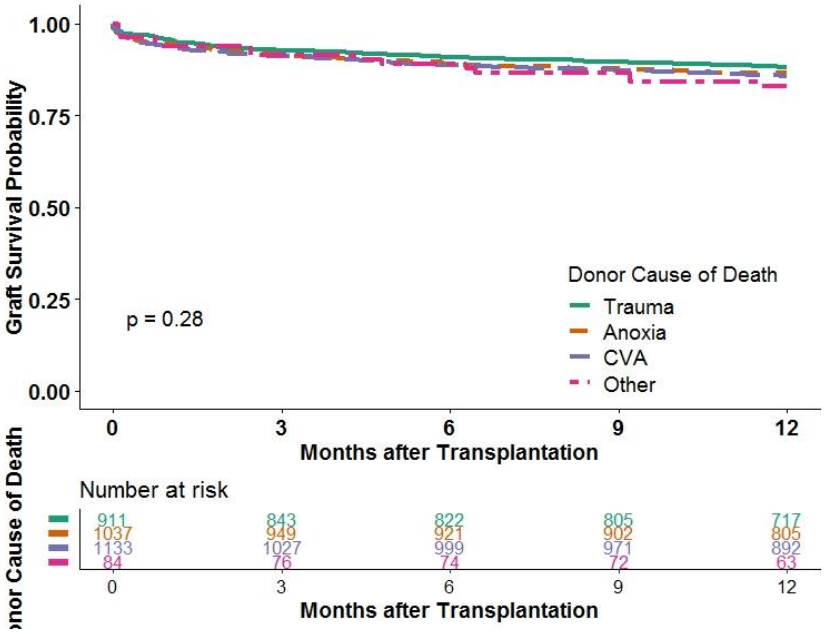

Figure 17. Kaplan Meier survival curves by cause of death.

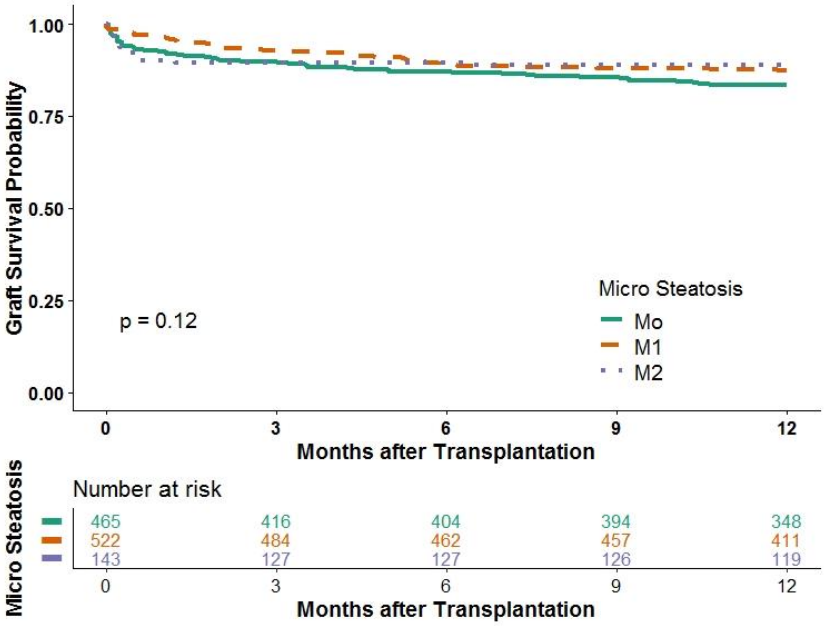

Figure 18. Kaplan-Meier survival curves by microsteatosis stage.

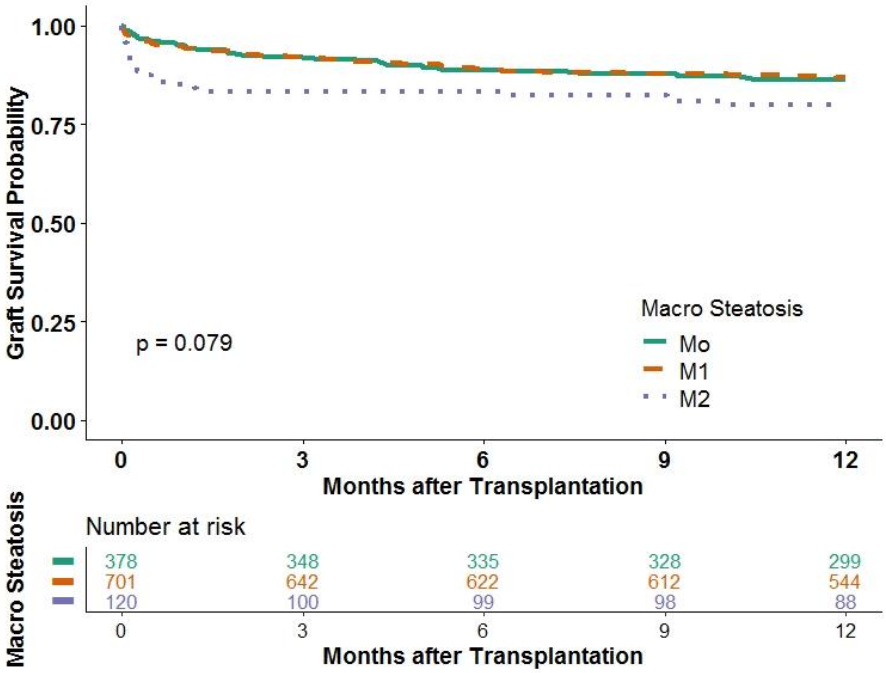

Figure 19. Kaplan-Meier survival curves by macrosteatosis stage.

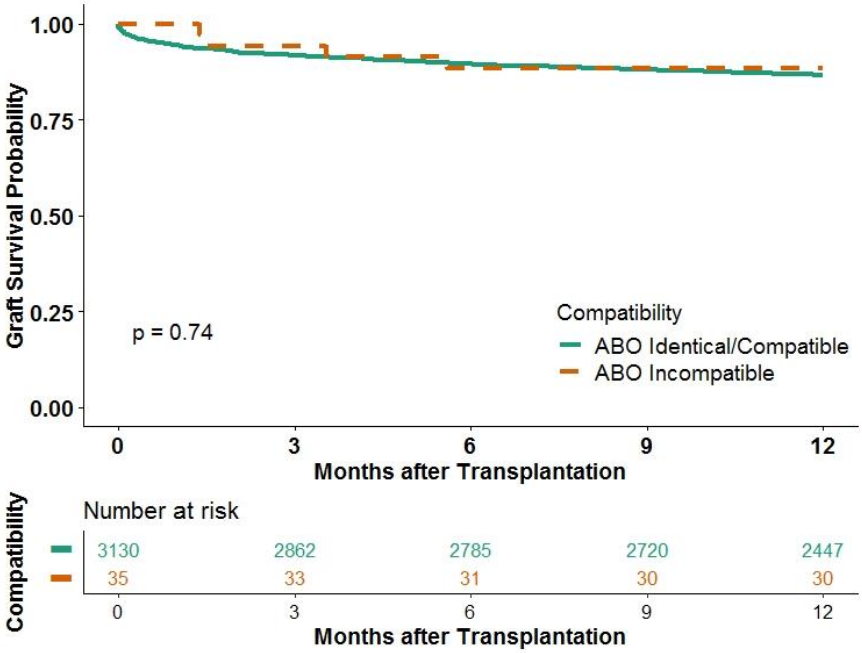

Figure 20. Kaplan-Meier survival curves by ABO compatibility.

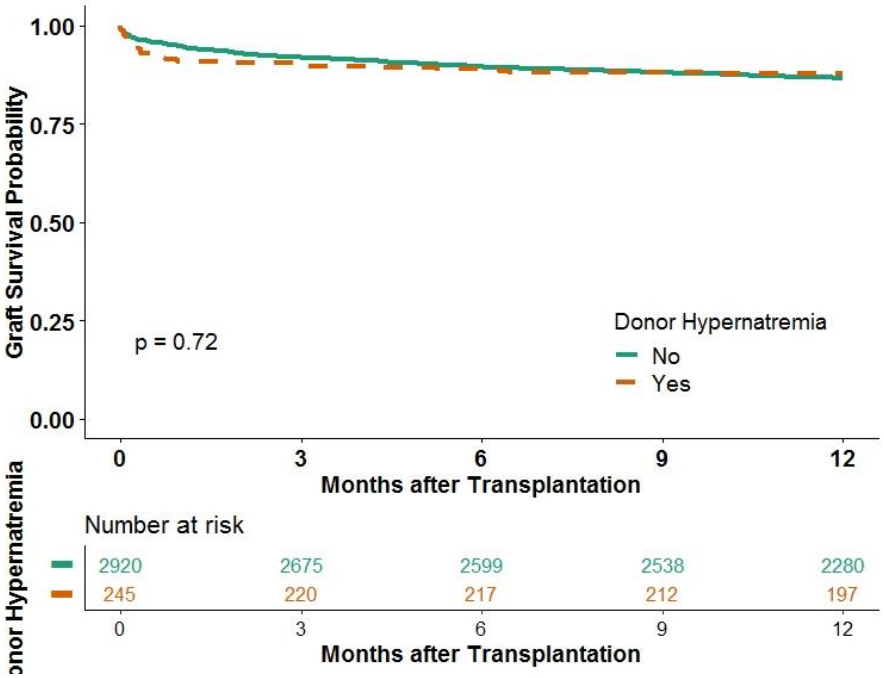

Figure 21. Kaplan-Meier survival curves by hypernatremia.

Figure 22 depicts Kaplan-Meier graft survival curves of NAFLD/CC recipients who received Public Health Service increased risk and non-increased risk donors. The log-rank test compared survival experience between the two donor risk categories and found no statistically significant difference (p=.96). Table 18 contains information about graft survival probability at 1-year post LT and the 95% CIs.

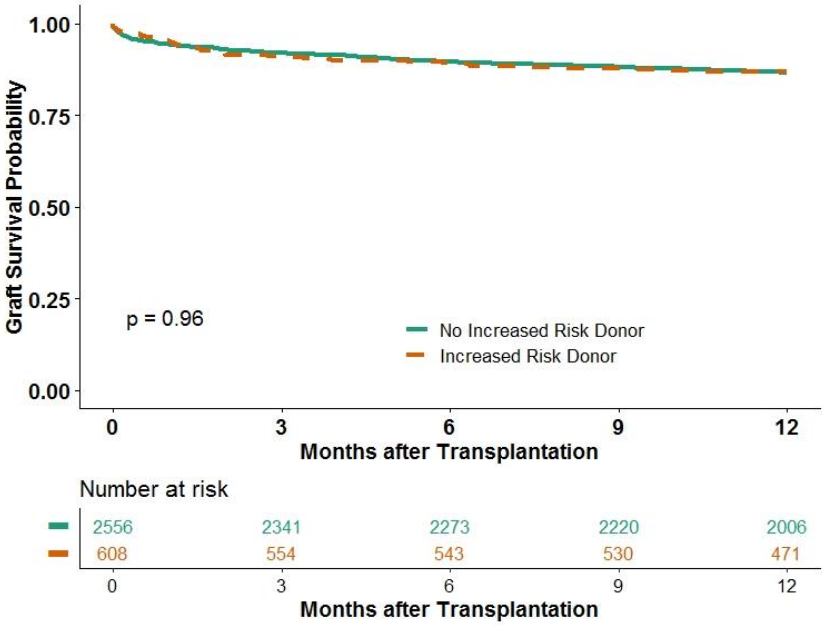

Figure 22. Kaplan-Meier survival curves by public health increased donor risk.

Table 18

One-year post LT Graft Survival Probability and 95% Confidence Intervals

Variable	Level	1-year survival	95% CI
Total	Overall		
Gender	Male	.87	(.84, .88)
	Female	.86	(.84, .88)
Donor diabetes	No diabetes	.87	(.86, .88)
	No insulin dependent	.90	(.87, .94)
	Insulin dependent	.78*	(.72, .84)
Donor hypertension	No hypertension	.87	(.85, .89)
	Hypertension	.86	(.84, .88)
Donor hypernatremia	Hypernatremia	.88	(.84, .92)
	No hypernatremia	.87	(.85, .88)
Micro steatosis	Mo	.83	(.80, .87)
	M1	.87	(.84, .90)
	M2	.89	(.84, .94)
Macro steatosis	Mo	.86	(.83, .90)
	M1	.87	(.84, .89)
	M2	.80	(.73, .87)
Donor DCD	DBD	.87	(.86, .89)
	DCD	.77***	(.72, .83)
Donor cause of death	Trauma	.88	(.86, .90)
	Anoxia	.87	(.85, .89)
	CVA	.86	(.84, .88)
	Other	.83	(.75, .92)
Size match	Normal for size	.87	(.86, .89)
	Small for size	.87	(.83, .90)
	Large for size	.81*	(.77, .85)
ABO compatibility	Identical/compatible	.87	(.85, .88)
	Incompatible	.88	(.79, .99)

Note. * $p<.05$, ** $p<.01$, *** $p<.001$.

Research Question 1

The first research question was based on whether there is a relationship between post-transplant graft survival among NAFLD/CC recipients and a number of donor characteristics (age, gender, height, weight, BMI, the cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, hypernatremia). To answer this question, I considered a semiparametric approach or a multivariable Cox PH regression model using graft survival outcomes, which included intrinsic donor factors and a nonparametric machine learning approach or random survival forests (RSF).

The initial list of candidate predictors, based on literature review and combined with knowledge matter, included 13 donor's variables: age, sex, height, weight, BMI, BSA, hypertension, the cause of death, hypernatremia, DCD, MDRD, HCV, and HBsAb. I analyzed variable distributions and patterns of missing data in the preliminary phase. The distributions of HCV and HBsAb status were too narrow to allow the inclusion in the model. I excluded HBsAg because it was missing in a large number of subjects. I removed four extremely high values for MDRD because they were considered as potential errors.

Cox PH Approach

I analyzed donor height, donor BMI, and donor BSA separately in alternative models because of collinearity, and I compared the models using the Akaike Information

Criteria (AIC). At least one of the donor factors considered was missing in 47 cases (or 1.5% of cases). Because the sample size was large enough for adequate power, and the sample was representative of the target population, I conducted complete cases analysis.

The effective sample size available was sufficiently large to allow fitting a saturated pre-specified model with all predictors, including the non-significant in the univariate analysis. I used smoothing transformations of continuous predictors to relax the linearity assumption and prevent residual confounding. I tested model distributional assumptions using smoothed scaled Schoenfeld residuals for each predictor and the graphical visualization. I did not observe any trend against time and no major violations. I tested the validity of the proportional hazard assumption for each covariate and globally. The global test of proportional hazard was not statistically significant (p= .245) indicating that the proportionality of hazards was met at significance level α=.05.

Dunkler, Plischke, Leffondré, & Heinze (2014) recently proposed a variable selection strategy which combines significance and change in estimation criterion, the augmented backward elimination, which enables assigning a specific role to independent variables. This strategy allows the inclusion in the model of "passive variables," regardless of their significance, just based on subject-matter knowledge. I applied an augmented backward elimination to reduce the number of predictors in the final model, in 1000 bootstrap samples drawn from the original data, with a level of significance set to α=.2 and the threshold of the relative change-in-estimate criterion 'τ' set to .1. This

strategy allowed to include into the model donor age and DCD regardless of their statistical significance, as known predictors of graft failure.

The independent donor variables selected in the final model included: age, height, diabetes, DCD, and MDRD. Harrell (2015) suggested that at least 10–20 events are needed per degree of freedom, as a rule of thumb. The study sample included 412 events and approximately 20 degrees of freedom to spend to fit the model, which used 12 degrees of freedom. I tested the overall significance of the Cox PH model or the model goodness of fit using the likelihood ratio test ($\chi^2(11) = 48.68$, $p < .0001$) indicating that the model was statistically significant and adequate in predicting the graft survival experience of NAFLD/CC recipients of LT.

The results of the selected Cox regression model are presented in Table 19, which shows the estimated coefficients, the adjusted hazard ratios (AHR) along with the 95% confidence intervals (CI), of each categorical predictor, for each parameter used in the splines. Recipients of DCD grafts were more than twice likely to lose their grafts within 1-year post LT (AHR=2.17, 95% CI=1.60, 2.95). Receiving donors with insulin-dependent diabetes was associated with an increased risk of graft failure within 1-year post LT (AHR=1.71, 95% CI= 1.24, 2.38). The final RCS regression model results in Table 19 include estimated coefficients for each parameter used in the splines, which do not have an immediate interpretation but can be better described graphically. Tables 20-22 provide useful interpretations of the RCSs variables.

Table 19

Multivariate Cox PH Model for Donor Variables Predicting Liver Graft Function

Variable	Estimated β SE(β)	Wald χ^2	AHR (95% CI)
Donor type			
DBD	Reference		
DCD	.776 (.156)	4.96	2.17 (1.60, 2.95)**
Donor diabetes			
No Diabetes	Reference		
Non-insulin dependent	-.344 (.230)	-1.49	0.71 (1.24, 2.38)
Insulin dependent	.539 (.167)	3.23	1.71 (1.24, 2.38)*
MDRD linear	-.004 (.003)	-1.34	1.00 (0.99, 1.01)
MDRD’	.001 (.003)	0.43	1.00 (0.99, 1.01)
Donor height linear	-.031 (.011)	-2.90	0.97 (0.95, 0.99)*
Donor height’	-.064 (.034)	1.87	1.07 (1.00,1.14)
Donor height’’	-.261 (.163)	-1.60	0.77 (0.56, 1.06)
Donor age linear	.009 (.014)	0.60	1.01 (0.98, 1.04)
Donor age’	-.038 (.045)	-0.83	0.96 (0.88, 1.05)
Donor age’’	.012 (.125)	0.95	1.13 (0.88, 1.44)

Note. NAFLD/CC recipients (n=3,165). β =estimated coefficient of Cox PH model, SE=standard error, AHR=adjusted hazard ratio. CI=confidence intervals.
*p<.01, **p<.001

Table 20

Selected Estimates for Donor Age from the Multivariate Cox PH Regression

Donor Age (yrs)	AHR	95% CI
20	1.01	(0.76, 1.33)
40	1.04	(0.95, 1.14)
45	Reference	
50	0.97	(0.89, 1.05)
60	1.00	(0.85, 1.17)

Note: Donor age (yrs.) adjusted to donor height of 172 cm, no diabetes, DBD donor, MDRD of 69. AHR=adjusted hazard ratio, CI=confidence intervals.

Table 21

Selected Estimates for Donor MDRD from the Multivariate Cox PH Regression

MDRD	ARH	95% CI
30	1.14	(0.97, 1.33)
50	1.06	(0.99, 1.14)
60	1.03	(1.00, 1.06)
69	Reference	
80	0.96	(0.95, 0.99)
100	0.92	(0.87, 0.98)
120	0.88	(0.79, 0.98)

Note: MDRD adjusted to no diabetes, DBD, donor height of 172 cm, donor age of 45 yrs. AHR=adjusted hazard ratio, CI=confidence intervals.

Table 22

Selected Estimates for Donor Height from the Multivariate Cox PH Regression

Donor height (cm)	AHR	95% CI
130	2.67	(1.41, 5.07)
140	1.97	(1.26, 3.07)
160	1.08	(0.90, 1.29)
172	Reference	
180	1.01	(0.89, 1.45)
180	0.84	(0.57, 1.23)

Note: Donor height (cm) adjusted to donor age of 45 yrs., no diabetes, DBD donor, MDRD of 69. AHR=adjusted hazard ratio, CI=confidence intervals.

Table 21 summarizes the AHR and 95% CI for selected MDRD values. Compared to a median reference donor with MDRD of 69, liver allografts from donors with an MDRD of 100 provided a reduction of 8% in the risk of graft failure within 1-year post LT (AHR=0.92, 95% CI=0.79, 0.98). Compared to a median donor of 172 cm height, livers from donors of 140 cm height were associated with 97% higher risk of graft failure (AHR=1.97, 95% CI 1.26, 3.07). This finding indicated that holding all other variables constant to their reference values, liver allografts from donors with a height of 140 cm were almost twice more likely to fail within 1-year post LT, compared to grafts from donors with a height of 172 cm (Table 22).

