Impacts of Donor Birth Sex on Liver Transplant Mortality among Individuals with Alcoholic Liver Disease (ALD)

Abstract

Alcoholic Liver Disease (ALD) leads to an estimated 30,910 deaths per year in the United States, for a mortality rate of 9.3/100,000 per year (CDC, 2024). Among patients who undergo liver transplant, recipients of livers from female donors tend to experience worse outcomes and higher rates of post-transplant mortality (Legaz, 2019). In particular, many studies have found that men who receive female donor livers are significantly more likely to experience graft failure than patients with other donor-recipient relationships (Lai, 2018). Little research exists on the relationship between donor sex and post-transplant outcome among individuals with ALD, specifically.

This study examines electronic health record data from a major transplant center in Atlanta, Georgia from the years 2013-2023 to identify the relationship between donor sex and post-transplant survival at 1 and 3 years in patients with Alcoholic Liver Disease. A number of potential covariates, including patient and donor age, donor circumstance of death, patient MELD score, and donor-recipient BMI difference were tested as potential mediators in the relationship between donor sex and survival.

The results of chi-square analysis found that contrary to the literature, female-female transplants performed significantly worse than other donor-recipient pairings, including female-male pairings. Stepwise logistic regression identified significant associations between female-female pairings and donor and recipient age, donor circumstance of death, and diabetes status. These covariates were not significant in explaining mortality rates in other donor-recipient pairing groups.

The existing literature suggests that among all-cause liver transplants, female-male pairings may experience poor outcomes due to a mismatch in estrogen levels between donor and recipient. This study hypothesizes that female-male transplants outperformed female-female transplants in this case due to the role of excessive alcohol consumption on estrogen production among recipients with ALD.

Impacts of Donor Birth Sex on Liver Transplant Mortality among Individuals with Alcoholic Liver Disease (ALD)

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Acknowledgements

I want to thank my committee members Dr. Casanova and Jessica Tarabay for their assistance in planning and executing this research, and for navigating the thesis process with me. I additionally want to thank Jessica Tarabay for continuing to mentor me following my Applied Practice Experience under her supervision, and for providing the dataset that formed the basis of this research. I would like to thank Jithin Sunny, my parents, Pam and Bruce McGuffey, and all of my friends and loved ones that supported me during this process, let me bounce ideas off of them, and took pity on me when my SAS code wouldn’t run. Thank you to the healthcare professionals and selfless organ donors who make life-saving organ transplant possible.

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Chapter I. - Introduction

Topic Selection

This study uses deidentified electronic medical record (EMR) data from a single American transplant center from the years 2013 to 2023. During this period, the hospital completed 1401 total liver transplants.

The transplant cases were divided into broad disease categories, which were not mutually exclusive. Patients were categorized as having one or more of the following disease categories based on their primary diagnoses at time of transplant: Alcoholic Liver Disease; Hepatic and Biliary Cancers; Non-Alcoholic, Non-Hepatitis Cirrhosis; Hepatitis; Acute Liver Injury; Metabolic Diseases; and Complications Relating to a Prior Transplant. A full list of diseases that were included in each category can be found in the appendix. While transplants for other causes than those listed occurred, an “other” category was omitted because the wide range of conditions included in this category would make any analysis too broad to be useful.

Chi-square analyses and T-tests were performed within each disease category (including a total, all-cause category) to determine the relationships between potential independent variables and the dependent variables of interest (patient survival at 1 and 3 years post-transplant). The variables investigated were Patient sex, Patient Age, Patient social vulnerability index (SVI), Patient race/ethnicity, Patient MELD score at transplant, Total time on waitlist, Diabetes at transplant, Donor Sex, Donor Age, and Donor circumstance of death. Full results of the 1-year survival analyses can be found in the appendix. No variables that were found not significant at 1 year post-transplant were significant at 3 years post-transplant, and these values were omitted for space.

The Alcoholic Liver Disease cohort (N=370) and Donor Sex variable were selected for further analysis, as this was one of only two combinations that yielded statistically significant correlations with survival at 1 and 3 years at the 95% confidence level (p=0.0445 and 0.0251, respectively). Patient race/ethnicity was found to be significant within the Non-alcoholic, non-hepatitis cirrhosis category, but this association was not chosen for further analysis because of small sample sizes within racial categories and relative inconsistency in primary diagnosis within this disease category. All further analysis was conducted using only the Alcoholic Liver Disease dataset.

Overview of Alcoholic Liver Disease (ALD)

Alcoholic Liver Disease (ALD) describes a progressive series of liver disorders caused by overconsumption of alcohol (Patel, 2023). The primary stage, alcoholic steatosis, or alcoholic fatty liver, is typically reversible with abstinence from alcohol, but it is estimated that about 3% of individuals with alcoholic steatosis progress into the final stage of Alcoholic Liver Disease, Alcoholic cirrhosis, each year (Han, 2021). The secondary stage is Alcoholic Hepatitis, which is characterized by fibrosis (scarring) of the liver, a rapid increase in serum bilirubin levels and jaundice, and is frequently associated with fever, coagulopathy, and hepatomegaly (enlarged liver). Annually, approximately 10% of individuals with Alcoholic Hepatitis will progress on to Alcoholic cirrhosis, and 5-15% will die. The final stage, known as Alcoholic cirrhosis, is characterized by significant buildup of scar tissue in the liver, and is associated with a variety of serious complications, including hepatomegaly, splenomegaly, and portal hypertension (including ascites, pedal edema, and encephalopathy) (Patel, 2023). Additionally, Alcoholic cirrhosis is a significant risk factor for the development of Hepatocellular Carcinoma (HCC) and other hepatic and biliary cancers (Gitto, 2020). Alcoholic cirrhosis develops in approximately 15-20% of excessive drinkers during their lifetime (Han, 2021). Between the years 2009 to 2016, the number of patients requiring liver transplant for alcoholic cirrhosis increased by 63.4%, and mortality among patients aged 25-34 years increased by 10.5%.

