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Determinants of racial disparities in outcomes from liver transplantation

By

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Doctor of Philosophy

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B.S.P.H., University of Miami, 2015

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An abstract of

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Abstract

Black patients experience significant and persistent disparities in survival after liver transplant, the only treatment for end-stage liver disease. The association of race, survival, and shorter-term outcomes, such as hospital admission, remains unclear. The overall goal of this project was to identify determinants of racial disparities in hospital admission and survival among liver transplant recipients.

In **Aim 1**, we used national data from a population-based registry of transplant recipients to determine whether the association of race with post-transplant survival differed by characteristics of the transplant center. While Black patients had lower post-transplant survival than White patients overall, racial disparities varied substantially across transplant centers. We did not find significant effect modification by center volume, proportion of minority patients, quality rating, or geographic region.

In **Aim 2**, we estimated the association between patient race and risk of hospital readmission within six months of transplant (**Aim 2A)**, and did not find a clinically meaningful difference in hospitalization between Black and White patients. In a mediation analysis, we found that readmission within six months of transplant did not impact the association between race and survival (**Aim 2B**).

In **Aim 3**, we used data from the Emory Transplant Center (ETC) to estimate the association between race and aspects of post-transplant hospitalization not collected in national data. We found that disparities in hospital admission rates arose in the late post-transplant period. Black patients were more likely to have rejection as a cause of admission, and were more likely to be admitted emergently than White patients.

In this dissertation, we identified substantial variation in racial disparities after liver transplantation across transplant centers that was not explained by selected characteristics. While race was not associated with readmission within six months of transplant in a national cohort, preliminary data from the ETC suggests that disparities in hospital admissions may arise beyond six months. Black patients appeared to have different causes of readmission than White patients, and differences in admission urgency may point to opportunities to prevent these admissions. Further research is needed to identify modifiable factors associated with racial disparities in hospital admissions and survival after liver transplant.

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This dissertation is dedicated to the memory of William McClellan, who believed it was possible long before I did.

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Chapter 1: Background and Literature Review

Chronic Liver Disease, End-Stage Liver Disease and Hepatocellular Carcinoma

Chronic liver disease (CLD) occurs when inflammation of the liver leads to the development of scar tissue that replaces healthy tissue, a process known as fibrosis[1]. Hepatic cirrhosis, or cirrhosis, occurs when fibrosis advances to the point that liver function becomes impaired, and is typically irreversible[2]. Cirrhosis can be classified by clinical states (Table 1.1) or by the presence or absence of decompensation. Patients with decompensated cirrhosis have developed complications associated with decreased liver function, including ascites, variceal bleeding, jaundice, or hepatic encephalopathy; patients with compensated cirrhosis have not yet experienced these complications. Decompensated cirrhosis is also referred to as end-stage liver disease (ESLD) and is accompanied by markedly increased mortality risk (20 – 57% per year)[3].

Table 1.1. Cirrhosis state definitions[4].

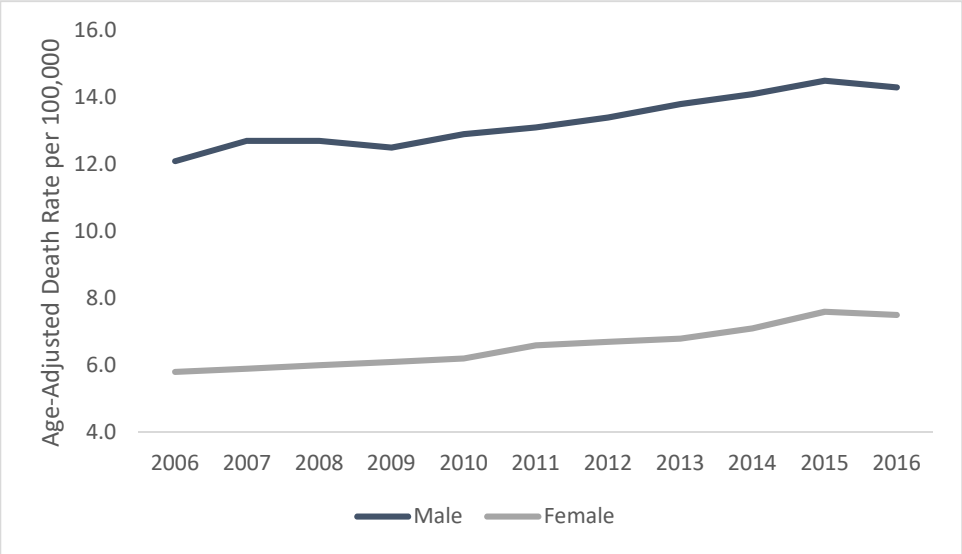
Clinical States of Cirrhosis	**Description**
State 1	Compensated cirrhosis without varices
State 2	Compensated cirrhosis with varices
State 3	Decompensated cirrhosis with variceal bleeding
State 4	First non-bleeding decompensation (ascites, jaundice, or encephalopathy)
State 5	Further decompensation (bleeding and ascites, jaundice and encephalopathy)

State 6	Late advanced decompensation (refractory ascites, infections, persistent encephalopathy, other organ system dysfunction)

Epidemiology of CLD and ESLD in Adults

In 2016, 4.9 million adults in the United States reporting having liver disease (2.0% of the population) and approximately 40,000 deaths were attributable to liver disease[5]. Liver disease is more prevalent among those aged 45 – 65, American Indians or Alaska Natives, Hispanics, those with less than a high school diploma, those living in poverty, and patients insured by Medicaid[5]. Death rates from liver disease have been steadily increasing since 2006 in both males and females (Figure 1.1)[6] and are highest in the West and the South[7].

Figure 1.1. Annual age-adjusted mortality rates from chronic liver disease and cirrhosis per 100,000 in the United States, stratified by sex, 2006 – 2016.



Liver disease can be caused by several different etiologic mechanisms, including viral infections, genetic disorders, autoimmune disorders, exposure to hepatotoxins, and lifestyle factors[1]. One major cause is chronic hepatitis C (HCV) infection, which affects approximately 3.5 million people in the United States[8]. Risk factors for HCV include injection drug use, HIV,

chronic hemodialysis, and receipt of clotting factor or blood transfusions before advanced blood testing became available[9]. Approximately 10% of those who are infected with HCV will develop cirrhosis over a period of 20 to 30 years; risk factors for progression include being male, being older than 50 years, using alcohol, having nonalcoholic fatty liver disease, being co-infected with HIV or HCV, and being on immunosuppressive therapy[9].

Another major disease etiology is alcoholic liver disease (ALD). In 2015 there were 21,028 deaths from ALD, representing 63% of all alcohol-induced deaths and over half of all deaths from liver disease[10]. While the amount of alcohol ingested is the most important risk factor for ALD[11], there is not a linear relationship between alcohol ingested and development of cirrhosis. Other risk factors for ALD include the type of alcohol consumed (beer or spirits are associated with increased risk) and pattern of drinking (binge drinking and drinking outside of mealtimes are associated with increased risk). While ALD is more common in men, women appear to be more susceptible to alcohol-mediated hepatotoxicity and may develop ALD at lower levels of alcohol consumption. Similarly, while binge drinking is less common among racial and ethnic minorities[10], alcoholic cirrhosis rates are higher among Black and Hispanic males compared to White males.

Non-alcoholic fatty liver disease (NAFLD) is another cause of liver disease that has increased in incidence due to the obesity epidemic. NAFLD includes a spectrum of severity ranging from nonalcoholic fatty liver (NAFL), which is typically asymptomatic, to nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. Extrapolation of National Health and Nutrition Examination Survey (NHANES) data suggests that over 400,000 people in the U.S. have NASH cirrhosis, and 4.1 million have NAFLD-associated fibrosis[12]. NAFLD is commonly associated with the metabolic syndrome and its associated comorbidities, including obesity, diabetes mellitus, and dyslipidemia[13]. Additional risk factors for NAFLD include increasing age, male sex,

and Hispanic ethnicity[13]. The growing prevalence of the metabolic syndrome and NAFLD-associated fibrosis predicts a rise in the prevalence of NASH cirrhosis in the coming years.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer[14]. HCC may develop during the course of liver disease[1], and nearly all cases occur in people with cirrhosis or chronic viral hepatitis[15]. There were approximately 40,000 cases of HCC diagnosed in 2018, and incidence has tripled since 1980[14], making HCC the cancer with the most rapid increase in incidence in the United States. If diagnosed early and within certain clinical criteria, HCC patients may benefit from liver transplantation[15]. HCC was the leading indication for liver transplantation in the United States in 2015[16].

Liver Transplantation

Liver transplantation is the only curative treatment option for patients with ESLD, and provides the best survival outcomes for selected patients with HCC[17]. The first liver transplant in the United States was performed in 1967[18], and since then there have been over 160,000 transplants[19]. The greatest challenge in the field of liver transplantation is the dearth of donor organs relative to the size of the population waiting for transplant. As of October 30, 2018, there were 13,691 candidates waiting for a liver; in 2017, only 8,082 liver transplants were performed[20]. Since there is no long-term treatment option for ESLD patients equivalent to maintenance hemodialysis for end-stage renal disease (ESRD) patients, this shortage of donor organs results in many patients dying while waiting for a liver.

Living Donor Liver Transplantation

One option for patients who need a liver transplant is to receive a living donor transplant. The living donor donates a portion of their liver to the transplant candidate, and their remaining

liver regenerates after the surgery. Living donor liver transplants are rare, making up approximately 4% of liver transplants in 2017[20], and the vast majority of these are adult-to-child transplants. Adult-to-adult living donor transplants do offer survival benefits to recipients[21], but they are much less common than deceased donor transplants. One reason that adult-to-adult living donor liver transplants are rare is that it is a technically challenging surgery, with increased risk to the donor due to the portion of liver transplanted (the right lobe for adults, compared to the left lateral lobe for children). Another reason that adult-to-adult living donor liver transplants are rare is that they are not typically recommended for patients with high MELD, due to lack of benefit. For these reasons, this dissertation will focus on deceased donor liver transplantation.

Deceased Donor Allocation

Livers are currently allocated on the basis of need, quantified using the Model for End-Stage Liver Disease (MELD) score. The MELD score is used for patients 12 and older and ranges from 6 to 40, with higher values indicating increased disease severity. The MELD score is used to predict 90-day mortality on the waiting list, and was selected to guide deceased donor liver allocation policy due to its high predictive ability across a broad range of liver disease etiologies and severity[22]. The MELD score is calculated using the lab values for creatinine, bilirubin, international normalized ratio (INR), and serum sodium[23] (Figure 1.2).

Figure 1.2. Formula to obtain MELD scores for a given patient over 12 years of age.

$$MELD_i = (0.378 * \ln(bilirubin) + 1.120 * \ln(INR) + 0.957 * \ln(creatinine) + 0.643) * 10$$

$$MELD = MELD_i + 1.32 * (137 - \mathrm{Na}) - (0.033 * MELD_i * (137 - \mathrm{Na})$$

For conditions where MELD does not accurately represent disease severity, most notably for HCC patients, standardized exception points are assigned to ensure these patients receive appropriate priority for transplantation[22]. For patients with equal MELD scores, waiting

time will determine their priority on for receipt of transplantation. Organs are not allocated on the basis of MELD for Status 1A and 1B patients. Status 1A patients are those who experienced acute liver failure (ALF) and have a life expectancy of hours to days, and Status 1B patients are pediatric patients (< 18 years of age) with severe illness. Status 1A and 1B patients make up less than 1% of the transplant waiting list[24].

The United Network for Organ Sharing (UNOS) facilitates deceased donor organ allocation in the United States. When a donor organ becomes available, patients on the waiting list that are not compatible with the donor on a variety of characteristics, including blood type, height, and weight, are screened out. For the remaining candidates, priority is assigned based on medical urgency (assessed using MELD) and geographic proximity to the donor. There are three tiers of proximity: local (in the same Donor Service Area [DSA] as the donor), regional (in the same allocation region as the donor) and national (remaining candidates in the nation).

Donor livers are offered to appropriate transplant candidates in the following categories, in order: local or regional Status 1A candidates, local or regional Status 1B candidates, local candidates with a MELD of 35 or greater, regional candidates with a MELD of 35 or greater, local candidates with MELD 15 – 35 in order of MELD score, regional candidates with MELD 15 – 35 in order of MELD score, national Status 1A or 1B candidates, national candidates with MELD > 15 in order of MELD score, and finally candidates with MELD < 15 (first locally, regionally, and then nationally). The receiving transplant center has the discretion to either accept or decline the organ offer.

Indications and Evaluation for Transplant

The presence of cirrhosis alone does not necessitate a liver transplant. Liver transplantation is broadly indicated in patients with ESLD and HCC for whom liver transplantation would extend life expectancy or improve quality of life[18]. The American

Association for the Study of Liver Diseases (AASLD) recommends that ESLD patients be evaluated for transplant once hepatic dysfunction results in a MELD score of $\geq$ 15[25].

Transplant evaluation is a lengthy process designed to determine whether candidates have any major comorbid conditions that may preclude successful liver transplant, ongoing substance abuse that may result in poor transplant outcomes, psychosocial issues or lack of social support that may be a barrier to having major surgery or interfere with their ability to adhere to immunosuppression after transplant, and any comorbidities that need to be treated before transplant[25]. The evaluation process varies by transplant center, however, it generally includes a financial screening, medical evaluation, surgical evaluation, anesthesia evaluation, and support services evaluation (Table 1.2)[26]. Potential contraindications include AIDS, active alcoholism or other substance abuse, advanced cardiac or pulmonary disease, malignant cancer, persistent non-adherence to medical care, uncontrolled sepsis, and inability to afford immunosuppressive medication after transplant[27]. Transplant centers have substantial freedom in deciding which candidates they will list for transplantation.

Table 1.2. Liver transplant evaluation process[26].

Event	**Description**
Referral	Referred to transplant center
Financial screening	Obtain approval from insurance companies for evaluation
Medical evaluation	
Hepatology assessment	Confirm diagnosis, optimize management
Laboratory testing	Assess hepatic function, electrolytes, renal function, viral serology, markers of other causes of liver disease, tumor

	markers, ABO-Rh blood typing, insulin clearance, creatinine clearance, urinalysis and urine drug screen
Cardiac evaluation	Electrocardiography, echocardiography, stress testing, cardiology consult (if risk factors are present and/or age 40 or older)
Hepatic imaging	Ultrasonagraphy for portal vein patency, CT or MRI for tumor screening
General health assessment	Chest X-ray, prostate cancer screening, Pap smear and mammogram, colonoscopy
Transplant surgery evaluation	Assess technical issues, discuss procedure risks
Anesthesia evaluation	Cardiopulmonary risk stratification for procedure; management of liver-related anesthetic considerations including hepatopulmonary syndrome, portopulmonary hypertension
Ancillary support services	
Psychiatry or psychology	If prior history of substance abuse, psychiatric illness, or adjustment difficulties
Social work	Address potential psychosocial issues and possible impact of transplantation on patient's social system
Financial counseling	Itemize costs of transplant and post-transplant care, help develop financial management plans

Nutritional support	Assess nutritional status and patient education

Care of the Liver Transplant Recipient

Immediately after surgery, most liver transplant recipients are admitted to the Intensive Care Unit (ICU) for hemodynamic, respiratory, and metabolic monitoring and support[28] before being transferred to the surgical ward[29]. Potential surgical complications include surgical or medical (coagulopathy) bleeding, thrombosis of the liver, leak or stricture of the biliary connection to the new liver, and infection. Potential medical complications in the immediate post-operative period include infections, respiratory complications, acute kidney injury, cardiovascular disease, neurologic complications, coagulopathies, and diabetes mellitus[27]. In the absence of these complications, discharge planning is possible by the second week after liver transplant; after discharge, a significant proportion of patients need either inpatient or home physical rehabilitation. Patients are seen frequently in the first 2-3 months post-operatively to assess surgical recovery, liver function and adequacy of immunosuppression[27].

Patients are required to take immunosuppression medication throughout the life of the allograft to prevent immune-mediated injury. Potential side effects of immunosuppression medications include increased risk of infection, chronic kidney injury, metabolic complications including diabetes and hypercholesterolemia, and cancer[30]. In addition to immunosuppression, long-term medical concerns for liver transplant recipients include cardiovascular disease and renal failure (the leading non-hepatic causes of mortality after liver transplant[31,32]), recurrent liver disease, and return to substance use (especially alcohol)[33]. The AASLD guidelines for long-term care of liver transplant recipients focus on reducing cardiovascular risk factors, suppressing or eradicating specific infections, improving surveillance for cancer, monitoring liver function, and preventing or treating recurrent liver disease[33].

Outcomes of Liver Transplantation

Optimizing outcomes from transplant is important to both patients and transplant centers. Transplant outcomes – most notably graft survival and overall survival - are used as quality metrics for the evaluation of transplant center performance, designation as Centers of Excellence, and reimbursement from the Centers for Medicare & Medicaid Services (CMS)[34]. CMS flags centers with poor outcomes, and these centers may be subject to probation or closure. In addition, centers with poor outcomes may be censured by UNOS or have contracts canceled by payers. Other outcomes, such as resource utilization and hospital readmission, are also important due to their impacts on long-term recipient health and cost of care.

Graft and Overall Survival

Graft survival refers to the functioning of the transplanted organ. Graft survival is often calculated in one of two ways. Death-censored graft survival is calculated from the date of transplant to the date of graft failure and censored for loss to follow up or death with a functioning graft. Graft survival (not censored for death) is calculated from the date of transplant to the date of graft failure or death censored for loss to follow up. Patient survival refers to overall survival and is calculated from the date of transplantation to the date of death, censored for loss to follow up. Graft survival and patient survival at one year after transplant is a quality metric used to assess transplant center performance[34]. One-year graft survival is currently at 89%, and 1-year overall survival is at 91%[20]. As 1-year survival continues to improve, attention has shifted to even longer-term outcomes. UNOS and the Organ Procurement and Transplantation Network (OPTN) both report three- and five-year graft and overall survival[20] (Table 1.3).

Table 1.3. Overall and graft survival for deceased donor liver transplant recipients in the United States, 2008 – 2015[20].

	Graft Survival (95% CI)	**Overall Survival (95% CI)**
1 – year	89.1% (88.7%, 89.4%)	91.2% (90.8%, 91.5%)
3 – year	80.0% (79.5%, 80.5%)	82.8% (82.2%, 83.3%)
5 – year	71.9% (71.3%, 72.4%)	75.0% (74.5%, 75.6%)

Predictors of Graft and Overall Survival – Patient Factors

Patient-level factors have been the primary focus of studies aiming to identify predictors of graft and overall survival. As graft failure is highly predictive of mortality, risk factors for graft failure and for overall mortality are similar. A study by Asrani et al.[35] using national-level data from the Scientific Registry of Transplant Recipients (SRTR) and center-level data from Baylor University, found that ventilator support, age > 60, hemodialysis, diabetes, or serum creatinine $\geq$ 1.5 mg/dl without hemodialysis were all associated with graft failure. Dave et al.[36] also used national level data to study graft loss among women, and found that young Black women were at particularly high risk for graft loss when compared to either young White women or older Black women. A single center study in Michigan[37] found that non-adherence to immunosuppression medication among liver transplant recipients was common and associated with increased risk of graft failure. A single center study in Italy[38] found that bilirubin, cold ischemia time, and MELD $\geq$ 25 were associated with increased graft loss within one year of transplant, while HCV-positivity and serum sodium concentration were predictive of patient survival.

One controversial topic is the ability of pre-transplant MELD to predict post-transplant survival. A systematic review[39] of studies that used pre-transplant MELD to predict survival after transplantation found that the majority of studies reported an association, but the predictive ability was often low (c-statistic < 0.70). Rana et al.[40] developed a score to predict survival after transplant that included several recipient characteristics, such as age > 60, BMI > 35, previous transplants, previous abdominal surgery, albumin < 2.0 g/dL, pre-transplant dialysis, pre-transplant ICU admission, MELD score > 30, pre-transplant life support, encephalopathy, portal vein thrombosis, and ascites. However, this score had low sensitivity (45%) and specificity (85%) and has not been widely adopted[41]. Many of the factors identified in this score involved pre-transplant resource utilization and disease severity, which have been found to be associated with survival in other studies. Bitterman et al.[42] conducted a study using SRTR data and found that pre-transplant ICU admission increased the risk of early post-transplant mortality independent of disease severity (as measured by MELD score). Van Wagner et al.[31] used OPTN data to study early cardiovascular mortality after transplant, and found that age, pre-operative hospitalization, ICU and ventilator status, calculated MELD, and portal vein thrombosis were all significantly associated with early CVD mortality.

Predictors of Graft and Overall Survival – Donor Factors

Characteristics of the organ donor also play a role in patient outcomes. Feng et al.[43] developed a Donor Risk Index using OPTN data from 1998 to 2002 in order to quantify the impact of donor characteristics on risk of graft failure. The DRI includes advanced donor age (relative to age < 40), donation after cardiac death (DCD), cause of death as a cerebrovascular accident (CVA) or anoxia (relative to trauma), receipt of a split/partial graft, non-White race, lower height, increased cold ischemia time (the time between the chilling of an organ after its blood supply is cut off and its warming after its blood supply is restored), and regionally or nationally shared organs (as opposed to local). The DRI is still widely used today, although

some[44] have called for it to be updated with MELD-era data and adapted to recipients with nonalcoholic fatty liver disease, who make up a larger portion of the disease population now than when the DRI was developed.

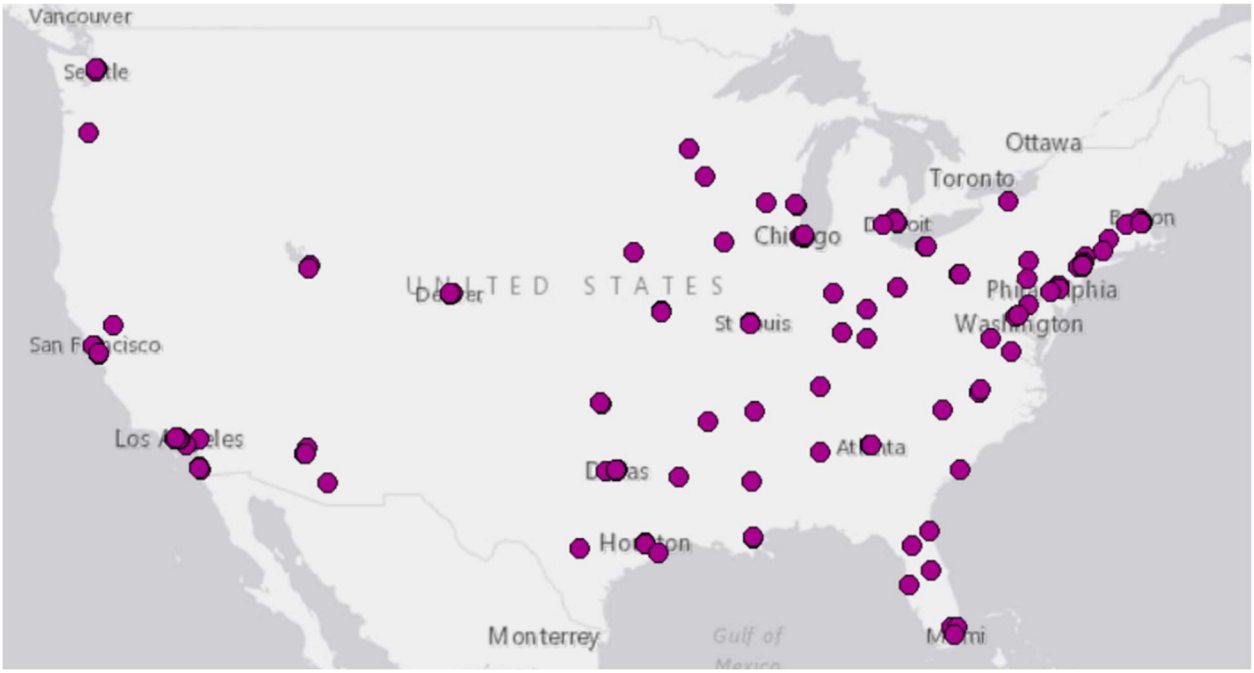
Donor race as a risk factor is controversial. Some studies have suggested that receiving an organ from a Black donor increases the risk of graft failure; however, Asrani et al.[45] found that after adjustment for transplant center, age, height, hepatitis B, recipient serum creatinine, and recipient HCV status, this association was not significant. However, racial mismatch may play an important role in graft failure and overall survival[46-48]; Black patients that receive organs from White donors appear to fare worse than Black recipients who receive organs from Black donors.