Figure 23 illustrates the adjusted hazard of graft failure as a function of donor age (yrs.), as follows: (A) Donor MDRD (B) and donor height (cm) (C), holding all other

variables constant at representative levels set at their reference category or mean values (DBD donors, without diabetes, with MDRD of 69, of 45 years, with a height of 172 cm).

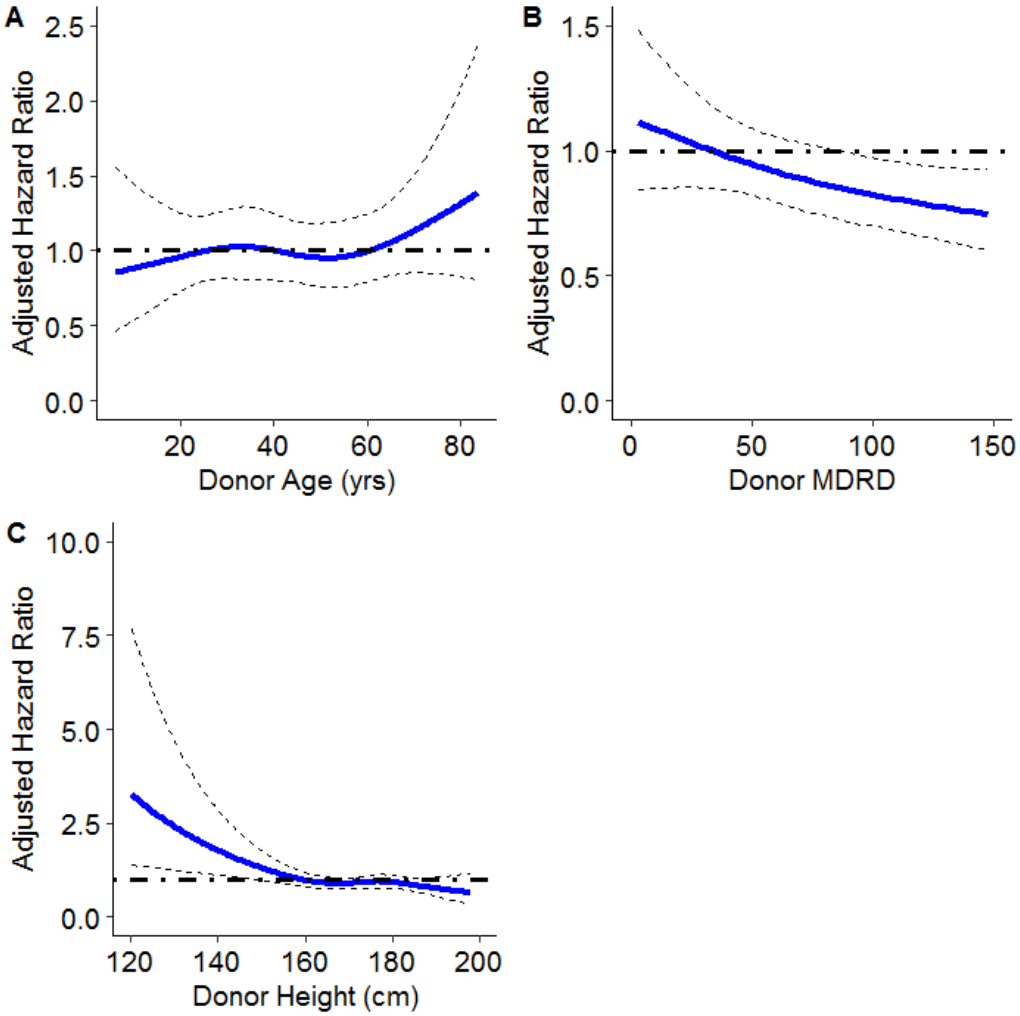

Figure 23. Restricted cubic splines of the association between donor age (A), donor MDRD (B) and donor height (cm) (C) and adjusted relative hazard of graft failure at 1-year post LT.
Note. The model is adjusted for the following variables set at reference category: donor type (DBD), diabetes (No), or median category: MDRD (69), donor age (45 yrs.), donor height (172 cm).

When compared to an average reference donor, donor age was not associated with the risk of graft failure, as shown in Figure 23 (A). The risk of graft failure decreased, as MDRD increases as displayed in Figure 23 (B). Decreasing donor height was associated with an increased risk of graft failure, as shown in Figure 23 (C).

After fitting a Cox PH model that included splines, I computed hazard ratios by comparing specific values of a variable, with a single reference value. From Figure 23 (A), the 95% CI of the AHR includes one for each value of donor age, compared to an average donor. From Table 20, the AHR for a 50-year donor compared to a 45-year donor was 0.97 (95% CI=0.89, 1.05). From Figure 23 (B), donors with MDRD 80 or greater were associated with improved survival.

The Donor Intrinsic DQ-NAFLD Score

The DQ-NAFLD risk score is an estimate of the relative risk of posttransplant graft failure for an adult recipient from a cadaveric donor, compared to a reference donor: a 45-year DBD donor of 172 cm height, with no diabetes and MDRD of 69. From the Cox PH model, the risk for subject j is expressed as:

$$\lambda(t|x_j) = \lambda_0(t) r_j(t)$$

I used the coefficients of the Cox PH model in conjunction with individual covariates to estimate DQ-NAFLD risk score for an individual. The risk score for a subject ‘j’ is the hazard ratio for that person relative to the baseline, as shown in Equation 10:

$$DQ - NAFLD_{(j)} \qquad (10)$$

$$= \exp\big(\beta_1 \text{ x I}\big(DCD_{(j)}\big) + \beta_2 x\ MDRD_{(j)} + \beta_3\ x\ MDRD'_{(j)} + \beta_4 x\ height_{(J)}$$

$$+ \beta_5\ x\ height'_{(j)} + \beta_6\ x\ height''_{(j)} + \beta_7\ x\ age_{(j)} + \beta_8\ x\ age'_{(j)}$$

$$+ \beta_9\ x\ age''_{(j)} + \beta_{10} \text{ x I}\big(Non\ Insulin\ Dependent_{(j)}\big)$$

$$+\ \beta_{11} \text{x I}(Insulin\ Dependent_{(j)}\ ))$$

$for\ j=1....N$

Where I(e)=1 if the event is true, I(e)=0 otherwise,

The predictors, donor's age, height, and MDRD, are expressed as restricted cubic splines. I modeled the predictor MDRD as RCR with 3 knots, $t_1 = 17$, $t_2 = 69$, $t_3 = 137$. The nonlinear term is:

$$MDRD^i_{(j)} = (MDRD_{(j)} - t_1)^3_+ - \frac{(t_3 - t_1)}{(t_3 - t_2)}\ x\ \big(MDRD_{(j)} - t_2\big)^3_+$$

$$+ \frac{(t_2 - t_1)}{(t_3 - t_2)}\ x\ \big(MDRD_{(j)} - t_3\big)^3_+$$

I modeled the predictor donor height as RCS with 4 knots, $t_1 = 154$, $t_2 = 167$, $t_3 = 176$, $t_4 = 188$. The nonlinear terms are:

$$height'_{(j)} = (height_{(J)} - t_1)^3_+ - \frac{(t_4 - t_1)}{(t_4 - t_3)}\ x\ \big(height_{(J)} - t_2\big)^3_+$$

$$+ \frac{(t_3 - t_1)}{(t_4 - t_3)}\ x\ \big(height_{(J)} - t_4\big)^3_+$$

$$height''_{(j)} = (height_{(J)} - t_2)^3_+ - \frac{(t_4 - t_2)}{(t_4 - t_3)}\, x\, \left(height_{(J)} - t_3\right)^3_+$$

$$+ \frac{(t_3 - t_2)}{(t_4 - t_3)}\, x\, \left(height_{(J)} - t_4\right)^3_+$$

I modeled the predictor donor age as RCS with 4 knots, $t_1 = 18$, $t_2 = 35$, $t_3 = 52$, $t_4 = 71$. The nonlinear terms are:

$$age'_{(j)} = (age_{(j)} - t_1)^3_+ - \frac{(t_4 - t_1)}{(t_4 - t_3)}\, x\, \left(age_{(j)} - t_2\right)^3_+ + \frac{(t_3 - t_1)}{(t_4 - t_3)}\, x\, \left(age_{(j)} - t_4\right)^3_+$$

$$age''_{(j)} = (age_{(j)} - t_2)^3_+ - \frac{(t_4 - t_2)}{(t_4 - t_3)}\, x\, \left(age_{(j)} - t_3\right)^3_+ + \frac{(t_3 - t_2)}{(t_4 - t_3)}\, x\, (age - t_4)^3_+$$

Where $(z)_+$ is equal to z if z > 0, and 0 otherwise.

Replacing the estimated model coefficients, the Equation 10 became:

$$DQ - NAFLD_{(j)} = \exp[0.77 \text{ x I}\left(DCD_{(j)}\right) -$$

$$0.04\, x\, MDRD_{(j)} + 0.001\, x\, \left(MDRD_{(j)} - 17\right)^3_+ - \frac{(137-17)}{(137-69)}\, x\left(MDRD_{(j)} - 69\right)^3_+ +$$

$$\frac{(69-17)}{(137-69)}\, x\, \left(MDRD_{(j)} - 137\right)^3_+ - 0.031\, x\, height_{(J)} - 0.064\, x\, \left(height_{(J)} - 154\right)^3_+ -$$

$$\frac{(188-154)}{(188-176)}\, x\, \left(height_{(J)} - 167\right)^3_+ + \frac{(176-154)}{(188-176)}\, x\left(height_{(J)} - 188\right)^3_+ -$$

$$0.261\, x\left(height_{(J)} - 67\right)^3_+ - \frac{(188-167)}{(188-176)}\, x\left(height_{(J)} - 176\right)^3_+ +$$

$$\frac{(176-167)}{(188-176)}\, x\, \left(height_{(J)} - 188\right)^3_+ + 0.009\, x\, age_{(j)} - 0.038\, x\, (age - 18)^3_+ -$$

$$\frac{(71-18)}{(71-52)}\, x\, \left(age_{(j)} - 35\right)^3_+ + \frac{(52-18)}{(71-52)}\, x\left(age_{(j)} - 71\right)^3_+ + 0.012\, x\, \left(age_{(j)} - 35\right)^3_+ -$$

$\frac{(71-35)}{(71-52)}\ x\ (age_{(j)}\ -52)_{+}^{3}+\frac{(52-35)}{(71-52)}\ x\ (age_{(j)}\ -71)_{+}^{3}+$

$0.344\ x\ \mathrm{I}(Non\ Insulin\ Dependent_{(j)})+0.539\ x\ I(Insulin\ Dependent_{(j)})]$

Validation of the Donor Intrinsic DQ-NAFLD Model

I conducted an internal validation to assess the performance of the final chosen model. The apparent performance of the model on the data used to fit the model will be better than the performance of the model in another set of data. The bootstrap approach described by Harrell et al. (1996) allows quantifying the overfitting or "optimism" inherent in predictive accuracy. I estimated the optimism by taking 1000 bootstrap samples with replacement from the full data and evaluating the difference between model performance in each bootstrap sample and model performance on the whole sample. I estimated the "optimism" as the average of these differences across 1000 bootstrap samples. I then subtracted the estimate of optimism from the naïve estimate of predictive ability to obtain the bias-corrected predictive ability.

Validation of model discrimination. Discrimination of the final model indicated by the Harrell's C-statistic represents the proportion of pairs of subjects that can be ordered such that the subject with higher predicted survival is the one who survived longer (not always possible, based on censoring). The C-statistic summarizes the predictive power of the DQ-NAFLD. The C-statistic ranges from 0.5 to 1.0, with higher values indicating greater discriminatory power, or the ability to separate more successful from less unsuccessful graft outcomes along the DQ-NAFLD scale. The apparent or naïve C-statistics was equal to 0.598, while the bootstrap optimism corrected C-statistics

was 0.587. A C-statistic nearly 0.60 is only moderately predictive. This result is consistent with other donor risk models since multiple factors are affecting graft survival not included in the DQ-NAFLD model. A model that accounts for more sources of variation would have a higher C-statistics. However, the goal of this intrinsic donor risk model was to summarize graft failure risk based on donor characteristics alone and not to describe all sources of variation (Rao et al., 2009).

Figure 24 displays the estimated relationship between DQ-NAFLD risk score calculated from the intrinsic model and log hazard ratio for graft failure at 1-year post LT.

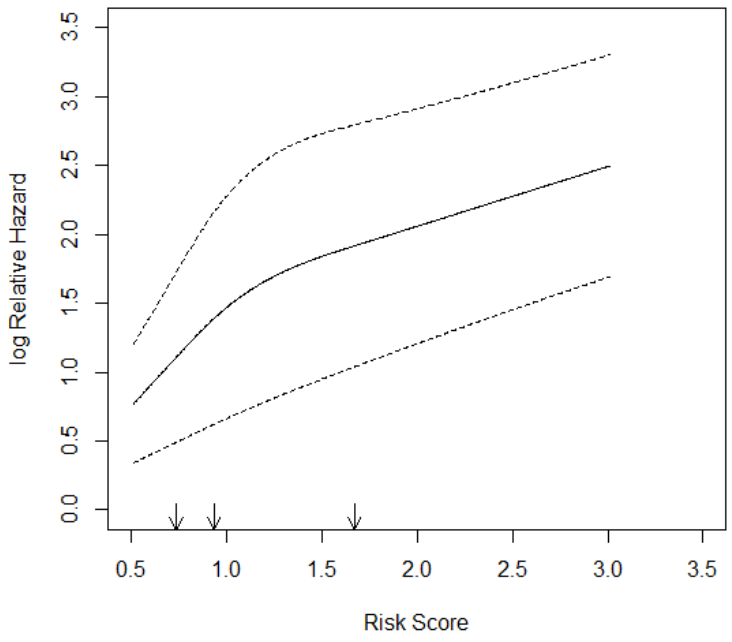

Figure 24. Restricted cubic spline estimates of the relationship between DQ-NAFLD risk score and log relative hazard of graft failure at 1-year post LT.
Note. Knots at 0.74, 0.93 and 1.67.

I estimated the relationship using a RCS with 3 knots at 0.71; 0.95; and 1.66. I further illustrated the discrimination of the final model by grouping patients in categories of the DQ-NAFLD risk score. I used the cutoffs of 0.71 (first knot) and 1.65 (third knot) obtained from the estimated spline transformation of the risk score to identify, low, medium, and high-risk donors. The Kaplan-Meier curves in Figure 25 show that the 1-year graft survival post LT was statistically significantly different across risk categories of the DQ-NAFLD score ($\chi^2(2) = 28.07$, $p < .0001$). After adjusting for multiple testing, recipients of high-risk donors based on the DQ-NAFLD score were more likely to experience liver graft failure within 1-year post LT, compared to medium risk (p <.0001) and low risk (p <.0001).

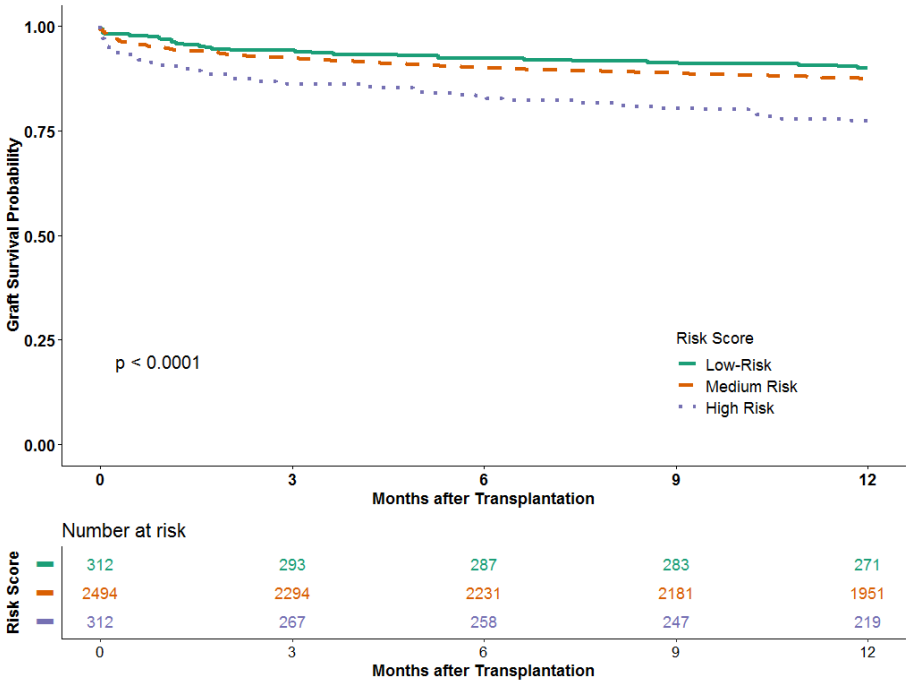

Figure 25. Kaplan-Meier graft survival by risk score.

Validation of model calibration. I validated the model for calibration accuracy in predicting the probability of graft surviving 1-year post LT. The model calibration plot in Figure 26 illustrates the agreement between observed and predicted estimated graft survival probability within 1-year post LT in the NAFLD/CC population. The blue curve in Figure 26 represents the estimated overfitting-corrected calibration curve. Well-calibrated models have a slope of 1, while models providing too extreme predictions have a slope less than one. The calibration curve slope indicates some overfitting. The bootstrap estimated calibration of slope shrinkage was 0.83, suggesting that about 17% of the fitted model is noise.

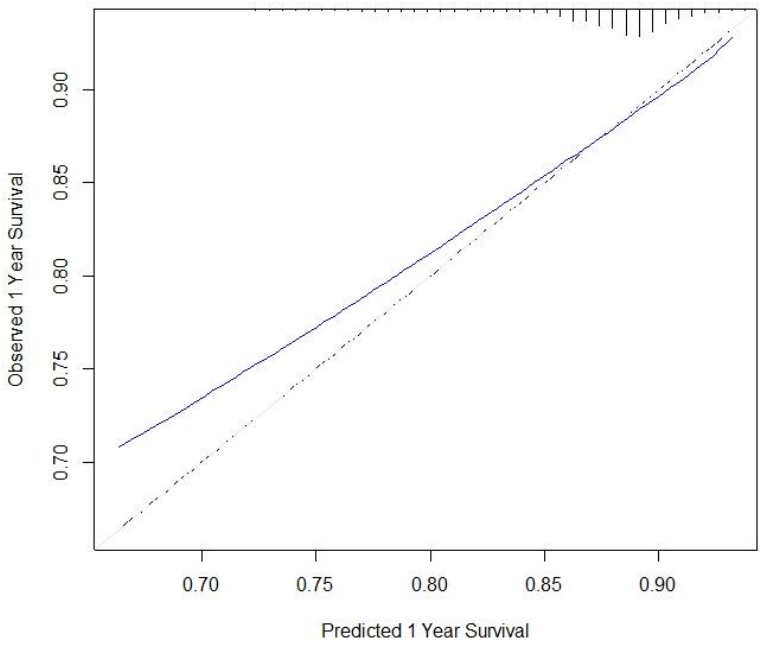

Figure 26. Bootstrap estimate of calibration accuracy for 1-year from the final Cox PH model.
Note. The blue curve corresponds to 1000 bootstrap corrected estimates.

Nomogram of the Intrinsic DQ-NAFLD Cox Model

I used the multivariable Cox PH model to build a nomogram depicted in Figure 27 for predicting 1-year graft survival probability. The nomogram shows the impact of each predictor on the outcome graphically. Points are assigned to each independent variable, donor age, donor MDRD, donor diabetes, DCD status, and donor height, according to the degree of their impact on graft survival. The nomogram allows estimating the probability of 1-year graft survival for a NAFLD/C recipient of LT when donor predictor variables are provided. The nomogram assigns to each independent donor variable in the model a point, and the total points are projected to a probability of graft survival scale that ranges for 0 to 1.