The most significant risk factor for the development of ALD is the severity of the patient's alcohol intake (Patel, 2023). Despite the fact that alcohol abuse is twice as common among men as it is among women, women are more susceptible to Alcoholic Liver Disease at lower rates of alcohol consumption, and often experience worse outcomes (Guy, 2013). Women consuming over 7 drinks per week experience higher incidence of ALD than men who consumed over 14 drinks per week. However, many studies have found significant discrepancies between sexes in the diagnosis of alcoholic cirrhosis, with men in some clinics being diagnosed more than women by a factor of 2 to 1. Obesity also appears to have a synergistic effect with alcohol consumption in the development of ALD (Han, 2021). Obese individuals have a significantly higher risk of developing ALD than non-obese individuals with similar levels of alcohol consumption. Among heavy drinkers, high BMI (26.3 vs 24.2 kg/m) and presence of diabetes (20.5% vs 6.5%) was significantly more common in individuals with ALD than those who had not developed the disease. Concurrent liver diseases such as Hepatitis C infection also greatly increase the risk of ALD and lead to more significant liver damage and greater mortality. Onset is typically between the ages of 40 and 50, but the proportion of individuals aged 25-34 with ALD has increased significantly in recent years (Patel, 2023).

Many individuals with Alcoholic Cirrhosis require liver transplantation, as cirrhosis is irreversible and frequently leads to organ failure. Additionally, individuals with Alcoholic Hepatitis that has not yet progressed to alcoholic cirrhosis may also be candidates for transplant if they are not responding well to other treatments and have MELD scores greater than 26 (Patel, 2023). MELD, or the Model for End-Stage Liver Disease, is a score assigned to a patient seeking listing for transplant based on the severity of their condition and their likelihood of mortality without a transplant in the next 90 days. Higher MELD scores indicate patients at higher mortality risk and will place that patient higher in priority listing for organs as they become available. There are serious ethical concerns related to the use of transplantation for patients with ALD, particularly that the limited supply of viable organs is being used to treat individuals that may not comply with post-transplant care such as the cessation of alcohol use. Most transplant centers utilize a 6-month rule to determine whether ALD patients are eligible for liver transplant (Gitto, 2020). This rule requires patients seeking transplant to prove at least 6 months of sobriety from alcohol prior to being cleared for transplant. However, it is unclear whether adoption of this rule actually decreases recidivism among transplant patients, and some patients with advanced disease may require transplant prior to 6 months. Survival following transplant is high- survival rates 1 year post-transplant range in various studies from 81-97%, while survival rates 3 years post-transplant range from 78-92% (Shroeder, 2023). The rate of alcoholic recidivism is fairly stable at around 17% of individuals who receive a transplant (Patel, 2023). Survival rates and rates of recidivism are essentially the same between patients with alcoholic cirrhosis and patients with alcoholic hepatitis (Gitto, 2020). However, access to transplantation remains an issue. It is estimated that only about 1.2% of eligible candidates actually receive a liver transplant annually, due both to limited supply of viable livers and the relative difficulty of receiving transplant referrals. Transplant is particularly inaccessible for individuals who have not yet progressed to alcoholic cirrhosis, as only about 27% of transplant programs in the United States will consider patients with alcoholic hepatitis (Patel, 2023). Alcoholic hepatitis patients make up only 1.37% of total liver transplants.

The most common causes of post-transplant mortality are cardiovascular disease and Hepatocellular Carcinoma (HCC) (Gitto, 2020). Patients with ALD also tend to have higher risk of cardiovascular disease prior to transplant than the general population, given their increased rates of diabetes, obesity, and hypertension. However, immunosuppressive treatments post-transplant can exacerbate these issues and sometimes lead to the development of these issues in patients who did not experience them previously. While certain conditions like HCC are more common among patients who relapse, all liver transplant patients experience a twofold risk of the development of new cancers and malignancies as compared to the general population. These account for approximately 40% of post-transplant deaths. Cancers and other malignancies in transplant patients are not only common, but also frequently more aggressive than similar conditions in the general public, with overall mortality rates of about 55%.

Role of Donor and Recipient Sex

Studies of all-cause liver transplant outcomes tend to agree that women experience higher rates of acute liver failure following transplant than men (Chen, 2023). Women are more likely to experience waitlist mortality, are more likely to receive organs with high donor risk indexes and are more likely to receive urgent transplants due to high MELD scores (Andacoglu, 2024). Some studies have argued that MELD scores tend to underestimate the severity of disease in women, due in part to how Creatinine levels, which tend to be higher in men, are figured into the score (De Simone, 2020). However, the only study identified by this review that specifically focused on women with ALD found that female patients experienced lower rates of graft rejection than men did. Ultimately, the mortality rates for men and women in this and other studies were very similar, despite possible differences in cause (Legaz, 2019, Andacoglu, 2024).

Another factor often found to have a significant impact on post-transplant outcomes is the sex of the organ donor. One systematic review found that across 7 studies, Donor-Recipient Sex discrepancy was associated with higher rates of graft failure post-transplant, particularly among male patients who received livers from female donors (Lai, 2018). Another study supported this finding by showing that Female-Male transplants continued to have higher mortality rates than other categories even after 15 years post-transplant. It also found that Male-Female transplants had the lowest mortality rates, while Male-Male and Female-Female transplants were essentially the same, suggesting that sex discrepancy is a factor independent of donor sex (Schoening, 2016). One study found that risk associated with a female donor was also related to recipient age. Among patients over 45, females receiving transplants from female donors had significantly better survival than males who received transplants from female donors, but patients under 45 had similar outcomes regardless of sex. Recipient age did not appear to have an effect on outcomes when the donor was male (De Simone, 2020). Existing literature proposes several other variables that may help to explain differences in outcomes between these groups. Sim et al. found that post-transplant outcomes were related both to donor sex and donor robusticity, as measured by the Skeletal Muscle Index (SMI) (2023). For patients with male donors, increased donor robusticity was associated with greater mortality, while for patients with female donors, increased robusticity was a predictor of greater survival. Another study found that donor risk index value and recipient kidney function were both strongly associated with post-transplant survival and related to donor sex (Schoening, 2016). This data was not available for analysis in the present study. Female donors in one study were found to have higher rates of death due to “cerebro-vascular accidents” and were less likely to have died due to trauma or anoxia, as opposed to male donors (Andacoglu, 2024). It is unclear, however, whether this led to increased mortality among recipients of female donor livers in this study. Many researchers have hypothesized that the impact of donor-recipient sex discrepancies can be attributed to differences in anatomical size between men and women. However, donor-recipient sex difference remains a significant predictor of post-transplant outcomes even when controlling for differences in physical size (Lee, 2018). This particular study also found that donor sex/sex discrepancy lost significance as female donors exited peak fertility at ages 36-40, which they described as associated with “poor ovarian reserve”. This suggests a potential role of sex-specific hormonal differences in mediating the relationship between donor sex and recipient survival. An expansion on this research in 2023 found that the typical increase in graft failure associated with Female-Male transplants disappeared when female donors were greater than 40 years old or had developed macrosteatosis (fatty liver deposits) (Han). Both age over 40 and macrosteatosis are associated with a decline in hepatic estrogen signaling in women, offering a likely mechanism for the hormonal differences hypothesis. Hepatic estrogen signaling is associated with improved healing capacity post- liver injury in women. While this mechanism is protective in certain instances and may even help explain why female recipients of male donor livers do not appear to experience the same negative consequences of hormonal mismatch, there is a downside. When female livers are transplanted into hormonally male bodies, the sudden decrease in estrogen (what the study calls “rapid defeminization”) can lead to increased risk of graft failure for these male patients. When the donating female was experiencing reduced estrogen production due to age or macrosteatosis, the hormonal shift was less pronounced, and the risk to male patients was decreased.