Transmission of infectious diseases from the donor to the recipient, including HIV, HCV, and HBV, is an area of public health concern. The U.S. Public Health Service published guidelines in July 2013 for designating donors as being at “increased risk” for potential transmitting latent infectious diseases. Factors that would classify a donor as “increased risk” include men having sex with men in the previous 12 months, injection drug use in the previous 12 months, people who have had sex in exchange for money or drugs in the preceding 12 months, or people who have had sex with a person known or suspected to have HIV, HBV, or HCV infection in the preceding 12 months[49]. Due to the increase in non-medical opioid use, there has been a rapid rise in donors classified as increased risk; nearly 20% were classified as increased risk in 2017[50]. Studies have found that increased risk donor organs are less likely to be utilized[51,52], but that they have similar or better graft and overall survival than non-increased risk organs[49].

Predictors of Graft and Overall Survival

There are approximately 150 centers currently performing adult liver transplantation in the United States (Figure 3). These centers are variable in their surgical expertise, donor and recipient selection criteria, and medical management protocols for post-transplant patients. This results in variation in transplant outcomes. Some studies have attempted to identify center-level characteristics that predict graft and overall survival in order to explain this variation.

Figure 1.3. Locations of adult liver transplant centers in the United States.



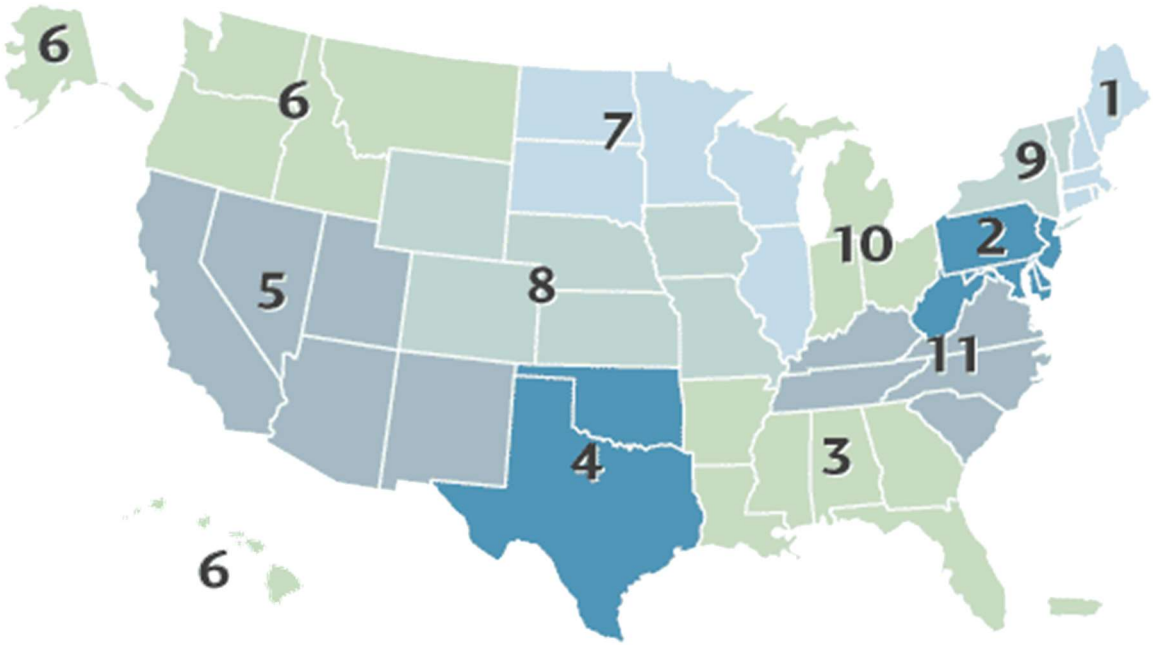
Asrani et al.[53] found that rates of graft loss per year varied from 5.9% in centers in the lowest quartile to 20.2% in centers in the highest quartile, independent of region and DSA. They did not find an association between center volume and graft failure but noted that centers with a high graft failure rate served a higher proportion of Black patients. However, Ozhathil et al.[54] found that high volume centers (HVCs) tended to use lower quality donor livers but achieve better allograft and patient survival compared to low volume centers (LVC). They attributed these findings to greater levels of expertise in these centers.

SRTR creates program-specific reports for transplant centers that include information on outcomes to facilitate patient decision making. Previously, they used a three-tier system to rank patient outcomes ("better than expected", "as expected" or "worse than expected"), in which the vast majority of centers were classed as "as expected". In an attempt to provide more useful information to patients, they recently released a 5-tier center-level quality rating system (1 = lowest, 5 = highest) for transplant programs based on the comparison of observed patient survival to expected survival[55]. Wey et al.[56] estimated the association with center quality rating at the time of listing and 1-year patient survival, and found that each additional tier was associated with a 7% decreased risk of mortality among liver patients. However, this rating system is controversial[57], with detractors citing its volatility as a major flaw[58].

Predictors of Graft and Overall Survival – Geography

Aside from transplant center-level variation in outcomes, outcomes vary by geographic region (Figure 1.4). Halldorson et al.[59] found that centers in areas of high competition (in DSAs where there is more than one center) listed more patients and used higher risk organs, but also performed transplantation for patients at a higher risk for graft failure and death. Hayashi et al.[60] found that Region 9 (including New York and Western Vermont) was more aggressive in listing patients and using high risk organs, with a corresponding decrease in graft survival that was statistically significant when compared to all other regions.

Figure 1.4. United Network for Organ Sharing (UNOS) regions.



Distance from the transplant center also plays an important role in post-transplant outcomes. Goldberg et al.[61] used Veterans Affairs (VA) data to demonstrate that greater distance from a VA transplant center, or any transplant center, was associated with a greater likelihood of death after transplant. However, this relationship is likely not linear[62], and was not observed in the U.K.[63] Area-level socioeconomic status is often associated with health outcomes, however, area-level socioeconomic status has not been associated with liver transplant outcomes in previous studies. We[62] used SRTR data and found that area-level socioeconomic status, as measured by the Community Health Score (CHS), was associated with mortality on the liver transplant waiting list, but not with survival after receiving a liver. Yoo et al.[64] also found that there was no association between neighborhood income and graft or overall survival.

Unplanned Hospitalization after Transplant

Transplant providers see liver recipients many times in the weeks following transplantation to monitor liver function and immunosuppression. In addition to these planned visits, many transplant recipients have unplanned readmissions – defined as unexpected admissions to the hospital requiring emergency medical care after an index hospitalization – in the weeks and months after transplant. These additional hospitalizations are a large contributor to the cost of liver transplantation[65] and are detrimental to both quality of life and long-term outcomes for patients[66]. Reducing unplanned readmissions is an area of high priority to the CMS[67], and while liver transplantation is not among the procedures included in the Hospital Readmissions Reduction Program, future expansions of this program may target costly, complicated procedures such as transplantation.[68]

Prevalence of Readmissions

Estimates of the prevalence of readmissions among liver transplant recipients, particularly early readmissions, are less precise than estimates of survival due to a lack of national registry data. One study that used the University Health Consortium[69] estimated that the overall 30-day readmission rate was 37.9%, with half of these patients being readmitted within 7 days of discharge. Nearly half (48%) of all liver transplant recipients were readmitted within 30 days. This study also found significant center-level variation in readmissions, with rates among hospitals ranging from 26.3% to 50.8%. Another study that used SRTR data[70] found that the hospitalization rate was 2.76 per patient year. A third study[69] that linked inpatient claims data with UNOS data found that 24.7% of liver transplant patients who were alive at discharge spent 30 or more days hospitalized in their first year after transplant. A single center retrospective study found that after 7 days post-discharge, 6% of liver transplant recipients had

at least one emergency department (ED) visit and 5% had at least one readmission; these proportions increased to 15% and 16% at 30 days, and to 35% and 45% at 30 days.[71]

Causes of Readmission

A single center study at the University of Cincinnati Medical Center found that the most common reasons for hospital readmission in the first 30 days after liver transplantation included infection (19.5%), renal insufficiency (9.3%), vomiting or diarrhea (8.5%) and pulmonary edema (7.6%). After 30 days, the most common reasons for hospital readmission were infection (24.8%), acute cellular rejection (8.5%) and biliary complications (7.1%).

Predictors of Readmission

Predictors of readmission vary by the time window considered. One study using the University HealthSystem Consortium[72] found that MELD, diabetes, hemodialysis, DRI, and discharge to a rehabilitation facility were all significantly associated with 30-day hospital readmission. In a study specifically examining hospitalization due to major adverse cardiovascular events (MACE)[73], age, alcoholic cirrhosis, NASH, pre-LT creatinine, baseline AF and stroke were all independently associated with MACE hospitalizations within 30 days. In a study of the state inpatient admissions databases for Florida and California[74], discharge to inpatient rehabilitation was associated with decreased odds of 30-day readmission when compared to discharge to home.

Several single center studies[62,67,6] have identified predictors of 90-day readmission, including renal function, MELD score at transplant, pre-LT admission to the hospital, age, length of stay, and hepatitis C infection. Reoperation, which involves an unplanned readmission, was required in 29.7% of liver transplant recipients within 90 days in the University HealthSystem Consortium[75]. Hemodialysis, illness severity, public insurance, MELD, and DRI were all associated with 90-day risk of reoperation. Longer-term studies of readmission are less

common. One national study using SRTR[70] found that recipient age, hepatitis C, diabetes, poor renal function, and receipt of a transjugular intrahepatic shunt procedure before LT was associated with risk of readmission within 6 months. In a single center study among Chinese liver transplant recipients[76], hepatic malignancy, previous abdominal surgery, complications, rejection, infection, and return to the operating room were associated with hospital readmissions in the first year after transplant.

Readmissions and Long-Term Outcomes

Patients who have unplanned readmissions after transplant are at increased risk for poor long-term outcomes, although the relevant time window is not clearly defined. One single-center study[77] found that patients who required readmission within 30 days had significantly lower survival than patients who did not. A study using SRTR data[70] found that the death rate was 22% higher for each readmission in the first 6 months after transplant. It is unclear whether unplanned readmission may play a causal role in poor long-term outcomes (for example, through increased exposure to infections), may simply be a marker for patients with poor prognosis, or both.

Preventing Readmission after Liver Transplant

While many studies have focused on identifying risk factors for readmission among liver transplant recipients, there have been relatively few that have translated these into actionable items to prevent readmission. The Carolinas Healthcare System implemented a quality improvement program at their transplant center aimed at reducing readmissions after liver transplant that included expanded multispecialty clinic access, coordinated “observation” stays in place of admissions, outpatient endoscopy to address biliary complications, and promoting local hospital lodging after discharge.[66] After implementing this program, 30-day readmission rates declined from 40% in the two years prior to 20% in the year after implementation[78]; the

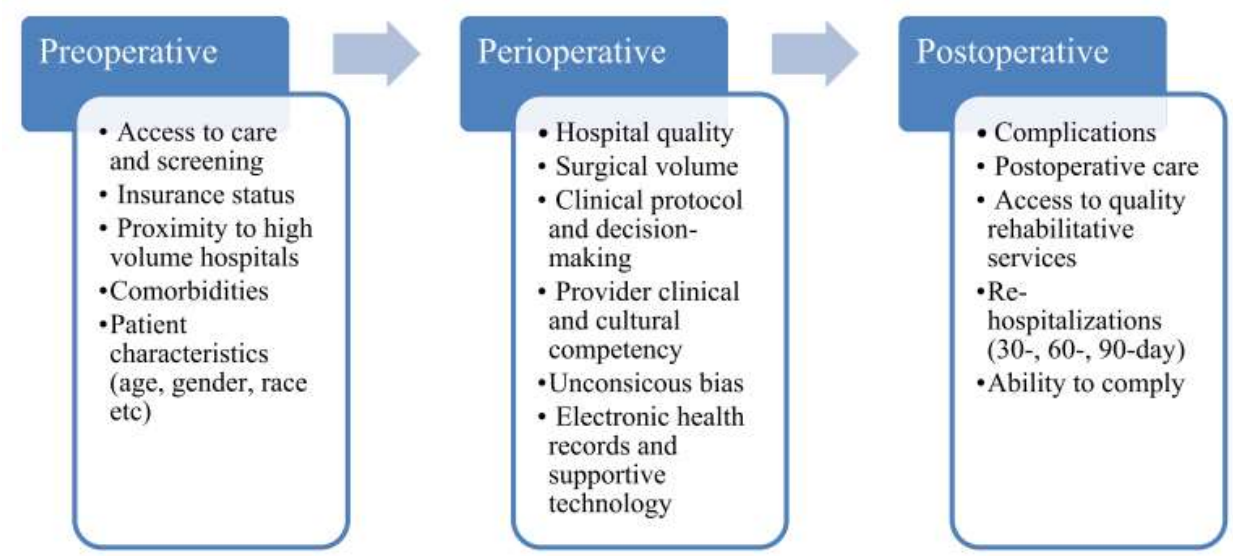
program was also successful in reducing 90-day readmissions.[79] Similarly, the University of Pennsylvania implemented a nurse practitioner-based post-transplant care program intended to improve continuity of care, increase the patient-to-provider ratio, and expand access to clinic visits, phone calls, and messages. They also found significantly reduced risks of readmission at 30 days (HR: 0.60, 95% CI: 0.39 – 0.90) and 90 days (HR: 0.49, 95% CI: 0.34 – 0.71).[80]

While they have not been studied in preventing readmissions among liver transplant recipients, multidisciplinary care teams have been found to improve quality of care, patient satisfaction, and clinical outcomes in other areas of hepatology.[81] In a systematic review of interventions to reduce hospital readmissions across all outcomes, Hansen et al.[82] categorized interventions into three groups: pre-discharge (patient education, discharge planning, medication reconciliation, appointment scheduled before discharge), post-discharge (timely follow-up, timely PCP communication, follow-up calls, patient hotlines, home visits), and "bridging" interventions (transition coaches, patient-centered discharge instructions, provider continuity). Bundled interventions appeared to be more successful than single interventions, but no intervention or bundle of interventions consistently reduced readmissions across the randomized controlled trials evaluated.

Disparities in Outcomes for Black Liver Transplant Recipients

As with many other health outcomes, there are substantial and well-documented disparities in liver transplant outcomes among Black patients compared to non-Hispanic White patients[83-85]. These disparities can be experienced at multiple time points along the health care trajectory, as described by Torain et al.[86] (Figure 1.5).

Figure 1.5. Potential avenues of surgical disparities within the health care trajectory[86].



Disparities along the Health Care Trajectory

Preoperative

Disparities in liver transplant outcomes likely begin as far upstream as disparities in the incidence and treatment of early liver disease. Acute HCV infection, binge drinking, NASH and ALD are all less common among Black patients than White[11,87,88]. However, HCV mortality is higher among Black patients[88] (likely due to limited access to care), and there is some evidence that Black patients are more susceptible to the damaging effects of alcohol at lower levels of consumption than White patients[11]. Further, Black patients have less access to primary care (for cirrhosis screening) and specialty care (for cirrhosis management), which may increase the risk of progression to decompensated cirrhosis among those with chronic liver disease.

The study of racial disparities in access to liver transplantation is challenging due to the lack of a registry of ESLD patients, such as the one that exists for end-stage renal disease patients (the United States Renal Data System, or USRDS). Despite this challenge, several

studies have identified racial disparities in access to transplantation in various populations. One single-center study of a VA hospital[89] found that Black patients were 85% less likely to be appropriately referred for liver transplant than their White counterparts. In a study that linked Pennsylvania inpatient records with transplant listing data, Bryce et al. found that Black ESLD patients were less likely to undergo evaluation, listing or transplantation, and that disparities were more pronounced in the earlier stages (evaluation and listing).[90]

Disparities have also been observed among surrogate ESLD populations. Among those listed for liver transplantation, Black patients are more likely to be listed at a higher MELD, potentially indicating delayed referral to transplant.[91] Among those diagnosed with hepatocellular carcinoma[92,93], who are captured by population-based cancer registries, Black patients are significantly less likely to undergo any treatment – particularly transplantation – than their White counterparts (6.3% vs. 3.4%). When liver waitlisting data is compared to population mortality data[94], Black patients have significantly lower access to transplant than White patients (liver waitlisting ratio [LWR]: 0.085 in Black patients vs. 0.154 in White patients).

Perioperative

There are few studies on racial disparities in perioperative factors, such as clinical decision-making, unconscious bias, and cultural competency, in liver transplant. Our preliminary analyses[95] indicate that a higher proportion of Black patients are treated in low-quality centers compared to high-quality centers, as rated by the SRTR 5-tier system. However, racial disparities in survival are more pronounced in high-quality centers. When compared to White patients who receive care in the lowest-quality centers, White patients who receive care in higher-quality centers have superior outcomes. However, Black patients in higher-quality

centers do not experience superior outcomes to Black-patients in lower quality centers, implying they do not derive the same benefit from increasing center quality as White patients.

Postoperative

Racial disparities in post-operative outcomes of liver transplantation are well documented (Table 1.4). In a study linking inpatient claims with UNOS data[69], investigators found that Black patients had 5 fewer days alive and out of the hospital (DAOH, a measure of disease burden in liver transplant recipients) in the first year of transplant than White patients, after adjusting for socioeconomic and geographic factors. Several studies using national data[96-98] have identified racial disparities in overall survival after liver transplantation. In a study using the University HealthSystem Consortium[99], Black recipients had higher risk of both graft failure (HR: 1.28, 95% CI: 1.14, 1.44) and death (HR: 1.31, 95% CI: 1.15, 1.50) after transplant even after controlling for recipient and donor characteristics, geographic region, donor service area, and individual hospital effects. However, some studies at selected academic transplant centers have demonstrated no short- or long-term disparities in survival by race, potentially indicating that disparities in survival are not inevitable.[100]

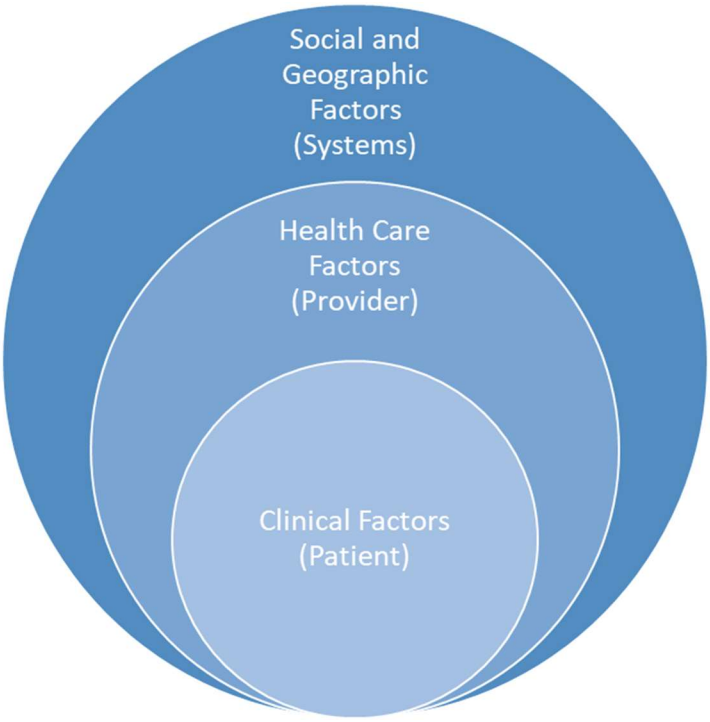
Table 1.4. Graft and patient survival after liver transplantation in the United States, by race[20].

	Graft Survival		**Patient Survival**	
	Black	White	Black	White
1 year after transplant	87.5%	89.0%	90.1%	91.1%
3 years after transplant	75.1%	80.6%	78.7%	83.4%
5 years after transplant	65.7%	72.5%	69.4%	75.6%

Potential Determinants of Disparities

As a theoretical framework for this dissertation, I will consider three unique categories of mechanisms of racial disparity in liver transplant outcomes: clinical (patient-level), health care (provider-level), and social (systems-level) factors[101]. While these categories are unique, they may interact with each other to influence racial disparities in outcomes (Figure 1.6).

Figure 1.6. Potential mechanisms of racial disparities in liver transplant outcomes.



Clinical Factors

Clinical factors, or individual-level disease attributes, are potential mechanisms for racial disparities in poor liver transplant outcomes. One proposed factor explaining racial disparities in outcomes is illness acuity. A study of ICU patients in California hospitals found that Black patients had more acute disease at ICU admission, and that adjustment for severity of illness resulted in the attenuation of racial disparities in hospital mortality and length of stay.[102] In a study of general surgery patients, Black patients experienced a higher burden of comorbidities

including hypertension and diabetes; after accounting for comorbidity, race was not associated with morbidity or mortality after surgery.[103] Black ESLD patients do present for transplant at a higher MELD than White patients[97], which could be due to differences in health-seeking behaviors, access to primary and specialty care, and care practices. Black ESLD patients may also experience a higher burden of comorbid conditions. However, disparities in outcomes persist after adjustment for these factors. In addition, liver transplant recipients are a highly selected group and undergo rigorous medical testing before transplantation, which should equalize some of the differences in underlying health status between the two groups.

Differences in underlying disease etiology may also play a role in liver transplant outcomes. Black patients are less likely than White patients to be listed for ALD or NASH, and more likely to be listed for hepatitis C (Table 1.5); this is consistent with racial differences in disease incidence. Wong and Ahmed[104] used SRTR data to evaluate the combined effect of disease etiology and race on liver transplant outcomes and found that Black patients had significantly lower survival than White patients among those with HCV and alcoholic liver disease, but not with other disease etiologies.

Table 1.5. Cause of underlying liver disease among Black and White liver transplant patients, 2012 – 2017[20].

	Black (N, %)	White (N, %)
Alcohol	428 (7.9)	10,641 (21.6)
Hepatitis C	2,125 (39.1)	13,022 (26.4)
Hepatocellular carcinoma	535 (9.8)	4,742 (9.6)
Non-alcoholic steatohepatitis	130 (2.4)	7,235 (14.7)

Other	2,218 (40.8)	13,672 (27.7)

Race-mismatch between donors and recipients has also been suggested to play a role in racial disparities and outcomes and may be modified by differences in underlying disease etiology. Layden et al.[47] conducted a prospective cohort of patients undergoing liver transplantation for HCV and found that Black patients with White donors had more severe fibrosis progression after transplantation than either White patients with White donors or Black patients with Black donors. The same authors conducted a similar study using national data and found that Black patients with White donors had a 66% higher mortality when compared to White recipients with White donors, while Black patients with Black donors had 18% lower mortality. Pang et al.[105] found that this detrimental association between race-unmatched grafts was only observed in those patients who were HCV positive, suggesting an alteration of the graft-host relationship by HCV. However, Silva et al. found a significant association (HR: 0.66, 95% CI: 0.49, 0.88) between race-matching and overall survival among Black liver transplant recipients for whom HCC was the primary indication.[48]

Medication adherence is another proposed mechanism for racial disparities in liver transplant outcomes. Non-adherence to medication is common among liver transplant recipients (22% – 62%), and has been associated with increased risk of graft failure[37] and number of readmissions[106]. Little is known about differences in immunosuppression adherence by race. Serper et al.[106] conducted data collection at two transplant centers and found that low levels of health literacy were associated with decreased adherence to immunosuppression medication after liver transplant. Health literacy is lower among Black patients compared to White patients[107]; if health literacy is strongly associated with decreased adherence, then it may represent a potential mechanism of racial disparities in liver transplant outcomes. In a study by Wedd et al. examining patient portal use after transplantation, which has been suggested to

improve medication adherence and health outcomes, Black liver transplant recipients were less likely to interact with the portal.[108]

Health Care Factors

A second potential mechanism of racial disparities in liver transplant outcomes is differences in access to and quality of health care. A review by Herbert et al.[109] on attributing racial differences in outcomes to quality of hospital care, identified three major pathways by which disparities occur: minority-serving hospitals providing worse quality care (between-hospital disparity), minorities receiving worse quality of care than nonminority patients at all hospitals (within-hospital disparity), and differences in upstream factors such as access to primary care and social support (hospital-independent factors); these pathways are not mutually exclusive.