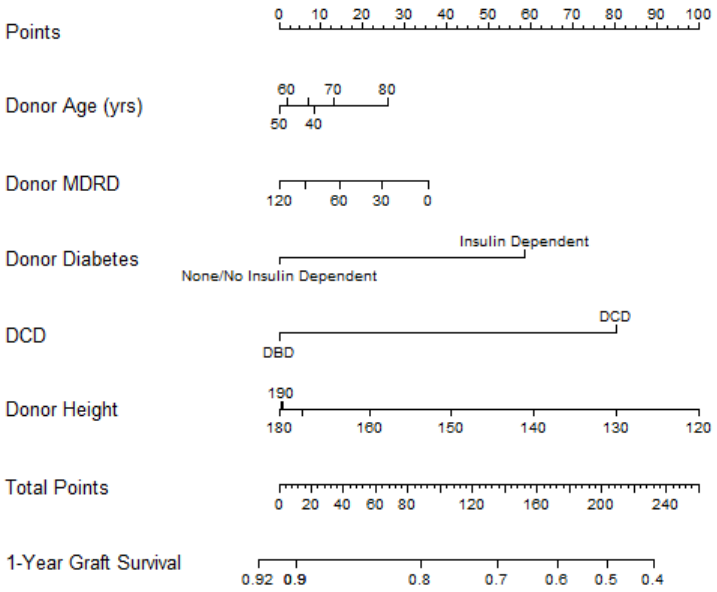

Figure 27. Nomogram from the fitted Cox PH model of intrinsic donor factors for predicting graft failure in NAFLD/CC.

The nomogram can be used to obtain manually predicted points for each subject from a regression model. Once the reader manually totals the points, the predicted values can be read at the bottom. For example, a recipient of LT from a donor who was 60-year-old (point 2), insulin dependent (points 62), DBD (points 0) with MDRD of 70 (points 15) and with a high of 170 (points 10), for a total of 86 points, had an estimated probability of liver graft survival at 1 year equal to 0.82.

Random Survival Forest (RSF)

RSF algorithm developed by Ishwaran et al. (2008) is a non-parametric tree-based learning machine method that, unlike the Cox PH model, requires no distributional assumption of the candidate predictors. RSF utilizes randomly selected bootstrap samples from the data to grow survival trees and can be used to identify and rank important risk factors for graft failure within 1-year posttransplant. I conducted an RSF based on trees grown from a sample of 3,165 NAFLD/CC recipients of LT and nine independent donor factors for the prediction of graft survival post LT. I created a random forest of 1000 survival trees with a pre-specified number of predictors randomly selected before each node split set to three, with node size set to 10, or terminating nodes with no fewer than ten observations. Table 23 summarizes details of the RSF parameters I used to grow the forest and the generalization error estimate from the forest. The overall estimated prediction error rate for the random survival forest was 35.26%.

Table 23

RFS Algorithm Result Using Random Log-Rank Splitting Criteria

Parameter	Value
Sample size	3115
Number of events	412
Number of trees	1000
Forest terminal node size	10
Average number of terminal nodes	219
Number of variables tried at each split	3
Total number of variables	9
Number of random split	10
Error rate	35.26%

Out-of-bag prediction error. Each bootstrap sample selects approximately 63.2% of the data to train each tree. As the RSF is built, the remaining 36.8% of observations (the Out-of-Bag (OOB) sample), can be used to test each tree and estimate the OOB error, which is an unbiased estimate of the true error, a measure of the predictive ability of the forest (Breiman, 1996). Hastie, Tibshirani, and Friedman (2009) showed that the OOB prediction error estimates are almost identical to n–fold cross validation estimates. This feature of the RSF allows obtaining internal model fit and validation in the same algorithm. Figure 28 depicts the RSF generalization error as a function of the number of trees and shows that the forest tends to stabilize after a few hundred trees. The OOB error estimate was 35.26%, indicating that the forest was reasonably good in predicting 1-year graft survival post LT. The OOB Harrell's C-statistics was .64, indicating a better predictive ability of the RSF, compared to the Cox PH model.

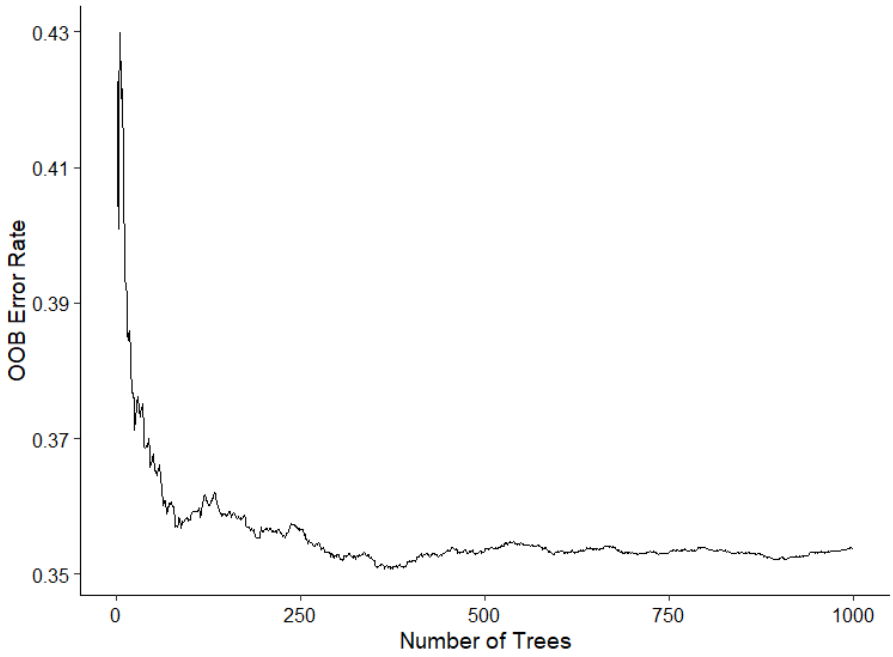

Figure 28. The OOB error for RSF for 1000 trees.

Variable importance in random survival forests. I used the RSF to assess the relative importance of variables. I considered two different criteria of ranking variables: variable importance (VIMP), and minimal depth. VIMP ranks the most important variables according to their impact on the predictive ability of the forest, and minimal depth assumes that variables with high predictive impact are those that most frequently split at the root node. Figure 29 illustrates the VIMP and the minimum depth plots showing the top variables contributing to the predictive accuracy of the forest, with higher values indicating more importance for the VIMP measures and lower values more importance for the minimal depth measure. Table 24 summarizes the ranking of variables. Donor sex, hypertension, and hyponatremia were the least important factors

based on both criteria. The top donor's variables averaging the two measurements were height, age, MDRD, diabetes, and DCD.

Table 24

Results for the Variable Importance Measures for Donor's Characteristics

Variable	Depth	Depth rank	VIMP	VIMP rank
Height (cm)	1.75	1	0.038	3
Diabetes	1.75	2	0.020	5
DCD	1.87	3	0.017	6
Age (yrs.)	1.92	4	0.039	2
MDRD	1.96	5	0.042	1
Cause of death	2.43	6	0.026	4
Sex	3.92	7	0.017	7
Hypernatremia	4.09	8	0.005	9
Hypertension	4.26	9	0.014	8

Note. Variables considered in the RSF for NAFLD/CC recipients of LT.

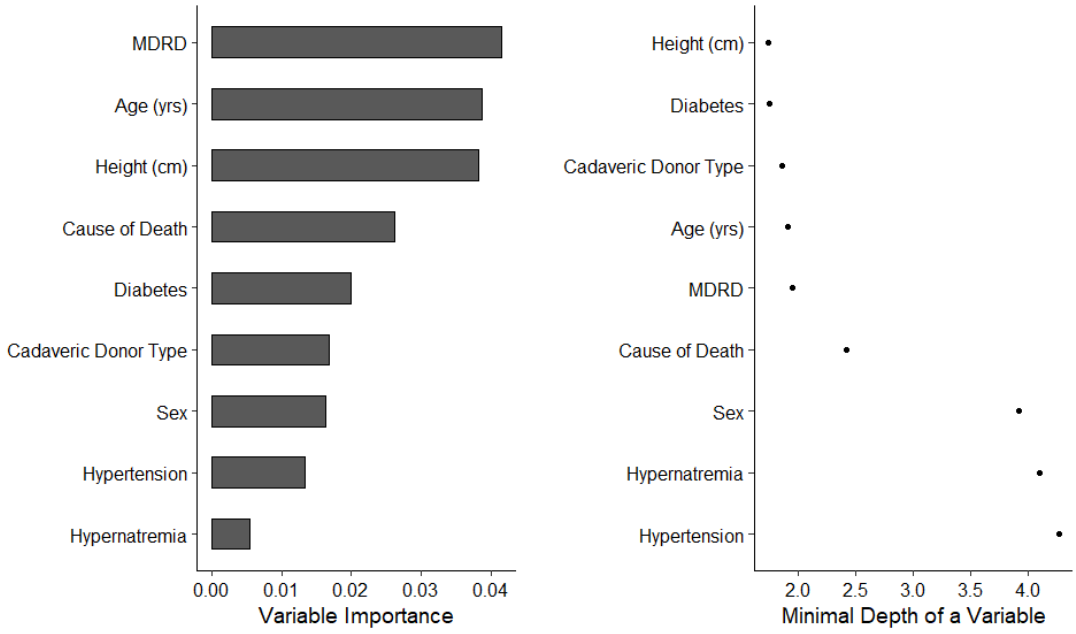

Figure 29. Variable importance, minimal variable depth of donor characteristics using RSF to model liver graft failure for NAFLD/CC.

Variable dependence. Although the RSF is considered a "black box" approach, graphical methods can help examine the dependency of the forest prediction on the independent variables. Variable dependence plots show the predicted response relative to a covariate of interest. The top donor's variables identified using minimal depth, and VIMP that contributed most to the predictive accuracy of the forest were further analyzed to explore how the forest predicted graft failure or death depends on these variables. Figures 30 illustrates the relationship among height, cadaveric donor type, age, and MDRD on 1-year graft survival post LT for NAFLD/CC patients. Blue circles events and red dots indicate censored cases, i.e., graft failure or death within 1-year. Boxplots indicate the distribution of predicted survival for all cases within each cadaveric donor

group (Figure 30) or diabetes group (Figure 31) and show that recipients of DCD donors or recipients of insulin-dependent diabetes have lower predicted graft survival. Variable dependence of predicted 1-year graft survival on continuous variables, donor's height, age, and MDRD are depicted in Figure 30. Censored cases are marked in red and events in blue. Loess smooth curve indicates the survival trend with increasing values. Recipients of donors taller than 160 cm, with high MDRD and younger than 60 years have higher predicted graft survival within 1-year post LT. Variable dependence can be interpreted only in general terms as a graft survival prediction for a patient, as a function of the values of all covariates in that particular patient.

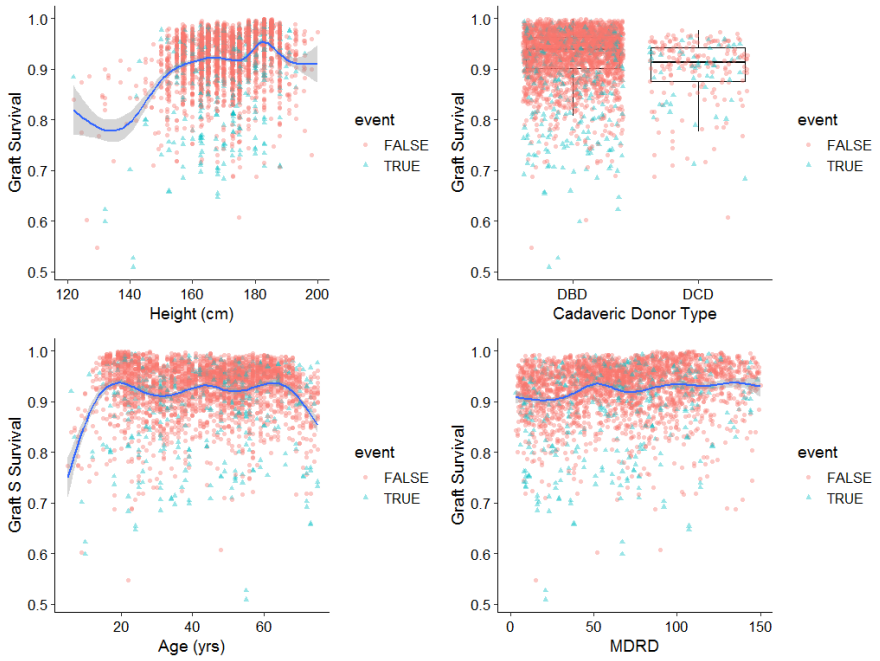

Figure 30. Variable dependence of 1-year graft survival post LT on height, cadaveric donor type, age and MDRD.

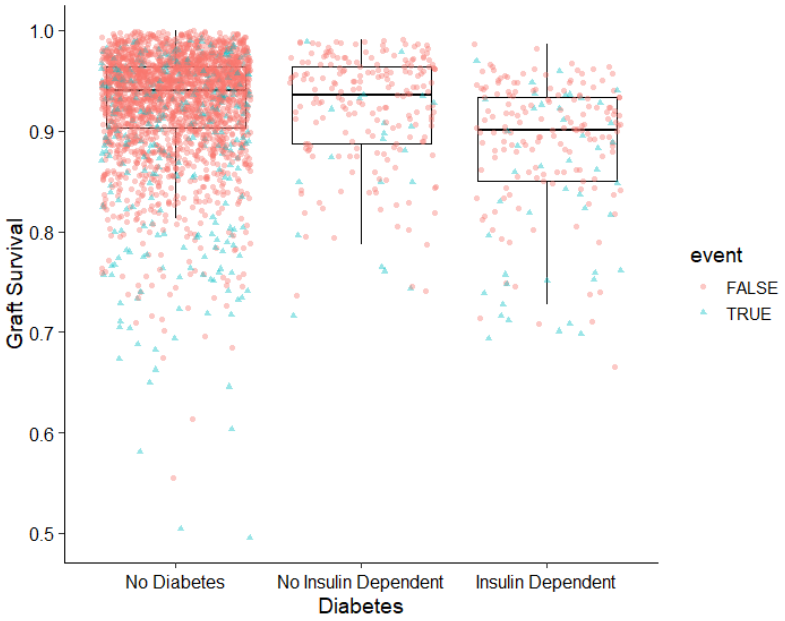

Figure 31. Variable dependence of 1-year graft survival post LT on diabetes.

Research Question 2

The second research question was based on whether there are relationships between post-transplant graft survival among NAFLD/CC recipients and transplant factors (cold ischemia time, ABO matching, and size matching). Univariate analyses showed that ABO compatibility and CIT modeled as RCS with four knots were both not statistically significantly associated with graft survival at 1-year post LT. The CIT, a significant predictor of graft survival in other studies (Feng et al., 2006), although not significant, was included in the model because of clinical relevance. The overall significance of the Cox PH model or the model goodness of fit was tested using the likelihood ratio test (χ^2 (6) = 49.21, p <.0001), indicating that the model was statistically

significant and adequate in predicting the graft survival experience of a NAFLD/CC recipients of LT.

ABO continued to be not statistically significant when adjusted for CIT and size match. Compared to normal for size grafts, livers large for size (AHR=1.52, 95% CI=1.15, 2.02) was associated with an increased risk of graft failure of 52% within 1-year post LT (Table 25). Table 25 shows the estimated coefficients of transplant-related predictors of graft survival at 1-year post LT, including each parameter used in the splines, and the AHRs along with the 95% CIs. Figure 32 provides a useful interpretation of association between CIT and the adjusted relative hazard and show that, after adjusting for ABO and size match at their reference category, for each value of the CIT, the 95% CI of the estimated AHR includes one, indicating that CIT is not statistically significantly associated with the hazard of graft failure at 1-year post LT.

Table 25

Multivariate Cox PH Model for Transplant Variables Predicting Liver Graft Failure.

Variable	Estimated β SE (β)	Wald χ^2	AHR (95% CI)
ABO compatibility			
ABO compatible	Reference		
ABO incompatibility	-.121 (.501)	-0.24	1.28 (0.78, 2.01)
Donor/recipient size match			
Normal for size	Reference		
Small for size	.069 (.164)	0.42	1.07 (0.78, 1.48)
Large for size	.423 (.144)	2.92	1.52 (1.15, 2.02)***
CIT linear	.042 (.011)	0.39	0.97 (0.86, 1.01)
CIT’	-.114 (.421)	-0.27	1.45 (0.94, 2.23)
CIT’’	.389 (1.266)	0.31	0.31 (0.09, 1.05)

Note. NAFLD/CC recipients (n=3165). β =estimated coefficient of Cox PH model, SE=standard error, AHR=adjusted hazard ratio, CI=confidence interval.
***p<.001

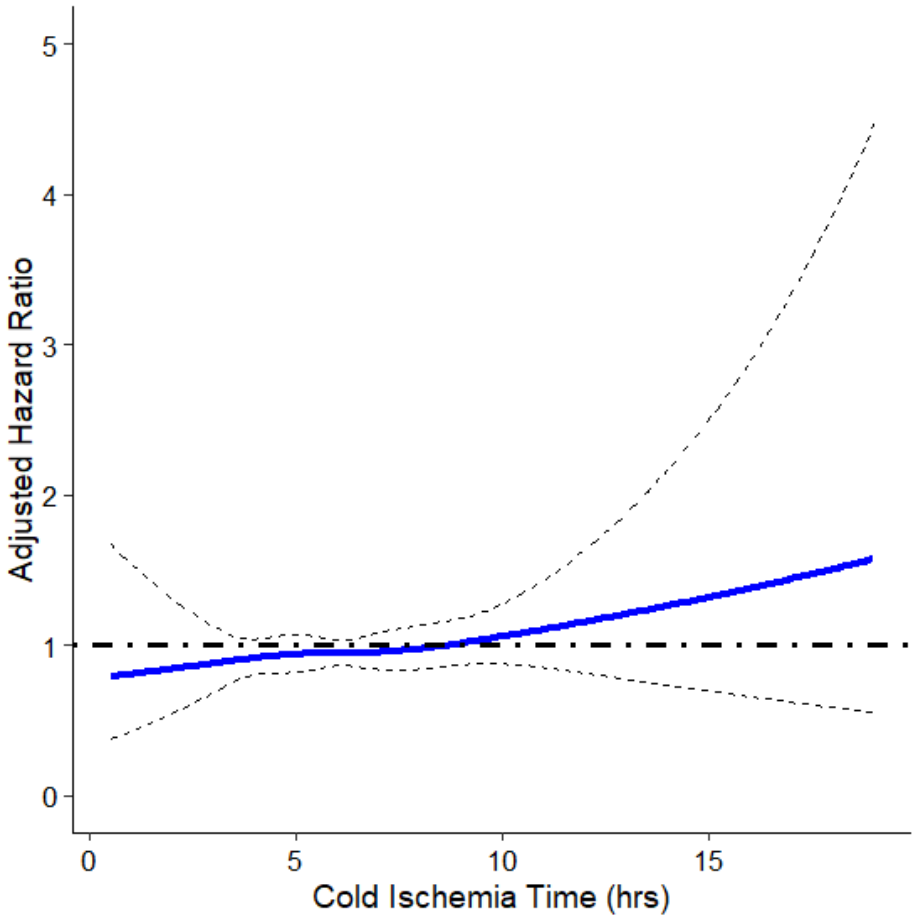

Figure 32. Restricted cubic splines of the association between CIT and relative hazard of graft failure at 1-year post LT.
Note. The model is adjusted for the following variables set at reference category: ABO compatibility (compatible), donor/recipient size match (normal for size).

Research Question 3

Research question three explores the relationships between post-transplant graft survival among NAFLD/CC recipients and a number of donor characteristics (age, gender, height, weight, BMI, the cause of death, hypertension, diabetes, donor after circulatory death, HCV status, HBsAb status, HBsAg status, MDRD, hypernatremia) and

transplant factors (CIT, ABO matching, size matching) after adjusting for characteristics of recipients of liver transplant (age, gender, biological MELD).To answer the third research question, I developed an extended version of the intrinsic donor model that included in addition to donor factors, recipient and transplant factors. At the first step, I used a priori information based on subject-specific knowledge and literature review to derive a working set of candidate independent variables known as relevant predictors or covariates for the study question to consider during statistical modeling. Next, I excluded variables whose distributions were too narrow or with a substantial amount of missing data, and this led to a final list of candidate predictors. I used Cox PH regression to examine the association between selected donor, recipient and transplant variables, and with the outcomes.