Research Question

This study aims to identify the relationship between donor sex and liver transplant patient survival at 1 and 3 years among individuals with alcoholic liver disease (ALD). It seeks to understand whether other variables, such as donor/recipient anatomical size mismatch, donor age, MELD score, or donor cause of death may be significant mediators in the relationship between donor sex and liver transplant survival.

Chapter III. - Methods

The original dataset pulled from EPIC patient electronic health records contained some obvious errors, likely due to typos, in the categories of Patient and Donor Height, Weight, and BMI. To address this, all values for Height and Weight that were outside the middle 98th percentile for these values for each sex in the US were removed (Male Height middle 98th percentile =156.3cm-191.9cm; Male Weight middle 98th percentile = 52.8kg-154.9kg; Female Height middle 98th percentile = 144.4cm-177.1cm; Female Weight middle 98th percentile = 44.3kg-137.5kg), and new BMIs were calculated (CDC, 2016). This reduced the total number of patients included in the analysis for these variables, as certain patients or their donors did not have valid height and/or weight values (new N=254). When conducting analysis on other independent variables, the full 370 sample size was used.

Patients were categorized first as either having received a liver from either a Male or Female donor, then by having a same-sex liver donation or an opposite-sex liver donation, and a new variable was created for the specific donor-recipient sex relationship (i.e. Male-Male, Female-Female, Male-Female, and Female-Male). Mortality was coded as alive at 1 year (yes/no) or alive at 3 years (yes/no). Chi-square analysis was conducted to determine the relationship between each donor sex/patient-donor sex difference category with 1 and 3 year survival post-transplant.

Chi-square and t-tests were performed to identify additional differences between the group of patients who received male livers and those who received female livers. These results would highlight covariates such as donor age, recipient time on waitlist, or diabetes status, that may help explain any differences in survival odds between the two groups that may be identified later in the analysis. The same process was then completed using male versus female recipients to identify if trends from the previous step were simply a result of the fact that female livers tend to go to female recipients, and male livers tend to go to male recipients, when such a match is possible.

Tests for collinearity were conducted so that variables with high Variance Inflation Factors (VIFs) and high Pearson's correlation could be removed.

Interaction variables were created between each sex category and each potential covariate.

Each independent variable and interaction variable was then tested using stepwise logistic regression against the dependent variables of 1- and 3- year survival, with a confidence interval of 95%.

Chapter IV. - Results

At 1 year post-transplant, patients of both sexes who had received a liver from a female donor had one year mortality rate of 12.5%, while patients of both sexes receiving a male liver had one year mortality of 6.41% (p=0.0445). Patients of both sexes who received female livers had three year mortality of 16.42%, while patients of both sexes receiving male livers had three year mortality of 8.66% (p=0.0251).

Chi-square analysis of cross- vs same-sex donor-recipient transplants found that there was no statistically significant difference in 1 year survival for patients who received a liver from a donor of their same sex vs patients who received a liver from a donor of the opposite sex (p=0.7063). The same was true of 3 year survival (p=0.4254). However, when all possible donor-recipient combinations were analyzed (Male-Male, Female-Female, Male-Female, and Female-Male), the chi-square p-value had marginal significance at 3 year survival (0.0526). The differences in mortality between these categories are shown in Table 1.

Table 1.

Donor-Recipient Sex combination	1 yr mortality %	3 yr mortality %
Male-Male	6.16	9.03
Female-Female	16.13	21.31
Male-Female	6.82	8.05
Female-Male	9.46	12.33

Recipient characteristics were analyzed stratified by recipient birth sex (Table 2). Male and female recipients did not differ significantly in their age, time on the waitlist, BMI, SVI, or

MELD score. In addition, there was no significant difference in the age of the donor between male (38.1 years) and female (39 years) recipients (p=0.57).

Table 2.

Recipient Characteristics by Recipient Sex				
Recipient characteristics	Female recipient (N=150)	Male recipient (N=220)	Mean Difference (F-M)	p-value
Recipient Age	53.8533	54.8955	-1.0421	0.3831
Total days on waitlist	132.8	153.2	-20.4491	0.3781
Recipient BMI	29.3900	28.8689	0.5211	0.5883
Recipient-Donor BMI difference	0.5534	-0.5490	1.1024	0.4141
MELD score at transplant	28.1733	28.8864	-0.7130	0.4505
SVI	0.6406	0.6162	0.0243	0.3524

Characteristics of recipients of both sexes, stratified by the sex of the donor, are shown in Table 3. There was a significant difference in the age of the donor between male (42.0 years) and female (36.4 years) donors; female donors were on average, 5.6 years older than male donors (p=0.0006).

Table 3.

