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Racial and Ethnic Differences in Graft Loss Among Female Liver Transplant Recipients

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Abstract

Background.—Racial differences in post-liver transplantation (LT) outcomes are identified in predominantly male cohorts. Despite known sex differences in a spectrum of liver-related outcomes, it is not known how race influences graft outcomes in women.

Methods.—Using the Scientific Registry of Transplant Recipients, we examined race and ethnicity and graft loss (death or retransplant) in women transplanted from 2002 to 2012. Covariates included recipient and donor characteristics, socioeconomics, and medical comorbidities.

Results.—The eligible cohort (n = 15,860) included 11,051 Caucasians, 2171 Hispanics, 1876 African Americans (AAs), and 762 Asian women with median follow-up of 3.1 years. Five-year graft survival was lower in AA women (60%) compared with Caucasians (71%), Hispanics (70%), and Asians (73%) ($P < .001$). Graft loss was 45% higher among AA women <40 years at transplant compared with AA women aged 50 to 59 (hazard ratio 1.45, 95% confidence interval 1.17–1.81) and aged 60 to 69 years (hazard ratio 1.33, 95% confidence interval 1.03 – 1.71), and risk increased after age 60 among Caucasians ($P < .001$ for race-age interactions). Increased graft loss among young AA women was limited to the first 2 years post-LT ($P = .002$).

Conclusion.—Younger AA women are at particularly high risk for graft loss, which predominates in the first 2 years post-LT. Prospective studies of immunosuppression adherence and pharmacokinetics, particularly in relation to patient age, may help to explain the mechanisms underlying the higher rates of graft loss in younger AA women.

THERE is growing recognition of the importance of individualized medicine, including gender-specific models of care. Sex differences in coronary and stroke risk, for example, have resulted in the incorporation of sex in clinical prediction models to better prognosticate

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cardiovascular outcomes [1,2]. Similarly, sex differences in risk of progressive kidney disease have led to the incorporation of sex in validated prediction tools for identifying individuals at risk for renal failure [3]. Sex differences are evident in the natural history and treatment response of many chronic liver diseases [4]. However, because men comprise the majority of liver transplant (LT) recipients, few studies have focused on unique aspects of transplant outcomes and management in women. With the number of transplanted women steadily rising [5], there is a growing need for sex-specific studies in this context. Like sex-specific models in other disease states, these data may help to improve the care of women in the LT setting.

African Americans (AAs) comprise approximately 10% of the more than 6000 LTs performed each year in the Unites States [6,7]. With the introduction of the Model for End-Stage Liver Disease (MELD) in 2002, racial and ethnic disparities in organ allocation have improved [8,9], specifically resulting in increased rates of LT among AAs. Although more AA patients are receiving LTs, studies of post-LT outcomes continue to note worse patient and graft survival in this population [6,10–14]. A recent publication from the Scientific Registry of Transplant Recipients (SRTR) identified ~30% higher risk of graft loss in AAs compared with Caucasians, independent of age, disease etiology, center quality, donor risk index, and composite measures of socioeconomic status [13]. The reasons for decreased survival in AAs are not known, though no prior studies have explored whether causes of graft failure differ by race. Prior studies also derive from male predominant cohorts without exploring graft outcomes among women of racial and ethnic minorities.

In the current study, we aimed to investigate racial and ethnic differences in post-transplant graft loss among women, with specific interest in comparing AA women to other racial and ethnic groups. We additionally sought to explore whether cause of graft failure among female transplant recipients differed by racial and ethnic group.

METHODS

Cohort Inclusion and Exclusion

This is a retrospective cohort study of women from the SRTR database. Eligible patients were women ≥ 18 years of age receiving a LT between March 1, 2002, and May 31, 2012. Women with retransplantation (n = 1340) or multiorgan transplants (n = 164) other than simultaneous liver-kidney transplants and women reporting "other uncategorized" racial and ethnic groups (n = 189) were excluded. This study was approved by the University of California, San Francisco Institutional Review Board.

Primary Predictor and Outcome

Race or ethnicity was the primary predictor. All women reporting Hispanic ethnicity were coded as Hispanic. The other groups included AAs, Caucasians, and Asians. The primary outcome was graft loss defined as a retransplant or death.

As an exploratory analysis, the association between race, age at transplant, and causes of graft failure were examined. Cause of graft failure was ascertained from the "Transplant Recipient Follow-up" form collected at 6 months and annually thereafter following LT.

Causes of graft failure included chronic rejection, primary nonfunction, recurrent hepatitis, recurrent non-hepatitis disease, vascular complications, biliary complications, infection, and noncompliance. These are reported as "yes," "no," and "unknown," with "unknown" coded as "no" for analysis. "Unknown" was reported in only 3% to 5% of patients. Noncompliance as cause of graft failure was collected in 2004 onward, therefore available in a subset of women. Categories of graft failure were not mutually exclusive.

Recipient demographic and socioeconomic factors included age at listing and transplant, insurance type, and level of education. Other recipient factors included disease etiology, history of hepatic decompensation (ever diagnosis of ascites, encephalopathy, or variceal bleeding), hospitalization pre-LT, time on wait list, functional status, metabolic comorbidities including history of diabetes, hypertension requiring medication, body mass index (BMI), dialysis use, height, weight, and pre-LT MELD score. Donor factors included deceased or living donor type, organ sharing, Centers for Disease Control high-risk donation, and components of the donor risk index [15].