Model Building

The pre-specified list of candidate predictors included donors' age, gender, diabetes, MDRD, hypertension, hypernatremia, the cause of death, and donor DCD, recipient's age, gender, and biological MELD, organ size match, ABO compatibility, and cold ischemia time. To reduce the number of predictors in the final model, I applied an augmented backward elimination in 1000 bootstrap samples drawn from the original data, with the level of significance 'α' set to 0.2 and the threshold of the relative change-in-estimate criterion 'τ' set to 0.1 (Dunkler, Plischke, Leffondré, & Heinze, 2014). This strategy allowed to include into the model regardless of their statistical significance donor age, DCD and CIT, as known predictors of graft failure.

The total number of complete cases included 3,118 recipients of LT, while 47 or 1.5% of cases were missing. I conducted a complete case analysis, and there were no significant interactions. The final selected parsimonious model included eight predictors from the initial set: recipient's age and MELD score, donor's age, DCD, MDRD, diabetes, donor/recipient size match, and CIT. The overall likelihood ratio test was $\chi^2(19) = 70.91$ ($p < .0001$). This test evaluates the omnibus null hypothesis that all model coefficients were 0, which was rejected against the alternative hypothesis that the selected Cox PH regression model was statistically significant, and adequate in explaining the graft survival experience of NAFLD/CC recipients of LT patients.

I used smoothing transformations of continuous predictors to relax the linearity assumption and prevent residual confounding. I tested the model distributional assumption using smoothed scaled Schoenfeld residuals for each predictor and graphical visualization. I did not observe any trends against the log of time. The global test of proportional hazard ($p=.08$) supported the validity of the proportional hazard assumption at the $\alpha=.05$ level of significance.

Model Selected

The independent variables selected in the final model included: recipient's age and MELD score, donor's age, DCD, MDRD, diabetes, donor/recipient size match, and CIT. Harrell (2015) suggested as a rule of thumb that at least 10–20 events are needed per degree of freedom. The study sample included 412 events and approximately 20 degrees of freedom to spend-to-fit the model, which used 19 degrees of freedom. The available

effective sample size was sufficiently large to allow the fit of an initial saturated pre-specified model, where I considered all predictors, including the non-significant in the univariate analysis. I tested the overall significance of the Cox PH model or the model goodness of fit using the likelihood ratio test with $\chi^2(19) = 70.91$, $p < .0001$), indicating that the model was statistically significant and adequate in predicting the graft survival experience of a NAFLD/CC recipients of LT.

The results of the Cox regression model selected presented in Table 26 include the estimated coefficients, the standard errors as well as the AHRs along with the 95% CIs of each categorical predictor, for each parameter used in the splines. Recipients of livers from donors with insulin-dependent diabetes were almost twice more likely to lose their liver allograft within 1-year post LT (AHR=1.77, 95% CI=1.27, 2.46), compared to recipients of donors with no diabetes. Receiving a DCD liver allograft was associated with a 2.5-fold increased risk of graft failure (AHR=2.51, 95% CI=1.83, 3.46). NAFLD/CC recipients of large for size livers were 1.4 times more likely to lose their liver allograft or die within 1-year post LT than recipients of normal for size donors (AHR=1.45, 95% CI=1.08, 1.92). The final RCS Cox regression model results presented in Table 26, include estimated coefficients for each parameter used in the splines that do not have an immediate interpretation.

Table 26

Multivariate Cox PH Model for Donor, Recipient and Transplant Variables Predicting Liver Graft Failure

Exposure	Estimated β SE(β)	Wald χ^2	AHR (95% CI)
Donor age linear	-0.004 (0.014)	-0.29	1.00 (0.91, 1.02)
Donor age'	0.007 (0.044)	0.16	1.01 (0.92, 1.02)
Donor age''	0.002 (0.123)	0.01	1.00 (0.79, 1.27)
MDRD linear	-0.004 (0.003)	-1.74	1.00 (0.99, 1.00)
Mdrd'	0.002 (0.003)	0.99	1.00 (1.00, 1.00)
Donor diabetes			
Non-diabetic	Reference		
Non-insulin dependent	-0.313 (0.231)	-1.36	0.73 (0.46, 1.15)
Insulin dependent	0.572 (0.168)	3.41	1.77 (1.27, 2.46)***
Cadaveric donor type			
DBD	Reference		
DCD	0.922 (0.162)	5.69	2.51 (1.83, 3.46)**
CIT	-0.007 (0.109)	-0.07	0.99 (0.80, 1.23)
CIT'	0.083 (0.423)	0.20	1.09 (0.47, 2.49)
CIT ''	-0.118 (0.285)	-0.09	0.89 (0.07, 11.03)

(*table continue*)

Exposure	Estimated β SE(β)	Wald χ^2	AHR (95% CI)
Donor/recipient size			
Normal for size	Reference		
Small for size	0.149 (0.168)	0.89	1.16 (0.84, 1.61)
Large for size	0.369 (0.147)	2.52	1.45 (1.08, 1.92)
MELD			
MELD <15	Reference		
MELD score 15-24	-0.169 (0.151)	-1.12	0.84 (0.63, 1.13)
MELD score 25-34	0.199 (0.160)	1.24	1.22 (0.89, 1.67)
MELD score ≥35	0.285 (0.171)	1.66	1.33 (0.95, 1.86)
Recipient age linear	-0.002 (0.015)	-0.12	0.99 (.97, 1.10)
Recipient age'	0.037 (0.029)	1.25	1.04 (.98, 1.01)
Recipient age ''	-0.248 (0.226)	-1.10	0.78 (.50, 1.21)

Note. NAFLD/CC recipients (n=3,115), β =estimated coefficient of Cox PH model, SE=standard error, AHR=adjusted hazard ratio, CI=confidence interval.
* p<.05, ** p<.01, *** p<.001

Tables 27-29 provide a useful interpretation of RCS. After fitting a Cox PH model that includes splines, I computed hazard ratios by comparing specific values of a continuous variable, with a single reference value. I calculated AHRs, and 95% CIs constructed from splines for donor age (Table 27), for CIT (Table 2), and donor MDRD (Table 28), at selected predictor values. From Table 28, compared to a reference donor

with MDRD of 69, liver allografts from donors with an MDRD of 30 provided an increase in the risk of graft failure within 1-year post LT of 17% (ARH=1.17, 95% CI= 1.01, 1.37).

Table 27

Estimated AHRs and 95% CI for Selected Values of Donor Age from the Multivariate Cox PH Regression

Selected donor age (yrs.)	ARH	95% CI
20	1.05	(0.80, 1.39)
30	1.01	(0.85, 1.21)
45	Reference	
60	1.09	(0.92, 1.28)

Note. AHR=adjusted hazard ratio, CI=confidence interval.

Table 28

Estimated AHRs and 95% CI for Selected Values CIT from the Multivariate Cox PH Regression

Selected CIT (hrs.)	AHR	95% CI
3	0.98	(0.72, 1.35)
5	0.98	(0.89, 1.08)
5.9	Reference	
10	1.24	(0.98, 1.58)

Note. AHR=adjusted hazard ratio, CI=confidence interval.

Table 29

Estimated AHRs and 95% CI for Selected Values of MDRD from the Multivariate Cox PH Regression

Selected MDRD	ARH	95% CI
30	1.17	(1.00, 1.37)
45	1.08	(0.84, 1.39)
60	1.03	(1.00, 1.06)
69	Reference	
80	0.96	(0.94, 0.99)
90	0.94	(0.91, 0.98)

Note. AHR=adjusted hazard ratio, CI=confidence interval.

Figures 33-35 show the predicted relative risk of graft failure as a function of donor age, CIT, and donor MDRD, holding all other variables constant at representative levels (DBD, no diabetes, 45-year old, donor MDRD of 69, CIT of 5.9) by MELD score. The solid blue line represents the estimated adjusted hazard ratio or relative risk for the Cox regression model with restricted cubic splines and dashed lines represent the 95% confidence interval of the estimate. If the 95% confidence interval includes 1, the hazard ratio is not significant. I did not observe any association between donor age and 1-year graft survival in each MELD score category (Figure 33). Decreased CIT is associated with improved 1-year graft survival for recipients for MELD score 15-24 (Figure 34).

Figure 35 (A and B) shows that the relative risk of graft failure increases as MDRD decreases, respectively, for MELD score <15 and MELD score 15-24. No association between MDRD and the risk of 1-year graft failure for other MELD score categories.

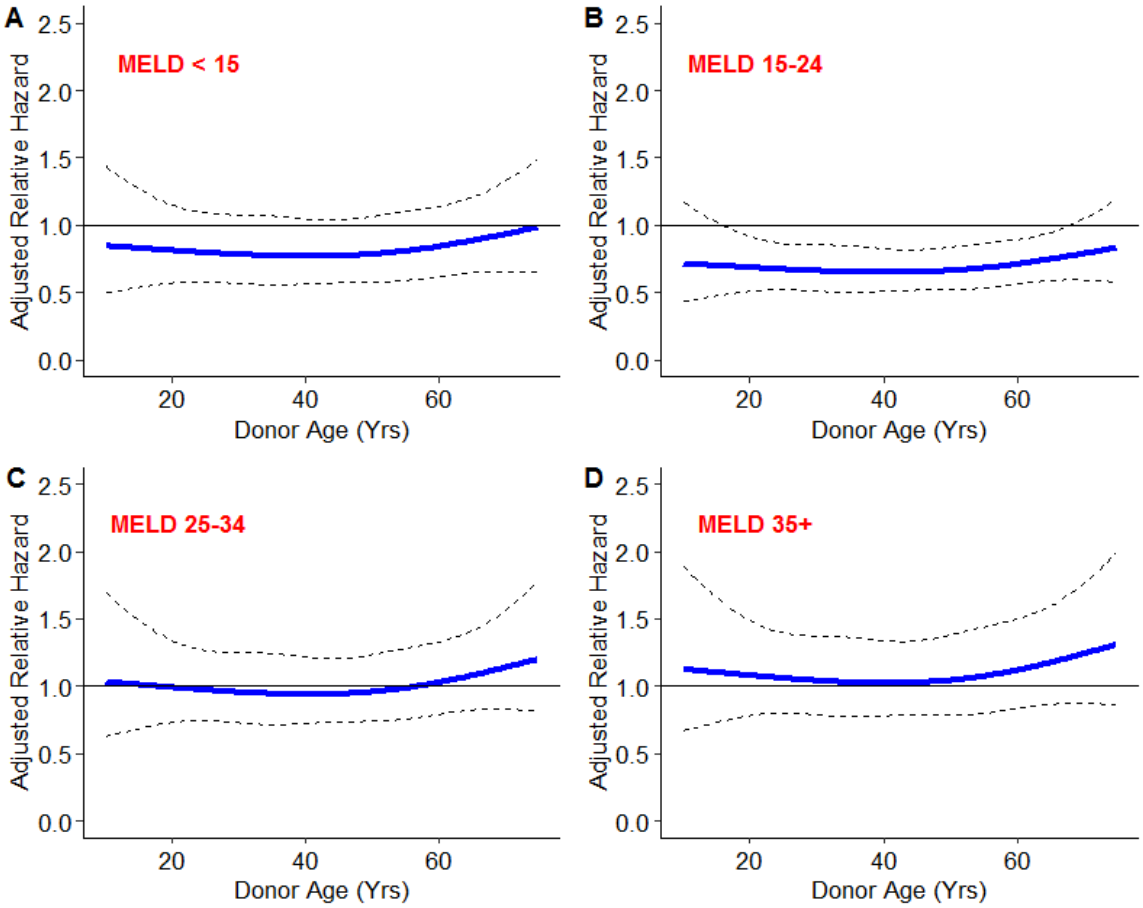

Figure 33. RCS relationships between donor age (yrs.) adjusted to reference values by MELD score: <15 (A), 15-24 (B), 25-34 (C), > 35 (D).
Note. The model is adjusted for the following variables set at reference category: donor type (DBD), diabetes (No), or median category: MDRD (69), normal for size donors, and CIT of 5.9 hours.

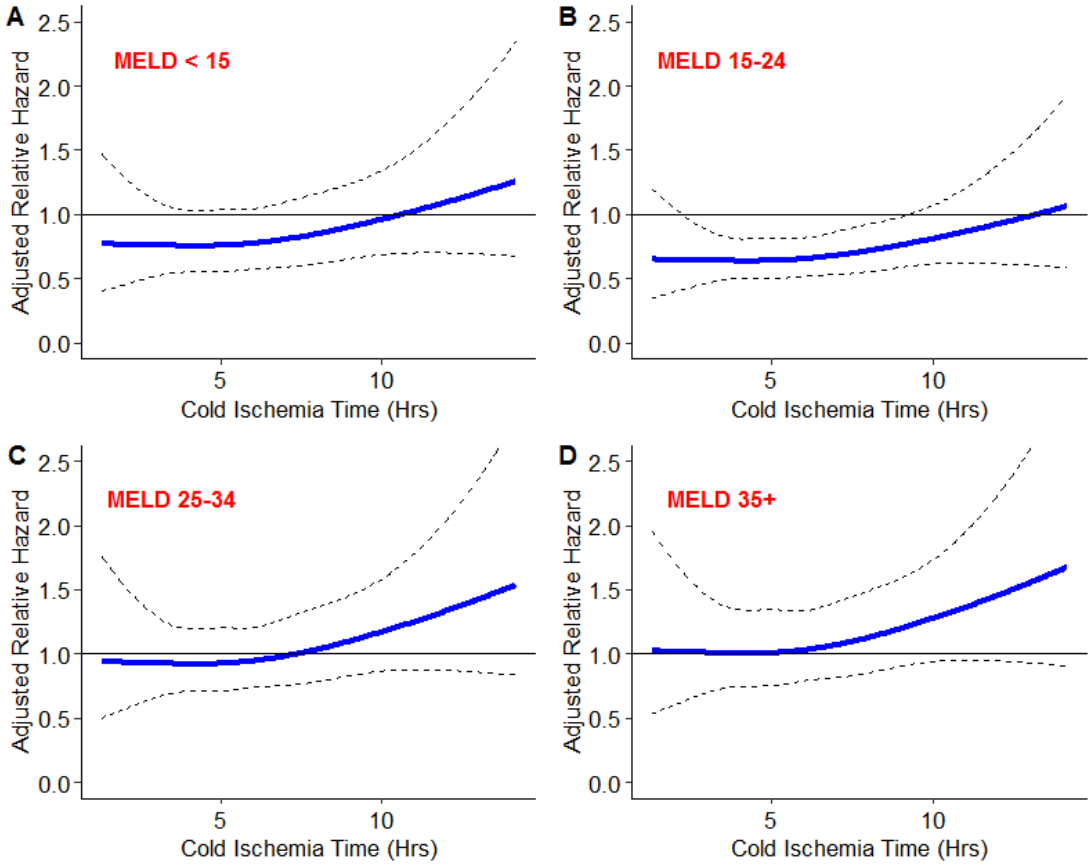

Figure 34. RCS relationships between CIT (hrs.) adjusted to reference values by MELD score: <15 (A), 15-24 (B), 25-34 (C), > 35 (D).
Note. The model is adjusted for the following variables set at reference category: donor type (DBD), diabetes (No), or median category: MDRD (69), donor age (45 yrs.), and normal for size donors.

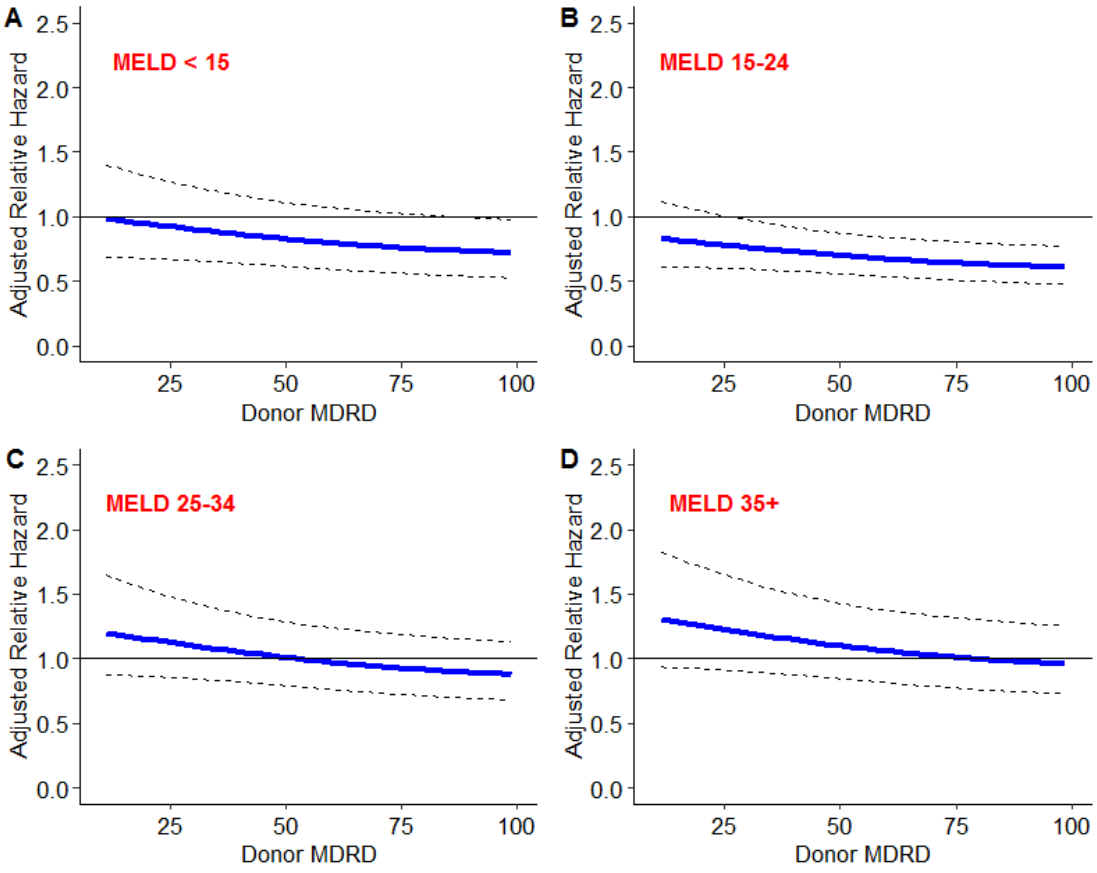

Figure 35. RCS relationships between donor MDRD adjusted to reference values by MELD score: <15 (A), 15-24 (B), 25-34 (C), > 35 (D).
Note. The model is adjusted for the following variables set at reference category: donor type (DBD), diabetes (No), or median category: donor age (45 yrs.), normal for size donors, and CIT of 5.9 hours.

The extended DQ-NAFLD risk score is an estimate of the relative risk of posttransplant graft failure for an adult recipient from a particular cadaveric donor, compared to a reference 45-year old donor, DBD, with a height of 172 cm, with no

diabetes and MDRD of 69, with an estimated graft normal for size, a 60-year old recipient with MELD score between 15 and 24, and with CIT of 5.9 hours. The Cox PH model assumes that the risk for subject j is:

$$\lambda(t|x_j) = \lambda_0(t) r_j(t)$$

I used the coefficients of the Cox PH model in conjunction with individual covariates to estimate extended DQ-NAFLD risk score for an individual. The risk score for a subject 'j' is the hazard ratio for that person relative to the baseline, as shown in Equation 11:

$$\begin{aligned} Extended\ DQ - NAFLD_{(j)} \quad (11) \\ = \exp\big(&\beta_1\, x\ Donor\ Age_{(j)} + \beta_2\, x\ Donor\ Age'_{(j)} + \beta_3\, x\ Donor\ Age''_{(j)} \\ &+ \beta_4\, x\ MDRD_{(j)} + \beta_5\, x\ MDRD^{i}_{(j)} + \beta_6 x\ I\big(Non\ Insulin\ Dependent_{(j)}\big) \\ &+ \beta_7 x\ I(Insulin\ Dependent_{(j)}) + \beta_8\, x\ I(DCD_{(J)}) + \beta_9\, x\ CIT_{(J)} \\ &+ \beta_{10}\, x\ CIT'_{(j)} + \beta_{11}\, x\ CIT''_{(j)} \\ &+ \beta_{12}\ x\ I\big(Small\ for\ Size_{(j)}\big) + \beta_{13} x\ I(Large\ for\ Size) \\ &+ \beta_{14}\, x\ I(MELD\ (15-24)_{(j)}) + \beta_{15}\, x\ I(MELD\ (25-34)_{(j)}) \\ &+ \beta_{16}\, x\ I(MELD\ (\geq 35)_{(j)}) + \beta_{17}\, x\ Recipient\ Age_{(j)} \\ &+ \beta_{18}\, x\ Recipient\ Age'_{(j)} + \beta_{19}\, x\ Recipient\ Age''_{(j)}\ \big) \end{aligned}$$

Where I(e)=1 if the event is true, I(e)=0 otherwise

$for\ j=1....n$

I expressed the predictors: donor age, MDRD, CIT and recipient age as RCSs.