Recipient Characteristics by Donor Sex				
Recipient characteristics	Female donors (Mean) (N=136)	Male donors (Mean) (N=234)	Mean Difference (Pooled) (Female-Male)	P-value (Pooled) *Significant at 95% CL

Recipient Age at Transplant	53.3676	55.1154	-1.75 years	0.1505
SVI	0.6481	0.6133	0.0348	0.1907
Total Days on Waitlist	159.5	136.4	23.0439	0.3294
Recipient BMI	29.5333	28.6941	0.8392	0.3497
Recipient-Donor BMI Difference	-2.1492	1.0341	-3.1834	0.0114*
Recipient MELD Score	27.2353	29.3889	-2.1536	0.0248*

BMI difference and MELD score were significantly different for recipients of livers from male donors vs livers from female donors. Individuals who received livers from female donors tended to have lower BMIs than their donors, while individuals receiving livers from males tended to have higher BMIs than their donors, indicating some level of anatomical size mismatch. Patients receiving female donor livers had lower MELD scores at time of transplant than individuals receiving male donor livers, suggesting that recipients of male livers had progressed further in end-stage liver disease by the time of transplant. Chi-square and T-tests were used to identify differences between patients that received male donor livers versus those that received female donor livers to identify other variables that might potentially play a role in relationships between donor sex and post-transplant survival. These are shown in Table 4.

Table 4.

		Female donor (N=136)	Male donor (N=234)	p-value
Deceased Donor Circumstance of	Natural Causes:	56.62%	35.62%	0.0002*

Death	Accident:	11.76%	14.16%	
	MVA:	11.03%	22.32%	
	Homicide:	2.21%	9.87%	
	Suicide:	11.76%	14.59%	
	None of the Above	6.62%	3.43%	
Recipient Diabetes	Yes:	11.03%	86.32%	0.4612
	No:	88.97%	13.68%	
Recipient Race/Ethnicity	White	73.53%	73.93%	0.6039
	Black	21.32%	16.67%	
	Hispanic	2.94%	4.27%	
	Asian	2.21%	4.27%	

Male donors were significantly more likely to have died from motor vehicle accidents and homicide, while female donors were significantly more likely to have died of natural causes. Rates of mortality from non-MVA accidents and suicide were similar, with male donors being slightly more likely to die in these circumstances.

The same relationships were then analyzed by recipient birth sex (Table 5).

Table 5.

		Female recipient (N=136)	Male recipient (N=234)	p-value
Deceased Donor Circumstance of Death	Natural Causes:	46.31%	41.36%	0.7953
	Accident:	13.42%	13.18%	
	MVA:	16.78%	19.09%	
	Homicide:	8.05%	6.36%	

	Suicide:	12.08%	14.55%	
	None of the Above	3.36%	5.45%	
Recipient Diabetes	Yes:	14%	11.82%	0.5361
	No:	86%	88.18%	
Recipient Race/Ethnicity	White	69.33%	76.82%	0.1668
	Black	24%	14.55%	
	Hispanic	3.33%	4.09%	
	Asian	2.67%	4.09%	

There were no statistically significant differences between male and female recipients for donor cause of death, recipient diabetes diagnosis, or recipient race. Additionally, recall that each of these variables was independently tested for significance against 1- and 3- year survival using chi-square tests during the topic selection phase, and only Donor Sex was found to be significant in predicting 1- and 3- year survival. To understand why donor sex is significant, the interactions between donor sex and the other independent variables were analyzed using logistic regression.

Before conducting logistic regression, tests were conducted to identify possible collinearity between independent variables. The variable "BMI Difference" had a VIF of 7.87490, and the variable "Weight Difference" had a VIF of 7.55410. Pearson correlation found that these two variables were highly correlated (0.90096, $p<.0001$). "Weight Difference" was removed as an independent variable from the logistic regression analysis. The statistically significant results of the stepwise logistic regression between each independent variable and survival at 1 year are shown in the table below. A full list of the independent variables tested and their variable names in SAS can be found in the appendix.

Table 6.

Sex Category	Interaction Variable	Survival Odds Ratio (95% CI)	P-value
F-F	Recipient Age	0.996 (0.995-0.997)	<0.0001
F-F	MVA Donor Death	1.32 (1.029-1.692)	0.0289
F-F	Homicide Donor Death	0.476 (0.283-0.800)	0.0054
F-M	Suicide Donor Death	0.628 (0.486-0.811)	0.0005
Female Donor	Recipient Diabetes	0.87 (0.773-0.978)	0.0165

Stepwise logistic regression found 5 statistically significant relationships at 1 year post-transplant. The interaction between recipient age at transplant and a Female-Female sex difference had a small negative association with survival at 1 year (OR: 0.996, $p<0.0001$). This suggests that among female patients with female donors, each 1 year increase in recipient age reduced the odds of 1-year survival by about 0.4%. This association did not exist for any other donor-recipient sex difference. The interaction between a donor who died in a motor vehicle accident and a Female-Female sex difference had a positive association with 1 year survival (OR: 1.32, $p=0.0289$), suggesting that female patients who received livers from females who had died in a motor vehicle accident were 1.32x more likely to survive 1 year post-transplant than similar patients whose donor died of natural causes. This may relate to a difference in age between individuals who died of natural causes versus those that died due to a trauma. However, no significant relationship was found between donor age and donor circumstance of death. The interaction between a donor who died of homicide and a Female-Female sex difference had a negative relationship with 1 year survival (OR: 0.476, $p=0.0054$), and the interaction between a donor who died of suicide and a Female-Male sex difference had a negative relationship with 1 year survival (OR: 0.628, p=0.0005). These both suggest that having a donor who died of homicide or suicide has a negative impact on 1 year survival, but only in cases of females who received livers from females, and males who received livers from females, respectively. Female patients who received livers from female donors who died via homicide were only about half as likely to survive to 1 year post-transplant as similar patients whose donors died of natural causes. The interaction between Donor Sex and Recipient diabetes had a negative association with survival at 1 year (OR: 0.87, p=0.0165). Since Male was the reference value for Donor Sex, this indicates that any patient who received a liver from a female donor and also had diabetes was only 87% as likely to live to 1 year post-transplant as patients in other categories.

The statistically significant results of stepwise logistic regression between each independent variable and recipient survival at 3 years are shown in the table below.

Table 7.

