The impact of donor and recipient race on survival after hepatitis C-related liver transplantation

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Abstract

Background—Both donor and recipient race impact outcomes after liver transplantation (LT), especially for hepatitis C virus (HCV). The interaction and simultaneous impact of both on patient survival is not clearly defined. The purpose of this study was to examine the impact of donor and recipient race on recipient and graft survival after HCV-related LT using the United Network for Organ Sharing (UNOS) database.

Methods—16,053 recipients (75.5% white, 9.3% black, and 15.2% Hispanic) who underwent primary LT for HCV between 1998–2008 were included. Cox regression models were used to assess the association between recipient/donor race and patient survival.

Results—A significant interaction between donor and recipient race was noted (p=0.01). Black recipients with white donors had a higher risk of patient mortality (adjusted HR 1.66; 95% CI: 1.47–1.87) compared to that of white recipients with white donors. In contrast, the pairing of Hispanic recipients with black donors was associated with a lower risk of recipient mortality compared to that of white recipients with white donors (adjusted HR 0.64 (95% CI: 0.46–0.87). Similar results were noted for graft failure.

Conclusion—In conclusion, the impact of donor and recipient race on patient survival varies substantially by the matching of recipient/donor race.
Keywords

Hepatitis C virus (HCV); liver transplantation; race; survival

Introduction

Hepatitis C virus (HCV) is the main indication for liver transplantation in the United States (1, 2). However, patients transplanted for HCV have lower patient and graft survival compared to patients undergoing liver transplantation for other indications (3–6). Among those with HCV, the severity of disease progression and mortality after transplantation is highly variable (7–14).

Previous studies have illustrated racial disparities for patient and graft survival after liver transplantation (4, 15–19). Recently, Ananthakrishnan et al. showed using the United Network for Organ Sharing (UNOS) database that black recipients had decreased patient survival while Hispanics had higher survival rates compared to white recipients two years after transplant (15). In this study, the negative impact of black race on survival was most pronounced for those transplanted for HCV. Velidedeoglu et al similarly found recipient race to be important in HCV positive recipients, but not in HCV-negative recipients (4). A more recent study also utilizing the UNOS data examined the effects of race on outcomes among persons undergoing liver transplantation for HCV. In this study by Pang et al., black recipients of livers from black donors experienced graft failure rates similar to those of white recipients (20). However, black recipients who received livers from white donors had significantly lower graft survival rates compared to black recipients of livers from black donors. Conclusions of other studies regarding the effect of donor race on outcomes after liver transplantation have been inconsistent (17, 21–23), but these studies have not uniformly considered donor-recipient race matching or indication for liver transplantation.

Identifying risk factors impacting mortality in patients transplanted for HCV is an important step to improving outcomes. While both recipient and donor race have been associated with worse liver transplant outcomes, a careful analysis assessing the interaction and simultaneous impact of both, specifically for HCV, has not been completed. Therefore, the purpose of this study was to use nationwide transplant data to assess the impact of different pairings of donor and recipient race on recipient survival after transplantation for HCV.

Results

Study Population

There were 16,053 recipients in the final analytic cohort, which included 12,118 white recipients (75.5%), 1,489 black recipients (9.3%) and 2,446 Hispanic recipients (15.2%). In general, black recipients (BR) had less favorable clinical parameters than the other two groups; they were, for example, older than white (WR) and Hispanic recipients (HR) (53.2±6.9 BR, 52.0 ± 7.1 WR, 52.0±7.9 HR; p<0.002), had lower mean albumin levels (2.7±0.7BR, 2.9±0.7 WR, 2.8±0.7HR; p<0.002) higher INR (1.9±1.1 BR, 1.7±1.1 WR, 1.8±1.1 HR; p<0.001) and creatinine levels (1.8±1.8 BR, 1.3±1.1WR, 1.4±1.3HR; p<0.001). Black and Hispanic recipients were more often female (30.4% and 28.9%) compared to white recipients (22.7%). Additionally, white recipients had lower mean MELD scores (18.7±8.5) compared to BR and HR’s (20.4±8.7 and 20.6±9.5; p<0.001). Importantly, however, there were no significant differences between the three race groups with regards to organ sharing region, DCD donor rates, mean cold ischemia time, donor age or donor BMI. Detailed descriptive statistics can be found in supplemental table 1.
Predictors of Patient Survival