I modeled the predictor donor age as RCS with four knots, $t_1 = 18$, $t_2 = 35$, $t_3 = 52$, $t_4 = 71$. The nonlinear terms are:

$$Donor\ Age'_{(j)} = (Donor\ Age_{(j)} - t_1)^3_+ - \frac{(t_4 - t_1)}{(t_4 - t_3)}\ x\ \left(Donor\ Age_{(j)} - t_2\right)^3_+ + \frac{(t_3 - t_1)}{(t_4 - t_3)}\ x\ \left(Donor\ Age_{(j)} - t_4\right)^3_+$$

$$Donor\ Age''_{(j)} = (Donor\ Age_{(j)} - t_2)^3_+ - \frac{(t_4 - t_2)}{(t_4 - t_3)}\ x\ \left(Donor\ Age_{(j)} - t_3\right)^3_+ + \frac{(t_3 - t_2)}{(t_4 - t_3)}\ x\ \left(Donor\ Age_{(j)} - t_4\right)^3_+$$

I modeled the predictor MDRD as RCS with three knots, $t_1 = 17$, $t_2 = 69$, $t_3 = 137$. The nonlinear term is:

$$MDRD^i_{(j)} = (MDRD_{(j)} - t_1)^3_+ - \frac{(t_3 - t_1)}{(t_3 - t_2)}\ x\ \left(MDRD_{(j)} - t_2\right)^3_+ + \frac{(t_2 - t_1)}{(t_3 - t_2)}\ x\ \left(MDRD_{(j)} - t_3\right)^3_+$$

I modeled the predictor CIT as RCS with four knots, $t_1 = 3.1$, $t_2 = 5.1$, $t_3 = 6.6$, $t_4 = 10$. The nonlinear terms are:

$$CIT'_{(j)} = (CIT_{(J)} - t_1)^3_+ - \frac{(t_4 - t_1)}{(t_4 - t_3)}\ x\ \left(CIT_{(J)} - t_2\right)^3_+ + \frac{(t_3 - t_1)}{(t_4 - t_3)} x\ \left(CIT_{(J)} - t_4\right)^3_+$$

$$CIT''_{(j)} = (CIT_{(J)} - t_2)^3_+ - \frac{(t_4 - t_2)}{(t_4 - t_3)} x\ \left(CIT_{(J)} - t_3\right)^3_+ + \frac{(t_3 - t_2)}{(t_4 - t_3)}\ x\ \left(CIT_{(J)} - t_4\right)^3_+$$

I modeled the predictor recipient age as RCS with four knots, $t_1 = 42$, $t_2 = 57$, $t_3 = 64$, $t_4 = 70$. The nonlinear terms are:

$$Recipient\ Age'_{(j)}$$

$$= (Recipient\ Age_{(j)} - t_1)_+^3 - \frac{(t_4 - t_1)}{(t_4 - t_3)} x \left(Recipient\ Age_{(j)} - t_2\right)_+^3$$

$$+ \frac{(t_3 - t_1)}{(t_4 - t_3)} x \left(Recipient\ Age_{(j)} - t_4\right)_+^3$$

$$Recipient\ Age''_{(j)}$$

$$= (Recipient\ Age_{(j)} - t_2)_+^3 - \frac{(t_4 - t_2)}{(t_4 - t_3)}\ x \left(Recipient\ Age_{(j)} - t_3\right)_+^3$$

$$+ \frac{(t_3 - t_2)}{(t_4 - t_3)}\ x \left(Recipient\ Age_{(j)} - t_4\right)_+^3$$

Where $(z)_+$ is equal to z if z > 0, and 0 otherwise.

Replacing the estimated model coefficients, Equation 11 is obtained:

$$Extended\ DQ - NAFLD_{(j)}$$

$$= \exp\Bigg(-0.004\ x\ Donor\ Age_{(j)}$$

$$+ 0.007\ x\ \Bigg(\left(Donor\ Age_{(j)} - t_1\right)_+^3 - \frac{(t_4 - t_1)}{(t_4 - t_3)}\ x\ \left(Donor\ Age_{(j)} - t_2\right)_+^3$$

$$+ \frac{(t_3 - t_1)}{(t_4 - t_3)}\ x\ \left(Donor\ Age_{(j)} - t_4\right)_+^3\Bigg)$$

$$+ 0.002\ x\ \Bigg(\left(Donor\ Age_{(j)} - t_2\right)_+^3 - \frac{(t_4 - t_2)}{(t_4 - t_3)}\ x\ \left(Donor\ Age_{(j)} - t_3\right)_+^3$$

$$+ \frac{(t_3 - t_2)}{(t_4 - t_3)}\ x\ \left(Donor\ Age_{(j)} - t_4\right)_+^3\Bigg) - 0.004\ x\ MDRD_{(j)}$$

$$+ 0.002\ x\ \Bigg(\left(MDRD_{(j)} - t_1\right)_+^3 - \frac{(t_3 - t_1)}{(t_3 - t_2)}\ x\ \left(MDRD_{(j)} - t_2\right)_+^3$$

$$+ \frac{(t_2 - t_1)}{(t_3 - t_2)}\ x\ \left(MDRD_{(j)} - t_3\right)_+^3\Bigg)$$

$$- 0.313\ x\ I\left(Non\ Insulin\ Dependent_{(j)}\right)$$

$$+\ 0.572\ x\ I(Insulin\ Dependent_{(j)}) +\ 0.922\ \ x\ I(DCD_{(J)})$$

$$- 0.07\ \ x\ CIT_{(J)} + 0.083\ x\ (\left(CIT_{(J)} - t_1\right)_+^3 - \frac{(t_4 - t_1)}{(t_4 - t_3)}\ x\ \left(CIT_{(J)} - t_2\right)_+^3$$

$$+ \frac{(t_3 - t_1)}{(t_4 - t_3)} x\ \left(CIT_{(J)} - t_4\right)_+^3) - 0.118\ x(\left(CIT_{(J)} - t_2\right)_+^3$$

$$- \frac{(t_4 - t_2)}{(t_4 - t_3)} x\ \left(CIT_{(J)} - t_3\right)_+^3 + \frac{(t_3 - t_2)}{(t_4 - t_3)}\ x\ \left(CIT_{(J)} - t_4\right)_+^3)$$

$$+ 0.149\ x\ I\left(Small\ for\ Size_{(j)}\right) +\ 0.369x\ I(Large\ for\ Size)$$

$$- 0.169\ x\ I(MELD\ (15-24)_{(j)}) + \ 0.199\ x\ I(MELD\ (25-34)_{(j)})$$
$$+\ 0.285\ x\ I(MELD\ (\geq 35)_{(j)}) - 0.002\ x\ Recipient\ Age_{(j)}$$
$$+ 0.037\ x\ Recipient\ Age'_{(j)} - 0.248\ x\ Recipient\ Age''_{(j)} \Big)$$

Model Validation

I performed the internal validation to assess the performance of the final chosen model. The bootstrap approach described by Harrell et al. (1996) allows quantifying the overfitting or "optimism" inherent in predictive accuracy. I estimated the optimism by taking 1000 bootstrap samples with replacement from the full data and evaluating the difference between model performance in each bootstrap sample and on the whole sample. I estimated the optimism as the average of these differences across 1000 bootstrap samples. I then subtracted this estimate of optimism from the naïve estimate of predictive ability to obtain the bias-corrected predictive ability.

Validation of model discrimination. Discrimination of the final model indicated by the Harrell's C-statistic represents the proportion of pairs of ordered subjects such that the subject with higher predicted survival is the one who survived longer. The C-statistic summarizes the predictive power of the DQ-NAFLD and ranges from 0.5 to 1.0. High values indicate greater discriminatory power, or the ability to separate "more successful" from "less unsuccessful" graft outcomes along the DQ-NAFLD scale. According to 1000 bootstrap samples, the apparent or naïve C- statistics was equal to .613, and the bootstrap optimism corrected C-statistics was .601. The extender DQ-NAFLD model provides only a slight improvement in accuracy, compared to the donor intrinsic DQ-NAFLD model. A

C-statistic nearly 0.60 is only moderately predictive. This ted result is consistent with other donor risk models since multiple factors not included in the DQ-NAFLD model affects graft survival.

Figure 36 displays the estimated relationship between DQ-NAFLD risk scores calculated from the extended model and log-hazard ratio for graft failure at 1-year post LT. The relationship was estimated using an RCS with three knots at 0.62, 0.69 and 1.73. I used the cutoffs of 0.62 (first knot), and 1.73 (third knot) obtained from the estimated spline transformation of the risk score to identify low, medium, and high-risk donors.

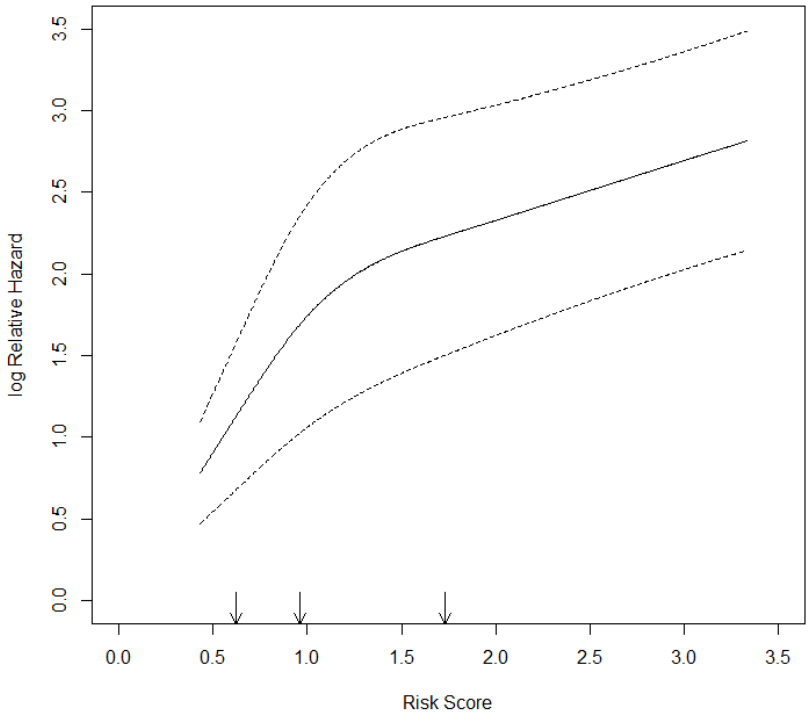

Figure 36. Restricted cubic spline estimates of the relationship between the extended DQ-NAFLD risk score and log relative hazard of graft failure at 1-year post LT.
Note. Knots at 0.62, 0.96 and 1.73.

The Kaplan-Meier curves and log-rank test in Figure 37 show that the 1-year graft survival post LT was statistically significantly different across risk categories of the DQ-NAFLD score ($\chi^2(2) = 45.4$, $p < .0001$). After adjusting for multiple testing, recipients of high-risk donors based on the DQ-NAFLD score were more likely to experience liver graft failure within 1-year post LT, compared to medium risk ($p < .0001$) and low risk ($p < .0001$).

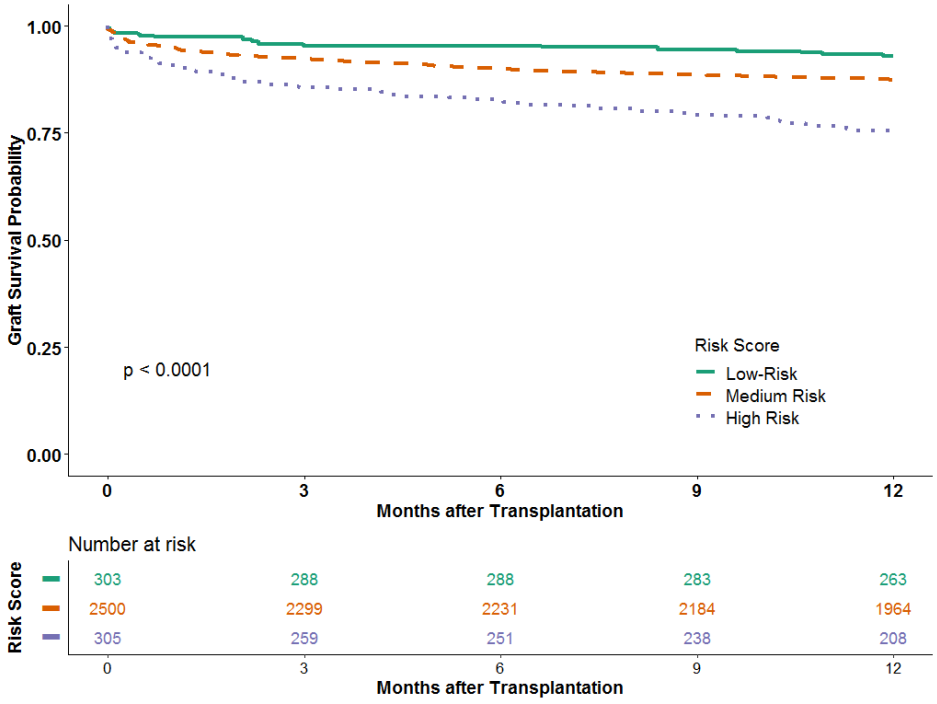

Figure 37. Kaplan-Meier graft survival by risk score.

Validation of model calibration. I validated the model for calibration accuracy in predicting the probability of graft survival 1-year post LT. The model calibration plot in Figure 38 determines the agreement between observed and predicted estimated graft

survival probability within a 1-year post LT in the NAFLD/CC population. The blue curve in Figure 38 represents the estimated overfitting-corrected calibration curve. The calibration curve slope indicates some overfitting. The bootstrap estimated calibration of slope shrinkage was 0.80, suggesting that about 20% of the fitted model is noise.

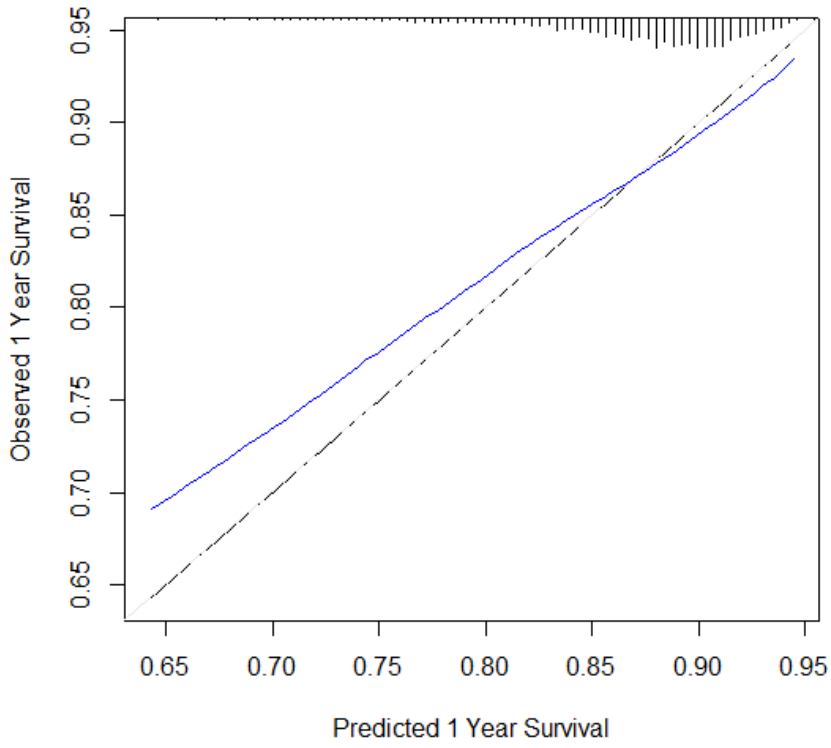

Figure 38. Bootstrap estimate of calibration accuracy for 1-year from the final Cox PH model.
Note. The blue curve corresponds to 1000 bootstrap corrected estimates.

Nomogram of the Extended DQ-NAFLD Cox Model

I used the multivariable Cox PH model to build a nomogram, as depicted in Figure 39, for predicting 1-year graft survival probability. The nomogram shows the impact of each predictor on the outcome graphically. Points are assigned to each independent donor, recipient, and transplant variables in the model according to the degree of their impact on graft survival. The nomogram allows estimating the probability of 1-year graft survival for a NAFLD/CC recipient of LT when the selected donor, recipient, and transplant predictor variables are provided. The nomogram assigns a point to each independent donor variable in the model, and the total points are projected to a probability of graft survival scale that ranges from 0 to 1. The nomogram can be used to obtain manually predicted points for each subject from a regression model. Once the user manually totals the points, the predicted values can be read at the bottom.

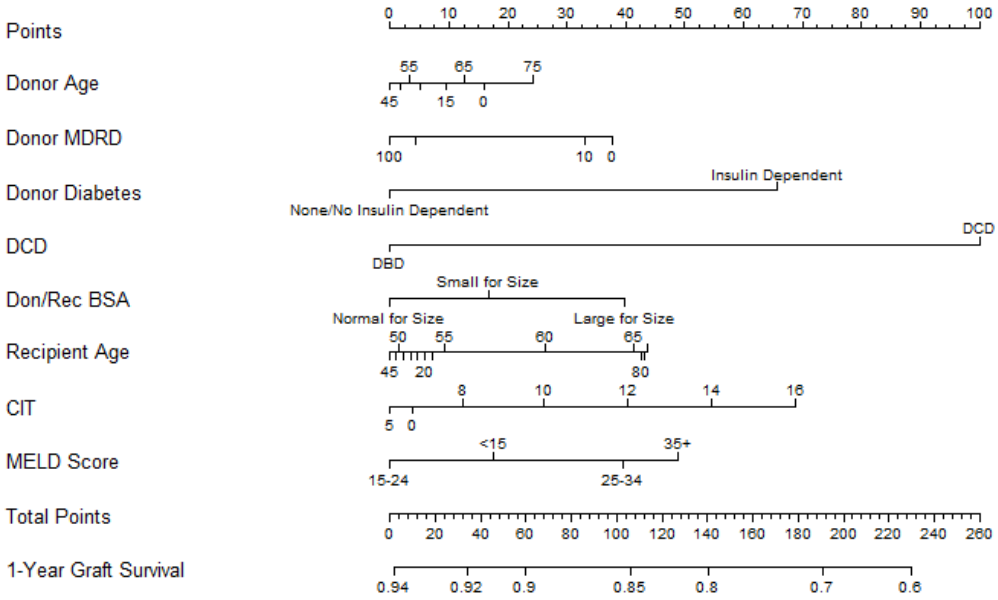

Figure 39. Nomogram from the fitted Cox PH model of extended donor factors for predicting graft failure in NAFLD/CC.

For example, a NAFLD/CC recipient of LT of 60 years (26 points) and MELD Score 18 (0 points) is considered herein matched with a DCD donor (100 points), 35-year-old (2 points), without diabetes (0 points), with MDRD of 80 (4 points), with an estimated CIT of 5 hours (0 points) and with an estimated graft large for size (40 points). The resulting total points are 172, which has an estimated probability of .78 for liver graft survival at one year.