Statistical Techniques

Patient characteristics were described using frequencies (percentages) and median with interquartile ranges (IQR) and compared across racial and ethnic groups using χ^2 and Kruskal-Wallis tests, as appropriate. Observation time was measured from the date of transplant to the first event (retransplant or death) or last follow-up date. The Kaplan-Meier method was used to estimate 1-, 3-, and 5-year graft survival and 95% confidence intervals (CI) by racial and ethnic groups. Survival differences were assessed with the log-rank test, and Bonferroni-adjusted P values were reported to account for multiple comparisons across racial and ethnic groups. Cox proportional hazards regression assessed risk of graft loss within 5 years post-transplant. We accounted for center-level clustering with robust sandwich estimates of standard error. Covariates with $P < .1$ in single predictor models were eligible for inclusion in multivariable model building. The final multivariable model was developed using backward selection of covariates and included those with a multivariable $P < .05$. To explore the racial and ethnic differences in graft loss, we tested for interactions between race and all covariates included in the final model. These included age at transplant, insurance type, disease etiology, hospitalization status, portal vein thrombosis, diabetes, functional status, dialysis use, receipt of MELD exception points, donor factors (age, sex, race, and cause of death), and cold ischemia time. Cause of graft failure was described with frequencies and percents by race and ethnicity and compared using Pearson exact χ^2 test. Cox proportional hazards regression evaluated cause-specific risk of graft failure by (1) race and ethnicity among women age <50 years, (2) race and ethnicity among women age 50 years, and (3) age <50 versus 50 years among AA women. Time from LT to each cause-specific graft failure was calculated and patients were censored at the date of last follow-up if "no" or "unknown" graft failure was reported. Analyses were performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc, Cary, NC, United States).

RESULTS

Cohort Characteristics by Race and Ethnicity

The eligible cohort included 15,860 women that underwent LT between 2002 and 2012, of whom 69.7% were Caucasian, 13.7% Hispanic, 11.8% AA, and 4.8% Asian. AA women had a lower median age at LT of 52 years (IQR 43–58) years, compared with Caucasians (55 years, IQR 48–61), Hispanics (55 years, IQR 47–61), and Asians (58 years, IQR 50–64). AAs were most likely to have hepatitis C virus (HCV) as the cause of liver disease as well as acute liver failure (ALF), while hepatocellular carcinoma as indication for LT was more than twice as high among Asian women than all other racial and ethnic groups. Level of education was similar between Caucasian and AA women, though Hispanics and Asians were more likely to have education of grade school level or less. Public insurance was more frequent in AA women than Caucasians and Asians, though most frequent among Hispanic women. AA women more frequently had hypertension requiring medication, a BMI >35 kg/m^2, and simultaneous liver-kidney transplant (SLK), although were less likely than Hispanic women to need pretransplant dialysis. Interestingly, AAs had a significantly lower median wait time than other racial and ethnic groups and were most likely to be in the intensive care unit (ICU) at time of LT ($P<$ .001). Regarding donor factors, AA women were least likely to receive living donor LT and most likely to receive Centers for Disease Control high-risk donors, although they had the lowest median donor risk index (Table 1).

Graft Survival by Race and Ethnicity

Graft loss occurred in 4156 women (26.2%) within 5 years of LT, which included 631 (33.6%) AAs, 552 (25.4%) Hispanics, 2795 (25.3%) Caucasians, and 178 (23.4%) Asians. Compared with other racial and ethnic groups, AA women had the lowest cumulative graft survival (log-rank $P<$ .001) (Fig 1). Graft survival at 1, 3, and 5 years was 82%, 69%, and 60% among AAs; 85%, 77%, and 71% among Caucasians; 85%, 76%, and 70% in Hispanics; and 86%, 78%, and 73% in Asians. In fully adjusted models, AA women had a 24% to 33% higher risk of graft loss compared with all other racial and ethnic groups ($P<$ .001). Additional factors associated with graft loss included older recipient age at LT, public insurance, HCV as cause of liver disease, hospitalization prior to LT (including those with ICU stay), diabetes, severely impaired functional status, dialysis, receipt of hepatocellular carcinoma exception, portal vein thrombosis, longer cold ischemia time, and donors that were male, Asian or Hispanic, older, or with non-head trauma as cause of death (Table 2). Lower level of education was not associated with graft loss (hazard ratio [HR] 1.03, 95% CI 0.89–1.19, $P=$.69).

Factors Associated With Graft Outcomes in African-American Women

To better understand the increased risk of graft loss among AA women, we assessed potential interactions by race and model covariates. This was specifically explored between AA and Caucasian women because Caucasians were the largest group in our cohort. As demonstrated in Fig 2, statistically significant age by race interactions were identified, specifically among women aged 50 to 59 ($P=$ .006) and 60 to 69 ($P=$ .007) at LT. Figure 2 demonstrates a lower risk of graft loss among AA women aged 50 to 69 years, compared with AA women <40 years of age. Alternatively, among Caucasian women, risk of graft loss

remained relatively stable from ages 18 to 59, with increasing risk of graft loss starting at age 60 years compared with younger Caucasian women. No race-by-age interactions were identified with Hispanic or Asian women (interaction *P* values   0.17).

The observed race-by-age interaction highlights an un-expected high-risk group within younger AA women. Specifically, risk of graft loss was 45% higher among AA women <40 years at transplant compared with AA women aged 50 to 59 (HR 1.45, 95% CI 1.17–1.81) and aged 60 to 69 years (HR 1.33, 95% CI 1.03–1.71). Likewise, AA women aged 40 to 49 also had a 34% higher risk of graft loss than AA women aged 50 to 59 (HR 1.34, 95% CI 1.08–1.67) with nonstatistically significant increased graft loss compared with those aged 60 to 69 (HR 1.23, 95% CI 0.96–1.57). Risk of graft loss was similar in AA women aged 40 to 49 years compared with <40 years (HR 1.08, 95% CI 0.85–1.38), indicating that AA women <50 years of age at LT represent the highest risk group.

Given the observed age-race interactions noted for AA women, we assessed whether patient characteristics varied by age. There were notable differences between younger and older AA women, with younger women appearing to be sicker prior to LT. Specifically, younger AA women had higher median MELD at transplant and shorter wait times and were more likely to have hepatic decompensation, to be in the ICU, and to have severely impaired functional status at time of transplant. These characteristics may to attributed to the more than 3-fold higher prevalence of ALF in younger (23.5%) compared with older (6.7%) AA women. On the other hand, AA women >50 were more than twice as likely to have hepatitis C, hypertension, and diabetes (Table 3).

Additional statistically significant interactions by AAs and other racial and ethnic groups included hospitalization within 90 days of transplant and pre-LT dialysis, but these factors were only associated with increased risk of graft loss among non-AA racial and ethnic groups (Table 4) therefore not explanatory of the higher risk of graft loss in AA women.