The Kaplan-Meier curves for patient survival by recipient race are displayed in Figure 1a with the univariable Cox regression proportional hazard ratios (HRs) displayed in Table 1. Blacks had a significantly higher risk of death, with a HR of 1.56 (1.44–1.71; p<0.001) compared to whites. There was also a trend for better survival among Hispanics compared to whites with a HR of 0.92 (0.84–1.01; p=0.07). When considering donor race alone, without regard to recipient/donor race matching, recipients who received a liver from a Hispanic donor had slightly increased mortality (HR: 1.11, p=0.03). There was no significant difference with regards to the impact of black and white donors on recipient survival when matching of recipient/donor race was not taken into account.

However, a significant interaction between donor and recipient race was observed (p=0.01) (table 1), which illustrated that the impact of donor race on patient survival varied by the race of the recipient. Because of this significant interaction, a categorical variable with a group for each recipient/donor race combination was created to better examine the impact of donor and recipient race on survival. The univariable Cox regression HRs for each recipient/donor race combination are displayed in Table 1. Compared to the white recipient/white donor group, white recipients with livers from Hispanic donors (HR: 1.20, 95% CI: 1.07–1.34, p=0.002), and black recipients with livers from white (HR: 1.76, 95% CI: 1.57–1.96, p<0.001) or Hispanic donors (HR: 1.51, 95% CI: 1.13–2.01, p=0.005) had a higher risk of death. Black recipients with black donors had similar survival compared to the white recipients/white donor group. Additionally, Hispanic recipients of livers from black donors appeared to have better outcomes compared to the reference group (HR: 0.71, 95% CI: 0.53–0.95, p=0.02). Kaplan-Meier curves for patient survival by recipient/donor race matching are displayed in Figure 1b.

Figure 2 provides the 1, 2, and 5 year cumulative survival rates by donor and recipient race, with the number of study subjects entering each time interval displayed. Black recipients who had white or Hispanic donors had the lowest survival rates compared to all other recipient/donor race combination groups after transplantation. The black recipient/white donor and black recipient/Hispanic donor groups were the only two to have 2 year cumulative survival rates below 80% and five year survival rates below 60%.

Multivariable Model

The adjusted multivariable HRs for death according to recipient/donor combination are displayed in Table 2. After adjusting for all other potentially confounding variables, black recipients with livers from white donors had the highest risk of death, with a controlled HR of 1.66 (1.47–1.87; p<0.001) compared to white recipients with livers from white donors. In this analysis, the HR for black recipients of Hispanic donor livers was no longer significantly increased. However, other recipient/donor race groups also showed significantly different outcomes compared to the white recipient/white donor group. Consistent with the univariable analysis, there was a higher risk of death among white recipients of livers from Hispanic donors (HR=1.19 [1.05–1.34; p=0.007]) and Hispanic recipients with black donors had improved survival (HR=0.64 [0.46–0.87; p=0.005]).

To assess the impact of missing database values on our results, a missing value analysis and fully conditional specification method was used with five imputations. The results of the final model did not change significantly. For example, the HR for death for black recipients of livers from white donors was 1.61 (1.44–1.9; p<0.001) in the analysis using imputed values.
Causes of death and graft failure

Cause of death and cause of graft failure were analyzed by recipient/donor race combinations. Graft failure was listed as the cause of death in 22.8% of the study population and the rate was not significantly different by recipient/donor race combination. When comparing only black recipients, graft failure as the cause of death was 23.6%, 17.2% and 29.2% for black recipients of white, black, and Hispanic donors, respectively (p=0.2). Of the 5,220 patients in the study population with graft failure, only 2,435 (46.6%) patients had information recorded regarding cause of graft failure. For subjects where this information was available, the overall rate of HCV recurrence listed as the cause of graft failure was 43.4%. For blacks with white donors and blacks with Hispanic donors, the rate was 51.0% and 48.4%, respectively. For blacks with black donors, HCV recurrence was the cause of graft failure in 30.3% (Figure 3, p=0.01).