There is a wealth of evidence that racial disparities are, at least in part, attributable to between-hospital disparity for some health conditions. Many studies have demonstrated that Black patients are more likely to be seen in lower quality hospitals. In a study of hospitals in the New York metropolitan area, Black patients were less likely to be seen at high-volume hospitals or by high-volume surgeries for ten surgical procedures for which a volume-outcome relationship had been established.[110] In a study of hospitals across in the United States, hospitals that were both low-quality and high-cost were found to be concentrated in the South, with a much higher proportion of elderly Black and Medicaid patients. These hospitals also had higher mortality rates for acute myocardial infarction and pneumonia.[111] In a study of Medicare and Medicaid beneficiaries hospital care was found to be highly concentrated by race; 5% of hospitals cared for approximately 45% of all Black patients, and 25% of hospitals cared for nearly 90% of elderly Black patients.[112] Creanga et al.[113] studied variation in the quality of obstetric care provided in minority serving hospitals, and found that Black-serving hospitals

performed worse than White-serving hospitals on 12 of 15 measured indicators (between-hospital disparity). They also found that Black and Hispanic patients at White-serving hospitals received worse quality of care than White patients (within-hospital disparity). Ly et al.[114] used Medicare data to study patient safety indicators in Black and White serving hospitals, and found that Black-serving hospitals performed significantly worse on 6 of 11 indicators (between hospital disparity). They also found that both White and Black patients had higher rates of potential safety events in Black-serving hospitals than White-serving hospitals. The importance of address between-hospital disparities was emphasized at a consensus meeting to set a national agenda for surgical disparities research, where improving care at facilities with a higher proportion of minority patients was identified as a research priority.[115]

As further evidence for the importance of between-hospital disparity, racial disparities in both quality of care and outcomes appear to be attenuated after adjustment for site of care and hospital factors. In a study using the University Health Consortium, Black patients were less likely than White patients to receive guideline concordant care for 12 of 13 healthcare quality measures. After adjusting for site of care, the magnitude of disparity was reduced.[116] In a study of the Nationwide Inpatient Sample, Black patients had higher mortality after emergency general surgery; however, this disparity was entirely explained by differences in hospital factors, including number of hospital beds and urban location. [117] Similarly, Taylor et al.[118] found that racial disparities in time to antibiotic treatment for septic patients were attenuated after adjustment for hospital-level differences.

There is also evidence supporting the presence of within-hospital racial disparities in treatment and outcomes. In a study of out-of-hospital cardiac arrests, Casey & Mumma found that non-White race was associated with lower rates of cardiac catheterization and worse neurologic recovery; they concluded that disparities in outcomes may be due to differences in in-hospital treatment.[119] Silber et al. compared surgical outcomes in teaching hospitals to non-

teaching hospitals, and found that the survival benefit of teaching hospitals was only experienced by White patients, not Black patients.[120] The authors hypothesized that this could be due to lower monitoring of Black patients compared to White patients, leading to delays in rescue. In a study using Medicare claims after general, orthopedic, and vascular surgery, receiving care at a teaching hospital was associated with improved outcomes after surgery; however, these benefits were not experienced by Black patients in these hospitals. [120] In a cross-sectional survey of medical providers at Johns Hopkins, implicit race and social class bias was present but was not associated with clinical decision-making in a series of vignettes. However, patient race and social class were associated with patient care in certain clinical scenarios, such as the increased likelihood of diagnosing pelvic inflammatory disease instead of appendicitis in young Black women compared to young White women.[121] This type of implicit bias may explain some within-hospital differences in care decisions by race.

Data on racial disparities in quality of care for liver disease patients are sparse. Chakrabati et al.[122] used National Inpatient Sample (NIS) data to study racial disparities in cirrhosis mortality. They found that Black patients were more likely to be seen in high-mortality hospitals, and after accounting for hospital-level characteristics, there were no differences in outcomes by race. Similarly, Nguyen et al.[123] found that Black patients with decompensated cirrhosis were less likely to receive certain treatments (palliative shunt or liver transplantation) when compared to Whites, which may contribute to disparate mortality. There are no published studies on variations among liver transplant recipients; however, our preliminary data suggest that there are both between-hospital and within-hospital disparities in this population.

Differences in the care received after transplant may also play a role in racial disparities in outcomes. Kothari et al.[124] used State Inpatient Databases for Florida and California to identify the outcomes of care fragmentation – defined as being readmitted to a different hospital than the one who performed the transplant – after liver transplant. They found that post-

discharge fragmentation increased the odds of both 30-day mortality and 30-day readmission. They also found that discharge to inpatient rehabilitation, compared to home, reduces the risk of mortality and time to first readmission after liver transplant[74]. In their sample, Black patients were much less likely to be discharged to inpatient rehabilitation than White patients.

Social Factors

Differences in social factors, particularly socioeconomic status (SES), often explain observed racial differences in health outcomes. SES shapes our physical and social environment, access to health-promoting resources, and interpersonal experiences; all of these factors can affect health. SES is also strongly determined by race, particularly in the United States. In a recent national study of inpatient surgical discharges, Witt et al.[125] found that racial disparities in surgical outcomes were explained by insurance and community characteristics, such as community-level SES.

However, this does not appear to be the case for racial disparities in liver transplant outcomes. Yoo et al.[64] used UNOS data to determine whether racial disparities were explained by education, neighborhood income, or insurance. They found that education and neighborhood income were not associated with graft or overall survival, while public insurance was associated with overall survival. Race remained strongly associated with survival after accounting for these factors. Similarly, Thammana et al.[126] found that racial disparities persisted in pediatric liver transplant outcomes after adjustment for SES. Most recently, Quillin et al.[98] used the University HealthSystem Consortium to assess the impact of SES on perioperative outcomes, including length of stay, in-hospital mortality, and 30-day readmissions. and found no significant associations.

SES is not the only social factor that has been shown to impact racial disparities in health outcomes. Other factors, such as discrimination, implicit bias, and residential

segregation, have all been associated with poor outcomes among Black patients. Dimick et al.[127] found that Black patients were more likely to undergo surgery at low-quality hospitals (as defined by a composite measure to predict procedure-specific mortality) in racially segregated regions; there was a strong relationship between living in a racially segregated area and the likelihood that Black patients had surgery at a low-quality hospital versus a high-quality hospital. In a study of outcomes from acute myocardial infarction, Black patients residing closest to lower-mortality hospitals were more often admitted to racially-segregated, high-mortality hospitals and to hospitals other than the closest one. Very little is known about social factors other than SES in the context of racial disparities in liver transplantation.

Summary of Critical Literature Review

Liver transplantation is the only life-saving therapy available for the growing population of ESLD patients in the United States. There are substantial disparities in transplant outcomes, including readmissions, graft survival, and overall survival, for Black patients when compared to White patients. There have been several studies on patient-level clinical factors associated with this disparity, including disease severity, etiology, and race-donor mismatch; however, these factors are unable to explain the persistent racial disparity in outcomes. Further research on the contribution of social and health care factors to liver transplant outcomes is critical to the development of multilevel interventions that reduce racial inequity and improve clinical care for all patients.

Chapter 2: Significance and Specific Aims

Study Motivation

Liver transplantation is the only curative treatment for ESLD, which kills approximately 50,000 people in the United States each year[128]. Black patients have lower graft function[99], inferior graft survival[129], and worse overall survival[130] after liver transplantation than White patients. This disparity remains after controlling for patient-level factors, such as socioeconomic status (SES)[64] and clinical covariates[99]. Center-level factors, such as center volume, are strongly associated with liver transplant outcomes[53,69,131], but it is unknown whether this association differs by patient race. Understanding the role of transplant centers in survival disparities is important because centers have strong incentives to improve patient survival[34] and provide the majority of post-transplant acute care[124]; high-disparity transplant centers are therefore ideal venues for targeted interventions to reduce racial disparities in survival. Further, identifying center characteristics that have a different effect on survival in Black patients than White patients may provide insight into the mechanisms underlying survival disparities, which are currently unexplained by patient-level factors.

While disparities in survival are well-documented, few studies have estimated the association between race and shorter-term outcomes, such as unplanned hospital readmissions, for liver transplant recipients. Such readmissions are common[68], costly[65], and associated with substantially increased risk of graft failure and death[66]. Hospital readmission after liver transplantation may be a marker to identify groups at high risk for poor outcomes, including mortality. If survival disparities are mediated by increased risk of hospital readmissions among Black patients, interventions that address the underlying determinants of readmission may be effective at reducing survival disparities.

The SRTR – the national registry of transplant recipients – documents whether recipients are hospitalized in the 6 months following transplant. However, there is no information collected on the timing of hospitalization within that interval, reasons for hospitalization, or the overall burden of hospitalization (frequently measured using days alive and out of the hospital [DAOH]); these characteristics provide important insight into the underlying mechanisms of hospitalization. Research on these factors largely relies on single-center studies and, to date, no studies have addressed whether there are differences in the timing of, burden of, or reasons for hospitalization by race. Such research could be used to generate hypotheses about the etiology of racial disparities in hospitalization after liver transplant.

Potential Application of the Results to Liver Transplantation

The results of this dissertation could be used to develop targeted, center-based interventions to improve outcomes among liver transplant recipients and ameliorate observed racial disparities in survival. Transplant centers are ideal venues for such interventions because they are strongly incentivized to improve patient outcomes by regulatory agencies, provide the majority of post-acute care for transplant recipients[124], and often participate in quality improvement initiatives[66,132]. In Specific Aim 1, I will identify characteristics of transplant centers with exacerbated racial disparities in outcomes. These centers represent appropriate locations for potential intervention. In Specific Aims 2A and 2B, I will estimate the association of race with a shorter-time outcome amenable to intervention (hospital readmission) and quantify the effect of that outcome on the relationship between race and survival. The results of these analyses will provide insight into whether hospital readmission is an appropriate target for our potential intervention. Finally, in Specific Aim 3, I will explore the association of race with characteristics of hospitalization. This analysis is hypothesis generating and intended to provide preliminary data on potential mechanisms of racial disparities in hospital readmission.

Potential Application of the Results Outside Transplantation

The results of this dissertation may also be useful outside of the field of transplantation. Black patients are at an increased risk of many chronic conditions, including cancer, diabetes, and cardiovascular disease; surgical intervention is often required for these conditions and disparities in outcomes exist across a range of surgical procedures[86]. This dissertation will contribute to the extant literature on racial disparities in surgical outcomes by providing insight into potential effect modification by place of care and by clarifying the relationship between race, hospital readmission, and survival.

Specific Aims

The objectives of this dissertation are to a) identify center-level factors associated with racial disparities in survival after liver transplantation, b) estimate the magnitude of racial disparities in hospital readmission and survival after liver transplantation, and c) explore differences in hospitalization characteristics by race among liver transplant recipients. The overarching research goal is to identify factors associated with racial disparities in short-term (hospitalization) and long-term (survival) outcomes of liver transplantation.

Specific Aim 1. To determine whether the association of race with post-transplant survival differs by center-level factors among Black and White patients who received a liver transplant between 2010 and 2017 in the United States (N = 33,997).

Hypothesis: *The association of race and survival will differ by center-level factors. For example, the disparity in survival among Black patients vs. White patients will be higher in SRTR Tier 1 centers than in SRTR Tier 5 centers.*

Specific Aim 2. A) To estimate the association of race with likelihood of hospital readmission within 6 months of hospital discharge after liver transplantation, among a retrospective cohort of

Black and White patients who received a liver transplant in the United States between 2010 and 2017. B) To estimate the controlled direct effect of race on survival after transplant after accounting for mediation by hospital readmission.

Hypothesis: (A) Black patients will have higher likelihood than White patients of hospital readmission within 6 months of discharge from receiving a liver transplant. (B) The controlled direct effect of race on survival will be meaningfully attenuated compared to the total effect of race on survival.

Specific Aim 3. To explore racial differences in the timing, burden, and reasons for hospitalization after discharge for liver transplantation among Black and White patients at the Emory Transplant Center (ETC) between 2010 and 2018 (N = 821).

This aim is hypothesis generating.

Chapter 3: Data Sources and Methods

Data Sources

Scientific Registry of Transplant Recipients

Specific Aims 1 and 2 are a retrospective cohort study of patients who received an orthotopic liver transplant in the United States between 2010 and 2017. Data on all solid organ transplant candidates and recipients in the United States are collected by the Scientific Registry of Transplant Recipients (SRTR), a disease registry maintained by the Minneapolis Medical Research Foundation. SRTR collects clinical and demographic variables about candidates for organ transplantation, as well as information about surgical procedures undergone by recipients, and characteristics of donor organs. After transplant, SRTR follows recipients at 6 months, 1 year, and then annually until death, re-transplantation, or loss to follow-up.

Emory Transplant Center

Specific Aim 3 is a retrospective cohort study of patients who received a liver transplant at the Emory Transplant Center (ETC) between 2010 and 2017. The ETC is the 7th largest transplant center in the country and performs approximately 120 liver transplants per year. Data will be obtained from the Emory Transplant Data Mart, an integrated data repository for all transplant recipients at the ETC that includes data from 5 hospitals and over 600 outpatient clinics as well as appointment data, billings/claims data, and laboratory data.

Study Population

Specific Aims 1 and 2

The cohort for Specific Aim 1 will be defined as patients who 1) are over 18 years of age, 2) received a liver transplant in the United States between January 1, 2010, and December 31, 2017), 3) are non-Hispanic Black or non-Hispanic White, 4) did not receive a simultaneous

transplant of another organ, and 5) had not had a prior liver transplant. Patients who had acute liver failure, acute alcoholic hepatitis, or received a living donor liver transplant will be excluded. The cohort for Specific Aim 2 will have the same criteria as Specific Aim 1, with an additional exclusion of patients who died during their initial post-transplant stay.

Specific Aim 3

The cohort for Specific Aim 3 will be defined as patients who 1) are over 18 years of age, 2) received a liver transplant at the Emory Transplant Center between January 1, 2010, and December 31, 2017), 3) are Black or non-Hispanic White, 4) did not receive a simultaneous transplant of another organ, 5) had not had a prior liver transplant, and 6) were discharged alive from the ETC. Patients who had acute liver failure, alcoholic hepatitis or received a living donor liver transplant will be excluded.

Variables

Exposure

The primary exposure for all aims is race, dichotomized as non-Hispanic Black or non-Hispanic White. In this study, race is considered a social construct and a proxy for the experience of individual and institutional racial discrimination as an adult; this is distinct from potential effects of race that arise from physical phenotype, parental physical phenotype, genetic background, and family socioeconomic status. Race is reported by the transplant centers to SRTR, and therefore it is unclear whether race is in this dissertation represents patient- or provider-reported race; it may be a mix of both depending on transplant center reporting practices.

Outcomes

The primary outcome of Specific Aim 1 and Specific Aim 2B is time to graft failure or death after liver transplant, which is the outcome metric used by SRTR in program-specific reports for transplant centers. Patients will be censored at the date of death, graft failure, loss to follow-up, or the end of the study period (December 31, 2019), whichever occurs first. Information on graft failure and overall survival is available in the follow-up file of SRTR.

The primary outcome of Specific Aim 2A is hospital readmission within 6 months (dichotomized as yes or no). Information on hospital readmission after transplantation is available in the follow-up file of SRTR.

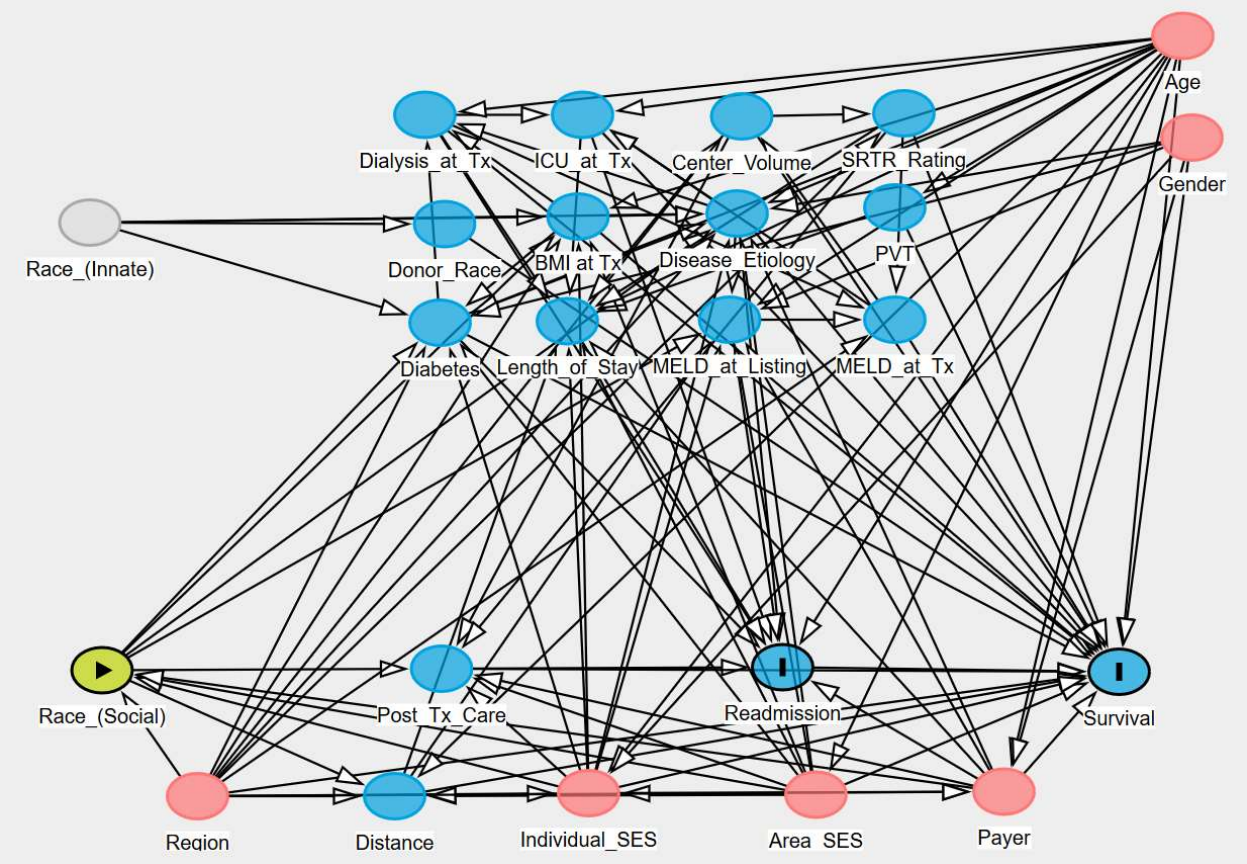
For Specific Aim 3, I will explore a variety of outcomes of interest related to the post-transplant hospital admissions. Outcomes are separated into two categories: patient-level outcomes and admission-level outcomes. The first patient-level outcome of interest is time to first admission. Previous research in kidney transplant recipients suggests that the determinants of admission vary by the timing of the window, so we considered three windows of admission risk: “early” (within 30 days of transplant discharge), “medium” (within 6 months of transplant discharge), and “late” (over the entire study period). Patients are censored at the date of their first admission, death, graft failure, date of last contact with the transplant center, end of the window or December 31st, 2019, whichever occurred first. The second patient-level outcome is the overall number of admissions to the ETC. The third patient-level outcome is the number of days alive and out of the hospital (DAOH), which has been previously validated as a measure of disease burden in liver transplant recipients[69]. DAOH was calculated as the number of days alive minus the number of days admitted to ETC, both in the first year after transplant and overall.

The first admission-level outcome is the length of stay for each admission, in days. The second is the reason for admission, defined using ICD-9 and ICD-10 codes. Codes were classified into six broad categories by two clinicians, including rejection, infection, surgical / technical, liver, renal, and frailty. Each admission could be caused by none, one, or multiple of these classifications. Other admission-level outcomes included urgency (whether admission was planned, urgent, or emergent) and intensity (whether the patient required ICU care during their admission).

Covariates

Causal Model

Figure 3.1. Proposed directed acyclic graph (DAG) for the relationship between race, admissions, and survival.



To create this DAG, I included all factors that predicted hospital readmission or survival after liver transplant identified through the literature review as well as plausible pathways between them. Assuming that race is a social construct and a proxy for institutional and individual discrimination, race is "caused" by region, individual socioeconomic status, area socioeconomic status, and payer. Age and gender are also on open biasing pathways between the exposure and the outcome.

Specific Aim 1

The purpose of Specific Aim 1 is to determine whether the association of race and survival differs by center-level characteristics. Our selected characteristics include transplant volume (dichotomized at the median), SRTR quality rating, and proportion of Black patients at the center (dichotomized at the median), and geographic region (collapsed from UNOS regions to Northeast, South, Midwest, and West). For this type of research question, it is necessary to adjust for confounding of the race-survival association, but not the center-survival association. Because our question of interest includes the overall public health impact of racial disparities (i.e. the crude association) as well as the transplant center perspective (i.e. the association adjusted for factors that occur prior to transplant), we used a sequential adjustment approach where we first presented the crude association, then adjusted for clinical covariates that occurred prior to transplant or at the time of transplant (age at transplant, year of transplant, MELD at transplant, underlying liver disease etiology, medical condition at transplant, body mass index [BMI] at transplant, donor risk index [DRI], portal vein thrombosis [PVT], history of diabetes, and dialysis at transplant), then additionally for sociodemographic confounders identified in the DAG (educational attainment, zip-code income, and primary payer), and finally additionally for center-level characteristics.

Specific Aim 2

The purpose of Specific Aim 2A is to estimate the association between race and readmission to the hospital within 6 months of initial transplant discharge. Analyses were adjusted using the sequential approach described in Aim 1.

The purpose of Specific Aim 2B is to estimate the controlled direct effect of race on survival after accounting for potential mediation by readmission, which require control of both exposure-outcome and mediator-outcome confounding. I will control for race-survival confounders including age, gender, region, educational attainment, zip-code income and primary payer. Based on the DAG as written, there are several possible minimally sufficient sets to control for confounding of the readmission-survival relationship, including (age, area SES, BMI, center volume, diabetes, dialysis at transplant, disease etiology, donor race, gender, ICU at transplant, individual SES, MELD at transplant, payer, region, and SRTR rating), (age, area SES, BMI, center volume, diabetes, disease etiology, donor race, gender, ICU at transplant, individual SES, MELD at transplant, portal vein thrombosis, payer, region, and SRTR rating), (age, area SES, center volume, gender, ICU at transplant, individual SES, length of stay, MELD at transplant, payer, race, and SRTR rating), (age, area SES, center volume, gender, ICU at transplant, individual SES, MELD at transplant, payer, race, region, and SRTR rating), and (age, ICU at transplant, individual SES, length of stay, MELD at transplant, payer, and post-transplant care). I will use the set (age, area SES, center volume, gender, ICU at transplant, individual SES, MELD at transplant, payer, race, region and SRTR rating) due to its combination of parsimony and reduced likelihood of measurement error based on the variables involved. I will conduct a sensitivity analysis using other potential sets of confounding variables

Specific Aim 3

The purpose of Specific Aim 3 is to explore the association of race with characteristics of post-transplant hospitalization, including timing, burden, and reasons for readmission. Analyses

will be adjusted sequentially, as described in Specific Aims 1 and 2A, with the exception of center-level factors, as all transplants in this aim occurred in the same center.

Analytic Methods

Aim 1

First, I will use descriptive statistics (mean, median, and proportion) to describe baseline characteristics clinical and demographic characteristics of the population. I will use Kaplan-Meier curves to estimate the bivariate association of race and survival, not adjusted for any other covariates.

One of the potential products of this dissertation is preliminary evidence for the development of targeted, center-based interventions to improve outcomes among liver transplant recipients and ameliorate observed racial disparities in survival. To identify appropriate centers for such intervention, we should target those where the most cases could potentially be prevented; identifying these subgroups requires the use of deviation from additive interaction as the measure of interest. Since the Cox proportional hazards model is on the multiplicative scale, it is less appropriate for this purpose than the additive hazards model, which is on the additive scale[109].

To answer my research question, I will fit a hierarchical additive hazards model to estimate the association between race and survival, accounting for the covariates listed above and potential effect modification by center characteristic. I will consider both statistical and clinical significance when evaluating effect modification. A total of four models will be fit (one for each center characteristic of interest). All analyses will be performed in R, using the “timereg” package for additive survival analysis[109].

Aim 2A

Descriptive statistics (mean, median, and proportion) will be used to describe baseline characteristics by race. Continuous variables will be compared using t tests, and categorical or binary variables will be compared using the chi-square test. To compare differences in the risk of hospital readmission after transplant, I will use multivariable log-binomial regression. To decide what covariates to include in the final model, I will use a DAG. I will use generalized estimating equations to account for clustering within centers.

Aim 2B

Our goal is to estimate the controlled direct effect of race on survival. This requires two assumptions: no exposure-outcome confounding and no mediator-outcome confounding. In a situation where mediator-outcome confounders are affected by exposure, marginal structural models using inverse probability of treatment weighting (IPTW) can be used. In this analysis, race would likely affect any given mediator-outcome confounder (such as disease etiology). In order to estimate the controlled direct effect of race on survival, I will conduct a mediation analysis using marginal structural Cox models with IPTW to account for potential confounders of the race-survival and readmission-survival associations. I will calculate two separate weights – one for potential confounders of the race-survival association (age, gender, region, individual SES, area SES, and payer) and one for potential confounders of the readmission-survival relationship (age, area SES, center volume, gender, ICU at transplant, individual SES, MELD at transplant, payer, race, region and SRTR rating). Analyses will be conducted in SAS 9.4[110].

Aim 3

Analyses will be divided into two categories of outcomes: patient-level and admission-level outcomes. For patient-level outcomes, we will use linear regression to estimate the association between race and DAOH, and Cox proportional hazards models to estimate the association between race and time to admission within 6 months. For admission-level

outcomes, we will use generalized estimating equations (GEE) to account for the potential for multiple admissions by the same patient. We will use linear regression to estimate the association between race and length of stay, log-binomial regression to estimate the association between race and cause of admission, log-binomial regression to estimate the association between race and ICU stay during admission, and multinomial logistic regression to estimate the association between race and acuity of stay. All analyses are presented first unadjusted, and then adjusted for demographic, clinical, and socioeconomic characteristics as described above.