Predicted DQ-NAFLD Scores

Figure 40 provides an insight into the distributions of the calculated DQ-NAFLD scores using the two models. In this figure, the variation of the donor predicted hazard ratios of graft failure within 1-year posttransplant using the two DQ-NAFLD models is presented. The observed DQ-NAFLD scores in the donor-only model ranged from 0.1 to 6.6 with a median value of 0.93 (*IQR*, 0.83, 1.11) while the observed scores in the extended DQ-NAFLD ranged from 0.26 to 4.2, with a median value of 0.96 (*IQR*, 0.76, 1.25). The DQ-NAFLD score can be interpreted as a measure of relative graft failure hazard rate compared with the median donor, which has a relative hazard failure rate of 1. Figure 41 displays the side by side of the DQ-NAFLD scores classified by risk group category using the two DQ-NAFLD models.

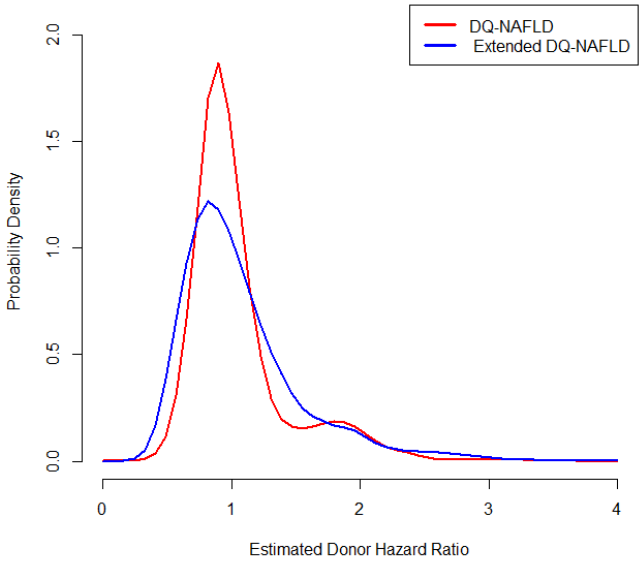

Figure 40. Kernel density distributions of DQ-NAFLD scores.

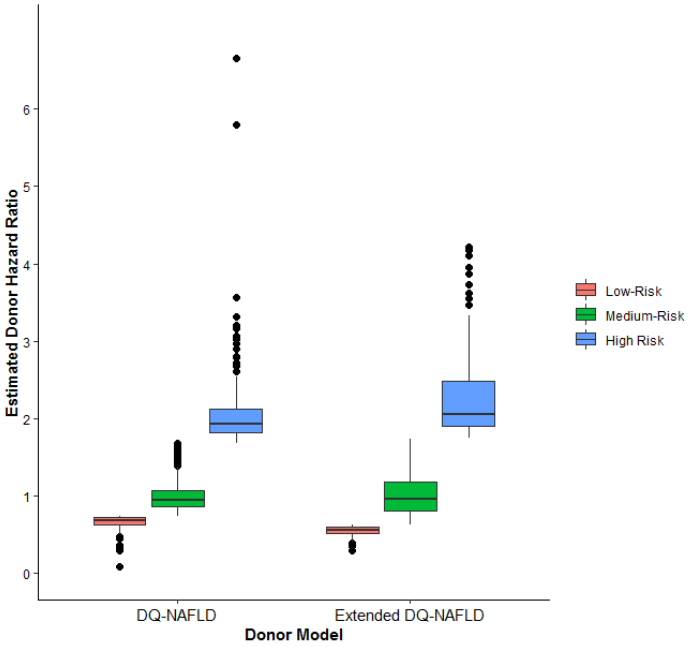

Figure 41. Side by side boxplots by DQ-NAFLD model and risk group.

Research Question 4

The fourth research question explores the relationships between post-transplant graft survival among NAFLD/CC recipients and the health risk status of the county were recipients reside, measured by the community health score (CHS). A total of 3017 NAFLD/CC recipients of LT had CHS data, and there were 397 events, i.e., graft failures or deaths within 1-year post LT. CHS data were not available for 148 study subjects. To answer the research question, I modeled CHS as RCS with four knots at 6, 12, 18, and 30 in a Cox PH model of graft survival. The corresponding global likelihood ratio test ($\chi^2(3) = 4.70$, p=.185) indicated that CHS was not statistically significantly associated with graft survival at 1-year post LT. Therefore, the null hypothesis of no association

between CHS and post-transplant graft failure is not rejected. Alternatively, I ued the knot positions as cutoffs to categorize CHS in five groups: CHS ≤ 6, 7 ≤ CHS ≤ 12, 13 ≤ CHS ≤ 18, 19 ≤ CHS ≤ 30, and HCS>30. I estimated survival curves using the Kaplan-Meier method for each of the five categories of CHS, as portrayed in Figure 42.

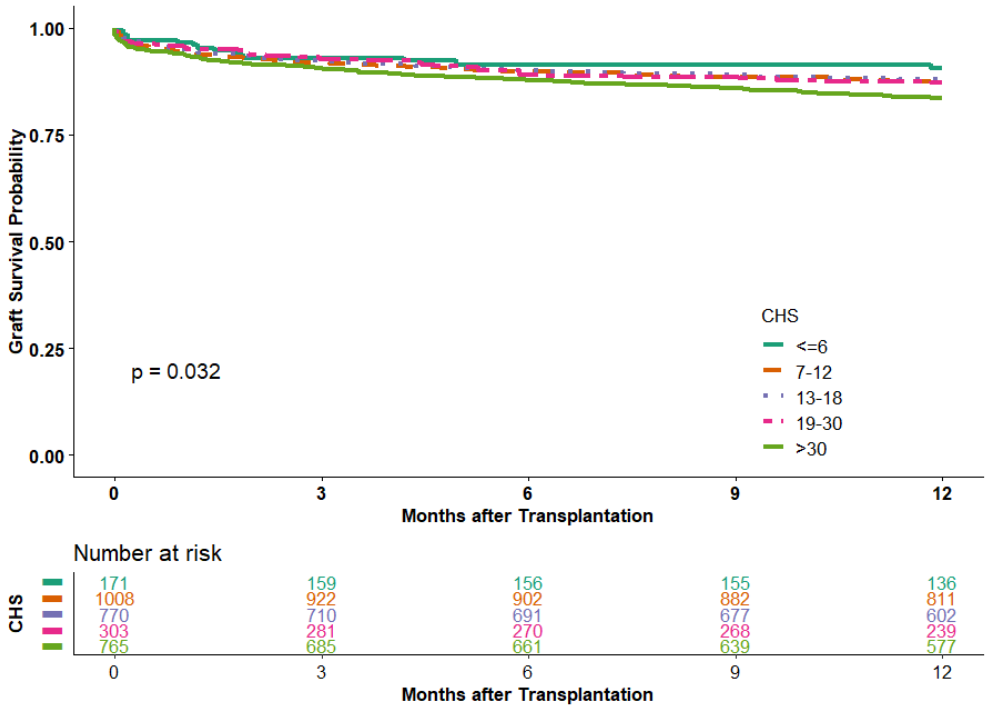

Figure 42. Kaplan-Meier graft survival by CHS with cut-off points obtained from the estimated spline transformation of the risk score.

I compared the survival curves using the log-rank test. The overall log-rank test ($\chi^2(4) = 10.6$, p=.0.032) indicated a statistically significant difference in graft survival experience among the CHS groups. I performed post hoc Benjamín and Hochberg adjusted multiple comparisons that control the false discovery rate to identify where the differences across groups lied. The pairwise corrections revealed that, compared to

recipients of LT who resided in low health risk counties (CHS<6), recipients who resided in counties with high community health risk (CHS >30) had a worse graft survival experience post LT (p = .041). All other pairwise comparisons were not statistically significant.

Similarly, when, I modeled CHS as a categorical predictor in a Cox PH model, the global likelihood ratio test ($\chi^2(4) = 10.34$, p =.04) revealed that CHS was statistically significantly associated with graft survival at 1-year post LT indicating that the null hypothesis of no association between CHS and graft survival is rejected. The association between CHS and 1-year graft survival tends to be conflicting depending on how CHS is modeled: significant when CHS is categorized, not significant when CHS is modeled as RCS.

Table 30 summarizes the results of the Cox PH model. Compared to the reference category of CHS <6, recipients of LT who reside in counties with CHS>30 were more likely to lose their liver allograft within 1-year post LT (HR=1.81, 95% CI 1.08, 3.05).

Table 30

Univariate Cox Regression Model for CHS Predicting Liver Graft Failure

Variable (CHS)	Estimated β SE(β)	Wald χ^2	AHR (95% CI)
< 6	Reference		
7-12	0.216 (0.265)	1.12	1.35 (0.78, 2.26)
13-18	0.255 (0.271)	0.94	1.29 (0.76, 2.20)
19-30	0.328 (0.297)	1.10	1.40 (0.78, 2.48)
>30	0.594 (0.265)	2.24	1.81 (1.08-3.05)*

Note. NAFLD/CC recipients (n=3017). β =estimated coefficient of Cox PH model, SE=standard error, AHR=adjusted hazard ratio. CI=confidence interval.* $p<.05$.

Choropleth graph (Figure 43) shows the donor graft survival aggregated by county by three groups of graft failures. The graph illustrates the county estimated graft survival at 1-years colored according to group value from light to dark blue, with darker colors indicating more favorable graft survival. Counties with unavailable information are indicated in black. The choropleth graph provides a visual illustration of the variation in graft survival across countries. There were 1145 counties represented in the analysis, and there were counties with few patients.

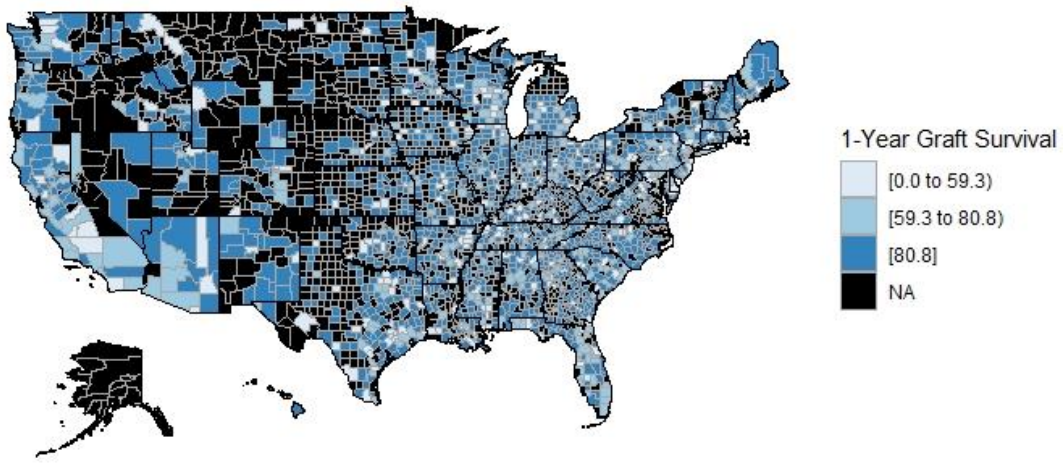

Figure 43. Choropleth graph of 1-year graft survival by county.

Research Question 5

The fifth research question was based on whether or not there was a relationship between post-transplant graft survival among NAFLD/CC recipients and the distance from recipient residence to the transplant center. I analyzed a total of 3,137 NAFLD/CC recipients of LT. There were 414 events; r graft failures or deaths within 1-year post LT.

I excluded from the analysis twenty-eight subjects with missing zip code data as I could not calculate the distance from their residence to the transplant center.

To answer the research question, I modeled distance from recipient residence to transplant center as RCS with four knots at 5, 27, 85, and 422 miles. The corresponding global likelihood ratio test ($\chi^2(2) = 4.10$, p=.25) indicated that distance from recipient residence to the transplant was not significantly associated with graft survival at 1-year post LT. Therefore, the null hypothesis of no association is not rejected. Alternatively, I used the knot positions as cutoffs to categorize distance to the transplant center in 5 groups: ≤5 (miles), 6-27 (miles), 28-85 (miles), 46-422 (miles), and >422 (miles). Figure 44 illustrates the Kaplan-Meier survival curve for the five distance groups. The log-rank test ($\chi^2(4) = 4.0$, p =.40) showed no differences in survival experience across the five distance from transplant center groups.

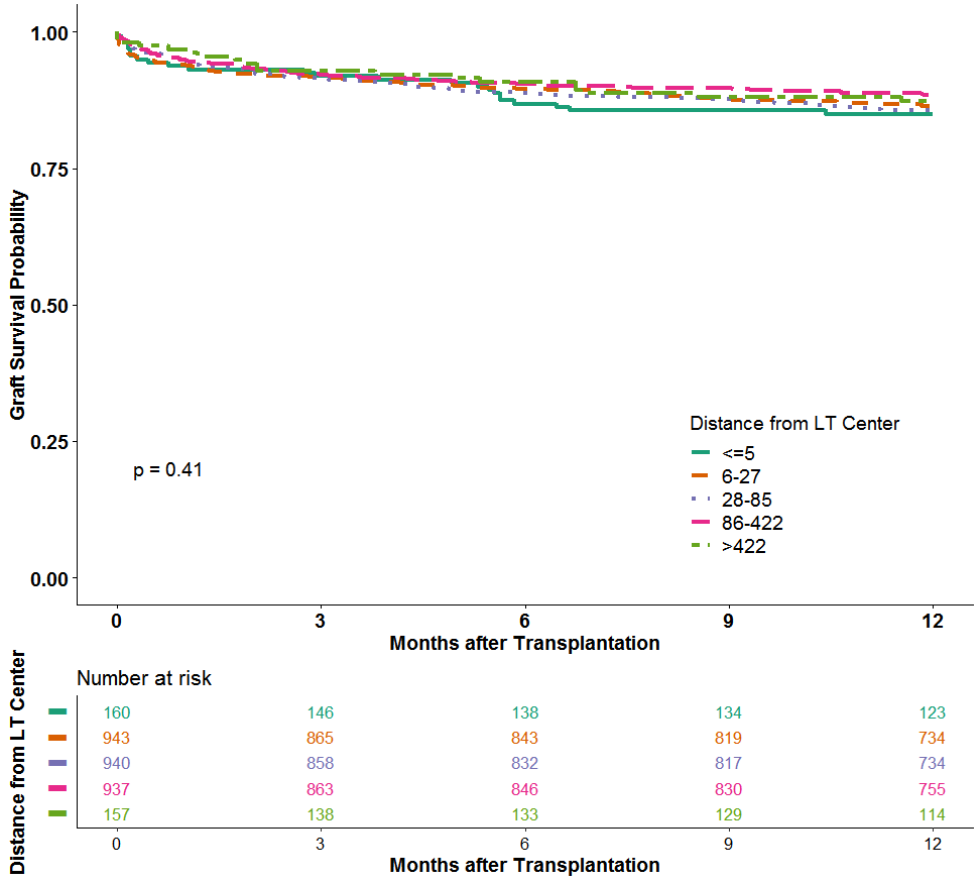

Figure 44. Kaplan-Meier graft survival by distance from transplant center with cut points obtained from the estimated spline transformation of the risk score.

Similarly, when I modeled the distance from transplant center as a categorical predictor in a Cox PH model, the global likelihood ratio test ($\chi^2(4) = 4.02$, $p = .40$) indicated that geographic distance was not associated with graft survival at 1-year post-transplant. Compared to the reference category of LT recipients' distance from the transplant center of ≤ 5 miles, all other recipients in other distance categories were as likely to lose their liver graft within 1-year post LT, as summarized in Table 31. These

results confirm that the null hypothesis of no association between distance and graft survival is not rejected.

Table 31

Univariate Cox Regression Model for Distance from Transplant Center Predicting Liver Graft Failure

Variable (Distance, miles)	Estimated β SE (β)	Wald χ^2	AHR (95% CI)
≤5	Reference		
6-27	-0.105 (0.222)	-0.474	.90 (0.58, 1.39)
28-85	-0.052 (0.221)	-0.234	.94 (0.62, 1.47)
86-422	-0.283 (0.226)	-1.256	.75 (0.48, 1.17)
> 422	-0.203 (0.307)	-0.660	.82 (0.45, 1.40)

Note. NAFLD/CC recipients (n=3017). β =estimated coefficient of Cox PH model, SE=standard error, AHR=adjusted hazard ratio, CI=confidence interval.

Research Question 6

Research question six was based on exploring relationships between DQ-NAFLD risk score and external community factors (CHS and distance from recipient residence to transplant center) among NAFLD/CC recipients of LT.

To answer the question, I developed a Cox PH model to measure the combined effect of DQ-NAFLD risk score category, distance from recipient residence to transplant center, and CHS on the risk of graft failure within 1-year post LT. There were 2971 observations, and 390 events, and no significant interactions. The model goodness-of-fit

tested using the likelihood ratio test ($\chi^2(10) = 39.05$, $p < .0001$) indicated model adequacy in explaining the graft survival experience of NAFLD/CC recipients of LT patients. The results of the Cox PH model are summarized in Table 32. Compared to recipients with low-risk donors based on the DQ-NAFLD score, recipients of medium risk livers (HR=1.57, 95% CI 1.12, 2.19) and high-risk livers (HR=2.57, 95% CI 1.84, 4.13) based on the DQ-NAFLD score were more likely to lose their grafts within the first-year post LT. Compared to the reference category of CHS <6, recipients of LT who resided in counties with CHS>30 were more likely to lose their liver allografts within 1-year post LT (HR=1.85, 95% CI 1.08, 3.17). The scatterplots in Figure 45 depict the direction and strength of the relationship between the donor risk score and community health score, respectively, Figure 45(A) and distance from transplant center Figure 45 (B).

Table 32

Multivariate Cox Regression Model for NAFLD/CC Risk Score and External Factors Predicting Liver Graft Failure.

Variables	Estimated β SE (β)	Wald χ^2	AHR (95% CI)
Risk Score			
Low	Reference		
Medium	0.452 (0.171)	2.95	1.57 (1.12, 2.20)*
High	1.014 (0.206)	4.91	2.76 (1.84, 4.13)***
CHS			
<6	Reference		
7-12	0.331 (0.276)	1.20	1.39 (0.81, 2.39)
13-18	0.280 (0.280)	1.00	1.32 (0.76, 2.29)
19-30	0.387 (0.312)	1.25	1.47 (0.80, 2.71)
>30	0.616 (0.274)	2.25	1.85 (1.08, 3.17)*
Distance			
< 6	Reference		
7-27	-0.181 (0.225)	-.81	0.83 (0.54, 1.30)
28-85	-0.086 (0.224)	-.38	0.92 (0.59, 1.4)
86-422	-0.299 (0.229)	-1.29	0.74 (0.47, 1.17)]
≥ 422	-0.245 (0.324)	-.75	0.78 (0.41, 1.48)

Note. NAFLD/CC recipients (n=2971), β =estimated coefficient of Cox PH model, SE=standard error, AHR=adjusted hazard ratio, CI=confidence intervals.
* *p*<.05, **p<.001, ***p<.0001.

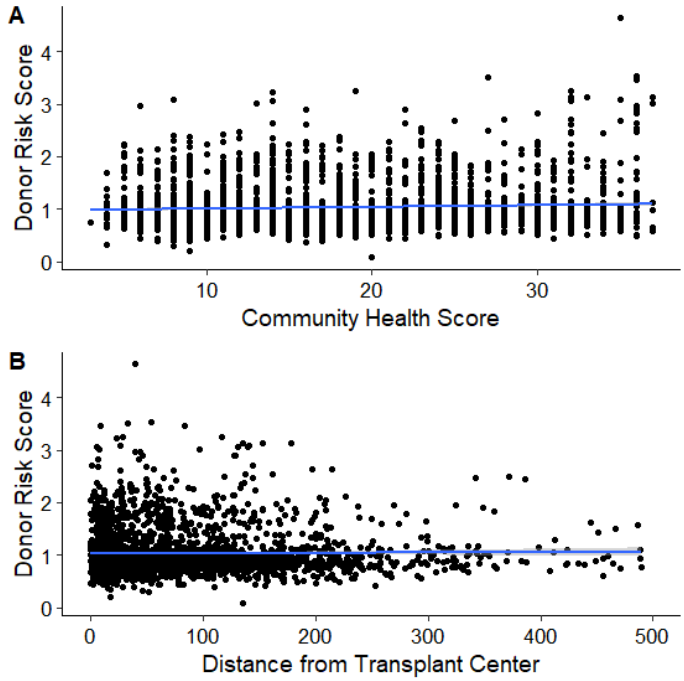

Figure 45. Scatterplot of NAFLD/CC donor risk score; (A) CHS, (B) distance from recipient residence to transplant center.