Sex Category	Interaction Variable	Survival Odds Ratio (95% CI)	P-value
None	Recipient Diabetes	0.86 (0.768-0.965)	0.0105
F-F	Donor Age	1.005 (1.000-1.011)	0.0458
F-F	Recipient Age	0.991 (0.986-0.995)	0.0001
F-F	MVA Donor Death	1.59 (1.174-2.159)	0.0029
F-F	Homicide Donor Death	0.477 (0.256-0.890)	0.0201
F-M	Suicide Donor Death	0.649 (0.476-0.884)	0.0063

The stepwise logistic regression found 6 statistically significant associations with recipient survival at 3 years post-transplant. First, it found that recipient diabetes, regardless of donor sex or donor-recipient sex difference, had a negative association with 3 year survival (OR: 0.86, p=0.0105). This suggests that donor sex becomes less significant as time goes on for patients with diabetes, as the analysis of 1-year survival found that diabetes was only significant when patients received a liver from a female donor. However, this contradicts the results of the chi-square test of diabetes status and 3-year mortality completed during topic identification, which did not find a statistically significant association (p=0.6818), suggesting that there may be an important interacting variable that this analysis is not picking up on. The regression analysis found that the interaction between donor age and Female-Female transplant had a very small positive association with 3 year survival (OR: 1.005, p=0.0458), suggesting that increased donor age actually marginally improves 3-year survival when both donor and recipient are female. The interaction between recipient age at transplant and Female-Female sex difference had a very small negative association with 3 year survival (OR: 0.991, p=0.0001). This is an increase of 0.513% greater mortality risk per year of increased age from 1-year survival, suggesting that recipient age becomes more important for longer survival periods, but only for female patients who receive livers from female donors. The interaction between a donor who died in a motor vehicle accident and Female-Female sex difference had a positive association with 3 year recipient survival (OR: 1.59, p=0.0029). This is an 18.87% improvement in survival probability at 3 years rather than 1 year for these patients. The interaction between a donor who died of homicide and Female-Female sex difference had a negative association with survival (OR: 0.477, p=0.0201), and the interaction between a donor who died of suicide and Female-Male sex difference had a negative association with survival (0.649, p=0.0063). These represent no significant change in survival odds from 1 to 3 years for these patients. Therefore, while a motor vehicle accident circumstance of death improves survival chances, and continues to improve as time goes on, homicide and suicide seem to stay consistently negative as predictors of post-transplant survival.

Chapter V. - Discussion

Interpretation of Results

The results of this study suggest that donor sex is a significant predictor of post-transplant mortality among patients with ALD. This analysis found that recipients of either sex who received a female donor liver had roughly double the 1- and 3- years post-transplant mortality compared to recipients who received male donor livers. This supports the existing literature that finds a similar discrepancy based on donor sex (Legaz, 2019). In contrast to some other studies, donor-recipient sex concordance (having received a same-sex or opposite-sex liver donation) was not found to be a significant predictor of 1 and 3 year mortality (Schoening, 2016). Also contrasting with the majority of the literature, this study found that Female-Female transplants had the highest mortality rates (16.13% at 1 year, 21.31% at 3 years) among any donor-recipient sex pairing. The majority of the existing literature finds that Female-Male transplants have the worst outcomes (with hazard ratios of between 1.8 and 2.3x increased risk of mortality as compared to other groups), and generally find that Female-Female and Male-Male transplants are relatively equal in mortality risk (Lai, 2018; Schoening, 2016). However, the existing literature is based on studies of all-cause transplants, and do not specifically address the impact of donor and recipient sex on transplants due to alcoholic liver disease.

Stepwise Logistic Regression found that one variable interaction- the interaction between Female-Female transplant and donor death in a motor vehicle accident- had a positive association with 1-year survival, improving survival probability for these patients by 1.32 times compared to patients with donors who died of natural causes. Four variable interactions had negative associations with 1-year survival: Female-Female sex difference and recipient age, Female-Female sex difference and donor death due to homicide, Female-Male sex difference and donor death due to suicide, and Female donor and diabetes. These differences could be attributed to differences between male and female donors- for instance, it was demonstrated that female donors were significantly older than male donors. However, donor age was itself not shown to be a significant predictor of survival using either t-tests or logistic regression. Similarly, there were significant differences in donor circumstance of death between male and female donors, but donor circumstance of death was not shown to be significant as a variable by itself. This suggests that female donor's livers may be more sensitive to a variety of factors like donor circumstance of death and diabetes than are male donor's livers, and these differences cannot be explained by other differences between the two groups, such as donor age.

The results were similar at 3-year survival. Donor death by homicide or suicide had almost identical negative associations with survival at 3 years as they did at 1 year for Female-Female and Female-Male pairings, respectively. The recipient survival benefit associated with donor death from motor vehicle accidents for Female-Female transplants increased at 3 years, suggesting that the role of donor circumstance of death may become more pronounced as time goes on post-transplant. Female-Female transplant patients appeared to benefit slightly from increased donor age at 3 years post-transplant. This is counterintuitive, not only because one would expect that older organs would perform worse than organs from younger donors, but also because female donors were found to be older on average than male donors, and yet female recipients with female donors still had the worst survival outcomes. Finally, at 3 years post-transplant, diabetes was found to be a significant predictor among patients of any sex, independent of the sex of the donor. It is likely that additional interacting variables were not picked up in this analysis, as this result contradicts the results of a chi-square analysis on these same variables conducted during the topic selection phase of the study.