Chapter 4: Aim 1

Abstract

Background: Little is known about the role that transplant centers may play in perpetuating racial disparities after liver transplantation, which are unexplained by patient-level factors. We examined variation in between- and within-center disparities among 34,114 Black and white liver transplant recipients in the United States from 2010 to 2017 using Scientific Registry of Transplant Recipient (SRTR) data.

Methods: We used Cox proportional hazards models to calculate transplant center-specific Black-white hazard ratios and hierarchical survival analysis to examine potential effect modification of the race-survival association by transplant center characteristics, including transplant volume, proportion of Black patients, SRTR quality rating, and region. Models were sequentially adjusted for clinical, socioeconomic, and center characteristics.

Results: After adjustment, Black patients experienced 1.11 excess deaths after liver transplant per 100 PY compared to white patients (95% CI: 0.65, 1.56), corresponding to a 21% increased mortality risk (95% CI: 1.12, 1.31). While there was substantial variation in this disparity across transplant centers, there was no evidence of effect modification by transplant center volume, proportion of minority patients seen, quality rating, or region.

Conclusion: We found significant racial disparities in survival after transplant, with substantial variation in this disparity across transplant centers that was not explained by selected center characteristics. This is the first study to directly evaluate the role transplant centers play in racial disparities in transplant outcomes. Further assessment of qualitative factors that may drive disparities, such as selection processes and follow-up care, is needed to create effective center-level interventions to address health inequity.

Introduction

Liver transplantation is the only potentially curative treatment for end-stage liver disease, which kills approximately 50,000 people in the United States each year.[128] Black patients have lower graft function,[99] inferior graft survival,[129] and worse overall survival[130] after liver transplantation than White patients. This disparity has remained consistent over time[133] and persists after controlling for patient-level factors, such as socioeconomic status[98] and clinical covariates.[99] Improving outcomes for these patients, who are already less likely to be waitlisted for transplant,[89,92] is critical to ensuring equitable benefit from liver transplantation.

Little is known about the role that transplant centers may play in perpetuating or mitigating racial disparities in liver transplant outcomes. The idea that transplant centers may play a role in racial disparities is particularly plausible because of the documented importance of center-level factors to liver transplant outcomes in general.[62,131] Understanding the role of transplant centers in outcome disparities is important because centers have strong incentives to improve patient survival[34] and provide the majority of post-transplant acute care[124]; high-disparity transplant centers are therefore ideal venues for interventions to reduce racial disparities in liver transplant outcomes. Targeted interventions could be developed by identifying specific centers or types of centers with exacerbated racial disparities. Further, understanding the role of transplant centers in racial disparities may provide insight into the mechanisms underlying these disparities, which are currently unexplained by patient-level factors.

The objective of this study was to explore the role of the transplant center in survival disparities among Black liver transplant recipients. First, we described differences in transplant center characteristics between Black and non-Hispanic White transplant recipients (between-hospital disparity) and estimated variation in racial disparities across transplant centers (within-hospital disparity). Next, we assessed whether differences in racial disparity between transplant centers arose from potential effect modification by transplant center characteristics. To do so,

we used data from the Scientific Registry of Transplant Recipients (SRTR) on Black and White liver transplant recipients in the United States from 2010 to 2017.

Methods

Data Sources and Population

Data on liver transplant recipients was obtained from SRTR, a population-based registry of all solid organ transplant candidates, donors, and recipients in the United States. We included 40,776 adult (age $\geq$ 18) patients who were non-Hispanic Black or white and received a deceased donor liver transplant between January 1, 2010 and December 31, 2017. Patients were excluded if they received a simultaneous transplant of another organ (n = 3,746), had a prior liver transplant (n = 1,690), had acute liver failure (n = 1,189), or had acute alcoholic hepatitis (n = 134).

Variables

Race was reported by medical providers and dichotomized to non-Hispanic Black or white. Our primary outcome of interest was time to graft failure or death. Survival time was calculated as the time between receipt of transplant and date of death or graft failure, whichever occurred first, and divided by 365.25 to give survival time in years. Patients were censored at loss to follow-up or the end of the study period (December 31, 2018).

To explore whether racial disparities in outcomes arose from differential prevalence of important center characteristics or from the differential effect of given center characteristics by race, we selected four potential center characteristics of interest. Center characteristics were selected by reviewing the literature on factors associated with transplant outcomes and factors associated with racial disparities in other surgical outcomes. Transplant volume was defined as the number of adult liver transplants performed by the center in the year that the recipient received their transplant and was classified into tertiles by year (called “low,” “medium” and

“high volume” centers). Proportion of Black patients was defined as the percentage of Black adult liver transplants performed by the center in the year that the recipient received their transplant, classified into tertiles (“low”, “medium”, and “high minority” centers). Transplant center quality was defined using the SRTR 5-tier system for observed outcomes. Briefly, tiers are assigned based on the hazard ratio distribution of observed graft and patient survival in the first year after transplant compared with expected post-transplant survival, with Tier 5 representing the best performance. Geographic region of the transplant center was assigned according to the U.S. Census regions (Northeast, Midwest, South, and West). All time-varying center characteristics, including transplant volume, proportion of minority patients, and center quality, were assigned by year of transplant in order to account for variation over time.

Clinical covariates included age, year of transplant, sex, Model for End-Stage Liver Disease (MELD) score at transplant (a measure of disease severity), underlying cause of disease, presence of hepatocellular carcinoma (HCC) recipient medical condition at transplant, body mass index (BMI), donor risk index (DRI), portal vein thrombosis (PVT), diabetes mellitus, and dialysis at transplant. Underlying cause of disease was categorized as hepatitis C, alcoholic liver disease, non-alcoholic steatohepatitis (NASH) and other. Candidate medical condition at transplant was categorized as: in intensive care unit (ICU), hospitalized but not in ICU, and not hospitalized. The DRI is a validated score used to estimate the risk of graft failure based on donor characteristics, including donor age, race, cause of death, cold ischemic time, height, whether the donation was after cardiac death, and whether the graft was a split or partial graft. Socioeconomic covariates included educational attainment, zip-code level income, and insurance type. Educational attainment of the patient at the time of listing was categorized as “less than high school,” “high school diploma,” “some college,” and “associate’s degree or higher.” Insurance type was assigned based on the primary payer for the transplant (categorized as “public”, “private”, or “other”).

Statistical Analysis

We described clinical, demographic, and transplant center characteristics of our population, both overall and by race. To characterize center-level variation in racial disparities, we used Cox proportional hazards models to calculate center-specific Black-white hazard ratios for centers that had transplanted at least one Black patient between 2007 and 2017, adjusted for clinical and socioeconomic characteristics.

We used hierarchical additive survival analysis to estimate the absolute survival difference between Black and white patients, and hierarchical Cox proportional hazards models to estimate the relative hazard ratio over the entire time period. Models were hierarchical to account for potential clustering of outcomes within transplant centers, where patients treated in the same transplant center may have more similar outcomes to each other than to patients treated elsewhere. We sequentially adjusted models by including clinical, socioeconomic, and center characteristics, as described above. Missing values were imputed for the 21% of patients missing at least one covariate through chained random forests and predictive mean matching using the missRanger package. The presence of effect modification of race by transplant center characteristics was assessed through both statistical significance (p for interaction < 0.05) and clinical significance (magnitude of difference between the associations). We also used hierarchical additive survival analysis and Cox proportional hazards modeling to estimate the association of center characteristics with survival separately for both white and Black patients.

We performed a supplementary analysis to further characterize center-level variation in racial disparities. Using center-specific hazard ratios, we classified centers into tertiles of disparity (low, medium, and high). We estimated Kaplan-Meier curves for Black and white patients at centers in each tertile to visualize survival differences within and between tertiles. All analyses were performed in R 3.5.3.

Results

Study Population

We identified 34,114 Black and white patients who received a liver transplant at 128 U.S. centers between January 1, 2010 and December 31, 2017. The median follow-up time was 3.5 years (IQR: 1.8, 5.9). Demographic and transplant center characteristics, stratified by race, are provided in Table 4.1. Approximately 10% (n = 3,609) of transplant recipients in this time period were Black, while 90% were white (n = 30,505). The mean age of transplant recipients at listing was 55.3 years, with a mean MELD at transplant of 20.9. The majority of transplant recipients were male (67.8%), although a higher proportion of Black recipients than white recipients were female (39.3% vs. 31.4%). Black patients were more likely to have high school education or less (48.4% vs. 41.9%), lower annual household income in the zip code (53,200 vs. 64,400), and public insurance (51.1% vs. 41.4%) than white patients. Underlying cause of disease etiology also varied by race, with Black patients being more likely to have hepatitis C (51.5% vs. 37.7%) but less likely to have alcohol-associated liver disease (7.0% vs. 18.5%) or NASH (5.1% vs. 17.2%) than white patients; Black patients were also less likely to have PVT (8.9% vs. 13.5%). Medical condition at transplant, recipient BMI, dialysis, and DRI did not vary substantially by race.

Racial Differences in Transplant Center Characteristics

As expected, the majority of transplant recipients (65.8%) received a transplant at a high-volume transplant center; this proportion did not vary substantially by race. The majority of Black patients received a transplant at a transplant center in the highest tertile of minority patients (62.7%), while only 28.8% of white patients received a transplant at these centers. Black transplant recipients were more likely than white patients to receive care at a Tier 1 (8.0% vs. 7.0%) or Tier 2 (28.7% vs. 24.1%) center, and less likely to receive care at a Tier 4 (21.6%

vs. 25.4%) or Tier 5 (12.1% vs. 13.9%) center. Over half of Black patients received their liver transplant in the South (54.0%), compared to 41.6% of white patients.

Variation in Racial Disparities in Survival by Transplant Center

Over the study period, there were 861 “events” (deaths or graft failures) among Black patients (23.8%) and 5,840 events among white patients (19.2%). Figure 1 displays center-specific Black-white hazard ratios, adjusted for clinical and socioeconomic variables. While there is substantial variation from center to center in terms of hazard ratios and confidence intervals, the majority of centers have a hazard ratio above 1, indicating worse outcomes among their Black patients.

Table 4.2 presents sequentially adjusted results from both additive and Cox proportional hazards models estimating the magnitude of racial disparities in survival. Unadjusted, Black patients had 1.23 excess deaths per 100 PY compared to white patients (95% CI: 0.78, 1.66); this corresponded to 24% higher hazard of poor outcomes after liver transplant (95% CI: 1.13, 1.37). There was no statistically significant interaction between any of the center characteristics considered and race. In low volume centers there were 1.16 excess deaths among Black patients per 100 PY (95% CI: -0.32, 2.64) and 1.43 per 100 PY in high-volume centers (95% CI: 0.89, 1.97). Survival differences were larger in centers that treated a low proportion of minority patients (1.49 per 100 PY, 95% CI: -0.18, 3.16) or a high proportion of minority patients (1.21 per 100 PY, 95% CI: 0.63, 1.79) compared to those with a medium proportion of minority patients (1.06 per 100 PY, 95% CI: 0.31, 1.81). Black-white survival differences were highest among the lowest-rated transplant centers (Tier 1 difference: 1.83, 95% CI: 0.25, 3.41; Tier 2 difference: 1.79, 95% CI: 0.92, 2.66) and similar between Tiers 3 (1.06, 95% CI: 0.28, 1.84), 4 (0.69, 95% CI: -0.20, 1.58), and 5 (0.86, 95% CI: -0.31, 0.20). Differences were highest in the Northeast (1.54 per 100 PY, 95% CI: 0.54, 2.54), similar in the Midwest (1.17, 95 CI: 0.18, 2.16) and the Southeast (1.15, 95% CI: 0.56, 1.74), and lowest in the West (0.80, 95% CI: -0.70,

2.29). The overall association between race and survival was slightly increased after adjustment for clinical factors alone (excess deaths among Black patients: 1.34 per 100 PY, 95% CI: 0.90, 1.78; HR: 1.27, 95% CI: 1.16, 1.38), but was attenuated after further adjustment for socioeconomic and center-level characteristics (excess deaths among Black patients: 1.11 per 100 PY, 95% CI: 0.65, 1.56; HR: 1.21, 95% CI: 1.12, 1.31). There was no statistically significant interaction between race and any of the center characteristics after adjustment for covariates. Patterns of associations stratified by center characteristics were similar in both the unadjusted and adjusted results.

Table 4.3 presents the association of center characteristics with survival, stratified by race, and adjusted for clinical, socioeconomic, and center-level characteristics. None of our pre-specified center-level characteristics were meaningfully or statistically significantly associated with survival among Black or white liver transplant recipients, after adjustment for patient and other center-level factors.

Supplementary Analyses

Figure 4.2 provides Kaplan-Meier curves for Black and white transplant recipients at low, medium, and high disparity centers. In low disparity centers, white patients had worse outcomes than white patients at medium or high disparity centers. Outcomes among white transplant recipients were better, while outcomes among Black transplant recipients are worse, with higher center-level disparity.

Discussion

In this analysis of Black and white liver transplant recipients in the United States, we sought to quantify racial disparities in survival, and determine whether differential distribution or effects of transplant center characteristics explained disparities. We found significant racial disparities in survival after transplant, with substantial variation in this disparity across transplant

centers. Disparities remained consistent regardless of transplant center volume, proportion of minority patients seen, quality rating, or region. The magnitude of center-level variation in racial disparities indicates that racial disparities may be influenced by transplant centers; however, this variation is not explained by our center characteristics selected *a priori*. This is the first study to directly evaluate the role transplant centers play in racial disparities in transplant outcomes.

Our findings are consistent with previous studies that have demonstrated persistent racial disparities in liver transplant outcomes. Several studies using SRTR[6,13,14] have identified racial disparities in overall survival after liver transplantation. These disparities were present before the development of the current MELD-based allocation system and have persisted into the MELD era.[5] In a recent study that linked University HealthSystem Consortium and SRTR data sources, Black liver transplant recipients were seen in lower quality centers and had higher risk of both graft failure and death after transplant than white recipients after controlling for recipient and donor characteristics, geographic region, donor service area, and individual hospital effects.[2] Our findings are consistent with those of this previous study; however, we did not seek to control for individual center effects but instead identify potential sources of between-center variation.

In contrast with previous studies, we did not find a significant association between transplant center volume, quality rating and outcomes among either Black or white liver transplant recipients. Axelrod et al previously found that recipients at low volume centers had 30% higher odds of mortality in the first year after liver transplant compared to high volume centers.[9] However, this study used data from 1996 to 2000. It is possible that over the past twenty years, care has improved substantially at low-volume centers, thus eliminating the disparity. Ozhathil et al.[15] found that high volume centers tended to use lower quality donor livers but achieve better allograft and patient survival for high-risk patients compared to low volume centers. They attributed these findings to greater levels of expertise in these centers.

Our finding that effect of center volume did not appear to differ among white and Black patients after controlling for patient risk profile may have obscured potential sub-group differences among high-risk patients.

We did not observe a significant association between SRTR quality rating and outcomes among white or Black patients. This is in contrast to a previous study by Wey et al.,[16] who demonstrated a 7% decreased risk of mortality among liver transplant recipients for each additional quality tier. The Wey study assigned patients to a tier at the time of listing, whereas we assigned patients to a tier according to their year of transplant; this may account for our difference in results. Further, tiers are assessed on the basis of 1-year survival, while we examined longer-term outcomes. It is possible that if we looked solely at 1-year outcomes we would have observed an association between quality rating and survival. However, this rating system has been the subject of substantial controversy in the field, partially because of its focus on the arbitrary end points of 1-year survival.[17,18] It is possible that other measures of quality of care – such as process measures – may be more relevant to both survival and racial disparities than those currently in use in the transplant community.

While racial disparities in transplant outcomes did not vary by our measured center characteristics, there were still centers with exacerbated racial disparities in survival. One potential explanation for this finding is that the center-level factors that matter for racial disparities are not those that we assessed. We selected our factors *a priori* based on previously published studies in the liver transplant literature and in the broader field of health services research, but we were limited to those that could be derived from available national surveillance data. Accurately measuring potentially important factors, such as candidate selection processes, structural center-level practices, and the accessibility and quality of follow-up care, may require more nuance than is typically found in administrative datasets such as the SRTR. Future research in this area should consider incorporating additional data sources as well as

conducting qualitative analysis of “high” and “low” disparity centers to generate new hypotheses in order to explore these and other factors that may be important for racial disparities.

Notably, centers with low racial disparities in survival did not necessarily have better outcomes for their Black patients than centers with high racial disparities. Instead, white patients at low disparity centers had worse outcomes than white patients at high disparity centers. This finding highlights the importance of understanding center-level drivers of racial disparities when thinking about potential interventions. The goal of such interventions is not for Black and white patients to have equally poor outcomes, so recommending practices from “low disparity” centers to “high disparity” centers may be inappropriate. Critical assessment of the mechanisms underlying disparities is the first step to designing interventions that truly address racial inequity in transplant outcomes. In addition, this assessment should be informed by both the magnitude of disparity and the underlying outcome rates in each population.[19] We provide both relative and absolute measures of racial disparity in this study to facilitate this assessment.

The results of our study must be interpreted in the context of its limitations. We chose to restrict our study to non-Hispanic Black and white patients, which limits the generalizability of our findings. We did so because Black patients are at highest risk for poor outcomes after liver transplant, whereas Hispanic and Asian patients have survival that is better than or comparable to white patients.[4] However, it is possible that disparities for these populations exist in specific transplant center contexts. Future studies may wish to specifically examine the effects of transplant center factors for these patient populations. Another potential limitation of our findings is the measurement of center-level characteristics. In addition to the limitations of administrative data discussed above, we may have induced measurement error by assigning center characteristics by the year of transplant. It is possible that center characteristics at precisely the time of transplant are important. However, we would not expect center characteristics to vary too substantially over the course of one year. Additionally, we would not expect errors in

attribution by time to be differential by race. Selection bias may also occur from differences in transplant center selection processes, which cannot be measured using current waitlisting data. There may be unmeasured confounding affecting our results. Differences between transplant centers may be explained by unmeasured clinical factors (i.e. underlying chronic conditions), social support, or neighborhood environment. Measures of socioeconomic data in SRTR are limited to education, which may be poorly reported, and zip-code level income. There is no measure of individual-level wealth or income, which may impact the influence of race on transplant outcomes. Finally, differences in racial disparities between individual transplant centers may vary over time or be due to random variation; we do not have sufficient data to evaluate statistical significance or time trends.

In conclusion, the magnitude of racial disparity in liver transplant outcomes varied across transplant centers but was not affected by transplant volume, proportion of minority patients served, quality rating, or region. Further assessment of qualitative factors that may drive disparities, such as selection processes and follow-up care, is needed to create effective center-level interventions to address health inequity.

Tables and Figures

Table 4.1. Demographic, clinical, and center-level characteristics of non-Hispanic Black and White liver transplant recipients in the United States, 2010 – 2017, Scientific Registry of Transplant Recipients.

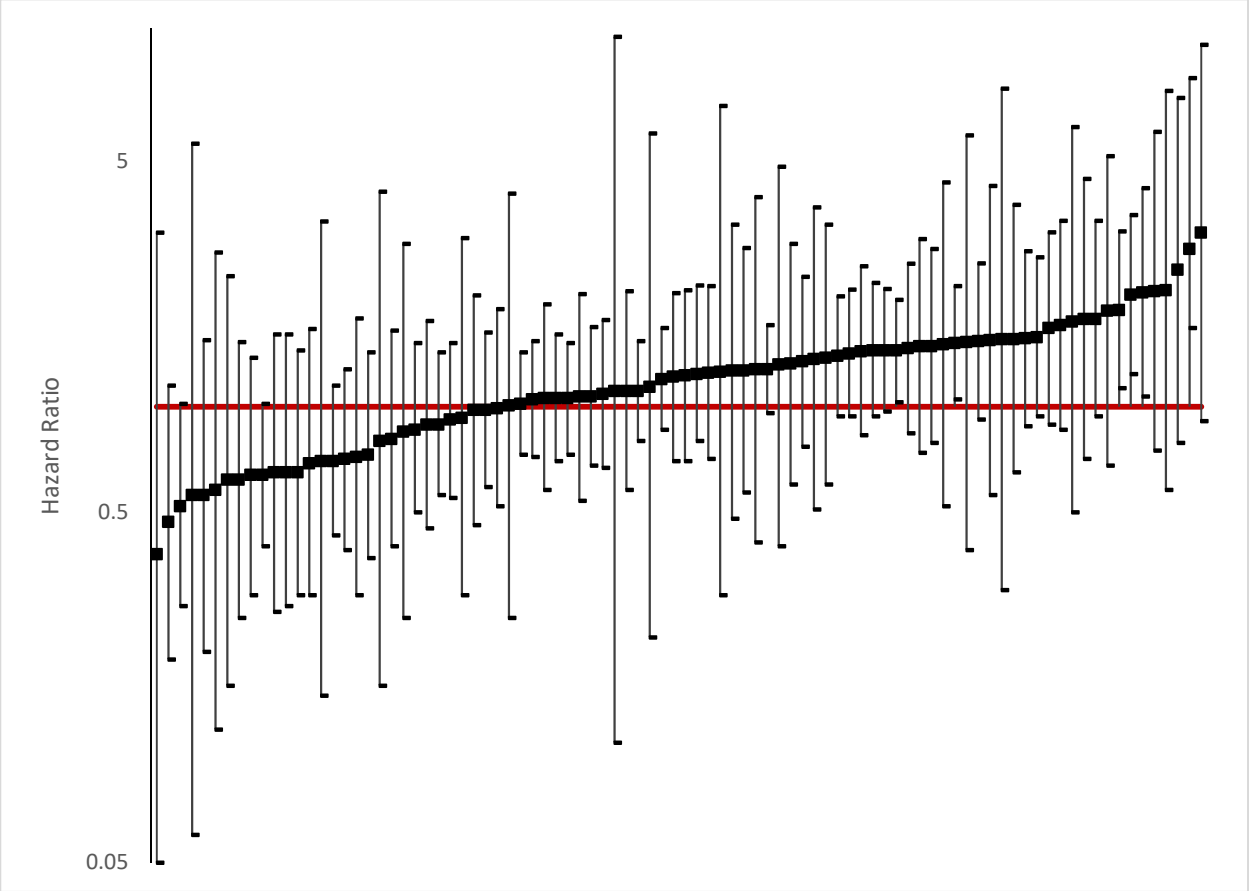
	Overall (N = 33,997)	**Black** (N = 3,617)	**White** (N = 30,080)
Center Characteristics			
Transplant volume (N, %)			
Low	2,708 (8.0%)	334 (9.2%)	2,374 (7.8%)
Medium	8,873 (26.1%)	895 (24.7%)	7,978 (26.3%)
High	22,416 (65.9%)	2,388 (66.0%)	20,028 (65.9%)
Proportion of minority patients at center (N, %)			
Low	9,070 (26.7%)	209 (5.8%)	8,861 (29.2%)
Medium	13,834 (40.7%)	1,137 (31.4%)	12,697 (41.8%)
High	11,093 (32.6%)	2,271 (62.8%)	8,822 (29.0%)
SRTR tier (N, %)			
1	2,413 (7.1%)	289 (8.0%)	2,124 (7.0%)
2	8,395 (24.7%)	1,037 (28.7%)	7,358 (24.2%)
3	9,954 (29.3%)	1,062 (29.4%)	8,892 (29.3%)
4	8,441 (24.8%)	775 (21.4%)	7,666 (25.2%)
5	4,636 (13.6%)	439 (12.1%)	4,197 (13.8%)
Missing	158 (0.5%)	15 (0.4%)	143 (0.5%)
Geographic region (N, %)			
Northeast	5,956 (17.5%)	744 (20.6%)	5,212 (17.2%)
Midwest	8,511 (25.0%)	655 (18.1%)	7,852 (25.9%)
South	14,673 (43.2%)	1,954 (54.0%)	12,719 (41.9%)
West	4,854 (14.3%)	263 (7.3%)	4,591 (15.1%)
Patient Characteristics			
Age (mean, SD)	55.3 (9.9)	53.7 (11.3)	55.5 (9.8)
Sex (N, %)			
Male	23,077 (67.9%)	2,196 (60.7%)	20,881 (68.7%)

Female	10,920 (32.1%)	1,421 (39.3%)	9,499 (31.3%)
Educational attainment (N, %)			
High school or less	14,498 (42.6%)	1,749 (48.4%)	12,749 (42.0%)
Some college	8,572 (25.2%)	918 (25.4%)	7,654 (25.2%)
Associate degree or higher	8,912 (26.2%)	687 (19.0%)	8,225 (27.1%)
Unknown	2,015 (5.9%)	263 (7.3%)	1,752 (5.8%)
Annual household income in zip code	63,200 (24,900)	53,200 (22,900)	64,400 (24,900)
Mean (SD)	63,200 (24,900)	53,200 (22,900)	64,400 (24,900)
Missing (N, %)	3,787 (11.1%)	252 (7.0%)	3,535 (11.6%)
Primary payer (N, %)			
Private	19,219 (56.5%)	1,741 (48.1%)	17,478 (57.5%)
Public	14,454 (42.5%)	1,852 (51.2%)	12,602 (41.5%)
Other	324 (1.0%)	24 (0.7%)	300 (1.0%)
MELD[1] at transplant (mean, SD)	20.9 (10.0)	21.5 (10.6)	20.9 (9.9)
Underlying cause of disease (N, %)			
ETOH[2]	10,551 (17.3%)	442 (7.0%)	10,109 (18.5%)
Hepatitis C	23,875 (39.2%)	3,240 (51.5%)	20,635 (37.7%)
NASH[3]	9,720 (15.9%)	319 (5.1%)	9,401 (17.2%)
Other	16,835 (27.6%)	2,290 (36.4%)	14,545 (26.6%)
HCC[4] (N, %)			
Yes	54,446 (89.3%)	5,519 (87.7%)	48,928 (89.5%)
No	6,534 (10.7%)	772 (12.3%)	5,762 (10.5%)
Medical condition at transplant (N, %)			
In ICU[5]	3,485 (10.3%)	399 (11.0%)	3,086 (10.2%)
Hospitalized, not in ICU	6,259 (18.4%)	699 (19.3%)	5,560 (18.3%)
Not hospitalized	24,253 (71.3%)	2,519 (69.6%)	21,734 (71.5%)
Recipient BMI[6]			

Mean (SD)	28.9 (6.7)	28.7 (7.3)	28.9 (6.6)
Missing (N, %)	104 (0.3%)	12 (0.3%)	92 (0.3%)
On dialysis (N, %)			
Yes	2,898 (8.5%)	272 (7.5%)	2,626 (8.6%)
No	31,099 (91.5%)	3,345 (92.5%)	27,754 (91.4%)
Portal vein thrombosis (N, %)			
Yes	4,412 (13.0%)	320 (8.8%)	4,092 (13.5%)
No	29,585 (87.0%)	3,297 (91.2%)	26,288 (86.5%)
Donor risk index (mean, SD)			
Mean (SD)	1.17 (1.0)	1.19 (0.8)	1.17 (1.0)
Missing (N, %)	1,662 (4.9%)	81 (2.2%)	1,581 (5.2%)

[1] Model for End-Stage Liver Disease
[2] Alcohol-associated liver disease
[3] Non-alcoholic steatohepatitis
[4] Hepatocellular carcinoma
[5] Intensive care unit
[6] Body mass index

Figure 4.1. Adjusted[1] center-specific Black-White hazard ratios for U.S. transplant centers, 2010 – 2017.