Discussion

In this study, the association of recipient/donor race matching and mortality was examined for HCV-related liver transplantation. Several important findings were observed. First, while black recipients appear to have higher mortality after liver transplantation for HCV, this is largely limited to black recipients who receive a liver from a white donor. The lowest cumulative survival rates were consistently observed in this group of patients, with 1, 2 and 5 year survival rates of 86%, 74%, and 56%. By contrast, black recipients of livers from black donors had 1, 2 and 5 year survival rates of 90%, 82% and 70%, rates which are not significantly different from white recipients with white donors (91%, 85% and 72%, respectively). While it appears that black recipients of livers from Hispanic donors may also have decreased survival rates after transplantation for HCV, this finding needs to be confirmed in larger studies given the small number in this group.

The second important observation is that the interaction between donor and recipient race and its impact on patient survival is not limited to black recipients. White recipients with Hispanic donors had a 19% increase in mortality compared to white recipients with white donors, even after adjustment for other differences in multivariable analysis. However, receipt of a liver from a black donor did not impact the outcome of white recipients. Finally, for Hispanic recipients, the best outcomes occurred in the subset of patients who received livers from black donors. Thus, all races studied were impacted in some way by recipient/donor race mismatching of organs.

The third observation is that, overall, Hispanics had a lower risk of death compared to white and black recipients. This was most pronounced in the subset of patients who received a liver from a black donor, with an adjusted HR of 0.64 (p=0.005) compared to the white recipient/white donor group.

These results extend the knowledge gained from prior studies. Several earlier studies have shown black recipients to have lower survival after liver transplantation (4,15–21), especially when transplanted for HCV (4, 15). This was observed in our study as well. However, in this study, we found that the lower survival among blacks was limited to those who received a liver from a white recipient. Similar results have been observed by Pang et al. who demonstrated that HCV-infected blacks transplanted with livers from white donors had lower graft survival (20). Interestingly, in their study, this result did not occur in patients transplanted for indications other than HCV. In addition, the white recipient/black donor combination led to worse outcomes, compared to whites with white donors (20). This result was not seen in our study, a finding that may be attributed to the different outcomes measured (patient survival in our study vs graft survival in the study by Pang et al.), or differences in study populations. The findings from these two studies emphasize the need to
consider both donor and recipient race when assessing mortality rates in those transplanted for HCV.

Past studies examining the impact of donor race have provided mixed results. Feng et al., in creating a donor risk index, found black donor race to be associated with worse outcomes (22). In a more recent study by Asrani et al., they did not find an association between black recipient race and liver graft failure after controlling for numerous variables, including transplant center (21). However, when analyses were stratified by recipient race, they did observe that black recipients of organs from white donors had an increased risk of graft failure. Comparing the results from these two studies to the present one is difficult for several reasons. First, the studies by Feng and Asrani included patients who had undergone liver transplantation for all indications (21,22). Prior studies have shown that the impact of recipient and donor race appears to be enhanced for HCV-related transplantation (4, 15).

Further, the study by Feng et al. did not appear to account for the interaction between donor and recipient race (20). While the study by Asrani et al. did assess for such an interaction, they did not include Hispanics, and they addressed the interaction by stratifying by recipient race (21). This allowed a comparison between groups of the same recipient race but HRs comparing to other race groups could not be calculated.