Based on these results, it can be said that the individual independent variables were not significant in predicting 1- and 3- year mortality alone, but rather the interaction between independent variables caused the differences in post-transplant survival. Recipients of female donor livers had reduced survival compared to recipients of male livers, with female recipients of female donor livers faring the worst across all groups, followed by male recipients of female donor livers, which was the group most commonly cited as having reduced post-transplant survival in the literature. Recipient age, donor circumstance of death, and diabetes status all appear to have had negative impacts on patient survival, but only when combined with Female-Female or Female-Male transplant sex relationships. While female donors were older on average than male donors, and there were significant anatomical size discrepancies (based on BMI), these factors were not found to be significant as variables independent of donor sex. So why did female patients receiving female livers experience the worst outcomes in this study, when the existing literature consistently shows that female-male transplants carry the greatest risk? The answer may lie in the body's reaction to excessive alcohol consumption. While the existing literature focuses on all-cause transplant outcomes, this study focuses specifically on patients who have a history of excessive alcohol consumption. Excessive alcohol consumption is associated with increased estrogen production and "feminization" of the liver, where the male liver becomes sensitive to the increased levels of estrogen in the body (Eagon, 2010). As discussed previously, a likely cause for poor outcomes in female-male transplants is the rapid “defeminization” of the female liver when it is transplanted into a male body (Han, 2023). While this may be the case in the average liver transplant, typical hormonal differences between men and women may become more complicated when one of the parties has a history of excessive alcohol consumption. If a male patient with a history of excessive alcohol use and associated higher-than-usual estrogen levels receives a female liver, the change in hormone levels may not be significant enough to lead to liver defeminization. In this case, men with alcoholic liver disease may actually experience a protective effect from their increased estrogen, as compared to non-alcoholic male patients who may receive a liver from a female donor. The risks typically associated with Female-Male transplants may be moderated enough by this effect to cause the difference in outcomes seen in this study. Among female recipients of female donor livers, donor and recipient age difference may become a more relevant factor and could explain how this group came to have the worst post-transplant outcomes. The study by Han et. al. found that the increased risk associated with female livers disappeared when the female donor was over the age of 40 or had certain conditions that would have reduced her estrogen production (2023). While a more in-depth analysis of the role of donor and recipient age gaps was outside the scope of this study, it would be a promising avenue for future research, as differences in hormone levels between women of different ages could theoretically explain this group’s poor outcomes. If true, this could also potentially explain this study’s finding that female-female transplant survival rates actually improved slightly as donor age increased.

Limitations & Future Research

One limitation of this study was the difficulty of accurately categorizing patients by disease. Patients were sorted non-exclusively by Primary Diagnosis at Transplant. Primary diagnoses at listing and secondary diagnoses were not included in analysis, and the impact of having multiple primary diagnoses was not studied. This study did not include analysis of drinking behavior or sobriety status after transplant due to unavailability of the data. Data relating to donor risk index and recipient kidney function, which were found to be significant in other studies, was not available. Of course, this study was also limited to a single transplant center, and the body of research would benefit from studies with more patients in additional settings.

The specific relationship between donor sex and post-transplant mortality among patients with alcoholic liver disease deserves significantly more research than currently exists. Additional research that incorporates behavioral and sobriety data may offer important insight into the trends observed in this study, particularly since men and women are known to have very different tolerances to alcohol consumption. Further study into the relationship between donor and recipient estrogen levels and post-transplant mortality, particularly for patients with ALD, may help to explain the results of this study and better place them in the context of broader liver transplant research. If future evidence supports the hypotheses put forth in this research, it could meaningfully impact the liver donation matching process to incorporate laboratory testing for hormone levels as a standard practice. This avenue of research may also come to include research into hormone therapies to mitigate the negative effects of donor-recipient hormone mismatch when ideal organ matching is not possible.

Conclusion

In an initial analysis of 1401 liver transplant patients at a major transplant center in Atlanta, Georgia, donor sex was found to be a significant factor in predicting post-transplant survival among individuals with Alcoholic Liver Disease- an association that was not found among patients with other types of liver disease. Among the 370 patients with ALD, recipients of female donor livers had mortality rates twice as high as recipients of male livers, and female recipients of female livers were found to be the most negatively impacted. Logistic regression found that female-female transplants interacted negatively with patient age, diabetes and certain donor circumstances of death, but actually improved outcomes as the age of the female donor increased. This contradicts existing research on all-cause transplant outcomes that consistently find that female-male transplants have the highest rates of graft failure and patient mortality. However, research into how female donor age and associated changes in estrogen levels impact the performance of liver transplants in male patients suggests that hormonal differences between donors and recipients may play an important role. Since alcohol is known to increase estrogen production in both sexes, the results of this study may differ from the existing literature because of the unique study population. Further research into donor-recipient hormonal differences may lead to additional screening during the organ donor matching process, or the use of hormone therapies to improve liver transplant outcomes.

Appendix

Disease Category	Primary Diagnosis EMR Entries
Alcoholic Liver Disease	Acute Alcohol-Associated Hepatitis With or Without Cirrhosis; Acute Alcoholic Hepatitis; Alcohol-Associated Cirrhosis Without Acute Alcohol-Related Hepatitis; Alcoholic Cirrhosis; Alcoholic Cirrhosis Type C/HCC; Alcoholic Cirrhosis With Hepatitis C; Alcoholic Cirrhosis/HCC; ETOH; ETOH/NASH; HCC & ETOH Cirrhosis; Other: HCC and Alcoholic Cirrhosis; Other: Toxic Metabolic/Alcoholic Cirrhosis
Hepatic and Biliary Cancers	Alcoholic Cirrhosis/ HCC; Cirrhosis: Type C and HCC; HCC & ETOH Cirrhosis; HCC and Cirrhosis; HCC & Alcoholic Cirrhosis; HCC/HCV; HCC/Cholangiocarcinoma; HCC and NASH; Other: Chronic Viral Hepatitis and Hepatocellular Carcinoma; Other: Cirrhosis: NASH/HCC; Other: HCC and Alcoholic Cirrhosis; Other: Hepatic Endothelioid Hemangioendothelioma; Other: Hepatoma (HCC) and HCV Cirrhosis; Cholangiocarcinoma (CH-CA); Fibrolamellar (FL-HC); Hepatoma- Hepatocellular Carcinoma; Hepatoma (HCC) and Cirrhosis; Other, Specify: i.e. Klatzkin Tumor, Leiomysarcoma
Hepatitis	Acute Alcoholic Hepatitis; Acute Liver Failure & HBV; Acute on Chronic AIH; Type B- HBSAG+; AIH; Alcoholic Cirrhosis Type C/HCC; Alcoholic Cirrhosis with Hepatitis C; Autoimmune Hepatitis; Cirrhosis: Chronic Active Hepatitis: Etiology Unknown; Cirrhosis: Type B and C; Cirrhosis Type B and D; Cirrhosis: Type B- HBSAG+; Cirrhosis: Type C; Cirrhosis: Type C & HCC; HBV; HCC and HCV; HCV; Hepatitis B Cirrhosis; Hepatitis C; Hepatitis B; Other: Acute Liver Injury - Ischemic Hepatitis;