Kaplan-Meier survival curves revealed notable temporal patterns in graft survival by race and ethnicity and age. Graft survival was lower among younger compared with older AA women during the first 2 years post-LT, but similar from 2 years post-LT onward (Fig 3). This temporal pattern persisted on multivariable analysis adjusted for insurance type, disease etiology and severity, diabetes history, dialysis, portal vein thrombosis, functional status, and donor factors. Adjusting for these factors, younger AA women had a 39% increased risk of graft loss within the first 2 years post-LT (HR 1.39, 95% CI 1.13–1.71, *P* =.002) followed by similar risk as older AA women from 2 years onward (HR1.08, 95% CI 0.76–1.54, *P* = .68). These findings suggest that increased graft loss among younger AA women is driven by factors that develop in the early post-LT period. There was no significant difference in risk of graft loss by age and time from LT among Caucasian (*P* =.09), Hispanic (*P* = .93), or Asian women (*P* = .62).

Exploratory Analysis of Causes of Graft Loss

Using available reported data, we explored whether cause of graft failure varied by race and ethnicity. Overall 1139 women (7.2% of cohort) had graft failure. The most common causes were recurrent hepatitis (40.3%), recurrent nonhepatitis causes of liver disease (26.2%), and

primary nonfunction (25.6%). No single cause was statistically greater among AA women than other racial and ethnic groups, although chronic rejection and noncompliance were numerically more frequent (Table 5). We then compared risk of specific etiologies of graft failure by age (Table 6). Compared with Caucasians <50 years, younger AA had a significantly higher risk of graft failure from chronic rejection, primary nonfunction, recurrent hepatitis, and infections, even after adjustment for donor risk index. Among older women, AAs had a significantly higher risk of graft failure from primary nonfunction, recurrent hepatitis and nonhepatic diseases, and noncompliance than Caucasian women. There was no significant racial difference in graft failure from chronic rejection among older women. When comparing younger to older AA women, only the risk of graft failure from chronic rejection was greater in younger AA women. Interestingly, no statistically significant difference in noncompliance was present in younger AA women compared with younger Caucasians (P = .14) or when compared with older AA women (P =.33). Likewise, increased risk of chronic rejection was noted in younger but not older AA women compared with Hispanics of similar age group.

DISCUSSION

In this racially diverse cohort, we identified a higher risk of graft loss in AA women, with a 24% to 33% increased risk compared with Caucasian, Hispanic, and Asian women. This risk was independent of demographics, socioeconomic factors, disease etiology, severity of liver disease, and donor characteristics. Importantly, a striking age-race interaction was evident with risk of graft loss highest in AA women less than 50 years of age at LT. Moreover, this risk was predominately during the first 2 years post-transplant, with younger AA women having a nearly 40% increased risk of graft loss during that time. Understanding the reasons for these striking racial differences in graft loss in women are essential to the implementation of future prevention strategies.

Prior studies from male predominant cohorts have noted consistently worse patient and graft survival in AAs that is not explained by potential confounding factors such as HCV, MELD at transplant, and socioeconomic status including insurance type and education [6,10,11]. In a recent publication, data from more than 12,000 transplant recipients were analyzed to more comprehensively investigate the role of detailed socioeconomic measures on observed racial differences in transplant outcomes [13,16]. Center volume, household income, education, and employment were included. Despite adjustment for robust measures of socioeconomic status, AAs continued to have a nearly 30% increased risk of death post-LT. Prior national data including men and women have shown that AAs with acute and chronic liver failure have lower access to the wait list than Hispanics and Caucasians [17]. Whether this pre-LT factor affects post-LT outcomes is not known. Referral patterns and distance to transplant center were not evaluated in our study but may be additional factors of importance in future studies of racial differences in post-LT outcomes [18].

Our study revealed previously unrecognized differences in risk of graft loss by age and race at transplant, with marked increased risk among younger compared with older AA women. A recent study of predominately women found that AAs transplanted for autoimmune hepatitis were on average 8 years younger than Caucasians, yet still had lower post-LT

survival. AAs in this study were also more likely to require retransplantation, although data on graft loss by age or rejection history as cause of graft loss were not available [19]. We observed similar increased prevalence of autoimmune conditions in younger compared with older AA women, as well as higher prevalence of ALF, which were the 2 most common causes of liver disease in this younger subgroup. Younger AA women were overall sicker at time of transplant with higher median MELD, longer ICU stay, and higher proportion with severe impairment of functional status. These differences may be attributed to their higher prevalence of ALF and might also explain the significantly shorter wait times among younger AA women.

In an effort to better understand observed age-race interactions, we explored causes of graft failure as secondary outcomes. Among all causes, only chronic rejection was significantly different between younger and older AA women, with younger AA women having nearly 4-fold higher risk of chronic rejection. Likewise among younger women, AAs had higher risk of chronic rejection compared with younger Hispanics and Caucasians. However, non-adherence as a cause of graft failure was not different be-tween these groups. It is important to note that causes of graft loss have not been validated in SRTR. Therefore, these exploratory findings do not provide conclusive explanations regarding increased risk of graft loss in younger AA women, but do support the need to evaluate factors related to chronic rejection beyond patient adherence.

Pharmacokinetic data have shown that for a given dose of tacrolimus African Americans have lower trough levels than Caucasians [20], and a recent study found that genetic differences in CYP3A5 enzyme production may explain observed racial differences in tacrolimus metabolism in kidney transplant recipients [21]. Another study found that AAs had a 70% higher risk for subtherapeutic tacrolimus levels, predominately in the first year after kidney transplant [22]. The median age of these recipients was also quite young at 42 years, although racial differences in tacrolimus levels by age were not explored. Studies of immunosuppression levels by race in liver transplantation have not been conducted. One could postulate that differences in target drug levels may be less apparent after LT given overall lower immunosuppression needs than after kidney transplant [23]. However, this may be most relevant within the first years following LT when immunosuppression needs are the greatest and may help to explain the increased graft loss that we observed in younger compared with older AA women within the first 2 years post-LT. If racial differences in drug metabolism contribute to increased graft loss among young AAs, alternative immunosuppressive protocols or intensified monitoring of immunosuppression levels may help to optimize graft outcomes. There is certainly need for detailed investigation of drug metabolism in AAs across age, including potential changes in drug metabolism over time.