There are well-documented differences between race groups in the natural history of HCV, such as a lower rate of spontaneous clearance of virus and a slower progression of HCV-related liver disease in blacks in the non-transplant setting (24–26). Combined with the well-known differences in HCV treatment response rates between race groups (27–30), it is reasonable to hypothesize that differences in mortality may be secondary to differences in HCV pathogenesis post-transplantation. In this study, we did find that among blacks, those with black donors had the lowest reported rates of HCV recurrence. Pang et al. also found a higher rate of graft failure due to HCV recurrence for black recipients, but did not stratify by donor race (20). Comparing graft failure etiologies based on UNOS data is problematic, however, as these data are often missing, standard criteria for determining the cause of graft failure are lacking, and biopsy confirmation of a diagnosis is not required. Further investigations on the differences in HCV recurrence according to recipient/donor race matching after liver transplantation are necessary to address this question.

While this study provides important findings, it is imperative to highlight its limitations. The UNOS database is a rich resource as it captures all transplants performed in the United States. However, as with any large database, it is limited in the information that it collects. As with many retrospective studies, detailed information regarding immunosuppression, treatment of HCV recurrence and rejection, and compliance to medical treatments is lacking. In addition, not all variables in the database are collected for all patients, and racial data are self-reported. Finally, there is no accompanying tissue repository to confirm outcomes or allow additional investigations. However, findings on survival from large retrospective databases often are the first to identify important observational findings that then can be confirmed with further investigation.

It might appear reasonable on the basis of the present study to recommend a change in donor matching policy to put liver allograft's from black donors into black recipients. However, we believe that a more comprehensive discussion is needed about access to and outcome after liver transplantation in African Americans in the US. A policy change to link black donors with black recipients could have the unintended consequence of restricting black patients access to liver transplantation, at a time when black patients are disadvantaged already in access to this therapy. Moreover, a broader global discussion is needed about donor-recipient matching, since it is clear, from this and other studies that the prognosis of the donor organ and recipient can be assessed with apriori knowledge of the donor and recipient

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race as well as other variables. However, instituting a policy to maximize the outcome after transplantation ('utility of transplantation') rather than giving priority to the sickest patient on the waiting list ('urgency') would be a radical change from present practices, and in conflict with the law governing transplantation, also known as 'the final rule'.

In conclusion, this study highlights that for HCV-related liver transplantation, the effect of recipient race varies according to the race of the donor, especially for black recipients. Future studies that assess mortality risk need to account for this interaction. Additionally, the mechanisms for the present observations need to be understood, both for their equity implications for patients of different races, as well because it may reveal important information about graft acceptance and success. Unfortunately, the donor pool for liver transplantations is limited, even more so if attempts are made to match donor and recipient races, particularly with respect to black recipients. There must be enhanced public awareness of the need for organ donation.

Methods
Study population
The analytic cohort was assembled using the UNOS database using a Standard Transplant Analysis and Research (STAR) file for all liver transplants performed in the United States from January 1, 1998 to Dec 31, 2008. Only donors and recipients with ethnicity defined as white, black/African American, or Hispanic/Latino, and non-status 1 adults (age 18 and over at the time of transplant) transplanted for HCV were included. Patients were included if HCV was listed in the dataset as a primary diagnosis / reason for transplant, and they were documented to be HCV sero-positive prior to transplant. Patients were excluded if they had undergone a prior liver transplant, or if they died within the first thirty days after transplantation.

Variables
The primary independent variables of interest were recipient and donor race, defined as white, black or hispanic. Recipient and donor demographic data included age at transplant, gender, body mass index (BMI), weight, height, and the presence of pre-transplant diabetes mellitus (DM). Insurance status of the recipient was recorded as either private or public/other. Recipient laboratory data at the time of transplant included: albumin, INR, creatinine, total bilirubin, serum glutamic pyruvic transaminase (SGPT), cytomegalovirus (CMV) serostatus, and calculated Model for End-Stage Liver Disease (MELD) score. The presence of hepatitis B virus (HBV) infection (defined as HBV surface antigen positivity) and / or hepatocellular carcinoma (HCC) in the recipient was also included in this analysis. Donor laboratory values for creatinine, SGPT, serum glutamic oxaloacetic transaminase (SGOT), total bilirubin and CMV serostatus were collected. The severity of illness of the recipient prior to transplant was further assessed by recording the need for hemodialysis in the week prior to transplant, life support and/or hospitalization at the time of transplantation and prior upper abdominal surgeries prior. Transplant-related variables examined included: cold ischemia time, donor cause of death (cerebrovascular accident (CVA) vs anoxia/other vs trauma), donation after cardiac death, use of deceased vs living donor organ, split vs whole liver allograft, share region for transplantation, time on wait list, year of transplantation, and length of stay after transplantation. Transplant region was also ascertained and included in analyses.