	Other: Chronic Viral Hepatitis C & Hepatocellular Carcinoma; Other: Hepatoma (HCC) and HCV Cirrhosis
Acute Liver Injury	Acute Injury; Abendazole, Fit 9 Enregy Supplement; Acute Hepatic Failure Unknown Cause; Acute Hepatic Necrosis; Acute Liver Failure; Acute Liver Failure & HBV; AHN: DRUG Atripla; AHN: DRUG Other Specify; AHN: DRUG Phentermine.; AHN: DRUG Tylenol; AHN: Other, Specify (E.G., Acute Viral Infection, Autoimmune Hepatitis - Fulminant); Consistant with DILI; Drug Induced Liver Injury; OLT 2012 Secondary to DILI, Decompensated Liver Di; Other: Accidental Tylenol Overdose; Other: Acute Hepatic Failure; Other: Acute Liver Injury; Ischemic Hepatitis; Other: Toxic Metabolic/ Alcoholic Cirrhosis
Non-Hepatitis, Non-Alcoholic Liver Cirrhosis	Non-Alc Cirrhosis; Choles Liver Disease: Sclerosing Cholangitis; Cirrhosis; Cirrhosis and Fibrosis; Cirrhosis: Autoimmune; Cirrhosis: Autoimmune/Graft Failure; Cirrhosis: Cryptogenic (Idiopathic); Cirrhosis: Drug/Indust Exposure Other; Cirrhosis: Drug/Indust Exposure Other Specify; Cirrhosis: Fatty Liver (Nash); Cirrhosis: Other, Specify (E.G., Histiocytosis, Sarcoidosis, Granulomatous); Cirrhosis: Sickle Cell; Cryptogenic Cirrhosis; Other: Cirrhosis: Nash/Hcc; Other: Cryptogenic Cirrhosis; Plm: Hepatoma (Hcc) and Cirrhosis; Sec Biliary Cirrhosis: Other Specify; Sclerosing Cholangitis; Primary Sclerosing Cholangitis; Other: Chronic Biliary Obstruction/Cirrhosis
Metabolic Disorders	Metabolic Disease; Alpha-1-Antitrypsin Deficiency; Metdis: Alpha-1-Antitrypsin Defic A-1-A; Metdis: Hemochromatosis - Hemosiderosis; Metdis: Maple Syrup Urine Disease; Metdis: Other Specify; Metdis: Primary Oxalosis/Oxaluria, Hyperoxaluria; Metdis: Wilson's Disease, Other Copper Metabolism Disorder; Other: Metdis: Primary

	Oxalosis/Oxaluria- Hyper
Complications Relating to a Prior Transplant	Prior Transplant; Alf Post Hepatectomy for Net; Alf Post Hepatectomy, Net; Chronic Rejection, Hat; Chronic Rejection/Poss Cholestatic Injury; Cirrhosis: Autoimmune/Graft Failure; Graft Failure; Graft Failure (Liver); Graft Failure: Liver; Hat; Hepatic Artery Thrombosis; Other: Chronic Allograft Rejection; Other: Hepatic Artery Thrombosis; Other: Pv Thrombosis/ Liver Abcess

Significance of Independent Variables by Disease Category, 1 year survival Chi-square value (p-value) *Significant at 95% CL								
	All Causes	ALD	Cancers	Hepatitis	Cirrhosis	Injury	Metabolic	Prior Transplant
Patient Sex	0.6771 (0.4106)	1.3003 (0.2542)	0.1745 (0.6761)	0.0317 (0.8587)	0.3418 (0.5588)	0.8988 (0.3431)	0.4118 (0.4118)	3.0784 (0.0793)
Donor Sex	0.2194 (0.6395)	4.0373 (0.0445)*	0.1933 (0.6602)	0.8542 (0.3554)	0.2922 (0.5888)	0.6710 (0.4127)	0.6863 (0.4074)	1.6872 (0.1940)
Patient Race/Ethnicity	2.6382 (0.7556)	0.7874 (0.9778)	1.2998 (0.7292)	3.8264 (0.2808)	10.0676 (0.0393)*	0.4148 (0.8127)	6.1765 (0.1033)	0.4285 (0.5127)
Patient Diabetes	0.2622 (0.6086)	0.2698 (0.6035)	2.7152 (0.0994)	0.3990 (0.9405)	2.3065 (0.5113)	-	0.2130 (0.6444)	0.6383 (0.7268)
Donor Circumstance of Death	4.0563 (0.5413)	2.4458 (0.7846)	6.7343 (0.2412)	3.7180 (0.5907)	0.8854 (0.9713)	6.2222 (0.2852)	0.8134 (0.9366)	1.2429 (0.9407)

Significance of Independent Variables by Disease Category, 1 year survival Mean Difference (Deceased-Survived, Pooled) (p-value) *Significant at 95% CL								
	All Causes	ALD	Cancers	Hepatitis	Cirrhosis	Injury	Metabolic	Prior Transplant
Patient Age	0.4718 (0.7441)	-0.4493 (0.8296)	-3.7356 (0.5368)	-3.3857 (0.4329)	0.2158 (0.9518)	2.9259 (0.8011)	-8.9706 (0.4024)	11.1556 (0.1421)
Donor Age	3.5518 (0.0528)	3.3939 (0.2239)	-9.2040 (0.2124)	6.5658 (0.1494)	2.6003 (0.5888)	-6.6296 (0.6630)	12.0882 (0.4127)	-3.6444 (0.6303)
SVI	-0.0411 (0.1554)	-0.0214 (0.6390)	0.0824 (0.4703)	-0.1183 (0.0827)	-0.0332 (0.6483)	0.1757 (0.4620)	0.0636 (0.8171)	-0.1854 (0.2222)
MELD Score	0.4822 (0.6904)	-2.7748 (0.0922)	0.7385 (0.8739)	0.1026 (0.9743)	-0.4205 (0.8793)	-10.5556 (0.2769)	-6.2941 (0.5373)	-3.1333 (0.6503)
Days on Waitlist	16.6436 (0.6928)	-32.3410 (0.4249)	-50.9368 (0.8207)	-26.5571 (0.8055)	224.0 (0.0589)	-82.4815 (0.6549)	106.9 (0.6111)	-134.4 (0.2530)