[1] Adjusted for age, sex, primary payer, educational attainment, zip-code income, MELD at transplant, underlying cause of disease, recipient medical condition at transplant, and center-level characteristics.

Table 4.2. Hierarchical additive hazards model and Cox proportional hazards model regressions for the association of race and survival, stratified by center-level characteristics, 2010 - 2017.

	Unadjusted		Clinical[1]		Clinical + Socioeconomic[2]		Clinical + Socioeconomic + Center[3]	
	Survival Difference per 100 PY (95% CI)	Hazard Ratio (95% CI)	Survival Difference per 100 PY (95% CI)	Hazard Ratio (95% CI)	Survival Difference per 100 PY (95% CI)	Hazard Ratio (95% CI)	Survival Difference per 100 PY (95% CI)	Hazard Ratio (95% CI)
Overall	1.23 (0.78, 1.66)	1.24 (1.13, 1.37)	1.34 (0.90, 1.78)	1.27 (1.16, 1.38)	1.20 (0.76, 1.64)	1.23 (1.12, 1.34)	1.11 (0.65, 1.56)	1.21 (1.12, 1.31)
Transplant volume								
Low	1.16 (-0.32, 2.64)	1.21 (0.95, 1.60)	1.27 (-0.22, 2.76)	1.22 (0.96, 1.55)	1.07 (-0.42, 2.56)	1.18 (0.93, 1.49)	0.94 (-0.55, 2.44)	1.14 (0.90, 1.46)
Medium	0.72 (-0.99, 1.55)	1.18 (1.01, 1.37)	0.83 (0.00, 1.66)	1.16 (1.00, 1.35)	0.63 (-0.20, 1.47)	1.12 (0.96, 1.30)	0.53 (-0.32, 1.37)	1.09 (0.94, 1.28)
High	1.43 (0.89, 1.97)	1.28 (1.14, 1.44)	1.54 (0.99, 2.09)	1.31 (1.18, 1.46)	1.42 (0.87, 1.97)	1.28 (1.15, 1.43)	1.36 (0.81, 1.91)	1.27 (1.15, 1.39)
Proportion of black patients at center								
Low	1.49 (-0.18, 3.16)	1.36 (1.02, 1.80)	1.49 (-0.18, 3.16)	1.30 (0.95, 1.78)	1.37 (-0.30, 3.04)	1.27 (0.93, 1.73)	1.33 (-0.35, 3.01)	1.26 (0.92, 1.72)
Medium	1.06 (0.31, 1.81)	1.20 (1.05, 1.37)	1.14 (0.38, 1.90)	1.22 (1.07, 1.39)	0.99 (0.23, 1.76)	1.19 (1.04, 1.36)	1.01 (0.25, 1.77)	1.19 (1.04, 1.37)
High	1.21 (0.63, 1.79)	1.25 (1.12, 1.39)	1.33 (0.75, 1.91)	1.26 (1.14, 1.39)	1.17 (0.58, 1.76)	1.22 (1.11, 1.35)	1.15 (0.56, 1.74)	1.22 (1.09, 1.34)
SRTR tier								
1	1.83 (0.25, 3.41)	1.37 (1.14, 1.65)	1.76 (0.18, 3.34)	1.34 (1.11, 1.62)	1.68 (0.10, 3.26)	1.33 (1.11, 1.60)	1.64 (0.05, 3.23)	1.32 (1.09, 1.58)
2	1.79 (0.92, 2.66)	1.35 (1.14, 1.61)	1.81 (0.94, 2.68)	1.35 (1.14, 1.61)	1.67 (0.79, 2.55)	1.31 (1.10, 1.57)	1.62 (0.73, 2.50)	1.30 (1.09, 1.54)
3	1.06 (0.28, 1.84)	1.21 (1.06, 1.37)	1.10 (0.31, 1.89)	1.22 (1.07, 1.38)	0.96 (0.17, 1.75)	1.19 (1.04, 1.35)	0.91 (0.11, 1.70)	1.17 (1.03, 1.33)
4	0.69 (-0.20, 1.58)	1.15 (0.98, 1.34)	0.90 (0.01, 1.79)	1.16 (1.00, 1.36)	0.75 (-0.15, 1.64)	1.13 (0.97, 1.32)	0.64 (-0.26, 1.54)	1.11 (0.95, 1.29)
5	0.86 (-0.31, 0.20)	1.18 (0.93, 1.50)	1.20 (0.03, 2.37)	1.25 (1.01, 1.56)	1.03 (-0.14, 2.20)	1.22 (0.98, 1.52)	0.95 (-0.23, 2.13)	1.20 (0.97, 1.49)
Geographic region								
Northeast	1.54 (0.54, 2.54)	1.29 (1.13, 1.49)	1.49 (0.48, 2.50)	1.26 (1.09, 1.46)	1.35 (0.34, 2.36)	1.23 (1.06, 1.43)	1.31 (0.29, 2.33)	1.22 (1.06, 1.41)

Midwest	1.17 (0.18, 2.16)	1.23 (1.03, 1.47)	1.05 (0.05, 2.05)	1.20 (1.01, 1.42)	0.85 (-0.15, 1.86)	1.15 (0.97, 1.37)	0.80 (-0.21, 1.81)	1.14 (0.95, 1.36)
South	1.15 (0.56, 1.74)	1.22 (1.07, 1.40)	1.35 (0.75, 1.95)	1.28 (1.13, 1.45)	1.23 (0.63, 1.83)	1.25 (1.10, 1.42)	1.19 (0.59, 1.79)	1.24 (1.11, 1.39)
West	0.80 (-0.70, 2.29)	1.20 (0.95, 1.52)	0.92 (-0.58, 2.42)	1.18 (0.96, 1.45)	0.81 (-0.69, 2.31)	1.15 (0.94, 1.42)	0.78 (-0.73, 2.28)	1.14 (0.93, 1.41)

[1] Adjusted for age, year of transplant, sex, MELD at transplant, underlying cause of disease, recipient medical condition at transplant, body mass index (BMI), donor risk index (DRI), portal vein thrombosis (PVT), history of diabetes, and dialysis at transplant.

[2] Adjusted for age, year of transplant, sex, MELD at transplant, underlying cause of disease, recipient medical condition at transplant, body mass index (BMI), donor risk index (DRI), portal vein thrombosis (PVT), history of diabetes, dialysis at transplant, educational attainment, zip-code income, and primary payer.

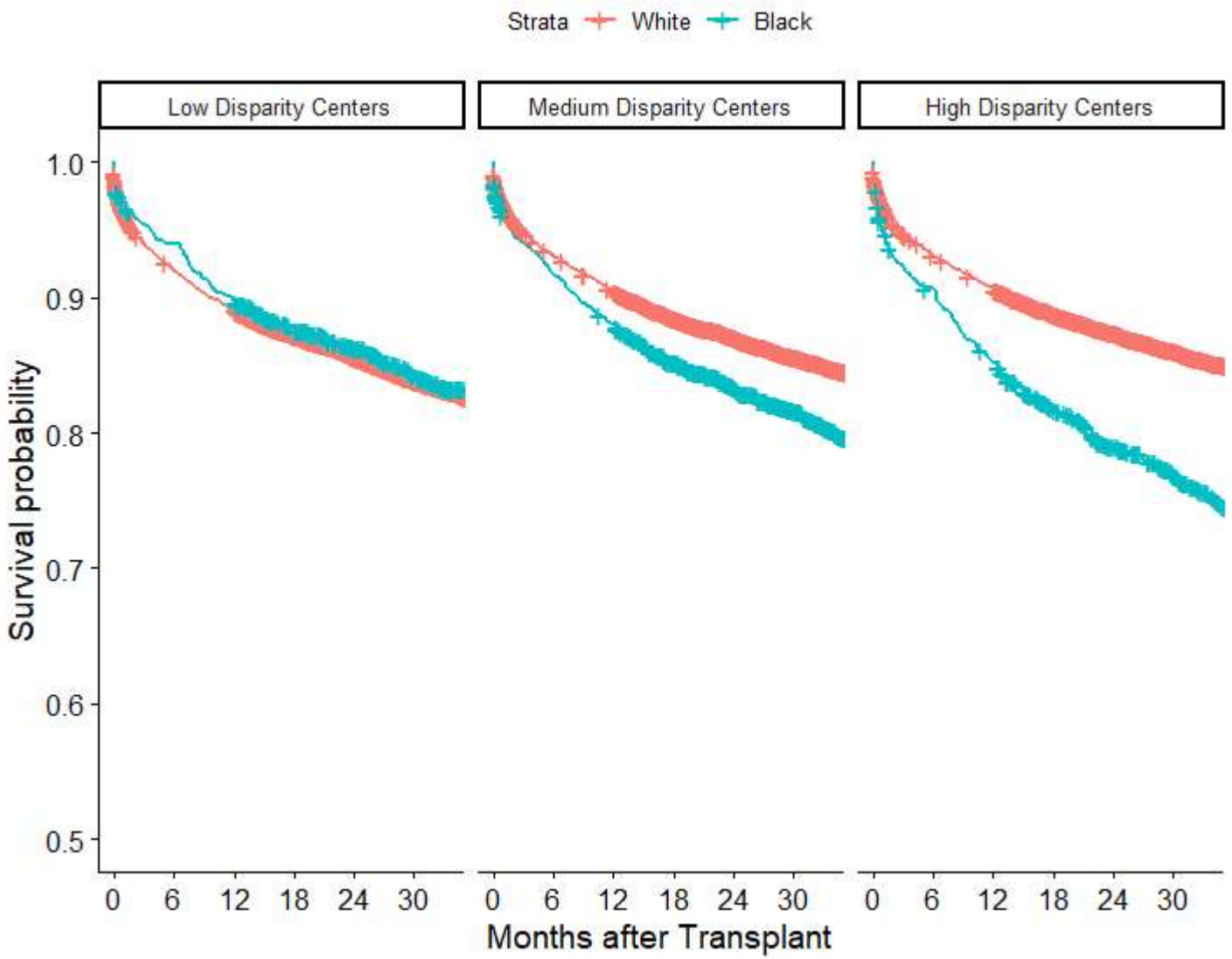
[3] Adjusted for age, year of transplant, sex, MELD at transplant, underlying cause of disease, recipient medical condition at transplant, body mass index (BMI), donor risk index (DRI), portal vein thrombosis (PVT), history of diabetes, dialysis at transplant, educational attainment, zip-code income, primary payer, and center-level characteristics.

Table 4.3. Adjusted[1] hierarchical additive hazards model for the association of center-level characteristics and survival, stratified by recipient race, 2010 - 2017.

Center-Level Characteristics	Within-White Survival Difference per 100 PY	Within-Black Survival Difference per 100 PY	Within-White Hazard Ratio	Within-Black Hazard Ratio
Transplant volume				
Low	0.29 (-0.23, 0.80)	-0.13 (-0.16, 1.38)	1.06 (0.94, 1.19)	0.96 (0.75, 1.24)
Medium	-0.13 (-0.44, 0.17)	-0.97 (-1.91, -0.03)	0.98 (0.90, 1.06)	0.83 (0.71, 1.00)
High (Ref)	Ref	Ref	Ref	Ref
Proportion of minority patients at center (N, %)				
Low (Ref)	Ref	Ref	Ref	Ref
Medium	-0.02 (-0.34, 0.30)	-0.34 (-2.15, 1.47)	1.00 (0.93, 1.08)	0.95 (0.66, 1.37)
High	0.05 (-0.32, 0.42)	-0.13 (-1.88, 1.62)	1.01 (0.93, 1.10)	0.98 (0.69, 1.37)
SRTR tier (N, %)				
1	0.18 (-0.41, 0.77)	0.87 (-1.01, 2.75)	1.04 (0.91, 1.18)	1.14 (0.87, 1.49)
2	0.29 (-0.14, 0.72)	0.97 (-0.43, 2.37)	1.06 (0.95, 1.18)	1.15 (0.86, 1.54)
3	0.23 (-0.19, 0.64)	0.20 (-1.15, 1.55)	1.04 (0.95, 1.15)	1.02 (0.80, 1.30)
4	0.15 (-0.26, 0.56)	-0.15 (-1.56, 1.26)	1.03 (0.93, 1.14)	0.95 (0.72, 1.26)
5 (Ref)	Ref	Ref	Ref	Ref
Geographic region (N, %)				
Northeast (Ref)	Ref	Ref	Ref	Ref
Midwest	-0.09 (-0.52, 0.33)	-0.56 (-1.92, 0.80)	0.98 (0.88, 1.08)	0.91 (0.75, 1.11)
South	-0.25 (-0.64, 0.14)	-0.44 (-1.55, 0.67)	0.95 (0.86, 1.04)	0.97 (0.80, 1.17)
West	-0.69 (-1.17, -0.20)	-1.32 (-3.08, 0.44)	0.87 (0.75, 1.01)	0.82 (0.68, 0.98)

[1] Adjusted for age, year of transplant, sex, MELD at transplant, underlying cause of disease, recipient medical condition at transplant, body mass index (BMI), donor risk index (DRI), portal vein thrombosis (PVT), history of diabetes, dialysis at transplant, educational attainment, zip-code income, primary payer, and center-level characteristics.

Figure 4.2. Kaplan-Meier curves for Black and White liver transplant recipients at low, medium, and high disparity transplant centers, 2007 – 2017.



Chapter 5: Aim 2

Abstract

Background: Unplanned hospital admissions are common, costly and detrimental to long-term outcomes after liver transplantation. While racial disparities in post-transplant survival are persistent and well-documented, little is known about racial disparities in post-transplant readmissions, or the role that these readmissions may play in perpetuating survival disparities. The two aims of this paper were to estimate the association between race and hospital readmission within 6 months of liver transplant, and to perform a mediation analysis to assess whether readmission meaningfully affected the association between race and survival.

Methods: Data were obtained from the Scientific Registry of Transplant Recipients (SRTR). We used log-binomial regression to estimate the association between race and readmission within 6 months of transplant, accounting for clinical, socioeconomic, and center characteristics. We used marginal structural Cox models with inverse probability of treatment weighting (IPTW) to estimate the controlled direct effect of race on survival, accounting for readmission within 6 months.

Results: We included 31,250 Black and White liver transplant recipients, of whom 45% were admitted to the hospital in the 6 months after transplant. After adjustment, Black patients had a slightly increased risk of hospital readmission within 6 months compared to White patients (RR: 1.03, 95% CI: 1.01, 1.06). Accounting for readmission did not meaningfully impact the association between race and survival, which remained significant (HR: 1.29, 95% CI: 1.19, 1.41).

Conclusions: Readmission within 6 months did not appear to play a meaningful role in racial disparities in post-liver transplant survival. More nuanced data on hospital admissions after transplant are needed to further elucidate this relationship.

Introduction

Unplanned readmissions to the hospital after liver transplantation are common[68], costly[65], and associated with substantially increased risk of graft failure and death[66]. While the causal role of unplanned readmissions in long-term outcomes of liver transplant recipients is unclear, growing evidence indicates that these additional hospitalizations are a large contributor to the cost of transplantation[65] and are detrimental to patient quality of life[66]. Accordingly, preventing hospital readmission is an increasingly prevalent target of transplant center quality improvement programs.[136] Such programs often involve expanding access to providers through dedicated multispecialty clinics, improving continuity of care following surgery, and promoting alternatives to readmission such as observation stays and local hospital lodging.[66,80] Early results of these programs are encouraging, with substantial reductions in 30-day hospital readmissions and ongoing research to clarify the effect of these programs on longer-term outcomes such as patient survival.[78-80]

Racial disparities in outcomes after liver transplant are persistent and well-documented, with Black patients experiencing worse graft and overall survival than patients of any other race.[20] However, little is known about the association between race and hospital readmission after liver transplant or the role that hospital readmissions may play in the known racial disparities in post-transplant survival. Hospital readmission after liver transplantation may simply be a marker to identify groups at high risk for poor outcomes, including mortality. However, if survival disparities are explained by an increased risk of hospital readmissions among Black patients, interventions that address the underlying determinants of readmission such as those described above may be effective at reducing racial disparities in survival following liver transplantation.

This paper had two objectives. The first was to estimate the association between race and hospital readmission within 6 months of liver transplant using national data from the

Scientific Registry of Transplant Recipients (SRTR). The second was to perform a mediation analysis to assess whether readmission within 6 months of transplant meaningfully affected the association between race and survival.

Methods

Data Sources and Population

Data on liver transplant recipients were obtained from SRTR, a population-based registry of all solid organ transplant candidates, donors, and recipients in the United States. We included 40,776 adult (age $\geq$ 18) patients from 127 transplant centers who were non-Hispanic Black or White and received a deceased donor liver transplant between January 1st, 2010 and December 31st, 2017. We chose to restrict our study to non-Hispanic Black and White patients because Black patients are at highest risk for poor outcomes after liver transplant, whereas Hispanic and Asian patients have survival that is better than or comparable to White patients, and we lacked sufficient sample size to draw inference about other racial and ethnic groups. Patients were excluded if they received a simultaneous transplant of another organ (n = 3,746), had a prior liver transplant (n = 1,690), had acute liver failure (n = 1,189), or had acute alcoholic hepatitis (n = 134). Patients were also excluded if they died prior to initial transplant discharge (n = 131) or were missing hospitalization information at 6 months (n = 631).

Variables

Our primary exposure was patient-reported race, dichotomized to non-Hispanic Black or White, and considered as a social construct, rather than a biologic categorization.[137] For our first aim, the primary outcome of interest was whether the patient was readmitted to the hospital within 6 months of initial transplant discharge, dichotomized to “yes” or “no”. We chose to examine rehospitalization within six months post-transplant because of data availability within

the SRTR system. For the second aim, the primary outcome of interest was time to graft failure or death. Survival time was calculated as the time between receipt of transplant and date of death or graft failure, whichever occurred first. Patients were censored at loss to follow-up or the at end of the study period (December 31st, 2018).

Relevant patient-level covariates for both aims included age, sex, individual-level socioeconomic status, zip-code level income, insurance type, MELD at transplant, underlying cause of disease, dialysis at the time of transplant, portal vein thrombosis (PVT), body mass index (BMI) and donor risk index (DRI). Individual-level socioeconomic status was measured using educational attainment at the time of listing as a proxy (categorized as “less than high school”, “high school diploma”, “some college”, and “associate’s degree or higher”). Insurance type was assigned based on the primary payer for the transplant (categorized as “public”, “private”, or “other”). Underlying cause of disease was categorized as hepatitis C, alcoholic liver disease, non-alcoholic steatohepatitis [NASH], hepatocellular carcinoma [HCC] and other. Candidate medical condition at transplant was categorized as in ICU, hospitalized but not in ICU, and not hospitalized. The DRI is a validated score used to estimate the risk of graft failure based on donor characteristics, including donor age, race, cause of death, cold ischemic time, height, whether the donation was after cardiac death, and whether the graft was a split or partial graft.

We also included covariates at the transplant center-level that were associated with either survival after transplant or racial disparities in other surgical outcomes. Transplant volume was defined as the number of adult liver transplants performed by the center in the year that the recipient received their transplant, and was classified into tertiles by year (called “low”, “medium” and “high volume” centers). Proportion of minority patients was defined as the percentage of Black adult liver transplants performed by the center in the year that the recipient received their transplant, classified into tertiles (“low”, “medium”, and “high minority” centers). Transplant

center quality was defined using the SRTR 5-tier system for observed outcomes.[138] Tiers were assigned based on the center in the year that the recipient received their transplant. Geographic region of the transplant center was assigned according to the U.S. Census regions (Northeast, Midwest, South, and West).

Statistical Analyses for Aim 1

The objective of this aim was to estimate the association between race and hospital readmission within 6 months. Clinical, demographic, and transplant center characteristics of our population were described overall and stratified by whether the patient was readmitted to the hospital within 6 months. Missing covariates were imputed with the missRanger package in R, using chained random forests with predictive mean matching. Less than 10% of observations were missing one or more covariate. Because the outcome of hospital readmission was common in the population, we used log-binomial regression to estimate risk ratios instead of logistic regression to estimate odds ratios. Bivariable associations between clinical, demographic, and transplant center characteristics and hospital readmission were estimated using log-binomial regression. We used hierarchical multivariable log-binomial regression to estimate the association between race and hospital readmission, adjusted for the clinical, demographic and transplant center characteristics described above, and accounting for potential clustering within transplant centers.

Statistical Analyses for Aim 2

The objective of this aim was to perform a mediation analysis assessing whether hospital readmission within 6 months meaningfully attenuated the association between race and survival. To estimate the controlled direct effect of race on survival after accounting for hospital readmission, we used marginal structural modeling with inverse probability of treatment weighting to balance the distribution of potential confounders between Black and White

patients.[139] Potential confounding of the race-survival and readmission-survival association was accounted for using stabilized inverse-probability weights. Confounders of the race-survival association included region, age, sex, educational attainment, zip-code income and payer. Confounders of the readmission-survival association included age, sex, educational attainment, zip-code income, payer, MELD at transplant, medical condition at transplant, transplant center volume, center quality rating, and UNOS region. We assessed violations of the positivity assumption, or the assumption that exposure was possible in each stratum of the covariates,[140] by examining the distribution of the probability weights.

To estimate the total direct effect of race on survival, we fit a Cox proportional hazards model that included race and was weighted using confounders from the readmission-survival association. To estimate the controlled direct effect, we fit a Cox proportional hazards model that included race and hospital readmission, weighted using the product of the weights for race-survival and readmission-survival confounding. Product terms between race and readmission were not included because there was no evidence of effect modification between race and readmission.

One limitation of this analysis is that we do not have date of hospital readmission to allow for censoring for death among those who died in the first six months after transplant. We performed a sensitivity analysis in which we excluded patients that died within the first 6 months of transplant to assess whether this affected our results. All analyses were performed in R 3.5.3 and SAS 9.4.