The strengths of our study include the use of a large national database and the ability to adjust for many confounding factors that may influence post-transplant outcomes. By further exploring interactions by race and age, we identified younger AA women as a particularly high-risk group. As noted above, an important limitation of our study is the lack of validated data on causes of graft loss in this cohort, which are also inconsistently reported. Therefore, our secondary analyses were indeed exploratory in nature. Additional factors that would be helpful in exploring graft loss by race include patterns of insurance coverage after transplant

and distance from transplant center, the latter of which has been shown to increase risk of graft loss in kidney transplant recipients [18]. Finally, detailed information on immunosuppressive therapy is lacking, a key aspect of interpreting racial differences in chronic rejection.

Sex-specific studies aim to expand the relatively nascent field of gender medicine. Historically, there have been limited data on the epidemiology and management of women, with resulting disparities in health outcomes [24,25]. There is now a growing recognition of sex-specific models of care, which have been incorporated into the management of women with cardiovascular and renal disease [1–3]. Although sex differences are evident in the natural history and treatment response of many chronic liver diseases [4], gastroenterology and hepatology rank among the lowest subspecialties in published sex-specific research [25]. With a focus on graft loss in women, the current study will expand existing literature of outcomes in AAs, with a goal improving management of the particularly high-risk group of young AA women in the early post-transplant years.

In summary, we identified novel differences in risk of graft loss by age and race among transplanted women. Younger AA women had an increased risk of graft loss, which predominately occurred within the first 2 years after LT. Future studies including investigation of immunosuppression use and drug metabolism may be especially fruitful areas of research to help to improve graft outcomes in this population.

ACKNOWLEDGMENTS

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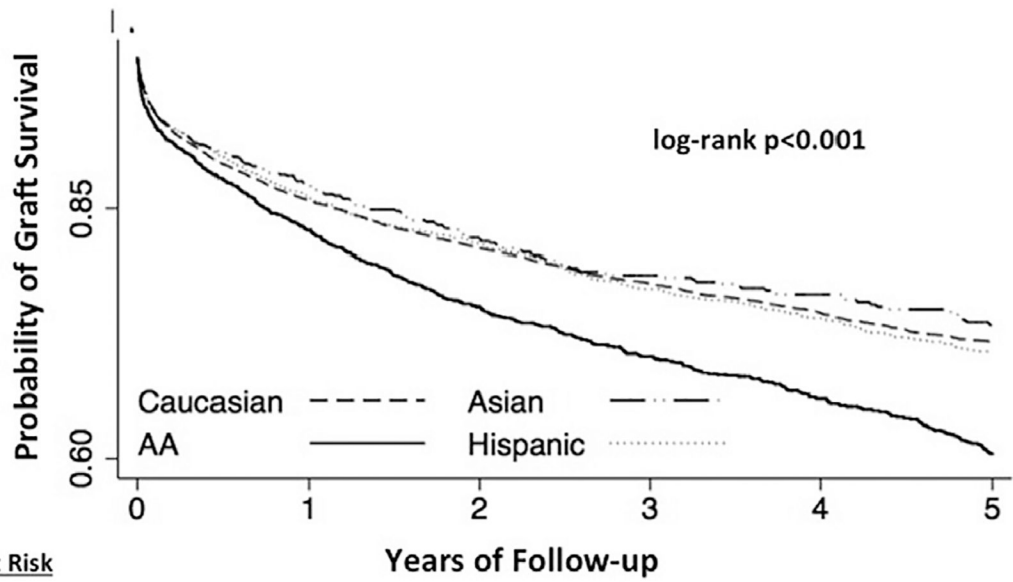
Fig 1.

African American (AA) women have lower graft survival than women of other race and ethnicities.
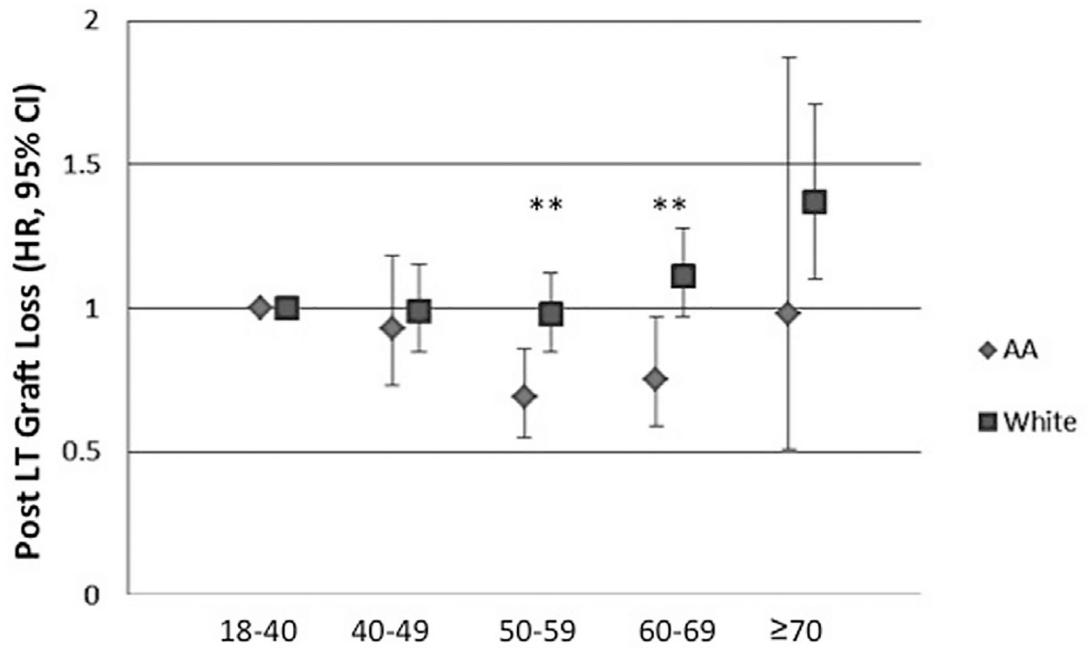
Age < 40 set as reference for respective racial groups. ** *Significant race by age interaction (p values <0.01)*