Summary of Results

In summary, the current study revealed that NAFLD/CC recipients of a liver transplant had different characteristics from recipients transplanted for other etiologies: they were sicker, as transplanted at a higher MELD score, older, and more obese, as having a higher BMI. The novel donor risk model tailored to this patient population is driven by four donor factors: insulin-dependent diabetes, DCD, height, and MDRD. Donor age did not have a strong impact on liver graft survival in the Cox PH model. However, in addition to the variables identified as strong predictors in the semiparametric model, the RSF selected donor age as a predictor of graft failure. An extended version of the intrinsic donor model, which included selected transplant and recipient factors, found

no association between donor age and 1-year graft survival in each MELD score category. Decreased CIT was associated with improved 1-year graft survival recipients with MELD score 15-24 but not for low MELD score (<15) or high MELD score (≥25). In addition to donor insulin-dependent diabetes, DCD, donor MDRD, donor/recipient size match, and recipient age had an impact on graft survival within 1-year post LT. NAFLD/CC recipients of LT had a higher probability of losing their graft within the first-year post LT. The study also revealed that receiving a Public Health extended high-risk donor did not increase the risk of graft survival.

In the context of community health scores, a difference in graft failure was observed at the extremes; between recipients of LT who resided in low health risk counties (CHS<6) versus recipients who resided in high health risk communities (CHS>30). The impact of community health scores on graft failure within 1-year post LT was observed in both univariate and multivariable Cox PH models. Findings suggested that in addition to donor quality, the environment in which the patient resides had an impact on the risk of graft failure. Residing far from the transplant centers was not associated with an increased risk of graft failure.

Chapter 5: Discussion, Conclusions, and Recommendations

The epidemic increase in the incidence of NAFLD has led to an increase in the prevalence of liver disease from NAFLD progression compared to other liver etiologies (O'Leary et al., 2011; Pais et al., 2016). Consequently, NAFLD has become one of the leading indications for liver transplant. The incidence of NAFLD has been intimately tied to the components of metabolic syndrome. NAFLD patients who progress to cirrhosis or HCC, leading to the need of a liver transplant, have to face two major obstacles: (a) the presence of comorbidities and (b) a low MELD score due to better liver functioning, placing them on the bottom of the wait list. Therefore, many of them may die while being on the liver transplant wait list due to organ shortage and low priority (O'Leary et al., 2011). Transplant centers are trying to increase the utilization of marginal donors to increase the donor pool. Donor risk models provide useful tools to help match marginal donors to the appropriate recipients.

Interpretation of the Findings

This study confirmed that NAFLD/CC patients have baseline characteristics different from other etiologies, which justifies the decision to develop donor risk models tailored for NAFLD/CC. Moreover, NAFLD/NASH recipients of LT had lower 1-year graft survival compared to other etiologies, reflecting their longer permanence on the wait list and comorbidities. The purpose of this retrospective study was to develop an intrinsic donor and an extended DQ-NAFLD score aimed at identifying the donor characteristics that can lead to poor posttransplant outcomes in this patient population.

The theoretical framework that guided this study was grounded in the socio-ecological model, which allowed me to explore the complex interplay among external environmental factors, expressed in terms of the county CHS and distance from the transplant center. Two sources of data, the SRTR database and the community health indicators, were adapted from the Robert Wood Johnson Foundation's community health rankings, making it possible to explore different levels of the socio-ecological model in the development of donor risk models.

The developed extended donor model improved only slightly the predictive accuracy but allowed the assessment of the additional impact of MELD score and CIT on posttransplant graft failure. Findings indicated that although the distance from the transplant center does not have an impact on post LT graft survival, the county where a patient resides has an impact. However, it is not clear whether the CHS is the appropriate metric to explain county discrepancies in health and socioeconomic risk.

Public Health Service Increased Risk

Increasing the donor pool by increasing the utilization of marginal donors can improve access to a scarce resource for NAFLD/CC candidate for LT. Potential organ donations at an increased risk for transmitting hepatitis B, hepatitis C, and human immunodeficiency virus are often discarded because the label associated to PHS increased risk organ carries a stigma that dramatically reduces the utilization of this organ source (Fleetwood, Lusciks, Poirier, Hertl, & Chan, 2016). However, the risk of transmitting disease in the era of nucleic acid testing is very low; still, patients are

reluctant to accepting PHS increased risk donors (Volk et al., 2017). This study demonstrated that the use of PHS increased risk donor livers did not alter significantly the risk of liver graft failure within 1-year post LT.

Kaplan-Meier graft survival curves between recipients of non-PHS increased risk versus PHS increased risk overlapped, suggesting that some of the underutilized PHS increased risk donors could be used for NAFLD/CC patients and not discarded due to stigmatization. This result is aligned with the findings from a study conducted by Pruett, Clark, and Taranto (2017) that showed that posttransplant outcomes, including 1-year patient and graft survival as well as the risk of unexpected transmission of HIV, HBV, or HCV after deceased donor kidney transplantation, did not change with the status of PHS extended risk donors. The finding that donor livers with PHS extended risk denomination did not alter the probability of graft survival in NAFLD/CC patients may be used to support patients' and physicians' decision-making regarding the use of PHS increased risk livers. This finding can also be used to help patients gauge the potential risk of undetected HIV, HBV, or HCV infection transmission versus refusing an organ for transplant and prolonging the stay on the wait list.

Intrinsic Donor DQ-NAFLD Model

Donor risk models have been previously proposed to evaluate donor quality of deceased donor livers to assist in decision-making. Feng et al. (2006) developed the first donor risk index using data in the pre-MELD era. This was followed by other developed risk models to predict posttransplant graft survival using donor, recipient, and transplant

factors (Blok et al., 2015; Braat et al, 2012; Dutkowski et al., 2011; Halldorson et al., 2009; Winter et al., 2018). These models have been used for risk stratification and validated in subsequent studies. However, none of these models is tailored for NAFLD/CC recipients of LT.

The intrinsic DQ-NAFLD donor model was developed using post-MELD and post-Share 35 data, and only included donor factors available at the time of donor offer that summarized the likelihood of graft failure after LT. The model reflects current practice and is tailored for NAFLD/CC recipients of LT. The model is driven by DCD, donor diabetes, MDRD, and donor height. Donor age, not a significant predictor in the Cox PH model, was included in the model to adjust the results because of clinical relevance, and also because it was used in other donor risk models. Donor diabetes, as a surrogate of liver steatosis, was not taken into account in previous donor risk models, while kidney function (expressed by the MDRD) was recently included to develop a donor quality index using the French liver transplant registry (Winter et al., 2018).

Macrosteatosis on donor biopsy, a known predictor of graft failure (de Graaf et al., 2012), was only available for 38% of donors who had biopsy data in SRTR. For this reason, macrosteatosis was not included in the multivariable donor risk models. The Kaplan-Meier curve shows a tendency of macrosteatosis donors with Stage M2 to have a worse but not statistically significant 1-year graft survival experience, compared to M0 and M1 stages of macrosteatosis when transplanted to NAFLD/CC recipients.

The DQ-NAFLD score represents the relative risk of posttransplant liver graft failure from the use of a particular deceased donor, compared to the average donor set at reference values for categorical predictors and average values of continuous covariates. For example, a donor with an estimated DQ-NAFLD of 1.45 will have an estimated risk of liver graft failure of 45% higher than the average reference donor. Lower DQ-NAFLD values are associated with increased donor quality and longer graft survival. Intrinsic donor DQ-NAFLD classifies liver organs as high, medium, or low risk. The observation of transplant practices and outcomes with these organs in NAFLD/CC recipients based on these estimated risk classifications can help identify subsets of NAFLD/CC recipients across these risk categories who can still achieve excellent outcomes. This is a definite step forward for an optimal allocation of donor livers to NAFLD recipients.

Impact of Transplant Factors

Fukazawa et al. (2013) proposed using the ratio of donor to recipient BSA index to estimate size match, and found that both small-for-size and large-for-size liver graft extremes can increase the risk of graft failure post LT. In a single-center study on adult and pediatric patients, Akdur et al. (2015) found that large-for-size liver grafts can cause abdominal compartment syndrome leading to graft failure. The current study revealed that, in the context of NAFLD/CC recipients of LT, receiving a large-for-size donor had a higher likelihood of graft failure compared to a normal-for-size done in both univariate and multivariate analyses.

Extended DQ-NAFLD Model

Among the candidate donor predictors considered, insulin-dependent diabetes, DCD, height, and MDRD were selected as stronger predictors of graft failure in the Cox PH model for the NAFLD/CC population. Additionally, donor age resulted as an important predictor of graft failure in the RSF model. With the addition of recipient and transplant factors, the extended version of the DQ-NAFLD improved only slightly the predictive ability of the model but allowed the prediction of the relative risk of a specified donor liver across different MELD score or different values of CIT.

The extended donor model revealed that donor/recipient size match affected graft survival. In particular, recipient age and reception of a large-for-size donor led to worsening graft survival. In both donor risk models, NAFLD/CC recipients using elderly donors did not experience a worse 1-year graft survival, suggesting that matching elderly donors to recipients with NAFLD/CC may be safe. Long term effects of old donors transplanted in NAFLD/CC recipients on graft and patient survival and other posttransplant outcomes should be further investigated.

Impact of Community Health Scores

Factors such as socioeconomic status, individual behavior, education, environmental risks, social support, access to healthy food, and health care vary widely by region and counties. Under the lens of the socio-ecological system, there are complex social and environmental determinants that increase or decrease the risk of poor posttransplant outcomes. Ross et al. (2017) included the CHS adapted from the Robert

Wood Johnson Foundation's community health rankings and found that disparities in health and economic conditions, and travel distance, had an impact on wait-list mortality.

To address the impact of external factors in the social-ecological model, I used in this analysis the CHS, a county-level measure of community health resources and risk. CHS is a score derived from multiple aspects of community health factors, such as access to care, and social and environmental risk factors, such as: (a) years of potential life lost, (b) proportion of children with low birth weight, (c) proportion of adults with poor or fair reported health, (d) adults' poor reported physical health days, (e) poor reported mental health days, (f) proportion of individuals reporting tobacco use, (g) adult obesity prevalence, (h) physical inactivity prevalence, (i) rate of preventable hospital stays, and (j) median annual household income. A cumulative score with a range from 0-40 was computed for each county (the county CHS), obtained by adding up scores from each of the 10 community health indices. Each county received a score of 0-4 based on quintile ranking (zero points if the county belonged to the 1st quintile for a particular index and one point for each subsequent quintile). NAFLD/CC recipients of LT who resided in high health risk counties with a CHS > 60 were more likely to lose their grafts within 1-year post LT compared to low health risk counties (p = .041) suggesting that the environment can play a role in post-transplant outcomes.

Impact of Geographic Distance from Transplant Center

Studies revealed that among patients eligible for a liver transplant, greater geographic distance from the transplant center was associated with a lower likelihood of

being listed or receiving a liver transplant (Goldberg et al., 2017). Although geographic distance has proven important on wait-list outcomes, this study has shown that greater geographic distance from the transplant centers was not associated with worsening 1-year graft survival post-transplant, suggesting that long-distance management of NAFLD/CC liver transplant recipients is not associated with worsening outcomes. However, the analysis was biased towards recipients that got transplanted.

Limitations of the Study

This study has several limitations that merit discussion. Retrospective nature of this quantitative study can only prove associations but not causation and can lead to confounding attributable to unobserved variables. The SRTR database I used in this study had a significant amount of missing data that were not analyzed. Donor biopsy was only present in 38% of cases; therefore, I did not include macrosteatosis in the multivariable models. This study revealed that donor insulin-dependent diabetes increased the likelihood of graft failure within 1-year post LT. Information about donor diabetes obtained from the donor next of kin might be inaccurate if the person interviewed had limited or erroneous information. The study was powered to develop multivariate donor risk models.

Consecutive sampling selection of all patients that met the inclusion criteria reduced selection bias. Therefore, inferences from SRTR studies are likely to generalize across United States. However, the model is expected to present some threats to external

validity and unlikely to generalize with data from non-US transplant centers with different policies and procedures (Massie, Kucirka, & Segev, 2014).

I calculated the distance from recipient residence to transplant center through zip code distances using the Haversine formula, which is the shortest distance between two points on the surface of a sphere, an approximation of the actual distance.

The aggregate nature of the community health factors can lead to model estimates that may be subject to ecologic bias. Moreover, at the county-level, the choropleth graph showed a county-based variation in liver graft survival. However, some counties had only a few study subjects, which can decrease the accuracy of the estimated graft survival by county. The small number of LT performed for NAFLD/CC recipients complicate the task of demonstrating that patients from disadvantaged counties all share the same elevated risk of poor outcomes making county rankings of transplant outcomes highly unstable.

Many factors can impact post-transplant outcomes, and both DQ-NAFLD models developed herein do not capture all aspects. Therefore, even if the models have shown that some donor factors have a large or small impact, they can only be used to support decision making at the time of donor acceptance, as several many other factors will play a role as well. For example, even though the analyses showed that, in both Cox PH models used to develop the DQ-NAFLD scores, donor age did not impact graft survival, it does not imply that it is safe to transplant each elderly donor to NAFLD/CC recipients. The

analysis was biased towards elderly donors that got transplanted, as transplant centers can reject older donors for several reasons.

Recommendations

This current study found that donor age is not a strong predictor of 1-year graft survival and may be extended in the future to explore whether older donors can be safely used to transplant NAFLD/CC recipients. The rate of steatosis among the general population is increasing, leading to an increasing number of cadaveric donors with hepatic steatosis. The progression from steatosis to fibrosis, and ultimately, cirrhosis is quite slow. However, in the current donor pool with an increasing prevalence of metabolic syndrome, the impact of donor steatosis on NAFLD/CC recipients and the likelihood to result in long term recurrence of NAFLD or NASH, compared to other etiologies, should be explored further.

The DQ-NAFLD, as well as other donor risk metrics, have been developed considering 1-year organ survival post-transplant. However, liver transplant recipients tend to gain weight within the first-year post LT. Therefore, some NAFLD/CC recipients of LT can develop recurrent NAFLD and NASH, and a smaller percentage can incur cirrhosis and require a re-transplant. Defining donor quality for NAFD/CC recipients of LT beyond 1-year graft survival but based on the recurrence of NAFLD in its progressive forms of NASH cirrhosis, can enhance the definition of donor quality and measure peculiar aspects of NAFLD/CC recipients. The SRTR database does not include post-LT complications needed to explore this aspect. However, data collected at the transplant

centers could be used to explore disease recurrence and the need for re-transplant in the short and long term

County differences in post-transplant graft survival do exist as the choropleth map revealed. These disparities are driven only in part by county socioeconomic status or CHS. The county aspect could be analized as a shared frailty term in a Cox PH model with a random effect to represent any unexplained variation in graft survival across counties, excluding low volume counties from the analysis. Moreover, CHS resulted as an independent predictor of graft failure when categorized, but not when modeled as RCS. This instability and conflicting result show the need for further validation of CHS in other populations. Further exploration of alternative county metrics and patient-level socioeconomic factors could contribute to explain county variation if used in risk adjustment donor models.

This study revealed that the use of PHS increased risk donors did not alter the probability of graft survival in NAFLD/CC patients. Different reasons can lead to the denomination of PHS extended risk donor, not all of them equally likely to increase the probability of undetected HIV, HBV, or HCV infection transmission. Therefore, further studies are needed to identify a subset of PHS increased risk donors that increase the risk of unintended transmission and graft failure.

Implications

The changing patterns in indication for LT herein pointed to the development of a post-MELD era post Share 35 donor quality score tailored to NAFLD/CC recipients. DQ-

NAFLD quantifies the quality of the liver graft by scoring the characteristics of the graft before LT. Therefore, it is a crucial factor for a better match between a liver graft and its recipient and can lead to a positive social change if used as a tool to assist both physicians and patients in the decision of graft usage.

The nomogram developed in this study using the DQ-NAFLD donor models, or a calculator created using the model estimates, can provide some information to patients and physicians of an expected outcome, which can be expressed in terms of expected 1-year survival or as expected AHR for a specific donor matched to a particular recipient.

Understanding and quantifying the impact of donor factors that do affect posttransplant graft survival, and donor factors that have minimal or no impact for this patient population, can contribute to freeing more donors to allocate to NAFLD/CC, who are at high risk of death while waiting for a liver. Moreover, understanding the impact of recipient factors, such as MELD, and transplant factors, such as CIT and donor/recipient size match, can help in achieving the ultimate goal of optimal donor/recipient matching.

Conclusion

Organ shortage leads to the utilization of non-optimal donors, and donor risk models provide a metric to quantify donor quality and help allocate non-optimal donors to appropriate recipients. However, many organs are discarded, some of which could be utilized with excellent results if adequately selected and matched to the appropriate LT candidates. Donor risk models provide the first step to match marginal donors to the appropriate recipients optimally. The creation and validation herein of DQ- NAFLD

donor risk models, tailored to NAFLD/CC recipients of LT, is a major step forward in the optimal utilization of a scarce resource for this patient population. NAFLD/CC is becoming one of the top indications for LT, but often NAFLD/CC candidates have low priority and high mortality on the wait list. The DQ-NAFLD score can contribute to NAFLD/CC LT candidates matched appropriately, who may die while on the wait list or may be removed because they are too sick to be transplanted. Moreover, understanding the impact of external geographic and community factors can help develop more accurate donor risk models adjusted for sociodemographic risk factors. Concerns remain that after adjusting for donor characteristics, posttransplant graft failure in NAFLD/CC recipients continues to be subjected to community disparities.

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Appendix A: County Health Indicators

County Health Indicators (CHI) are compiled annually using county-level measures from a variety of national and state data sources by the University of Wisconsin Population Health Institute and the Robert Wood Johnson Foundation. Since 2010, CHIs are available for almost all counties (over 30000 counties) and are used to compare county health status. The estimated CHI and their 95% CI are available for each county. Tables A1-A5 describe the CHSs by category: health outcomes, health behaviors, clinical care, social and economic factors, and physical environments. They indicate how each CHI is measured and the source of data and identify the selected group of indicators that will be used to develop the transplant community health score.