Results

Study Population

We included 31,250 Black and White liver transplant recipients who were transplanted between 2010 and 2017 and survived to initial discharge following transplantation. In this population, approximately 11% (n = 3,332) were Black. Overall, 45% of patients were readmitted to the hospital within 6 months of initial discharge (n = 14,143). Readmitted patients were more likely to be female (33.9% vs. 30.6%), have a higher MELD at transplant (21.6 vs. 20.0), to be in the ICU (11.2% vs. 8.0%) or hospital (20.3% vs. 16.1%) at the time of transplant, and to be on dialysis (9.6% vs. 6.9%). Readmitted patients were only slightly more likely to be Black (10.9% vs. 10.4%) and slightly less likely to have hepatocellular carcinoma (12.2% vs. 13.8%). Readmitted patients were less likely to be transplanted at a high volume center (63.4% vs. 67.8%), at a center with a low proportion of minority patients (27.9% vs. 25.9%), at a SRTR Tier 5 (high quality) center (12.6% vs. 14.5%), or at a center in the South (41.1% vs. 45.6%).

We describe characteristics of the 643 patients missing readmission information in Supplementary Table 5.1. Missingness does not appear to be differential by race. Patients missing hospital readmission information were slightly more likely to have public insurance (48.2% vs. 42.0%), to have alcohol-associated liver disease (27.2% vs. 19.0%), to be seen at a high-volume center (79.9% vs. 65.8%) and to reside in the Midwest (50.7% vs. 24.4%) than those not missing readmission information.

Race and Hospital Readmission

Table 5.2 presented unadjusted and adjusted risk ratios of hospital readmission within 6 months for demographic, clinical, and center-level characteristics. Prior to adjustment, Black patients had a 3% higher risk of readmission than White patients; this risk did not change with adjustment for covariates (adjusted RR: 1.03, 95% CI: 1.01, 1.06). Male patients had a 5% lower risk of readmission than female patients after adjustment for covariates (95% CI: 0.93, 0.96). Patients with public insurance had an 8% higher risk of readmission compared to patients with private health insurance (95% CI: 1.06, 1.10). Patients with hepatitis C (RR: 1.08, 95% CI:

1.06, 1.10), NASH (RR: 1.10, 95% CI: 1.08, 1.13), and other (RR: 1.05, 95% CI: 1.02, 1.07) underlying causes of liver disease had higher risk of readmission than patients with alcohol-associated liver disease. Unadjusted, patients with HCC had a lower risk of readmission (RR: 0.92, 95% CI: 0.89, 0.96), but this association was not significant after adjustment. Not being hospitalized at the time of transplant was associated with lower risk of readmission (RR: 0.90, 95% CI: 0.86, 0.93), while dialysis (RR: 1.10, 95% CI: 1.06, 1.13), PVT (RR: 1.04, 95% CI: 1.03, 1.05), and higher DRI (RR: 1.04, 95% CI: 1.03, 1.05) were associated with higher risk of readmission. Age, educational attainment, zip-code income, and recipient BMI were not associated with readmission risk.

Patients who received their transplant in a high volume center were less likely to be readmitted (RR: 0.95, 95% CI: 0.90, 0.99), as were patients who were seen in a center with a high proportion of minority patients (RR: 0.91, 95% CI: 0.87, 0.96). Compared to SRTR Tier 1 (low quality center), patients who received their transplant in a Tier 3 (mid-quality) center were 12% more likely to be readmitted (95% CI: 1.07, 1.18), but no other tier was associated with readmission risk. Patients in the South (RR: 0.89, 95% CI: 0.84, 0.94) and West (RR: 0.83, 95% CI: 0.77, 0.91) were less likely to be readmitted than patients in the Northeast.

Mediation Analysis

Estimates of the total and controlled direct effect of race on survival are presented in Table 5.3. Black patients were at 31% higher hazard of graft failure or death after liver transplant after adjusting for covariates, but not for hospital readmission (95% CI: 1.20, 1.42). Readmission was strongly associated with increased mortality risk (HR: 1.82, 95% CI: 1.72, 1.93). Accounting for hospital readmission did not attenuate the association between race and survival (controlled direct effect HR: 1.29, 95% CI: 1.19, 1.41).

In a sensitivity analysis, we assessed the impact of potential selection bias by limiting the cohort to those who survived longer than 6 months. Of the 867 patients who survived less than 6 months after transplant, 416 (48%) were readmitted to the hospital at least once. Excluding these patients from our analysis did not affect our results (data not shown).

Discussion

In this analysis of Black and White liver transplant recipients in the United States, Black patients had a slightly increased risk of hospital readmission within 6 months of liver transplant compared to White patients. While hospital readmission within 6 months was strongly associated with long-term survival, where hospitalized patients had an approximately 80% higher rate of mortality compared to non-hospitalized patients, hospital readmission did not appear to mediate the association between race and survival. After accounting for hospital readmission and other clinical and sociodemographic factors, Black patients still experienced nearly 30% higher risk of graft failure or death than White patients after liver transplant. The results of these analyses provide insight into the burden of hospital readmission among Black liver transplant recipients, and suggest that interventions to reduce hospital readmission may not necessarily reduce racial disparities in survival after liver transplant.

The high prevalence of readmission in our study (45% within 6 months) is consistent with previous work on readmission after liver transplant. In one study linking SRTR data with the University Health Consortium, 55% of liver transplant recipients were readmitted at least once in the first year after transplant.[69] In a study that linked SRTR and Medicare data from 2003 to 2010, 58% of patients were hospitalized in the first six months after liver transplant (2.76 hospitalizations per patient-year); this rate may be higher than our observed rate because of differences between the Medicare population and the overall population of liver transplant recipients or due to differences in the time period assessed.[70] This previous study did not find a

significant difference in readmission between Black and White patients, however, the Medicare population only represents approximately 12% of Black liver transplant recipients. The statistical significance in racial differences in readmission observed in our study is likely due to the larger sample size from including all liver transplant recipients. Other studies have also found small but statistically significant differences in the experience of hospital readmission among Black patients. For example, Bittermann et al. found that Black patients had five fewer days alive and out of the hospital in the first year after transplant than White patients after adjusting for clinical and demographic covariates.[69].

Racial disparities in survival after liver transplant are well-documented,[20] persistent over time,[133] and not explained by socioeconomic, neighborhood or transplant center characteristics.[99,141] The magnitude of racial disparity in survival we observed is similar to the magnitude observed in other studies.[97,99,104] Readmission after liver transplant is also associated with poor survival, although the relevant time window and potential causal relationship is not clearly defined. One single-center study[77] found that patients who required readmission within 30 days had significantly lower survival than patients who did not. A study using SRTR data[70] found that the death rate was 22% higher for each readmission in the first 6 months after transplant. To our knowledge, our study is the first to examine the role that readmission may play in racial disparities in survival following liver transplantation.

The underlying goal of this study was to provide insight into whether targeting hospital readmissions might be an effective strategy to reduce racial disparities in survival after liver transplantation. One interpretation of our findings is that hospital readmission is not a mediator of the association between race and survival, and therefore would not be a good intervention to reduce racial disparities. However, another possible interpretation is that hospital readmission in this study is not “well-defined” enough to determine whether it is a mediator. Sources of ambiguity and potential residual confounding, including why patients were readmitted and

whether readmission had a causal effect on survival, are unknown. Readmissions could be avoidable but necessary (because of something preventable by earlier intervention), unavoidable and necessary (because of something not preventable by earlier intervention), or not necessary. Similarly, readmissions could be life-saving, have no effect on patient survival, or actually cause death due to medical error or nosocomial infections acquired during the hospitalization.

The challenge of targeting hospital readmissions for quality improvement is illustrated by the Hospital Readmission Reduction Program (HRRP), a CMS program that linked 30-day readmission rates to financial penalties.[142] The HRRP resulted in a decline in hospital readmissions for certain conditions, including a narrowing of racial disparities in readmission rates.[143] However, the long-term impacts of the HRRP on patient outcomes were less clear, with some studies suggesting that patient mortality actually increased after the HRRP due to provider reluctance to readmit patients when medically necessary.[144] For the purposes of considering a readmission reduction program as an intervention for transplant centers to improve survival, readmissions should be preventable, and preventing the need for readmission should be life-saving. However, it is unclear from the available data what proportion of readmissions fulfill these criteria. While one strength of our study is its generalizability due to the use of nationally representative data, we are unable to explore more nuanced aspects of readmission, such as cause of readmission, whether the patient required intensive care, and readmission outcomes. Single center studies, while limited in scope, are needed to provide additional context to studies of readmission and survival.

Our findings must be interpreted in the context of their limitations. First, readmissions are reported to SRTR by the transplant center. If patients were readmitted to a different hospital, this information would not be available in SRTR. This is unusual for transplant patients, particularly within 6 months of transplant, who are typically be transferred to their transplant

center for acute care if readmitted to a different hospital.[124] However, this may be more common among patients who reside in rural areas or far away from their initial transplant center. If this occurs, our estimates of the prevalence of readmission would be an underestimate, and our results concerning racial differences in readmission risk may be biased towards the null if care fragmentation is more likely among Black patients than White patients. Second, we do not have information on the date of hospital readmission within the 6 month interval, which means that we cannot censor for death or loss-to-follow up in the first 6 months after transplant, resulting in potentially missing outcome data. Missing data becomes more of an issue over time, which is one reason why we restricted our study to the first time period available (6 months after transplant), where less than 6% of patients were missing information on hospital readmission. This missingness does not appear to be differential by race, suggesting that any bias would be toward the null. Additionally, a sensitivity analysis restricting the population to only those who survived the first six months after transplant did not change our results. Finally, we used mediation analysis to estimate the controlled direct effect of race on survival, which requires strong assumptions about confounding and positivity. While we assessed positivity using the propensity score for race and readmission and controlled for available confounders of the race-survival and readmission-survival associations, there may be unmeasured or incorrectly measured confounders that bias our observed results.

In summary, Black liver transplant recipients in the United States had a small increased risk of readmission within 6 months of transplant when compared to White patients, but readmission did not appear to influence the association between race and survival. While the use of national data improved the generalizability of our findings, a key limitation is the lack of nuanced data on the causes and effects of readmission. Future studies utilizing single-center data should focus on currently unmeasured factors that might reduce both mortality and

admission after liver transplant in order to inform interventions that address racial disparities in survival.

Tables and Figures

Table 5.1. Demographic, clinical, and center-level characteristics of liver transplant recipients in the United States, stratified by hospital readmission within 6 months, 2010 – 2017, Scientific Registry of Transplant Recipients.

	Overall (N = 31,250)	**Readmitted** (n = 14,143)	**Not Readmitted** (n = 17,107)
Patient Characteristics			
Age (mean, SD)	55.1 (10.0)	54.9 (10.2)	55.2 (9.9)
Race (N, %)			
Black	3,332 (10.7)	1,548 (10.9)	1,784 (10.4)
White	27,918 (89.3)	12,595 (89.1)	15,323 (89.6)
Sex (N, %)			
Female	10,029 (32.1)	4,797 (33.9)	5,232 (30.6)
Male	21,221 (67.9)	9,346 (66.1)	11,875 (69.4)
Educational attainment (N, %)			
High school or less	13,307 (42.6)	6,095 (43.1)	7,212 (42.2)
Some college	7,919 (25.3)	3,628 (25.7)	4,291 (25.1)
Associate degree or higher	8,232 (26.3)	3,672 (26.0)	4,560 (26.7)
Unknown	1,792 (5.7)	748 (5.2)	1,044 (6.1)
Annual household income in zip code			
Mean (SD)	63,200 (25,000)	62,900 (24,700)	63,400 (25,200)
Missing (N, %)	3,357 (10.7)	1,601 (11.3%)	1,756 (10.3)
Primary payer (N, %)			
Private	17,835 (57.1)	7,780 (55.0)	10,055 (58.8)
Public	13,123 (42.0)	6,237 (44.1)	6,886 (40.3)
Other	292 (0.9)	126 (0.9)	166 (1.0)
MELD at transplant (mean, SD)	20.7 (9.9)	21.6 (10.1)	20.0 (9.7)
Underlying cause of disease (N, %)			
ETOH	5,931 (19.0)	2,625 (18.6)	3,306 (19.3)
Hep C	11,710 (37.5)	5,254 (37.1)	6,456 (37.7)
NASH	5,776 (18.5)	2,727 (19.3)	3,049 (17.8)
Other	7,833 (25.1)	3,537 (25.0)	4,296 (25.1)
Hepatocellular carcinoma (HCC) (N, %)			
Yes	4,087 (13.1)	1,724 (12.2)	2,363 (13.8)
No	27,163 (86.9)	12,419 (87.8)	14,744 (86.2)
Medical condition at transplant (N, %)			
In ICU	2,953 (9.4)	1,582 (11.2)	1,371 (8.0)
Hospitalized, not in ICU	5,636 (18.0)	2,876 (20.3)	2,760 (16.1)
Not hospitalized	22,661 (72.5)	9,685 (68.5)	12,976 (75.9)
Recipient BMI			
Mean (SD)	29.9 (6.7)	28.9 (6.4)	28.9 (6.9)
Missing (N, %)	94 (0.3)	37 (0.3)	57 (0.3)
On dialysis (N, %)			
Yes	2,449 (7.8)	1,363 (9.6)	1,086 (6.3)
No	28,801 (92.2)	12,780 (90.4)	16,021 (93.7)

Portal vein thrombosis (N, %)			
Yes	3,912 (12.5)	1,823 (12.9)	2,089 (12.2)
No	27.338 (87.5)	12,320 (87.1)	15,018 (87.8)
Donor risk index (mean, SD)			
Mean (SD)	1.16 (0.98)	1.18 (0.96)	1.15 (1.0)
Missing (n, %)	1,537 (4.9)	843 (6.0%)	694 (4.1)
Center Characteristics			
Transplant volume (N, %)			
Low	2,508 (8.0)	1,195 (8.4)	1,313 (7.7)
Medium	8,173 (26.2)	3,980 (28.1)	4,193 (24.5)
High	20,569 (65.8)	8,968 (63.4)	11,601 (67.8)
Proportion of minority patients at center (N, %)			
Low	8,372 (26.8)	3,944 (27.9)	4,428 (25.9)
Medium	12,640 (40.4)	5,741 (40.6)	6,899 (40.3)
High	10,238 (32.8)	4,458 (31.5)	5,780 (33.8)
SRTR tier (N, %)			
1	2.233 (7.1)	952 (6.7)	1,281 (7.5)
2	7,620 (24.4)	3,398 (24.0)	4,222 (24.7)
3	9,182 (29.4)	4,450 (31.5)	4,732 (27.7)
4	7,812 (25.0)	3,490 (24.7)	4,322 (25.3)
5	4,258 (13.6)	1,776 (12.6)	2,482 (14.5)
Missing	145 (0.5)	77 (0.5)	68 (0.4)
Geographic region (N, %)			
Northeast	5,431 (17.4)	2,668 (18.9)	2,763 (16.2)
Midwest	7,627 (24.4)	3,678 (26.0)	3,949 (23.1)
South	13,634 (43.6)	5,827 (41.1)	7,807 (45.6)
West	4,556 (14.6)	1,970 (13.9)	2,586 (15.1)

Table 5.2. Log-binomial regression of demographic, clinical, and center-level characteristics on hospital readmission within 6 months, 2010 – 2017, Scientific Registry of Transplant Recipients.

	Unadjusted Risk Ratio (95% CI)	**Adjusted Risk Ratio (95% CI)**
Patient Characteristics		
Race		
White	Ref	Ref
Black	1.03 (0.99, 1.07)	1.03 (1.01, 1.06)
Age (per year)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Sex		
Female	Ref	Ref
Male	0.92 (0.90, 0.94)	0.95 (0.93, 0.96)
Educational attainment		
High school or less	Ref	Ref
Some college	1.01 (0.98, 1.04)	1.02 (1.00, 1.04)
Associate degree or higher	0.98 (0.95, 1.01)	1.01 (1.00, 1.03)
Annual household income in zip code		
Quartile 1	Ref	Ref
Quartile 2	1.01 (0.98, 1.05)	1.01 (0.99, 1.03)
Quartile 3	1.00 (0.96, 1.03)	1.00 (0.98, 1.02)
Quartile 4	0.98 (0.95, 1.02)	0.99 (0.97, 1.02)
Primary payer		
Private	Ref	Ref
Public	1.09 (1.06, 1.12)	1.08 (1.06, 1.10)
Other	0.99 (0.86, 1.12)	0.97 (0.92, 1.03)
MELD at transplant	1.01 (1.01, 1.01)	1.00 (1.00, 1.01)
Underlying cause of disease		
ETOH	Ref	Ref
Hep C	1.01 (0.98, 1.05)	1.08 (1.05, 1.11)
NASH	1.07 (1.03, 1.11)	1.10 (1.08, 1.13)
Other	1.02 (0.98, 1.06)	1.05 (1.02, 1.07)
HCC		
Yes	0.92 (0.89, 0.96)	0.98 (0.94, 1.02)
No	Ref	Ref
Medical condition at transplant		
In ICU	Ref	Ref
Hospitalized, not in ICU	0.95 (0.91, 0.99)	1.00 (0.97, 1.02)
Not hospitalized	0.80 (0.77, 0.83)	0.90 (0.86, 0.93)
Recipient BMI	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
On dialysis		
No	Ref	Ref
Yes	1.25 (1.21, 1.30)	1.10 (1.06, 1.13)
Portal vein thrombosis		
No	Ref	Ref
Yes	1.03 (1.00, 1.07)	1.03 (1.01, 1.05)
Donor risk index	1.04 (1.01, 1.07)	1.04 (1.03, 1.05)
Center Characteristics		
Transplant volume		
Low	Ref	Ref
Medium	1.02 (0.98, 1.07)	1.05 (1.00, 1.09)
High	0.92 (0.88, 0.96)	0.95 (0.90, 0.99)
Proportion of minority patients at center		
Low	Ref	Ref

Medium	0.96 (0.94, 0.99)	0.95 (0.92, 0.99)
High	0.92 (0.90, 0.95)	0.91 (0.87, 0.96)
SRTR tier		
1	Ref	Ref
2	1.05 (0.99, 1.10)	1.04 (0.98, 1.10)
3	1.14 (1.08, 1.20)	1.12 (1.07, 1.18)
4	1.05 (0.99, 1.11)	1.03 (0.98, 1.09)
5	0.98 (0.92, 1.04)	1.00 (0.93, 1.08)
Geographic region		
Northeast	Ref	Ref
Midwest	0.98 (0.95, 1.02)	1.00 (0.95, 1.05)
South	0.87 (0.84, 0.90)	0.89 (0.84, 0.94)
West	0.88 (0.85, 0.92)	0.83 (0.77, 0.91)

Table 5.3. Total and controlled direct effects for the association of race and survival accounting for mediation by hospital readmission.

	Total Effect[a]		Controlled Direct Effect[b]	
Race	HR	95% CI	HR	95% CI
Black	1.31	1.20, 1.42	1.29	1.19, 1.41
White	Ref	Ref	Ref	Ref
Readmission				
Yes			1.82	1.72, 1.93
No				

[a] Adjusted for age, gender, region, education, zip code income, and payer.

[b] Stabilized inverse probability weights used to account for potential confounding by sets of confounders and risk factors.

Supplementary Table 5.1. Demographic, clinical, and center-level characteristics of liver transplant recipients in the United States, stratified by hospital readmission within 6 months, 2010 – 2017, Scientific Registry of Transplant Recipients.

	Overall (N = 31,250)	**Missing Readmission** (n = 643)
Patient Characteristics		
Age (mean, SD)	55.1 (10.0)	55.6 (9.8)
Race (N, %)		
Black	3,332 (10.7)	46 (7.2)
White	27,918 (89.3)	597 (92.8)
Sex (N, %)		
Female	10,029 (32.1)	189 (29.4)
Male	21,221 (67.9)	454 (70.6)
Educational attainment (N, %)		
High school or less	13,307 (42.6)	250 (38.9)
Some college	7,919 (25.3)	179 (27.8)
Associate degree or higher	8,232 (26.3)	154 (24.0)
Unknown	1,792 (5.7)	60 (9.3)
Annual household income in zip code		
Mean (SD)	63,200 (25,000)	62,300 (22,300)
Missing (N, %)	3,357 (10.7)	204 (31.7)
Primary payer (N, %)		
Private	17,835 (57.1)	326 (50.7)
Public	13,123 (42.0)	310 (48.2)
Other	292 (0.9)	7 (1.1)
MELD at transplant (mean, SD)	20.7 (9.9)	22.2 (10.2)
Underlying cause of disease (N, %)		
ETOH	5,931 (19.0)	175 (27.2)
Hep C	11,710 (37.5)	227 (35.3)
NASH	5,776 (18.5)	99 (15.4)
Other	7,833 (25.1)	142 (22.1)
Hepatocellular carcinoma (HCC) (N, %)		
Yes	4,087 (13.1)	73 (11.4)
No	27,163 (86.9)	570 (88.6)
Medical condition at transplant (N, %)		
In ICU	2,953 (9.4)	80 (12.4)
Hospitalized, not in ICU	5,636 (18.0)	120 (18.7)
Not hospitalized	22,661 (72.5)	443 (68.9)
Recipient BMI		
Mean (SD)	29.9 (6.7)	29.0 (6.4)
Missing (N, %)	94 (0.3)	0 (0)
On dialysis (N, %)		
Yes	2,449 (7.8)	74 (11.5)
No	28,801 (92.2)	569 (88.5)
Portal vein thrombosis (N, %)		
Yes	3,912 (12.5)	89 (13.8)
No	27.338 (87.5)	554 (86.2)

Donor risk index (mean, SD)		
Mean (SD)	1.16 (0.98)	1.21 (0.53)
Missing (n, %)	1,537 (4.9)	16 (2.5)
Center Characteristics		
Transplant volume (N, %)		
Low	2,508 (8.0)	19 (3.0)
Medium	8,173 (26.2)	110 (17.1)
High	20,569 (65.8)	514 (79.9)
Proportion of minority patients at center (N, %)		
Low	8,372 (26.8)	192 (29.9)
Medium	12,640 (40.4)	310 (48.2)
High	10,238 (32.8)	141 (21.9)
SRTR tier (N, %)		
1	2.233 (7.1)	15 (2.3)
2	7,620 (24.4)	184 (28.6)
3	9,182 (29.4)	170 (26.4)
4	7,812 (25.0)	142 (22.1)
5	4,258 (13.6)	131 (20.4)
Missing	145 (0.5)	1 (0.2)
Geographic region (N, %)		
Northeast	5,431 (17.4)	92 (14.3)
Midwest	7,627 (24.4)	326 (50.7)
South	13,634 (43.6)	186 (28.9)
West	4,556 (14.6)	39 (6.1)

Chapter 6: Aim 3

Abstract

Background: The SRTR – the national registry of transplant recipients – documents whether recipients are hospitalized in the 6 months following transplant. However, there is no information collected on the timing or reasons for readmission; these characteristics provide important insight into the underlying mechanisms of hospitalization. Research on these factors largely relies on single-center studies and, to date, no studies have addressed whether there are differences in the timing of or reasons for hospital admission by race. Such research could be used to generate hypotheses about the etiology of racial disparities in hospitalization after liver transplant.

Methods: We used data from the Emory Transplant Center, a large Southeastern transplant center with a high proportion of Black patients, to describe racial differences in patient- and admission-level hospitalization outcomes after liver transplant. Patient-level outcomes included the timing of first admission and the overall burden of hospital admission, while admission-level outcomes included the reason, urgency, and intensity of admission. We used generalized estimating equations (GEE) to account for multiple readmissions per patient.

Results: We included 821 Black and White liver transplant recipients that experienced 2,262 post-transplant hospital admissions. Black patients had a lower hazard of readmission in the first six months after transplant (HR: 0.77, 95% CI: 0.55, 1.08) and a higher hazard after six months (HR: 1.37, 95% CI: 0.77, 2.43). For each admission, Black patients had a higher prevalence of rejection as a cause of readmission (PR: 1.40, 95% CI: 1.04, 1.89), and a lower prevalence of other causes. For each admission, Black patients were more likely to be admitted emergently (OR: 1.89, 95% CI: 1.29, 2.77), but less likely to go to the ICU (RR: 0.66, 95% CI: 0.48, 0.90).

Conclusions: At a single transplant center, Black patients appeared to have different etiologies of hospital admission after liver transplant compared to White patients. Differences in admission urgency and intensity may point to opportunities to prevent admissions among Black patients. Future research is needed to identify modifiable determinants of these admissions.

Introduction

Disparities in liver transplant outcomes for Black transplant recipients have been well-documented and persist after adjustment for clinical, socioeconomic, and transplant-center specific factors.[1,2] Understanding the determinants of these disparities and identifying opportunities for clinical intervention in the post-transplant period to address disparities is critical to ensuring equitable benefit from transplant for all patients. One such opportunity may be during readmission to the transplant center after initial discharge. Hospital admissions after transplant are common, costly, and associated with poor outcomes.[3] Little is known about racial disparities in hospital admissions after liver transplant, which are both an important health outcome on their own and may represent a good target for intervention to improve long-term outcomes while patients are accessible to clinicians.