Fig 2.
Risk of graft loss (hazard ratio [HR], 95% confidence interval [CI]) by race and age at liver transplantation (LT). Among African American (AA) women, risk of graft loss was higher for those transplanted aged 18 to 49 compared with 50 to 69 years. Alternatively, among Caucasians, risk remained similar through transplant aged 18 to 59 with increased risk of graft loss starting at age 60 years.
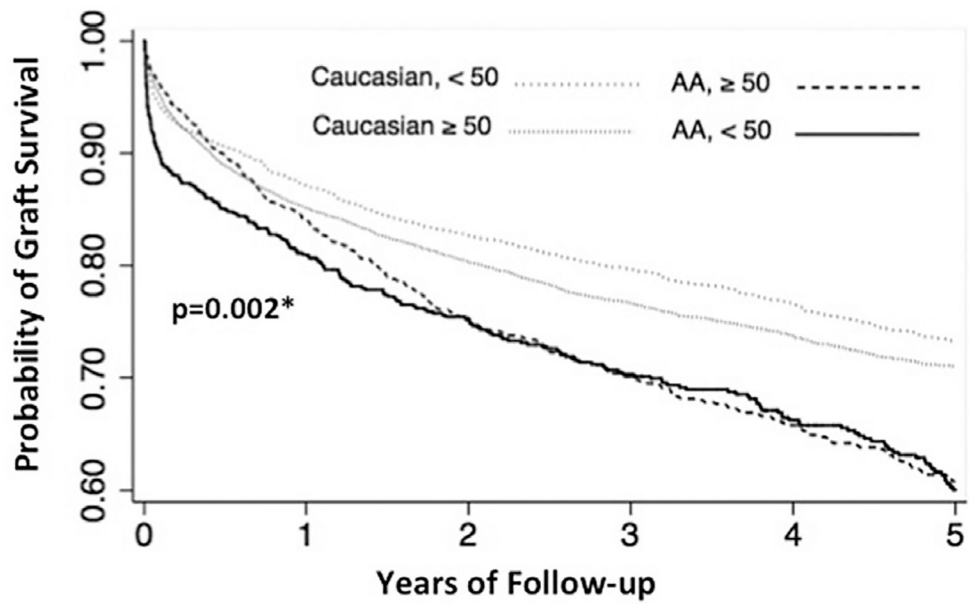
Fig 3.
Decreased graft survival in younger African American (AA) women occurs within the first 2 years post-transplant.

Table 1.

Characteristics of Women Transplanted From 2002 to 2012

	Total (n = 15,860)	Caucasian (n = 11,051)	African American (n = 1876)	Hispanic (n = 2171)	Asian (n = 762)	P Value
Recipient factors						
Median follow-up years (IQR)	3.1 (1.2–5.0)	3.3 (1.2–5.0)	2.9 (1.0–5.0)	3.0 (1.2–5.0)	3.1 (1.1–5.0)	<.001
Age at transplant (%)						<.001
18–39	12.6	11.3	20.2	13.1	10.1	
40–49	18.5	18.7	20.2	18.1	13.4	
50–59	38.6	39.1	38.9	38.3	32.8	
60–69	27.2	27.6	19.5	27.9	37.9	
70+	3.1	3.4	1.2	2.7	5.8	
Etiology (%)						<.001
Hepatitis C	32.4	30.3	39.4	36.6	33.3	
Autoimmune/cholestatic	18.8	19.6	21.3	17.2	8.5	
Cryptogenic/nonalcoholic steatohepatitis	17.4	19.0	6.1	23.4	7.7	
Alcohol	9.3	11.3	4.0	6.5	1.3	
Hepatitis B	2.5	1.0	3.5	1.1	25.9	
Acute liver failure	7.5	6.5	13.5	7.0	10.0	
Other	9.8	10.6	9.8	6.3	8.1	
MELD exception for HCC (%)	17.2	14.9	17.0	20.4	43.0	<.001
Education (%)						<.001
Grade school or less	4.9	2.1	2.3	18.9	13.5	
High school	38.7	39.0	38.9	39.7	31.5	
College/tech school	19.1	20.0	20.9	14.0	16.5	
Postgraduate	16.7	18.5	15.8	8.8	15.9	
Primary insurance (%)						<.001
Private	57.7	61.9	53.0	41.2	55.8	
Public	41.0	37.0	45.8	56.7	42.3	
Diabetes (%)	21.6	20.0	21.8	28.7	23.0	<.001
Hypertension treatment (%):	18.3	16.5	27.9	19.9	17.3	<.001
BMI (%)						<.001

	Total (n = 15,860)	Caucasian (n = 11,051)	African American (n = 1876)	Hispanic (n = 2171)	Asian (n = 762)	P Value
<25	35.6	35.9	29.6	31.0	58.5	
25–29.9	30.0	29.7	30.9	31.4	26.8	
30–34.9	19.4	19.1	21.5	21.9	11.3	
35–39.9	10.0	10.2	11.2	10.7	3.1	
40	5.0	5.0	6.8	4.9	0.3	
Dialysis (%)	10.9	10.3	10.6	14.9	8.7	<.001
Hepatic decompensation (%)	85.9	86.6	83.8	88.4	73.1	<.001
Portal vein thrombosis (%)	5.8	5.9	4.0	7.1	5.1	.004
Hospitalized within	35.5	35.0	35.6	39.8	30.1	<.001
90 days pre-LT (%)						
Functional status (%)						<.001
Excellent	9.9	10.4	8.5	8.4	11.9	
Good	21.2	21.9	19.5	17.6	26.8	
Restricted	30.8	31.5	30.0	30.4	23.5	
Severely impaired	27.2	25.2	30.1	34.5	28.1	
MELD at LT (median, IQR)	20 (14–30)	22 (14–28)	24 (17–32)	23 (15–32)	17 (9–29)	<.001
Waitlist time (median days, IQR)	65 (12–218)	67 (14–215)	40 (6–167)	82 (14–284)	66 (10–229)	<.001
Hospitalized (%)						<.001
ICU	16.0	14.4	20.0	19.0	19.6	
Non-ICU	17.3	16.1	18.7	22.8	15.5	
Not hospitalized	66.8	69.5	61.3	58.2	65.0	
Transplant/donor factors						
Simultaneous liver-kidney (%)	5.9	5.3	7.9	7.3	4.9	<.001
LDLT(%)	5.2	6.0	1.8	4.7	2.4	<.001
Organ sharing (%)						<.001
Local	66.5	65.1	67.1	71.0	71.8	
Regional	23.1	23.1	26.3	20.3	22.7	
National	10.5	11.8	6.6	8.8	5.5	
Male (%)	51.2	51.1	51.9	51.5	49.1	.60
Race/ethnicity (%)						<.001
Caucasian	67.0	71.3	60.4	55.0	55.9	