Outcomes
The primary outcome of interest was patient recipient death. Secondary outcomes of interest included cause of patient death and graft failure, and need for re-transplantation.
Statistical Analysis

Data were assessed for normalcy and erroneous data entry. To compare continuous variables across the three recipient race groups, ANOVA with Bonferroni correction for multiple comparisons was used. Categorical variables were compared using Chi-square tests. Kaplan-Meier curves were constructed to determine cumulative probabilities of survival. For the primary outcome of patient recipient death, Cox proportional hazards analyses were used to examine the association of race/ethnicity and other factors with this outcome. Potential violations of proportional hazards were assessed. Time to recipient death was calculated from date of transplant to death date. Patients lost to follow-up, re-transplanted, or alive at last data entry point were right censored at that time point. Univariable analyses were completed to assess for the association of both recipient and donor race, with the white donors and recipients serving as the reference category. Statistical interaction between donor and recipient race was assessed by incorporating an interaction term (donor race × recipient race) into the unadjusted model for patient survival. Due to its significance, a categorical variable with nine groups was created to account for all possible recipient/donor race combinations among Whites, Blacks, and Hispanics. For adjusted Cox analyses, the categorical recipient/donor variable and all other covariates that achieved significance at the 0.10 level in univariate models were considered. Multivariable models also included stratification by transplant region. Multivariable models were run excluding cases with missing data. To assess for the impact of missing values on the results, a fully conditional specification method with five imputations was used to replace missing values.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

HCV  Hepatitis C Virus
HBV  Hepatitis B Virus
HBsAg  Hepatitis B Surface Antigen
HCC  Hepatocellular Carcinoma
LT  Liver Transplantation
US  United States
ESLD  End Stage Liver Disease
BMI  Body Mass Index
HR  Hazard Ratio

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Figure 1a.
Patient survival by recipient race:
Figure 1b.
Patient survival by recipient and donor race
Figure 2.
Cumulative 1, 2 and 5 year survival by recipient / donor race
Figure 3.
Cause of death and graft failure in black recipients
### Table 1

Univariable Cox regression analysis: impact of race on death

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
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<tr>
<td><strong>Recipient Race</strong></td>
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<tr>
<td>Blacks vs white</td>
<td>1.56</td>
<td>1.41–1.71</td>
<td>&lt;0.001</td>
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<tr>
<td>Hispanics vs white</td>
<td>0.92</td>
<td>0.84–1.01</td>
<td>0.07</td>
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<tr>
<td><strong>Donor Race</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Black vs white</td>
<td>0.94</td>
<td>0.85–1.03</td>
<td>0.17</td>
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<tr>
<td>Hispanic vs white</td>
<td>1.11</td>
<td>1.01–1.21</td>
<td>0.03</td>
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<td>0.53–0.95</td>
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<td>Hispanic rec/Hispanic donor (N=633)</td>
<td>1.01</td>
<td>0.86–1.19</td>
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Table 2

Multivariable Cox regression: adjusted HRs for recipient / donor combination death**

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<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
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<td>Recipient/donor race combination (reference group: white recipient/white donor)</td>
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<td>Hispanic rec/white donor</td>
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<td>0.76–1.11</td>
<td>0.36</td>
</tr>
</tbody>
</table>

** Controlled for: Recipient: age, gender, height, diabetes, creatinine, albumin, total bilirubin, HCC, HBV, length of stay post-transplant, renal transplantation, prior abdominal surgery; location at time of transplantation; Donor: age, gender, height, diabetes, BMI, causes of death; CMV status, DCD status, sharing region, and stratified by transplant region.