Previously, we did not find racial differences in the risk of hospital readmission in the first six months after liver transplant using national data from the Scientific Registry of Transplant Recipients (SRTR). However, readmission risk alone does not provide a comprehensive description of the post-transplant hospitalization experience. SRTR does not collect more nuanced information on post-transplant hospitalization, such as the timing of admission, reasons for admission, or admission urgency and intensity; these characteristics provide important insight into the underlying mechanisms of hospitalization. Research on these factors relies on single-center studies but, to date, no studies have addressed whether there are differences in the timing of, burden of, or reasons for hospitalization by race. Such research could be used to generate hypotheses about the etiology of racial disparities in hospitalization after liver transplant and contribute to the design of clinical interventions to improve patient outcomes.

The objective of this study was to leverage clinical data from a large liver transplant center in the Southeast from 2010 to 2018 to describe racial differences in post-transplant

hospital admission characteristics. We considered both patient-level outcomes and outcomes at each admission to improve our understanding of potential mechanisms of disparity in post-transplant outcomes.

Methods

Study Population and Data Source

Data were obtained from the Emory Transplant Center (ETC) Data Mart, a repository that integrates clinical, billing, laboratory, and medical records from transplant recipients at Emory University. Patients were included if they were non-Hispanic Black or White adults (age $\geq$ 18) who received a deceased donor liver transplant at Emory University between January 1st, 2010 and December 31st, 2018 and were discharged alive from the ETC. Patients were excluded if they received a simultaneous transplant of another organ, had a prior liver transplant, had acute liver failure, or had acute alcoholic hepatitis. For patients with multiple transplants in this interval, only the first transplant was considered.

Variables

Race was abstracted from the medical record and dichotomized as Black or non-Hispanic White. We assessed several outcomes related to hospital admission after liver transplantation. Other patient-level covariates for included age at transplant, gender, zip-code level income, insurance type, underlying cause of disease, hepatocellular carcinoma (HCC), dialysis at time of transplant, body mass index (BMI) at transplant, MELD score at transplant, ICU at time of transplant and initial length of stay after transplant (except for DAOH analyses). Insurance type was assigned based on the primary payer for the transplant (categorized as “public” or “private”). Underlying cause of disease was categorized as hepatitis C, alcoholic liver disease, non-alcoholic steatohepatitis (NASH), and other.

Outcomes

Outcomes were separated into two categories: patient-level outcomes and admission-level outcomes. The first patient-level outcome of interest was time to first admission. Previous research in kidney transplant recipients suggests that the determinants of admission vary by the timing of the window, so we considered two windows of admission risk: admission in the first six months post-transplant, and admissions after six months post-transplant. Patients were censored at the date of their first admission, death, graft failure, date of last contact with the transplant center, end of the window or December 31st, 2019, whichever occurred first. The second patient-level outcome was the overall number of admissions to the ETC. The third patient-level outcome was the number of days alive and out of the hospital (DAOH), which has been previously validated as a measure of disease burden in liver transplant recipients[4]. DAOH was calculated as the number of days alive minus the number of days admitted to ETC, both in the first year after transplant and overall.

The first admission-level outcome was the length of stay for each admission, in days. The second was the reason for admission, defined using ICD-9 and ICD-10 codes. Codes were classified into six broad categories by two clinicians, including rejection, infection, surgical / technical, liver, renal, and frailty. Each admission could be caused by none, one, or multiple of these classifications. Other admission-level outcomes included urgency (whether admission was planned, urgent, or emergent) and intensity (whether the patient required ICU care during their admission).

Statistical Analyses

Clinical and demographic characteristics of our population were described, and bivariate associations between race and our outcomes were assessed using Chi-square or t-tests as appropriate. Analyses were divided into two categories of outcomes: patient-level and admission-level outcomes. For patient-level outcomes, we used linear regression to estimate the association between race and DAOH, and Cox proportional hazards models with an

interaction term between race and time to estimate the association between race and time to admission before and after 6 months. For admission-level outcomes, we used generalized estimating equations (GEE) to account for the potential for multiple admissions by the same patient. We used linear regression to estimate the association between race and length of stay, log-binomial regression to estimate the association between race and cause of admission, log-binomial regression to estimate the association between race and ICU stay during admission, and multinomial logistic regression to estimate the association between race and acuity of stay. All analyses were presented first unadjusted, and then adjusted for demographic, clinical, and socioeconomic characteristics.

Results

Population Characteristics

Between 2010 and 2018, there were 821 Black and White liver transplant recipients at the Emory Transplant Center, representing 2,262 post-transplant hospital admissions. Black patients comprised 23.1% of liver recipients and 26.2% of post-transplant admissions. On average (Table 6.1), liver recipients at ETC were 54 years of age (SD: 10.8 years), and predominantly male (62.4%) with private health insurance (63.8%). Hepatitis C was the most common indication for transplant among grouped diagnoses (28.4%), although a high proportion of patients had “other” diagnoses (34.8%). The majority of transplant admissions were classified as urgent (79.3%), and patients stayed an average of 17 days after receiving a transplant (SD: 16.8).

Stratified analyses indicate that Black and White patients differ on both sociodemographic and clinical characteristics. Black patients were younger (mean: 52.2 years vs. 54.6 years) and more likely to be female (47.9% vs. 34.5%) than White patients. The average annual income in zip code of residence was lower for Black patients (mean: $52,800)

compared to White patients (mean: $58,300). Black patients were more likely to have Hepatitis C as an underlying cause of liver disease (37.9% vs. 25.5%) but less likely to have HCC (7.4% vs. 13.6%) or diabetes (24.2% vs. 31.1%) at transplant.

Bivariate Associations

Table 6.2 provides bivariate associations between race and outcomes of interest after liver transplantation at ETC. At the patient level, Black patients had a similar number of admissions and days alive and out of the hospital compared to White patients. Differences emerged at the level of individual hospital admission. Black patients had a shorter average length of stay compared to White patients (5.9 days vs. 6.7 days, $p = 0.04$) and were less likely to be in the ICU during admission (11.8% vs. 15.7%, $p = 0.03$). However, Black patients were more likely than White patients to have an emergent admission (53.3% vs. 40.4%, $p < 0.001$), as opposed to an elective or urgent admission. Black and White patients differed significantly on their reason for admission. Black patients were significantly less likely than White patients to be readmitted for infection (25.6% vs. 40.0%, $p < 0.001$), surgical / technical complications (10.5% vs. 16.9%, $p < 0.001$), or renal concerns (34.2% vs. 39.3%, $p = 0.04$), and more likely than White patients to readmitted for rejection (25.0% vs. 14.4%, $p < 0.001$) or liver concerns (25.8% vs. 20.6%). There was not a significant difference in the proportion of patients admitted for frailty ($p = 0.30$).

Patient-Level Outcomes

Table 6.3 presents associations between race and the time to first admission after liver transplantation at ETC within and after 6 months. Unadjusted for any other variables, Black patients had a lower hazard of admissions within six months (HR: 0.82, 95% CI: 0.61, 1.11) or than White patients, and higher hazard of admission after six months (HR: 1.39, 95% CI: 0.84, 2.28). This pattern was similar after adjustment for clinical, demographic and socioeconomic

characteristics, Black patients had a lower hazard of admissions within six months (HR: 77, 95% CI: 0.55, 1.08) and a higher hazard of admission after 6 months (HR: 1.37, 95% CI: 0.77, 2.43); this association was not statistically significant.

Table 6.4 provides the mean number of hospital admissions after transplant, adjusted for clinical, socioeconomic, and demographic characteristics. In crude analyses, there was no difference between Black and White patients (mean difference: -0.09, 95% CI: -0.59, 0.42). Factors associated with the number of admissions were public insurance, relative to private (mean difference: 0.46, 95% CI: 0.01, 0.92), hepatocellular carcinoma (mean difference: -1.02, 95% CI: -1.56, -0.48), and elective transplant admission, relative to emergent (mean difference: -0.77, -1.49, -0.06). After adjustment, Black patients had fewer hospitalizations, but this association was not significant (mean difference: -0.21, 95% CI: -0.78, 0.34). The associations between insurance type, HCC, transplant type and number of readmissions remained significant, and alcohol-associated disease, relative to hepatitis C (mean difference: -0.75, 95% CI: -1.43, -0.06) was significantly associated with number of readmissions.

In the first year after transplant, Black patients had a similar number of DAOH compared to White patients in both unadjusted (mean difference: 0.02, 95% CI -6.9, 7.0) and adjusted analyses (mean difference: -0.5, 95% CI: -7.1, 8.2) (Table 6.5). There were no factors significantly associated with DAOH at one year in either adjusted or unadjusted analyses. Overall, Black patients had 20.3 fewer DAOH than White patients (95% CI: -167.7, 127.1), which increased to 48.4 fewer days when adjusted for other factors (95% CI: -201.8, 1.05). Higher annual average income in the zip code was associated with increased DAOH (adjusted mean difference: 34.9, 95% CI: 2.5, 67.2), while ETOH (adjusted mean difference: -309.3 days, 95% CI: -495.6, -123.0) and NASH (adjusted mean difference: -214.9, 95% CI: -412.4, -17.4) had significantly lower DAOH when compared to Hepatitis C. Patients with HCC also had fewer DAOH after transplant (adjusted mean difference: -326.2, 95% CI: -551.4, 100.9).

Admission-Level Analyses

Table 6.6 describes the association between race and admission length of stay after transplant, adjusted for clinical and demographic variables, at the level of the admission. Black patients had slightly shorter lengths of stay for each admission after transplant in both unadjusted (mean difference: -0.81 days, 95% CI: -1.89, 0.26) and adjusted (mean difference: -0.82 days, 95% CI: -2.10, 0.47) analyses; this difference was not statistically significant. The only variable significantly associated with admission length of stay was transplant length of stay, although the magnitude of the association was small (mean difference: 0.05 days, 95% CI: 0.03, 0.07).

Table 6.7 describes the association between race and primary cause of admission after transplant. Among those readmitted to ETC, Black patients were significantly more likely to be readmitted for rejection than White patients (prevalence ratio [PR]: 1.74, 95% CI: 1.13, 2.67); this association was attenuated but remained significant after adjustment (PR: 1.40, 95% CI: 1.04, 1.89). Female sex was also significantly associated with increased prevalence of admission for rejection (adjusted PR: 1.54, 95% CI: 1.15, 2.07).

In contrast, Black patients were less likely to have infection as the primary cause of admission (adjusted PR: 0.62, 95% CI: 0.45, 0.85). Other causes of liver disease, compared to hepatitis C, were more likely to be readmitted for infection (adjusted PR: 1.41, 95% CI: 1.04, 1.93). After adjustment for other factors, Black patients were 44% less likely to be readmitted for surgical / technical causes (PR: 0.56, 95% CI: 0.32, 1.00). Patients living in zip codes with higher annual income (adjusted PR: 0.85, 95% CI: 0.77, 0.94) and patients with diabetes (adjusted PR: 0.63, 95% CI 0.42, 0.94) were less likely to be readmitted for surgical / technical causes, and patients with elective, compared to emergent, admissions for transplant were more likely to be readmitted for surgical / technical causes (adjusted PR: 1.90, 95% CI: 1.20, 3.02).

Black patients had a similar prevalence of renal (adjusted PR: 0.93, 95% CI: 0.65, 1.94), hepatic (adjusted PR: 1.00, 95% CI 0.63, 1.59), or frailty-related (adjusted PR: 0.89, 95% CI: 0.53, 1.49) causes of admission to White patients. Women were more likely to be readmitted for frailty-related causes than men (adjusted PR: 1.53, 95% CI: 1.08, 2.18), and patients with HCC were also more likely to be readmitted for frailty-related causes (adjusted PR: 2.52, 95% CI: 1.46, 4.33).

Table 6.8 describes the association between race and type of hospital admission for each admission, with elective admissions as the reference group. Unadjusted for other factors, Black patients were more likely to have urgent (OR: 1.27, 95% CI: 0.90, 1.78) and emergent admissions than White patients (OR: 2.03, 95% CI: 1.45, 2.84). After adjustment, Black patients remained significantly more likely to have emergent admissions than White patients (OR: 1.89, 95% CI: 1.29, 2.77). Women (OR: 1.69, 95% CI: 1.21, 2.36), patients living in higher income zip codes (OR: 1.23, 95% CI: 1.12, 1.35), patients with public insurance (OR: 1.41, 95% CI: 1.09, 1.95), and patients with diabetes (OR: 2.23, 95% CI: 1.47, 3.18) were also more likely to have emergent, rather than elective, admissions. Type of admission at transplant was strongly inversely associated with admission urgency after transplant.

In crude analyses, Black patients were less likely than White patients to be admitted to the ICU during their hospital stay (RR: 0.75, 95% CI: 0.56, 1.00); this association was stronger after adjustment for clinical and demographic factors (RR: 0.65, 95% CI: 0.48, 0.90) (Table 6.9). There were no other significant associations with ICU admission.

Discussion

After adjustment for clinical and sociodemographic characteristics, Black patients at a large Southeastern transplant center differed from White patients in their post-transplant hospital admission characteristics. Black patients had more favorable or comparable outcomes

to White patients in the early post-transplant period, but experienced a higher burden of hospital admission overall. At each admission, Black patients had a higher prevalence of rejection as an indication for admission than White patients, and were more likely to be admitted emergently but less likely to require ICU admission during their hospital stay. These differences may provide insight into the underlying mechanisms of racial disparity in liver transplant outcomes.

Our findings that racial disparities in hospital admission timing and burden emerge in the late post-transplant period is consistent with previous work on survival disparities in liver transplant. Racial disparities in post-transplant survival grow over time, from a 1 percentage-point difference between Black and White patients in 1-year survival to a 6 percentage-point difference at five years. Ananthakrishnan et al. found that significant survival disparities among Black patients emerged at two years post-transplant, while graft survival disparities were evident at one year.[5] Research on post-transplant hospital admissions after kidney transplant found that demographic and socioeconomic factors were more important predictors of late than early admission.[6] As transplant center quality metrics move away from 1-year survival and towards longer-term outcomes[7], understanding and addressing the determinants of racial disparities in this late post-transplant period will become increasingly important.

One novel contribution of this study is the finding that reasons for admission differ by race. We found that, among patients who were readmitted, admission for rejection was more prevalent among Black patients than White patients; admission for any other cause was less prevalent. Rejection occurs when the liver allograft is injured by the recipient's immune system; transplant recipients are on lifelong immunosuppression regimens to avoid this complication. Medication adherence has been associated with the incidence of rejection in several studies.[8] Non-adherence to medication is common among liver transplant recipients (22% – 62%), but little is known about differences in immunosuppression adherence by race. Serper et al.[9] conducted data collection at two transplant centers and found that low levels of health literacy

were associated with decreased adherence to immunosuppression medication after liver transplant. In a study by Wedd et al. examining patient portal use after transplantation, which has been suggested to improve medication adherence and health outcomes, Black liver transplant recipients were less likely to interact with the portal.[10] Identifying barriers to adherence in this population may be one potential avenue of reducing disparities.

In our study, Black patients were more likely to admitted to the hospital emergently (compared to electively), but were less likely to require care in the ICU during their admission. The finding that Black patients are more likely to be admitted emergently is consistent with previous studies, which found that Black patients more likely to be admitted through emergency department than referral[11] and that admission source (referral vs. emergent) explained disparities in surgical outcomes for total knee replacement.[12] However, previous studies have found that Black patients are more likely to present to the hospital with higher illness acuity,[13] which is in contrast with what we found in this study. One potential explanation for this inconsistency is that Black liver transplant recipients are being admitted to the hospital for conditions that may be manageable in an outpatient setting. Racial disparities in access to care, particularly primary care, are well-established[14] and may partially explain our findings. In addition, Black patients may face structural barriers to care, such as transportation to the transplant center, that prompt physicians to admit them instead of potentially requiring multiple trips. Quality improvement programs that included coordinated “observation” stays in place of admissions and local hospital lodging after discharge have been shown to be effective in reducing admissions after liver transplant[15], and may be particularly effective at reducing admissions among Black patients if these structural barriers contribute to disparity.

This is a single center study and is subject to inherent limitations. We required center-specific data in order to address more nuanced aspects of hospital admission, but our results may not be generalizable to patients at other transplant centers. Notably, our center has twice

the national average proportion of Black patients, which increased our power to detect racial disparities but may also mean that our results do not reflect the experience of other transplant centers. In addition, we used ICD-9 and ICD-10 codes to classify reasons for admission at the time of admission, but these codes may change over the course of admission and therefore be misclassified. Finally, our reliance on center-level data means that we are excluding patients without continuity of care. While this is less common among transplant recipients than in other areas of medicine, if Black patients were more likely to experience care fragmentation then we may be differentially missing outcome data.

In summary, we identified several differences in post-transplant hospital characteristics by race in a large Southeastern transplant center. Relative to White patients and after adjustment for clinical and socioeconomic characteristics, Black patients experienced more favorable outcomes in the early post-transplant period, but this advantaged disappeared after the first year. At each admission, Black patients had a higher prevalence of rejection, a higher likelihood of emergent admission, and a lower likelihood of ICU stay. Further research to identify the determinants of these differences may contribute to the development of effective interventions to address preventable hospital admissions among Black patients, and potentially reduce persistent racial disparities in post-liver transplant outcomes.

Tables and Figures

Table 6.1. Clinical and sociodemographic characteristics of Black and White liver transplant recipients (N = 821) at Emory Transplant Center, 2010 – 2018.

	White (N = 631, 76.9%)	Black (N = 190, 23.1%)	Overall (N = 821)
Age at transplant (mean, SD)	54.6 (10.3)	52.2 (12.2)	54.1 (10.8)
Gender (N, %)			
Male	413 (65.5)	99 (52.1)	512 (62.4)
Female	218 (34.5)	91 (47.9)	309 (37.6)
Average annual income in zip code (mean, SD)	58,300 (19,500)	52,800 (17,000)	57,000 (19,100)
Primary payer (N, %)			
Public	209 (33.1)	64 (33.7)	273 (33.3)
Private	407 (64.5)	117 (61.6)	524 (63.8)
Missing	2 (0.3)	1 (0.5)	3 (0.4)
Underlying cause of disease (N, %)			
Hepatitis C	161 (25.5)	72 (37.9)	233 (28.4)
ETOH	132 (20.9)	20 (10.5)	152 (18.5)
NASH	141 (22.3)	8 (4.2)	149 (18.1)
Other	196 (31.1)	90 (47.4)	286 (34.8)
HCC (N, %)	86 (13.6)	14 (7.4)	100 (12.2)
On dialysis at transplant (N, %)	9 (1.4)	4 (2.1)	13 (1.6)
Diabetes at transplant (N, %)	196 (31.1)	46 (24.2)	242 (29.5)
BMI at transplant (mean, SD)	31.6 (16.8)	29.3 (6.5)	31.1 (15.1)
Missing (N, %)	39 (6.2)	15 (7.9)	54 (6.6)
MELD at transplant (mean, SD)	26.2 (7.1)	26.6 (8.3)	26.3 (7.4)
Transplant LOS (mean, SD)	17.1 (17.8)	16.3 (13.3)	16.9 (16.8)
Type of admission at transplant (N, %)			
Elective	65 (10.3)	15 (7.9)	80 (9.7)
Urgent	495 (78.4)	156 (82.1)	651 (79.3)
Emergent	71 (11.3)	19 (10.0)	90 (11.0)

Table 6.2**.** Bivariate associations between race and outcomes after liver transplantation at Emory Transplant Center.

Patient Level			
	White	Black	p-value
Number of admissions (mean, SD)	2.35 (3.07)	2.27 (3.19)	0.75
DAOH (mean, SD)			
1 year	352 (42.7)	352 (43.9)	0.99
Total	1,660 (908)	1,640 (912)	0.78
Admission Level			
	White	Black	p-value
LOS (mean, SD)	6.67 (13.3)	5.85 (5.6)	0.04
Type of admission (N, %)			< 0.001
Elective	217 (13.0)	50 (8.4)	
Urgent	777 (46.6)	227 (38.3)	
Emergent	675 (40.4)	316 (53.3)	
ICU during admission (N, %)	262 (15.7)	70 (11.8)	0.03
Reason for readmission			
Infection	667 (40.0)	152 (25.6)	< 0.001
Rejection	241 (14.4)	148 (25.0)	< 0.001
Surgical / Technical	282 (16.9)	62 (10.5)	<0.001
Liver	344 (20.6)	153 (25.8)	0.01
Renal	656 (39.3)	203 (34.2)	0.04
Frailty	210 (12.6)	64 (10.8)	0.30

Table 6.3. Association between race and time to first admission after liver transplantation at Emory Transplant Center, adjusted for clinical and demographic variables[a].

	Admission within 6 months		Admission after 6 months	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Race				
White	Ref	Ref		
Black	0.82 (0.61, 1.11)	0.77 (0.55, 1.08)	1.39 (0.84, 2.28)	1.37 (0.77, 2.43)
Age at transplant, per year increase	0.99 (0.98, 1.01)	0.99 (0.98, 1.01)	0.99 (0.97, 1.01)	0.99 (0.96, 1.01)
Gender				
Male	Ref	Ref	Ref	Ref
Female	1.05 (0.92, 1.35)	1.02 (0.77, 1.34)	0.81 (0.52, 1.26)	0.83 (0.50, 1.36)
Average annual income in zip code, per 10,000	0.95 (0.89, 1.020	0.95 (0.88, 1.02)	0.97 (0.87, 1.09)	0.96 (0.85, 1.09)
Primary payer				
Public	1.19 (0.92, 1.53)	1.12 (0.85, 1.48)	1.19 (0.76, 1.86)	1.28 (0.78, 2.09)
Private	Ref	Ref	Ref	Ref
Underlying cause of disease				
Hepatitis C	Ref	Ref	Ref	Ref
ETOH	1.03 (0.72, 1.48)	0.87 (0.59, 1.29)	0.77 (0.39, 1.53)	1.03 (0.49, 2.09)
NASH	1.21 (0.85, 1.71)	1.02 (0.68, 1.52)	1.02 (0.54, 1.89)	1.39 (0.66, 2.93)
Other	0.95 (0.69, 1.29)	0.85 (0.58, 1.26)	1.23 (0.72, 2.09)	1.41 (0.71, 2.80)
HCC	0.81 (0.55, 1.21)	0.93 (0.56, 1.54)	1.17 (0.60, 2.29)	1.18 (0.49, 2.82)
On dialysis at transplant	1.61 (0.71, 3.61)	1.49 (0.65, 3.41)	1.74 (0.43, 7.08)	1.86 (0.41, 0.84)
Diabetes at transplant	1.20 (0.93, 1.55)	1.25 (0.93, 1.67)	0.72 (0.45, 1.16)	0.82 (0.48, 1.40)
BMI at transplant, per point	1.00 (0.99, 1.01)	1.00 (0.98, 1.01)	0.99 (0.97, 1.01)	0.99 (0.96, 1.01)
MELD at transplant, per point	1.01 (1.00, 1.03)	1.01 (0.99, 1.03)	1.01 (0.98, 1.03)	1.00 (0.96, 1.03)
Transplant LOS	1.01 (1.00, 1.01)	1.00 (1.00, 1.01)	1.00 (0.99, 1.01)	
Type of admission at transplant				
Elective	0.81 (0.55, 1.19)	0.78 (0.52, 1.17)	1.08 (0.54, 2.18)	0.96 (0.46, 2.03)
Urgent	1.19 (0.74, 1.94)	1.00 (0.60, 1.68)	1.31 (0.55, 3.16)	1.52 (0.59, 3.93)
Emergent	Ref	Ref	Ref	Ref

Table 6.4. Association between race and number of readmissions after liver transplantation at Emory Transplant Center, adjusted for clinical and demographic variables[a].

	Number of Readmissions	
	Unadjusted	Adjusted
Race		
White	Ref	Ref
Black	-0.09 (-0.59, 0.42)	-0.21 (-0.78, 0.34)
Age at transplant, per year increase	-0.03 (-0.05, -0.01)	-0.04 (-0.06, -0.01)
Gender		
Male	Ref	Ref
Female	-0.02 (-0.45, 0.42)	-0.17 (-0.15, 0.09)
Average annual income in zip code, per 10,000	-0.05 (-0.16, 0.07)	-0.03 (-0.15, 0.09)
Primary payer		
Public	0.46 (0.01, 0.92)	0.48 (0.00, 0.96)
Private	Ref	Ref
Underlying cause of disease		
Hepatitis C	Ref	Ref
ETOH	-0.56 (-0.19, 0.07)	-0.75 (-1.43, -0.06)
NASH	0.10 (-0.54, 0.73)	-0.02 (-0.74, 0.70)
Other	-0.11 (-0.64, 0.43)	-0.15 (-0.82, 0.52)
HCC	-0.81 (-1.45, -0.16)	-0.68 (-1.50, 0.14)
On dialysis at transplant	0.83 (-0.86, 2.53)	0.72 (-0.98, 2.43)
Diabetes at transplant	0.02 (-0.44, 0.48)	0.23 (-0.29, 0.74)
BMI at transplant, per point	0.00 (-0.02, 0.01)	0.00 (-0.02, 0.01)
MELD at transplant, per point	0.00 (-0.03, 0.03)	0.00 (-0.04, 0.03)
Transplant LOS	0.01 (-0.01, 0.02)	0.00 (-0.01, 0.02)
Type of admission at transplant		
Elective	-0.77 (-1.49, -0.06)	-0.90 (-1.64, -0.16)
Urgent	0.10 (-0.83, 1.02)	-0.07 (-1.06, 0.92)
Emergent	Ref	Ref

Table 6.5. Association between race and days alive and out of the hospital after liver transplantation at Emory Transplant Center, adjusted for clinical and demographic variables[a].