	Total (n = 15,860)	Caucasian (n = 11,051)	African American (n = 1876)	Hispanic (n = 2171)	Asian (n = 762)	P Value
African American	15.6	15.3	22.8	11.9	13.6	
Hispanic	13.9	10.7	13.5	28.6	18.6	
Asian	2.9	2.2	2.7	4.0	10.6	
CDC high-risk organ (%)	6.6	6.2	8.2	6.9	7.2	<.001
Cause of death (%)						<.001
Anoxia	17.1	16.7	18.2	18.1	18.5	
Cerebrovascular/stroke	40.6	40.5	41.6	40.0	40.8	
Head trauma	34.5	34.1	35.4	35.0	36.2	
DRI (median, IQR)	1.44 (1.16–1.78)	1.44 (1.16–1.79)	1.40 (1.14–1.7)	1.45 (1.16–1.79)	1.45 (1.18–1.77)	<.001

Abbreviations: BMI, body mass index; CDC, Center for Disease Control; DRI, donor risk index; HCC, hepatocellular carcinoma; ICU, intensive care unit; IQR, interquartile range; LDLT, living donor liver transplantation; LT, liver transplant; MELD, Model End-Stage Liver Disease.

Table 2.

Factors Associated With Risk of Graft Loss

Variable	Univariable		Multivariable	
	HR (95% CI)	P Value	aHR (95% CI)	P Value
Race/ethnicity				
AA (ref)	1.00		1.00	
Caucasian	0.71 (0.65–0.77)	<.001	0.76 (0.70–0.84)	<.001
Hispanic	0.72 (0.65–0.81)	<.001	0.71 (0.63–0.80)	<.001
Asian	0.66 (0.56–0.78)	<.001	0.67 (0.57–0.80)	<.001
Age at transplant				
18–40 (ref)	1.00		1.00	
40–49	0.99 (0.89–1.11)	.90	0.94 (0.83–1.05)	.27
50–59	1.01 (0.91–1.12)	.84	0.90 (0.80–1.00)	.046
60–69	1.10 (0.99–1.22)	.08	1.00 (0.90–1.12)	.96
70+	1.42 (1.19–1.70)	<.001	1.28 (1.06–1.54)	.009
Public vs private insurance	1.25 (1.17–1.32)	<.001	1.13 (1.06–1.21)	<.001
HCV vs non-HCV	1.49 (1.40–1.59)	<.001	1.61 (1.51–1.72)	<.001
Hospitalized pre-LT	1.25 (1.16–1.34)	<.001	1.13 (1.05–1.22)	.002
Medical condition				
Not hospitalized (ref)	1.00		1.00	
ICU	1.47 (1.36–1.59)	<.001	1.37 (1.22–1.54)	<.001
Non-ICU	1.17 (1.08–1.27)	<.001	1.02 (0.92–1.13)	.70
Diabetes	1.18 (1.10–1.27)	<.001	1.16 (1.08–1.25)	<.001
Functional status				
Excellent (ref)	1.00		1.00	
Good	0.90 (0.80–1.02)	.08	0.90 (0.79–1.01)	.07
Restricted	1.02 (0.92–1.15)	.66	0.97 (0.86–1.08)	.55
Severe	1.34 (1.20–1.50)	<.001	1.15 (1.00–1.32)	.047
Dialysis pre-LT	1.35 (1.23–1.48)	<.001	1.22 (1.10–1.35)	<.001
HCC exception	1.11 (1.03–1.20)	.008	1.13 (1.03–1.23)	.008
Portal vein thrombosis	1.23 (1.09–1.39)	.001	1.21 (1.06–1.37)	.004

Variable	Univariable		Multivariable	
	HR (95% CI)	P Value	aHR (95% CI)	P Value
Cold ischemia time	1.03 (1.02–1.04)	<.001	1.03 (1.02–1.04)	<.001
Male donor	1.05 (0.99–1.12)	.09	1.14 (1.07–1.22)	<.001
Donor race				
Caucasian (ref)	1.00			
African-American	1.05 (0.96–1.14)	.27	1.00 (0.92–1.10)	.95
Asian	1.30 (1.10–1.53)	.003	1.26 (1.06–1.50)	.008
Hispanic	1.21 (1.11–1.32)	<.001	1.24 (1.13–1.36)	<.001
Donor age	1.01 (1.008–1.01)	<.001	1.01 (1.01–1.01)	<.001
Cause of death				
Head trauma (ref)	1.00		1.00	
Anoxia	1.16 (1.05–1.27)	.002	1.12 (1.01–1.23)	.03
CVA/stroke	1.41 (1.32–1.52)	<.001	1.22 (1.12–1.33)	<.001
LDLT	1.06 (0.91–1.23)	.48	1.29 (1.10–1.51)	.002

Abbreviations: aHR, adjusted hazard ratio; AA, African American; CI, confidence interval; CVA, cerebrovascular accident; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICU, intensive care unit; LDLT, living donor liver transplantation; LT, liver transplant.

Table 3.