Table A1

Community Health Indicators: Health Outcomes

Focus Area	CHI Measure	Description	Source	Used in Transplant CHS
Length of life	Premature death	Years of potential life lost before age 75 per 100,000 population (age-adjusted)	National Center for Health Statistics - Mortality files	Yes
Quality of life	Poor or fair health	Percentage of adults reporting fair or poor health (age-adjusted)	Behavioral Risk Factor Surveillance System	Yes
	Poor physical health days	Average number of physically unhealthy days reported in past 30 days (age-adjusted)	Behavioral Risk Factor Surveillance System	Yes
	Poor mental health days	Average number of mentally unhealthy days reported in past 30 days (age-adjusted)	Behavioral Risk Factor Surveillance System	Yes
	Low birthweight	Percentage of live births with low birthweight (< 2500 grams)	National Center for Health Statistics - Natality files	Yes

Notes: CHI: County health index; CHS: community health score.
Source: http://www.countyhealthrankings.org/

Table A2

Community Health Indicators: Health Behaviors

Focus Area	CHI Measure	Description	Source	Used in Transplant CHS
Tobacco use	Adult smoking	Percentage of adults who are current smokers	Behavioral Risk Factor Surveillance System	Yes
Diet and exercise	Adult obesity	Percentage of adults that report a BMI of 30 or more	CDC Diabetes Interactive Atlas	Yes
	Food environment index	Index of factors that contribute to a healthy food environment, 0 (worst) to 10 (best)	USDA Food Environment Atlas, Map the Meal Gap	No
	Physical inactivity	Percentage of adults aged 20 and over reporting no leisure-time physical activity	CDC Diabetes Interactive Atlas	Yes
	Access to exercise opportunities	Percentage of population with adequate access to locations for physical activity	Business Analyst, Delorme map data, ESRI, & US Census Tigerline Files	No
Alcohol and drug use	Excessive drinking	Percentage of adults reporting binge or heavy drinking	Behavioral Risk Factor Surveillance System	No
	Alcohol-impaired driving deaths	Percentage of driving deaths with alcohol involvement	Fatality Analysis Reporting System	No
Sexual activity	Sexually transmitted infections	Number of newly diagnosed chlamydia cases per 100,000 population	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention	No
	Teen births	Teen birth rate per 1,000 female population, ages 15-19	National Center for Health Statistics - Natality files	No

Notes: CHI: County health index; CHS: community health score.
Source: http://www.countyhealthrankings.org/

Table A3

Community Health Indicators: Clinical Care

Focus area	CHI measure	Description	Source	Used in transplant CHS
Access to care	Uninsured	Percentage of population under age 65 without health insurance	Small area health insurance estimates	No
	Primary care physicians	Ratio of population to primary care physicians	Area health resource file/American Medical Association	No
	Dentists	Ratio of population to dentists	Area Health Resource file/national provider identification file	No
	Mental health providers	Ratio of population to mental health providers	CMS, national provider Identification file	No
Quality of care	Preventable hospital stays	Number of hospital stays for ambulatory-care sensitive conditions per 1,000 Medicare enrollees	Dartmouth Atlas of Health Care	Yes
	Diabetes monitoring	Percentage of diabetic Medicare enrollees ages 65-75 that receive HbA1c monitoring	Dartmouth Atlas of Health Care	No
	Mammography screening	Percentage of female Medicare enrollees ages 67-69 that receive mammography screening	Dartmouth Atlas of Health Care	No

Notes: CHI: County health index; CHS: community health score.
Source: http://www.countyhealthrankings.org/

Table A4

Community Health Indicators: Social and Economic Factors

Focus Area	CHI Measure	Description	Source	Used in transplant CHS
Education	High school graduation	Percentage of ninth-grade cohort that graduates in four years	EDFacts	No
	Some college	Percentage of adults ages 25-44 years with some post-secondary education	American Community Survey	No
Employment	Unemployment	Percentage of population ages 16 and older unemployed but seeking work	Bureau of Labor Statistics	No
Income	Children in poverty	Percentage of children under age 18 in poverty	Small Area Income and Poverty Estimates	No
	Income inequality	Ratio of household income at the 80th percentile to income at the 20th percentile	American Community Survey	Yes
Family and social support	Children in single-parent households	Percentage of children that live in a household headed by single parent	American Community Survey	No
	Social associations	Number of membership associations per 10,000 population	County Business Patterns	No
Community safety	Violent crime	Number of reported violent crime offenses per 100,000 population	Uniform Crime Reporting - FBI	No
	Injury deaths	Number of deaths due to injury per 100,000 population	CDC WONDER mortality data	No

Notes: CHI: County health index; CHS: community health score.
Source: http://www.countyhealthrankings.org/

Appendix B: Donor Screening for Disease Transmission

Donor Screening

OPTN policy requires donor screening to determine if the potential donor has an infection that could be transmitted to recipients through the transplanted organ. All donors are screened for human immunodeficiency (HIV), hepatitis B (HBV), hepatitis C (HCV), syphilis, cytomegalovirus (CMV) and Epstein Barr viruses (EBV). Serological tests can screen donors who developed HIV, HBV, or HCV several months before organ donation. Federal law only prohibits the transplantation of HIV infected donors. Donor shortage and medical advances in treating viral infections lead to the utilization of organ with HCV and HBV infections. HBV and HCV-infected donors are typically offered to patients known to have the same infections, or to uninfected patients in urgent need for a transplant.

CDC High Risk and PHS Increased Risk Donors

OPTN policy also requires a medical and social history interview conducted with the deceased donor's close family members to assess potential donor social behaviors and past medical history. This information is used to identify at-risk of transmitting HIV, HBV, or HCV to transplant recipients. High or increased risk refers to a set of donor behaviors that can increase the risk of transmission, as described in Table B1.

Table B1

CDC High-Risk and PHS Increased-Risk Donors

CDC High Risk (1994)	PHS Increased Risk (2013)
MSM in the preceding 5 years	MSM in the preceding 12 months
Non-medical injection drug use in preceding 5 years	Non-medical injection drug use in preceding 12 months
Sex in exchange for money/drugs in preceding 5 years	People who have had sex in exchange for money or drugs in the preceding 12 months
Known or suspected to have HIV infection in the preceding 12 months	People who have had sex with a person known or suspected to have HIV, HBV, or HCV infection in the preceding 12 months
Women who have had sex with a man with a history of MSM behavior in the preceding 12 months	Women who have had sex with a man with a history of MSM behavior in the preceding 12 months
People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months	People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months
People who have had sex with a person who injected drugs by intravenous, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months	People who have had sex with a person who injected drugs by intravenous, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months
A child who is ≤18 months of age and born to a mother known to be infected with, or at increased risk for HIV infection (should not be used)	A child who is ≤18 months of age and born to a mother known to be infected with, or at increased risk for HIV, HBV, or HCV infection
A child who has been breastfed in the past 12 months by a mother known to have or at risk for HIV infection	A child who has been breastfed within the preceding 12 months and the mother is known to be infected with, or at increased risk for, HIV infection
Inmates of correctional systems	People who have been in lockup, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the preceding 12 months
Persons who cannot be tested for HIV infection because of refusal, inadequate blood samples (e.g. hemodilution that could result in false-negative tests), or any other reasons	When a deceased potential organ donor's blood specimen is hemodiluted, the donor should be considered at increased risk for HIV, HBV, and HCV infection because the donor's risk for infection is unknown

In 1994, the Centers for Disease Control (CDC) developed guidelines for high-risk behaviors to designate donors with an increased risk of transmitting HIV. In 2013 the CDC high-risk criteria were extended to include the screening of HBV and HCV in addition to HIV, and the U.S. PHS increased risk criteria was developed. PHS increased risk guidelines replaced the CDC high-risk guidelines.

The Nucleic Acid Testing (NAT), which has a much shorter window that serological tests, is required to screen these high-risk donors. The aim of the CDC high-risk and later of PHP increased risk designation was to inform candidates on the potential risk of HIV, HBV and HCV transmission from high-risk donors, recently infected, who tested negative on serologic testing or NAT but still potentially capable of transmitting these viral infections due to the window period between infection and seroconversion. PHP increased risk does not translate into donor quality. However, because of the designation, many of these organs are rejected with the perception that they can lead to poor survival. Acceptance practices vary by transplant program. Moreover, not all increase-risk donors have the same likelihood to transmit disease, but there is a wide variation: incarceration or sexual behaviors carry a much lower risk than intravenous drug use. However, because the risk of donor-derived HIV, HBV, or HCV transmission from a NAT negative donor is lower than 1%, often the risk of rejecting risk donors may be greater than the risk of accepting them.

Appendix C: Graphical Exploratory Analysis

Variable Distributions of Categorical Variables

Bar graphs visualize the frequency distribution of categorical variables and quantify the values within the categories of each variable to identify categories more frequents. (Describe). A review of the variable distributions revealed that only eight donors (or 0.2%) were HCV positive, and only two donors (or .06 %) were HBV Ag positive. Therefore, HCV and HBV were not considered in modeling and subsequent analyses because of the lack of predictive ability.

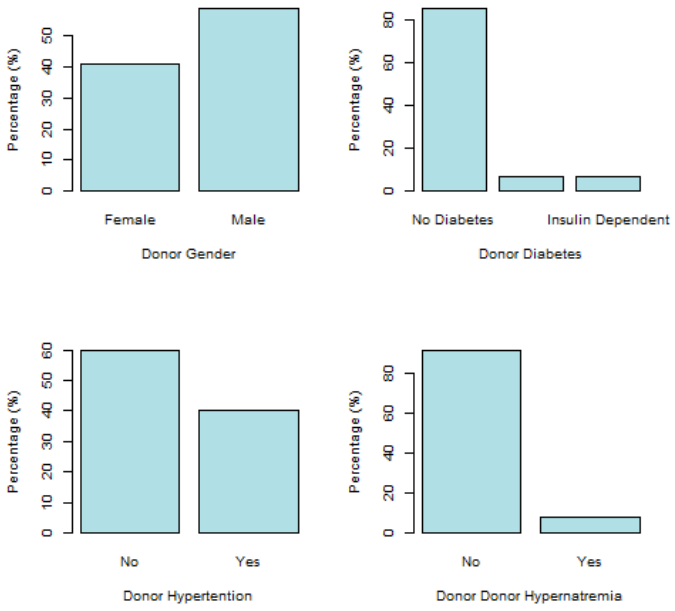

Figure C1. Bar chars of donor gender, diabetes, hypertension, hypernatremia.

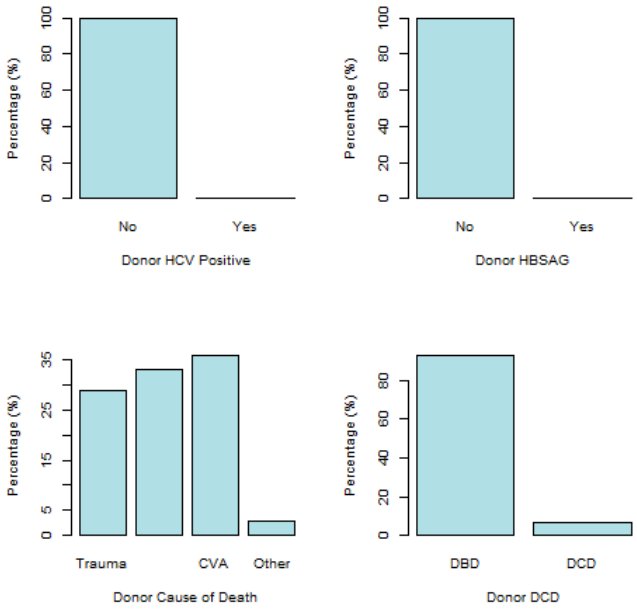

Figure C2. Bar chars of donor HCV, HBsAG, cause of death and DCD.

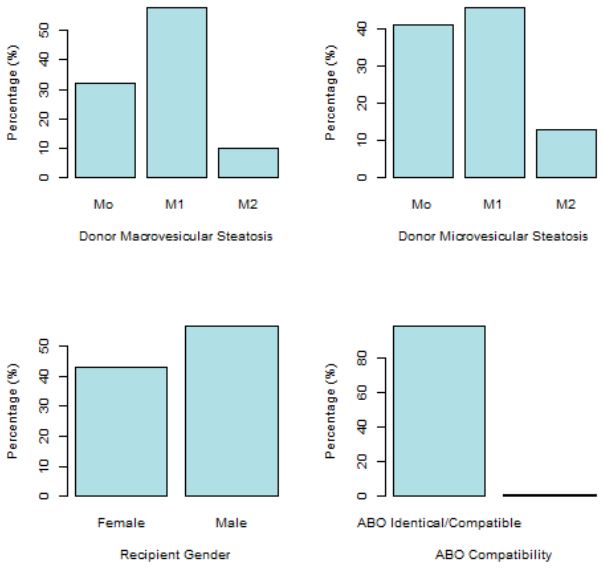

Figure C3. Bar chars of donor macrovascular steatosis, microvascular steatosis, recipient gender and ABO compatibility.

Distribution of Continuous Variables and Outlier Detection

The distribution of continuous variables was depicted using histograms with density and boxplots, to examine the shape of the distribution and detect the presence of outliers.

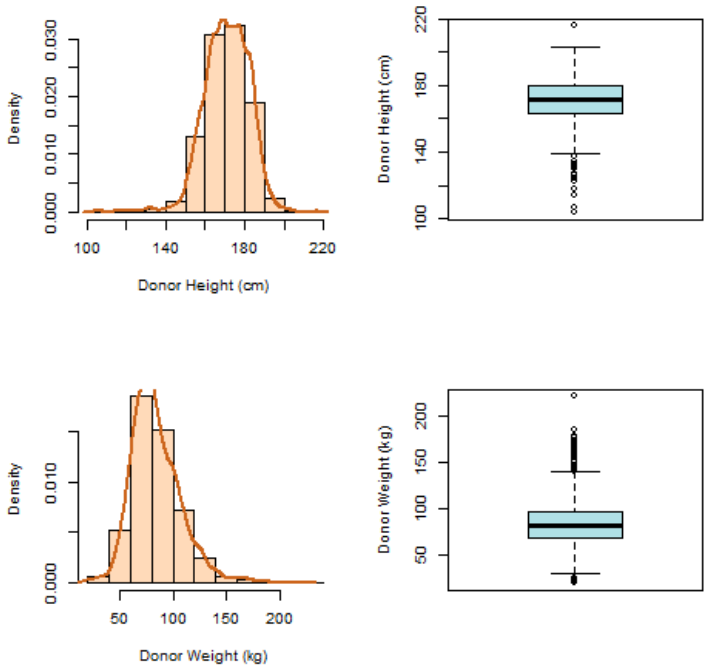

Figure C4. Histograms with density and boxplots o donor height and weight

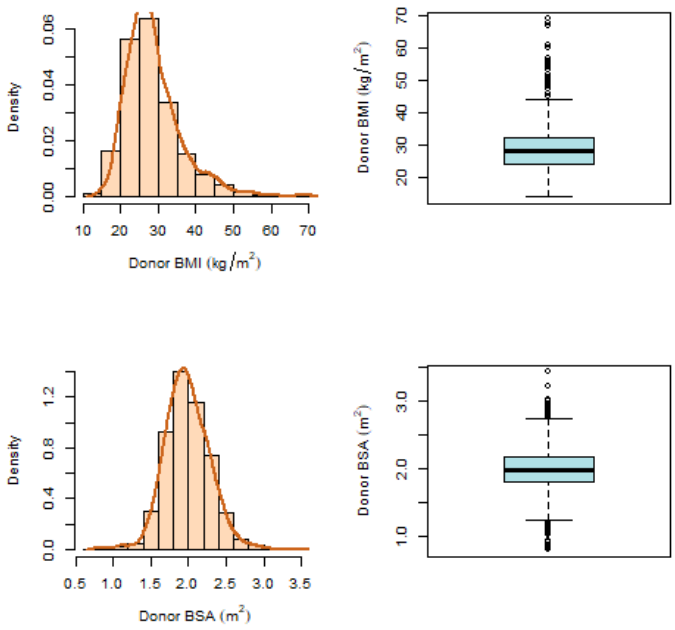

Figure C5. Histograms with density and boxplots o donor BMI and BSA

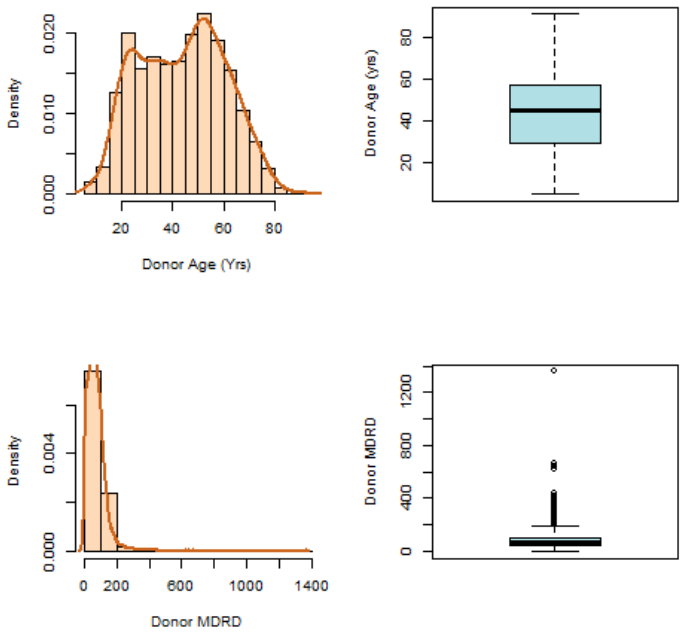

Figure C6. Histograms with density and boxplots of donor age and MDRD.

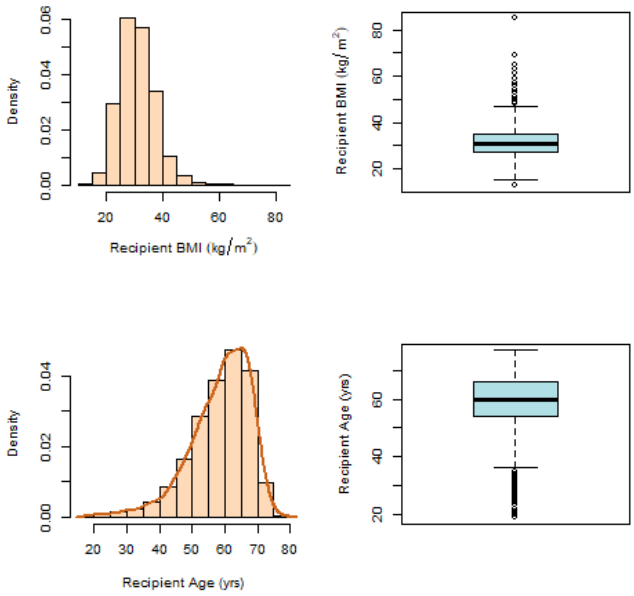

Figure C7. Histograms with density and boxplots of recipient BMI and age

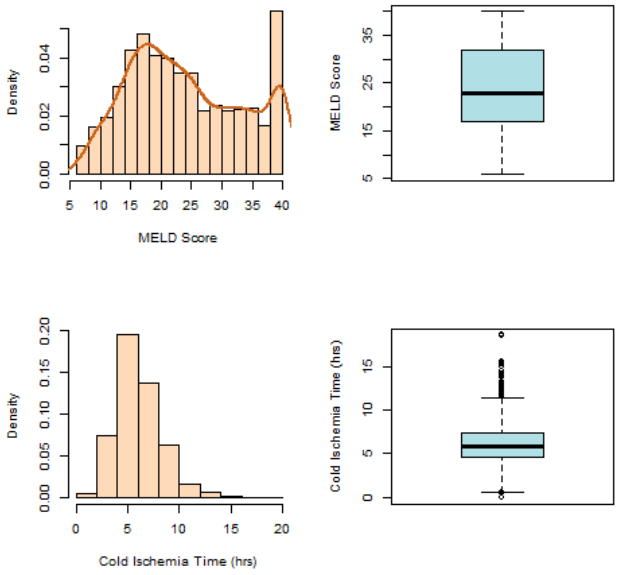

Figure C8. Histograms with density and boxplots of MELD score and cold ischemia time.

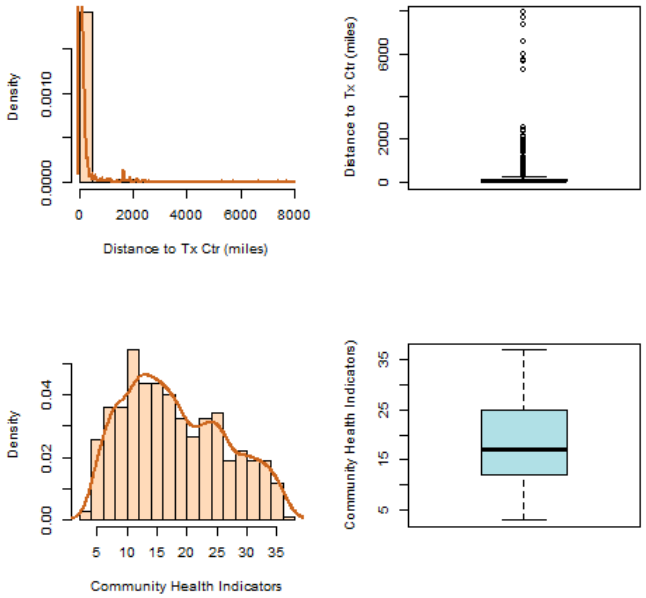

Figure C9. Histograms with density and boxplots of distance to transplant center and community health indicators.