	DAOH in first year		Total DAOH	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Race				
White	Ref	Ref	Ref	Ref
Black	0.02 (-6.9, 7.0)	0.5 (-7.1, 8.2)	-20.3 (-167.7, 127.1)	-48.4 (-201.8, 1.05)
Age at transplant, per year increase	-0.03 (-0.30, 0.24)	-0.01 (-0.3, 0.3)	-2.5 (-8.3, 3.3)	-5.0 (-11.3, 1.3)
Gender				
Male	Ref	Ref	Ref	Ref
Female	1.0 (-5.1, 7.1)	-0.2 (-6.7, 6.3)	1.4 (-126.9, 129.7)	-26.8 (-157.2, 103.6)
Average annual income in zip code, per 10,000	-0.5 (-2.0, 1.1)	-0.4 (-2.0, 1.3)	36.2 (3.4, 69.1)	34.9 (2.5, 67.2)
Primary payer				
Public	-2.6 (-8.9, 3.6)	-0.6 (-7.2, 6.0)	36.8 (-96.2, 169.7)	-0.40 (-132.5, 131.7)
Private	Ref	Ref	Ref	Ref
Underlying cause of disease				
Hepatitis C	Ref	Ref	Ref	Ref
ETOH	4.9 (-3.9, 13.6)	5.5 (-3.8, 14.8)	-353.0 (-537.2, -168.8)	-309.3 (-495.6, -123.0)
NASH	-5.4 (-14.2, 3.4)	-6.3 (-16.1, 3.6)	-199.0 (-384.3, -13.7)	-214.9 (-412.4, -17.4)
Other	-2.4 (-9.8, 5.0)	-0.1 (-9.2, 8.9)	-183.5 (-339.5, -27.4)	-90.4 (-272.6, 91.8)
HCC	-0.3 (-9.3, 8.7)	-2.7 (-14.0, 8.5)	-236.3 (-425.6, -46.9)	-326.2 (-551.4, -100.9)
On dialysis at transplant	-3.9 (-27.4, 19.7)	0.9 (-22.4, 24.2)	-585.1 (-1,081.5, -88.7)	-355.0 (-821.6, 111.6)
Diabetes at transplant	-0.9 (-7.3, 5.6)	-1.1 (-8.2, 5.9)	5.6 (-130.7, 141.9)	-62.1 (-203.4, 79.1)
BMI at transplant, per point	0.2 (-0.1, 0.3)	0.1 (-0.1, 0.3)	4.4 (0.3, 8.5)	4.8 (-0.8, 8.8)
MELD at transplant, per point	-0.3 (-0.7, 0.1)	-0.1 (-0.6, 0.3)	-30.3 (-38.4, -22.1)	-26.9 (-36.0, -17.9)
Type of admission at transplant				

Elective	6.0 (-3.9, 15.9)	2.3 (-7.8, 12.4)	-132.5 (-77.9, 342.8)	142.9 (-59.6, 345.3)
Urgent	-24.0 (-49.6, 1.6)	-15.1 (-28.5, 1.7)	-104.7 (-377.5, 168.1)	167.7 (-100.9, 436.3)
Emergent	Ref	Ref	Ref	Ref

Table 6.6**.** Association between race and admission length of stay after liver transplantation at Emory Transplant Center, adjusted for clinical and demographic variables[a].

	Admission Length of Stay	
	Unadjusted	Adjusted
Race		
White	Ref	
Black	-0.81 (-1.89, 0.26)	-0.82 (-2.1, 0.47)
Age at transplant, per year increase	0.00 (-0.08, 0.07)	0 (-0.06, 0.07)
Gender		
Male	Ref	Ref
Female	0.77 (-0.50, 2.04)	1.08 (-0.15, 2.3)
Average annual income in zip code, per 10,000	-0.43 (-0.97, 0.11)	-0.46 (-1.01, 0.09)
Primary payer		
Public	0.24 (-0.96, 1.44)	-0.11 (-1.45, 1.24)
Private	Ref	Ref
Underlying cause of disease		
Hepatitis C	Ref	Ref
ETOH	1.04 (-1.07, 3.15)	1.05 (-1.24, 3.34)
NASH	1.21 (-0.01, 2.43)	0.66 (-0.77, 2.09)
Other	1.38 (0.04, 2.71)	1.17 (-0.32, 2.67)
HCC	0.74 (-0.77, 2.25)	0.39 (-1.66, 2.44)
On dialysis at transplant	0.06 (-2.73, 2.85)	0.29 (-2.24, 2.83)
Diabetes at transplant	-0.40 (-1.57, 0.78)	0.32 (-0.79, 1.43)
BMI at transplant, per point	-0.03 (-0.10, 0.04)	-0.07 (-0.15, 0.02)
MELD at transplant, per point	0.02 (-0.04, 0.07)	-0.02 (-0.1, 0.05)
Transplant LOS, per day	0.04 (0.02, 0.06)	0.05 (0.03, 0.07)
Type of admission at transplant		
Elective	-1.84 (-5.02, 1.33)	-2.39 (-5.49, 0.7)
Urgent	-0.78 (-4.21, 2.65)	-1.92 (-5.07, 1.22)
Emergent	Ref	Ref

Table 6.7. Association between race and reason for admission after liver transplantation at Emory Transplant Center, adjusted for clinical and demographic variables[a].

	Rejection		Infection		Surgical / Technical		Renal		Hepatic		Frailty	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Race												
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.74 (1.13, 2.67)	1.40 (1.04, 1.89)	0.64 (0.47, 0.89)	0.62 (0.45, 0.85)	0.62 (0.33, 1.17)	0.56 (0.32, 1.00)	0.88 (0.62, 1.24)	0.93 (0.65, 1.33)	1.26 (0.82, 1.94)	1.00 (0.63, 1.59)	0.86 (0.52, 1.43)	0.89 (0.53, 1.49)
Age at transplant, per year	0.97 (0.96, 0.98)	0.99 (0.97, 1)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.01 (0.99, 1.02)	1.00 (0.99, 1.02)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	0.99 (0.98, 1.00)	0.99 (0.98, 1.01)	1.01 (1.00, 1.03)	1.01 (0.99, 1.02)
Gender												
Male	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Female	1.86 (1.35, 2.57)	1.54 (1.15, 2.07)	1.18 (0.97, 1.45)	1.22 (1.00, 1.48)	0.73 (0.49, 1.09)	0.69 (0.49, 0.99)	1.12 (0.91, 1.39)	1.18 (0.97, 1.43)	1.05 (0.75, 1.47)	1.12 (0.80, 1.57)	1.32 (0.92, 1.88)	1.53 (1.08, 2.18)
Average annual income in zip code, per 10,000	1.00 (0.91, 1.10)	1.02 (0.95, 1.1)	1.01 (0.94, 1.07)	1.00 (0.95, 1.05)	0.88 (0.80, 0.97)	0.85 (0.77, 0.94)	1.01 (0.95, 1.07)	1.02 (0.97, 1.08)	0.94 (0.85, 1.03)	0.93 (0.85, 1.03)	0.91 (0.81, 1.03)	0.90 (0.80, 1.02)
Primary payer												
Public	1.06 (0.72, 1.58)	1.06 (0.8, 1.39)	0.88 (0.71, 1.08)	0.84 (0.7, 1.02)	1.00 (0.68, 1.46)	0.93 (0.60, 1.43)	1.01 (0.82, 1.26)	1.05 (0.86, 1.29)	1.05 (0.74, 1.48)	0.95 (0.67, 1.35)	1.23 (0.86, 1.76)	1.14 (0.80, 1.62)
Private	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Underlying cause of disease												
Hepatitis C	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
ETOH	1.59 (1.02, 2.48)	1.27 (0.8, 2.01)	1.35 (0.94, 1.94)	1.25 (0.92, 1.71)	0.99 (0.59, 1.69)	0.90 (0.55, 1.47)	1.32 (0.94, 1.83)	1.29 (0.97, 1.73)	0.46 (0.26, 0.82)	0.43 (0.25, 0.74)	0.75 (0.41, 1.37)	0.77 (0.44, 1.35)
NASH	1.03 (0.64, 1.66)	0.99 (0.59, 1.66)	1.41 (1.03, 1.95)	1.2 (0.91, 1.58)	0.93 (0.56, 1.55)	1.04 (0.65, 1.68)	1.26 (0.91, 1.75)	1.10 (0.83, 1.44)	0.52 (0.34, 0.78)	0.45 (0.29, 0.69)	0.96 (0.57, 1.64)	0.72 (0.43, 1.23)
Other	2.06 (1.38, 3.07)	1.36 (0.86, 2.13)	1.28 (0.93, 1.76)	1.41 (1.04, 1.93)	1.05 (0.65, 1.70)	1.07 (0.68, 1.67)	1.01 (0.73, 1.40)	1.13 (0.79, 1.61)	0.90 (0.61, 1.34)	0.70 (0.43, 1.12)	1.13 (0.70, 1.83)	0.79 (0.47, 1.35)

HCC	0.93 (0.57, 1.52)	1.11 (0.66, 1.86)	1.09 (0.83, 1.43)	0.87 (0.63, 1.2)	1.35 (0.85, 2.12)	1.05 (0.63, 1.73)	1.12 (0.82, 1.52)	1.12 (0.78, 1.63)	1.11 (0.68, 1.82)	1.26 (0.69, 2.27)	2.19 (1.57, 3.28)	2.52 (1.46, 4.33)
On dialysis at transplant	1.26 (0.64, 2.49)	1.31 (0.8, 2.16)	1.13 (0.63, 2.03)	1.04 (0.66, 1.63)	0.31 (0.09, 1.09)	0.35 (0.10, 1.22)	1.33 (1.02, 1.74)	1.27 (0.88, 1.84)	0.65 (0.21, 1.98)	0.67 (0.23, 1.93)	1.40 (0.66, 2.97)	1.43 (0.74, 2.80)
Diabetes at transplant	0.61 (0.43, 0.87)	0.77 (0.54, 1.11)	1.01 (0.76, 1.35)	1.06 (0.85, 1.31)	0.69 (0.43, 1.08)	0.63 (0.42, 0.94)	1.06 (0.79, 1.42)	1.08 (0.84, 1.39)	0.92 (0.62, 1.36)	1.02 (0.68, 1.51)	0.90 (0.57, 1.44)	1.06 (0.70, 1.60)
BMI at transplant, per point	1.00 (0.98, 1.02)	1.01 (0.99, 1.02)	1.01 (1.00, 1.02)	1.00 (0.99, 1.01)	0.99 (0.97, 1.01)	0.99 (0.96, 1.01)	1.01 (0.99, 1.02)	1.00 (0.99, 1.02)	1.00 (0.98, 1.02)	1.01 (0.99, 1.03)	0.98 (0.95, 1.00)	0.97 (0.95, 0.99)
MELD score, per point	1.01 (0.99, 1.03)	1.01 (0.99, 1.04)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.97 (0.95, 0.99)	0.98 (0.96, 1.00)	1.02 (1.01, 1.03)	1.01 (1.00, 1.03)	1.00 (0.98, 1.02)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)	0.99 (0.97, 1.02)
Transplant LOS, per day	0.99 (0.98, 1.00)	0.99 (0.98, 1.01)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.99 (0.98, 1.00)	0.99 (0.98, 1.01)	1.01 (1.00, 1.01)	1 (1.00, 1.01)	0.99 (0.98, 1.00)	0.99 (0.98, 1.00)	1.01 (1.00, 1.01)	1.01 (1.01, 1.02)
Type of admission at transplant												
Elective	1.03 (0.69, 1.55)	0.89 (0.64, 1.23)	0.91 (0.68, 1.23)	0.97 (0.73, 1.30)	1.56 (0.92, 2.64)	1.90 (1.20, 3.02)	1.14 (0.83, 1.58)	1.18 (0.87, 1.60)	1.07 (0.66, 1.73)	1.21 (0.75, 1.94)	1.08 (0.58, 1.99)	1.15 (0.64, 2.08)
Urgent	0.79 (0.46, 1.34)	0.74 (0.42, 1.28)	0.97 (0.71, 1.32)	1.07 (0.77, 1.50)	0.85 (0.43, 1.67)	0.99 (0.49, 1.99)	1.34 (0.95, 1.88)	1.17 (0.82, 1.66)	0.85 (0.49, 1.48)	1.07 (0.60, 1.9)	1.44 (0.76, 2.74)	1.58 (0.76, 3.27)
Emergent	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

Table 6.8. Association between race and type of hospital readmission after liver transplantation at Emory Transplant Center, adjusted for clinical and demographic variables[a].

	Urgent vs. Elective		Emergent vs. Elective	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Race				
White	Ref	Ref	Ref	Ref
Black	1.27 (0.90, 1.78)	1.23 (0.83, 1.81)	2.03 (1.45, 2.84)	1.89 (1.29, 2.77)
Age at transplant, per year increase	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)	0.98 (0.97, 0.99)	0.97 (0.96, 0.98)
Gender				
Male	Ref	Ref	Ref	Ref
Female	2.03 (1.50, 2.74)	1.86 (1.33, 2.58)	1.83 (1.35, 2.47)	1.69 (1.21, 2.36)
Average annual income in zip code, per 10,000	1.06 (0.98, 1.15)	1.13 (1.03, 1.23)	1.16 (1.07, 1.26)	1.23 (1.12, 1.34)
Primary payer				
Public	1.10 (0.83, 1.47)	1.23 (0.89, 1.70)	1.17 (0.88, 1.55)	1.41 (1.09, 1.95)
Private	Ref		Ref	
Underlying cause of disease				
Hepatitis C	Ref	Ref	Ref	Ref
ETOH	0.98 (0.65, 1.48)	0.84 (0.54, 1.32)	0.88 (0.69, 1.33)	0.88 (0.56, 1.39)
NASH	1.65 (1.10, 2.45)	1.51 (0.95, 2.39)	1.15 (0.77, 1.72)	1.25 (0.78, 2.00)
Other	1.45 (1.03, 2.03)	1.11 (0.71, 1.72)	1.15 (0.83, 1.60)	0.93 (0.60, 1.44)
HCC	1.25 (0.79, 1.99)	1.52 (0.83, 2.79)	0.58 (0.35, 0.96)	0.82 (0.43, 1.55)
Diabetes at transplant	1.28 (0.94, 1.76)	1.38 (0.97, 1.97)	1.84 (1.34, 2.51)	2.23 (1.47, 3.18)
BMI at transplant, per point	1.02 (1.01, 1.05)	1.02 (1.00, 1.05)	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
MELD at transplant, per point	1.03 (1.00, 1.05)	1.04 (1.01, 1.06)	1.03 (1.00, 1.05)	1.03 (1.00, 1.05)
Transplant LOS, per day	1.00 (0.99, 1.00)	0.99 (0.98, 1.00)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
Type of admission at transplant				
Elective	0.70 (0.42, 1.16)	0.56 (0.31, 0.99)	0.48 (0.29, 0.80)	0.33 (0.19, 0.58)
Urgent	0.79 (0.42, 1.48)	0.59 (0.29, 1.22)	0.58 (0.32, 1.08)	0.53 (0.20, 0.82)
Emergent	Ref	Ref	Ref	Ref

Table 6.9. Association between race and ICU stay during admission liver transplantation at Emory Transplant Center, adjusted for clinical and demographic variables[a].

	ICU During Admission	
	Unadjusted	Adjusted
Race		
White	Ref	
Black	0.75 (0.56, 1.00)	0.66 (0.48, 0.90)
Age at transplant, per year increase	1.00 (0.99, 1.01)	0.99 (0.98, 1.00)
Gender		
Male	Ref	
Female	1.14 (0.87, 1.50)	1.22 (0.94, 1.57)
Average annual income in zip code, per 10,000	0.91 (0.83, 0.99)	0.92 (0.84, 1.01)
Primary payer		
Public	1.19 (0.93, 1.54)	1.12 (0.88, 1.44)
Private	Ref	Ref
Underlying cause of disease		
Hepatitis C	Ref	
ETOH	1.23 (0.85, 1.78)	1.12 (0.76, 1.64)
NASH	1.28 (0.90, 1.82)	1.13 (0.77, 1.64)
Other	1.04 (0.76, 1.44)	0.88 (0.59, 1.32)
HCC	1.10 (0.73, 1.65)	1.34 (0.80, 2.26)
On dialysis at transplant	1.51 (0.62, 3.68)	1.36 (0.55, 3.38)
Diabetes at transplant	0.98 (0.74, 1.29)	1.23 (0.93, 1.62)
BMI at transplant, per point	0.99 (0.97, 1.01)	0.98 (0.96, 1.00)
MELD at transplant, per point	1.01 (1.00, 1.03)	1.01 (0.99, 1.03)
Transplant LOS, per day	1.01 (1.00, 1.01)	1.01 (1.00, 1.01)
Type of admission at transplant		
Elective	0.86 (0.58, 1.30)	0.94 (0.63, 1.39)
Urgent	1.13 (0.73, 1.74)	0.94 (0.59, 1.51)
Emergent	Ref	Ref

Chapter 7: Public Health Implications and Future Directions

Summary of Findings

Black patients experience worse survival after liver transplantation, the only treatment option for patients with end-stage liver disease. Understanding the determinants of disparities in post-transplant outcomes is critical to ensuring equitable benefit from transplantation. Previous work in this area found that disparities persisted after adjustment for recipient and donor characteristics. This dissertation addressed gaps in the literature surrounding race and liver transplant outcomes by (1) examining the role of transplant centers in outcome disparities, (2) quantifying the role of hospital readmissions in survival disparities, and (3) exploring differences in post-transplant hospital admission characteristics by race.

The first dissertation study suggested that there was substantial variation in racial disparities across transplant centers, with center-specific hazard ratios spanning a 10-fold difference. However, racial disparities persisted after adjustment for center, and there was no significant effect modification of race by transplant center volume, proportion of minority patients at the center, quality rating, or geographic region. Upon further investigation, we found that centers in the lowest tertile of racial disparity had poor outcomes for both Black and White patients compared to centers in higher tertiles of disparity. This finding has at least two important implications for center level interventions. First, using practices from low-disparity centers to inform interventions for high-disparity centers may be inappropriate, as the goal of any intervention would be to ensure both health equity and good survival outcomes for all patients. Second, targeting interventions only to high-disparity centers may neglect an opportunity to improve survival among both Black and White patients, which are lower in low-disparity settings.

The second and third dissertation study focused on hospital admission after liver transplant as both an important outcome for patients and a potential marker of poor long-term survival. In the second dissertation study, we used national data to estimate the association of race with risk of hospital readmission within six months of transplant. We found that overall, 45% of patients were readmitted to the hospital within 6 months, and Black patients were 4% more likely to be readmitted than White patients; this association was not likely to be clinically meaningful. While we observed an overall significant racial disparity in survival, this association did not change after accounting for mediation by readmission within 6 months. While this finding could indicate that hospital readmission is not important to disparities in outcomes, it also could reflect the lack of nuance in hospitalization data available in national data collection systems.

In order to further explore hospital admission after transplant and its role in racial disparities, we used detailed data from the Emory Transplant Center. We explored a variety of outcomes related to the timing, etiology and intensity of hospital admissions after transplant. One of our major findings was that at Emory, Black patients had a lower likelihood of hospital readmission in the first six months after transplant; after this time, Black patients were more likely to be readmitted. This finding demonstrates the importance of considering relevant time periods when assessing disparities; disparities in survival also diverge significantly in the later post-transplant period. Another major finding was that the cause of admission varied by race. For Black patients, rejection was the most prevalent cause of readmission, while infection was the most prevalent cause for White patients. Black patients were 40% more likely to have rejection as a cause of admission than White patients even after adjustment for socioeconomic and clinical factors. Further exploration of factors driving this disparity, including medication adherence and immune system monitoring, may help identify modifiable factors to prevent these admissions. Finally, we found that Black patients were more likely to be admitted through the emergency room, but less likely to need intensive care during their hospitalizations. This

apparent paradox may actually be explained by lack of access to primary care, resulting in patients accessing the emergency room and being admitted for conditions that have the potential to be managed in an outpatient setting. Identifying determinants of care fragmentation after transplant and how it develops over time may help contextualize these findings.

Strengths and Limitations

One unique strength of this study is the combination of administrative and local transplant center data. The first two dissertation studies utilized a national, population-based registry of all transplant recipients in the United States, with virtually complete outcome data. This bolsters the generalizability of our findings and reduces the likelihood of selection bias from outcome misclassification. In our third dissertation study, we leveraged data from Emory's transplant center to investigate important clinical outcomes that are not collected through the national surveillance center. Notably, Emory has twice the national average proportion of Black liver transplant recipients, providing us with adequate power to examine racial differences in hospital admission outcomes after transplant.

One limitation present in all three dissertation studies, and inherent to the study of transplant outcomes, is bias from the transplant selection process. In order to be included in our population of transplant recipients, patients must have been referred, evaluated, and listed for a transplant. Transplant centers have total control over their waitlists, and each center has its own process for selecting transplant candidates that involves consideration of clinical, financial, and social factors. If transplant centers list patients differentially by race, and studies of transplant outcomes are conditional on receiving a transplant, then transplant listing becomes a conditioned-upon collider and opens biasing pathways between race, factors associated with both listing and outcomes, and outcomes. This type of bias is known as index event bias, and is similar to other types of collider stratification bias that plague outcomes studies (i.e. survival bias). This type of bias is particularly insidious in liver transplantation because there is no

information on the underlying population of ESLD patients that could be used to obtain unconditional estimates. Planned future work in this area includes a method to estimate the bounds of the potential bias from this source, which is relevant to both transplant outcomes studies and studies of outcomes from other health care procedures with some selection process.

Another limitation present in the second and third dissertation studies is the issue of selection bias due to care fragmentation. If patients are admitted to a hospital that is not their transplant center, data on that admission would not be recorded in their local center data (i.e. in Emory's Transplant Datamart) or reported to SRTR. This may potentially induce selection bias, especially if care fragmentation was differential by race. However, care fragmentation is less likely in the context of transplantation than other surgical outcomes, as transplant centers provide the vast majority of post-transplant acute care for their patients.

We had limited data on individual socioeconomic status, and relied primarily on proxy measures such as highest educational attainment, insurance status, and zip code poverty. While these variables are likely related to SES, they may not fully capture variation in the range of resources available to patients that affect post-transplant outcomes. In addition, we do not have information on factors such as social support that are also likely to play a role. In theory, the transplant selection process ensures that all patients have adequate resources and social support at the time of transplant, but levels of resources and support may change over time and contribute to diverging survival outcomes in the later post-transplant period.

Future Directions

The results of this study have informed several future research ideas and generated additional hypotheses surrounding racial disparities in liver transplant outcomes. One major area of additional research informed by this dissertation will be examining the role of transplant

selection processes in patient outcomes and outcome disparities. One of the major challenges in studying transplant center selection processes is the lack of a population-based data source on the pool of potential liver transplant candidates. Unlike end-stage renal disease patients, end-stage liver disease patients are not captured by a national surveillance system; studies of liver transplant populations therefore typically begin at waitlisting and are unable to capture the impact of transplant center selection. There are at least three future directions of research surrounding transplant selection processes informed by this dissertation work. First, efforts are underway to develop a method to estimate the bounds of the potential bias from this source, which is relevant to all transplant outcomes studies and could have a major impact on the field. Second, we will use local center data on evaluation, referral, and listing to examine how transplant selection varies by race. Third, we will use newly developed geographic catchment areas for transplant centers to calculate center-level listing rates, and examine how these listing practices are correlated with center outcomes and outcome disparities.

Our findings will also be used to develop future studies to further understand differences in the etiology of hospital admission by race, and to inform quality improvement efforts at Emory to prevent hospital admissions. First, our finding that rejection is the most prevalent cause of hospital admission among Black patients prompts further investigation into the role that medication adherence plays in this disparity. Identifying social determinants of medication adherence and ensuring appropriate access to immunosuppression monitoring may inform future interventions in this area. Second, further research is needed into how patient race impacts care fragmentation and primary care access after transplant, and how these factors in turn influence the urgency and intensity of subsequent hospital admissions. Third, we will undertake work to understand how pre-existing quality improvement programs at Emory intended to reduce readmissions (i.e. post-transplant hospital lodging) may be tailored to reduce racial disparities in admissions in the late-post transplant period.

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