Characteristics of African American Women by Age at Transplant

Recipient factors	Age < 50 y (n = 758)	Age	50 y (n = 1118)	P Values
Median follow-up years (IQR)	3.0 (1.0–5.0)		2.8 (1.0–5.0)	.59
Etiology (%)				<.001
Hepatitis C	120 (15.8)		619 (55.4)	
Autoimmune/cholestatic	233 (30.7)		168 (15.0)	
Cryptogenic/nonalcoholic steatohepatitis	50 (6.6)		65 (5.8)	
Alcohol	28 (3.7)		47 (4.2)	
Hepatitis B	40 (5.3)		26 (2.3)	
Acute liver failure	178 (23.5)		75 (6.7)	
Other	100 (13.2)		85 (7.6)	
MELD exception for HCC (%)	45 (5.9)		273 (24.4)	<.001
Education (%)				.046
Grade school or less	14 (1.8)		30 (2.7)	
High school	269 (35.5)		460 (41.1)	
College/tech school	173 (22.8)		220 (19.7)	
Postgraduate	119 (15.7)		177 (15.8)	
Primary insurance (%)				.02
Private	405 (53.4)		590 (52.8)	
Public	338 (44.6)		521 (46.6)	
Diabetes (%)	99 (13.1)		310 (27.7)	<.001
Hypertension treatment (%)	107 (14.1)		417 (37.3)	<.001
BMI (%)				<.001
<25	274 (36.1)		282 (25.2)	
25–29.9	205 (27.0)		374 (33.5)	
30–34.9	146 (19.3)		258 (23.1)	
35–39.9	85 (11.2)		125 (11.2)	
40	48 (6.3)		79 (7.1)	
Dialysis (%)	67 (8.8)		131 (11.7)	.046

	Age < 50 y (n = 758)	Age 50 y (n = 1118)	P Values
Hepatic decompensation (%)	652 (86.0)	920 (82.3)	.03
Portal vein thrombosis (%)	25 (3.3)	50 (4.5)	.20
Hospitalized within 90 days pre-LT (%)	273 (36.0)	395 (35.3)	.76
Functional status (%)			<.001
Excellent	62 (8.2)	98 (8.8)	
Good	129 (17.0)	236 (21.1)	
Restricted	189 (24.9)	374 (33.5)	
Severely impaired	260 (34.3)	305 (27.3)	
MELD (median, IQR)	26.0 (19.0–34.0)	22.0 (15.0–30.0)	<.001
Waitlist time (median days, IQR)	22.0 (3.0–137.0)	55.0 (9.0–185.0)	<.001
Hospitalized (%)			<.001
ICU	219 (28.9)	157 (14.0)	
Non-ICU	138 (18.2)	212 (19.0)	
Not hospitalized	401 (52.9)	749 (67.0)	
Transplant and donor-related factors			
Simultaneous liver-kidney (%)	38 (5.0)	111 (9.9)	<.001
LDLT (%)	15 (2.0)	19 (1.7)	.66
Organ sharing (%)			<.001
Local	453 (59.8)	806 (72.1)	
Regional	256 (33.8)	238 (21.3)	
National	49 (6.5)	74 (6.6)	
Male (%)	401 (52.9)	573 (51.3)	.48
Race (%)			.49
Caucasian	453 (59.8)	681 (60.9)	
African American	178 (23.5)	250 (22.4)	
Hispanic	108 (14.2)	146 (13.1)	
Asian	15 (2.0)	36 (3.2)	
CDC high-risk organ (%)	48 (6.3)	106 (9.5)	.01
Cause of death			.41
Anoxia	138 (18.2)	203 (18.2)	
Cerebrovascular/stroke	298 (39.3)	483 (43.2)	

	Age < 50 y (n = 758)	Age ≥ 50 y (n = 1118)	P Values
Head trauma	286 (37.7)	378 (33.8)	
DRI (median, IQR)	1.38 (1.14–1.67)	1.40 (1.14–1.71)	.32

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control; HCC, hepatocellular carcinoma; ICU, intensive care unit; IQR, interquartile range; LDLT, living donor liver transplantation; LT, liver transplant; MELD, Model End-Stage Liver Disease.

Table 4.

Graft Loss Estimates for Statistically Significant Interactions With Race and Ethnicity

	African American (HR 95% CI)	Caucasian (HR 95% CI) P Values[*]	Hispanic (HR 95% CI) P Values[*]	Asian (HR 95% CI) P Values[*]
Age at transplant (ref < 40 y)				
50–59	0.69 (0.55–0.86)	0.98 (0.85–1.12) P = .006		
60–69	0.75 (0.59–0.97)	1.11 (0.97–1.28) P = .007		
Dialysis pretransplant	0.88 (0.67–1.17)	1.21 (1.07–1.38) P = .01	1.60 (1.24–2.05) P = .004	1.41 (0.83–2.41) P = .06
Hospitalized within 90 d pre-LT	0.83 (0.68–1.01)	1.17 (1.07–1.29) P < .001	1.25 (1.002–1.56) P = .007	1.69 (1.14–2.52) P = .003

Abbreviations: CI, confidence interval; HR, hazard ratio; LT, liver transplantation. P values 0.1 for estimates not shown.

[*] Interaction P values with African American race.

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Table 5.

Etiology of Graft Failure by Race and Ethnicity

Cause of Graft Failure	Total (n = 1139)	Caucasian (n = 741)	African American (n = 211)	Hispanic (n = 142)	Asian (n = 45)	P Value
Chronic rejection	180 (15.8)	107 (14.4)	41 (19.4)	24 (16.9)	8 (17.8)	.34
Primary nonfunction	292 (25.6)	184 (24.8)	58 (27.5)	39 (27.5)	11 (24.4)	.82
Recurrent viral hepatitis	459 (40.3)	280 (37.8)	98 (46.4)	67 (47.2)	14 (31.1)	.02
Recurrent disease, nonviral hepatitis	298 (26.2)	206 (27.8)	50 (23.7)	29 (20.4)	13 (28.9)	.23
Vascular complications	124 (10.9)	92 (12.4)	16 (7.6)	12 (8.4)	4 (8.9)	.15
Biliary complications	150 (13.2)	108 (14.6)	22 (10.4)	14 (9.9)	6 (13.3)	.25
Infection	204 (17.9)	137 (18.5)	38 (18.0)	23 (16.2)	6 (13.3)	.78
Noncompliance [*]	66 (5.8)	42 (7.2)	17(9.7)	6 (5.2)	1 (3.2)	.39

[*]
Noncompliance data available in n = 905 women.

Table 6.