Independent Variables	Variable Name in SAS
1 Year Survival Post-Transplant	1 year survival yes/no
3 Year Survival Post-Transplant	3 year survival yes/no
Age of Recipient at Transplant	Age in Years At Transplant
Recipient Sex at Birth	Birth Sex
Recipient MELD Score at Transplant	MELD/PELD LAB score at transplan
BMI Difference (Recipient-Donor)	REAL BMI Diff
Recipient BMI at Transplant	REAL Recip BMI
Race/Ethnicity (Black, Hispanic, Asian) (Ref=White)	Race/Ethnicity Category (RaceB, RaceH, RaceA)
Recipient Social Vulnerability Index at Transplant	SVI
Donor Birth Sex	DSex
Presence of a Difference in Sex between Donor and Recipient	SexDiff
Sex Difference between Donor and Recipient (Female-Female, Male-Female, Female-Male) (Ref=Male-Male)	Sex_dif1 (Sex_dif3, Sex_dif4, Sex_dif5)
Recipient Total Chronological Days on Waitlist (>0)	Total Chronological Days on Wait
Recipient Diabetes Status at Transplant	Dia_yes
Deceased Donor Circumstance of Death (Accident, Motor Vehicle Accident, Homicide, Suicide, None of the Above) (Ref= Natural Causes)	Deceased Donor Circumstance of D (DACC, DMVA, DHOM, DUI, DNON)
Donor Age	Donor Age
Interaction between Donor Age and Sex Difference between Donor and Recipient (F-F, M-F, F-M)	interaction_donor_age3 interaction_donor_age4 interaction_donor_age5

Interaction between Recipient Age at Transplant and Sex Difference between Donor and Recipient (F-F, M-F, F-M)	interaction_transplant_age3 interaction_transplant_age4 interaction_transplant_age5
Interaction between Recipient SVI and Sex Difference between Donor and Recipient (F-F, M-F, F-M)	Interaction_svi3 interaction_svi4 interaction_svi5
Interaction between Recipient MELD score and Sex Difference between Donor and Recipient (F-F, M-F, F-M)	interaction_meld_lab3 interaction_meld_lab4 interaction_meld_lab5
Interaction between Total Chronological Days on Waitlist and Sex Difference between Donor and Recipient (F-F, M-F, F-M)	interaction_wait_days3 interaction_wait_days4 interaction_wait_days5
Interaction between Recipient Diabetes and Sex Difference between Donor and Recipient (F-F, M-F, F-M)	interaction_dia3 interaction_dia4 interaction_dia5
Interaction between Recipient-Donor BMI Difference and Sex Difference between Donor and Recipient (F-F, M-F, F-M)	interaction_bmi_diff3 interaction_bmi_diff4 interaction_bmi_diff5
Interaction between Recipient Race/Ethnicity (Black, Hispanic, Asian) and Sex Difference between Donor and Recipient (F-F, M-F, F-M)	interaction_raceb3 interaction_raceb4 interaction_raceb5 interaction_raceh3 interaction_raceh4 interaction_raceh5 interaction_racea3 interaction_racea4 interaction_racea5
Interaction between Donor Circumstance of Death (Accident, MVA, Homicide, Suicide, None of the Above) and Sex Difference between Donor and Recipient (F-F, M-F, F-M)	interaction_DACC3 interaction_DACC4 interaction_DACC5 interaction_DMVA3 interaction_DMVA4 interaction_DMVA5 interaction_DHOM3 interaction_DHOM4 interaction_DHOM5 interaction_DSUI3 interaction_DSUI4 interaction_DSUI5 interaction_DNON3

	interaction_DNON4 interaction_DNON5
Interaction between Donor Sex and Donor Age	interaction_Ddage
Interaction between Donor Sex and Recipient Age at Transplant	interaction_Drage
Interaction between Donor Sex and Recipient SVI	interaction_DSVI
Interaction between Donor Sex and Recipient MELD score	interaction_DMELD
Interaction between Donor Sex and Recipient Total Chronological Time on Waitlist	interaction_Dwait
Interaction between Donor Sex and Recipient Diabetes Status	interaction_Ddiab
Interaction between Donor Sex and Recipient-Donor BMI Difference	interaction_DBMI
Interaction between Donor Sex and Recipient Race/Ethnicity (Black, Hispanic, Asian)	interaction_DBlack interaction_DHisp interaction_DAsian
Interaction between Presence of a Difference in Sex between Donor and Recipient and Donor Circumstance of Death (Accident, MVA, Homicide, Suicide, None of the Above)	interaction_DDACC interaction_DDMVA interaction_DDHOM interaction_DDSUI interaction_DDNON
Interaction between Presence of a Difference in Sex between Donor and Recipient and Donor Age	interaction_SDdage
Interaction between Presence of a Difference in Sex between Donor and Recipient and Recipient Age	interaction_SDrage
Interaction between Presence of a Difference in Sex between Donor and Recipient and Recipient SVI	interaction_SDSVI
Interaction between Presence of a Difference in Sex between Donor and Recipient and	interaction_SDMELD

Recipient MELD Score	
Interaction between Presence of a Difference in Sex between Donor and Recipient and Recipient Total Chronological Days on Waitlist	interaction_SDwait
Interaction between Presence of a Difference in Sex between Donor and Recipient and Recipient Diabetes Status	interaction_SDdiab
Interaction between Presence of a Difference in Sex between Donor and Recipient and Recipient-Donor BMI Difference	interaction_SDBMI
Interaction between Presence of a Difference in Sex between Donor and Recipient and Recipient Race/Ethnicity (Black, Hispanic, Asian)	interaction_SDBlack interaction_SDHisp interaction_SDAsian
Interaction between Presence of a Difference in Sex between Donor and Recipient and Donor Circumstance of Death (Accident, MVA, Homicide, Suicide, None of the Above)	interaction_SDDACC interaction_SDDMVA interaction_SDDHOM interaction_SDDSUI interaction_SDDNON

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