Risk of Graft Failure by Race and Ethnicity and Age

Outcome	HR (95% CI)	P Value	aHR (95% CI)[*]	P Value
Among AA women < 50 vs 50 y				
Chronic rejection	3.83 (1.92–7.65)	<.001	3.84 (1.92–7.66)	<.001
Primary nonfunction	1.25 (0.74–2.09)	.40	1.26 (0.75–2.12)	.38
Recurrent disease, hepatitis	0.76 (0.50–1.15)	.19	0.76 (0.50–1.16)	.21
Recurrent disease, nonhepatitis	1.11 (0.64–1.94)	.71	1.13 (0.65–1.98)	.66
Vascular complications	1.95 (0.72–5.23)	.19	1.95 (0.73–5.25)	.19
Biliary complications	1.49 (0.65–3.45)	.35	1.53 (0.66–3.54)	.32
Infection	1.34 (0.71–2.54)	.37	1.37 (0.72–2.59)	.33
Noncompliance	1.59 (0.61–4.12)	.34	1.61 (0.62–4.18)	.33
Among women < 50, AA vs Caucasian				
Chronic rejection	3.25 (2.05–5.14)	<.001	3.28 (2.07–5.19)	<.001
Primary nonfunction	2.09 (1.33–3.28)	.001	2.13 (1.36–3.33)	.001
Recurrent disease, hepatitis	1.74 (1.18–2.57)	.005	1.74 (1.18–2.57)	.005
Recurrent disease, nonhepatitis	1.32 (0.82–2.10)	.25	1.37 (0.86–2.19)	.19
Vascular complications	1.22 (0.59–2.54)	.59	1.25 (0.60–2.59)	.56
Biliary complications	1.51 (0.77–2.96)	.23	1.60 (0.81–3.14)	.17
Infection	1.94 (1.12–3.35)	.02	1.98 (1.15–3.42)	.01
Noncompliance	1.74 (0.82–3.72)	.15	1.78 (0.84–3.81)	.14
Among women 50, AA vs Caucasian				
Chronic rejection	1.40 (0.74–2.66)	.31	1.40 (0.74–2.67)	.30
Primary nonfunction	1.93 (1.30–2.86)	.001	1.99 (1.34–2.96)	<.001
Recurrent disease, hepatitis	2.66 (2.00–3.54)	<.001	2.73 (2.05–3.63)	<.001
Recurrent disease, nonhepatitis	1.78 (1.18–2.69)	.006	1.85 (1.23–2.79)	.003
Vascular complications	0.89 (0.40–1.95)	.77	0.91 (0.42–2.01)	.82
Biliary complications	1.09 (0.58–2.06)	.78	1.15 (0.61–2.18)	.66

	HR (95% CI)	P Value	aHR (95% CI)*	P Value
Infection	1.58 (0.98–2.57)	.06	1.64 (1.01–2.66)	.05
Noncompliance	3.79 (1.62–8.86)	.002	3.85 (1.64–9.02)	.002
AA vs Hispanic, age < 50 y				
Outcome				
Chronic rejection	2.26 (1.18–4.34)	.01	2.27 (1.19–4.36)	.01
Primary nonfunction	1.66 (0.89–3.07)	.11	1.67 (0.90–3.10)	.10
Recurrent disease, hepatitis	1.46 (0.86–2.48)	.16	1.46 (0.86–2.48)	.16
Recurrent disease, nonhepatitis	1.95 (0.94–4.02)	.07	1.99 (0.96–4.19)	.06
Vascular complications	1.25 (0.47–3.37)	.65	1.27 (0.47–3.40)	.64
Biliary complications	1.35 (0.54–3.34)	.52	1.38 (0.56–3.44)	.49
Infection	1.77 (0.82–3.83)	.15	1.79 (0.83–3.87)	.14
Noncompliance	1.78 (0.60–5.31)	.30	1.80 (0.60–5.38)	.29
AA vs Hispanic, age 50 y				
Outcome				
Chronic rejection	1.42 (0.61–3.27)	.41	1.44 (0.62–3.28)	.41
Primary nonfunction	1.87 (1.09–3.20)	.02	1.99 (1.16–3.42)	.01
Recurrent disease, hepatitis	2.04 (1.39–2.99)	<.001	2.12 (1.44–3.12)	<.001
Recurrent disease, nonhepatitis	2.21 (1.22–3.99)	.01	2.38 (1.31–4.31)	.004
Vascular complications	1.89 (0.60–5.92)	.28	1.99 (0.63–6.28)	.24
Biliary complications	2.48 (0.92–6.71)	.07	2.91 (1.06–7.99)	.04
Infection	2.09 (1.04–4.19)	.04	2.24 (1.11–4.53)	.02
Noncompliance	11.35 (1.42–90.79)	.02	11.62 (1.45–93.06)	.02
AA vs Asian, age <50 y				
Outcome				
Chronic rejection	2.48 (0.76–8.12)	.13	2.51 (0.77–8.23)	.13
Primary nonfunction	1.70 (0.60–4.87)	.32	1.74 (0.61–4.97)	.30
Recurrent disease, hepatitis	8.46 (1.16–61.79)	.04	8.46 (1.16–61.80)	.04
Recurrent disease, nonhepatitis	1.38 (0.48–4.02)	.55	1.45 (0.51–4.26)	.48
Vascular complications	1.13 (0.24–5.22)	.88	1.15 (0.25–5.30)	.86
Biliary complications	1.37 (0.30–6.17)	.68	1.44 (0.32–6.49)	.64
Infection	2.25 (0.52–9.70)	.28	2.29 (0.53–9.89)	.27

	HR (95% CI)	*P* Value	aHR (95% CI)*	*P* Value
Noncompliance†	-	-	-	-
AA vs Asian, age 50 y				
Outcome				
Chronic rejection	1.31 (0.45–3.77)	.62	1.31 (0.46–3.78)	.62
Primary nonfunction	2.51 (1.11–5.71)	.03	2.60 (1.15–5.91)	.02
Recurrent disease, hepatitis	2.84 (1.56–5.15)	<.001	2.92 (1.61–5.30)	<.001
Recurrent disease, nonhepatitis	1.82 (0.86–3.86)	.12	1.89 (0.89–4.01)	.10
Vascular complications	1.90 (0.40–9.17)	.42	1.96 (0.41–9.46)	.40
Biliary complications	1.51 (0.48–4.74)	.48	1.60 (0.51–5.02)	.42
Infection	2.71 (0.95–8.11)	.06	2.87 (0.98–8.41)	.05
Noncompliance	4.62 (0.58–36.91)	.15	4.70 (0.59–37.65)	.14

Abbreviations: aHR, adjusted hazard ratio; AA, African American; CI, confidence interval; HR, hazard ratio.

*Adjusted for donor risk index.

†Limited events in Asian women.