Donor Factors Including Donor Risk Index Predict Fibrosis Progression, Allograft Loss, and Patient Survival following Liver Transplantation for Hepatitis C Virus

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Background: **The utilization of liver transplantation (LT) is limited by the availability of suitable organs. This study aimed to assess the impact of the donor risk index (DRI) and other donor characteristics on fibrosis progression, graft, and patient survival in hepatitis C virus (HCV)-infected LT recipients.** ***Methods:*** **HCV-infected LT recipients who had at least 2 post-LT protocol liver biopsy specimens available were included. Hazard ratio for bivariate analysis was computed using Cox proportional hazard regression analysis.** ***Results:*** **Of 312 recipients, 26.6% died over a median follow-up of 58.5 months (95% CI: 46.5–67.3). Fourteen patients underwent re-transplantation. Mean time to graft failure was 84.3 months, median follow-up: 59 months, 95% CI (48.2, 68.3). DRI >1.5 was significantly associated with patient and graft survival ($P = 0.04$). Of the subset of 104 individuals who underwent histological analysis, 67.3% progressed to ≥F2. On multivariate analysis, significant donor-specific predictors of fibrosis progression were: donor age >50 years and DRI >1.7.** ***Conclusions:*** **(1) Fibrosis progression in HCV-infected LT recipients is strongly associated with donor characteristics, specifically donor age and DRI. (2) DRI, an objective measure of donor quality, appears to correlate both with rate of histological progression and overall patient/graft survival. (J Clin Exp Hepatol 2016;6:109–114)**

Liver transplantation (LT) is widely accepted as a life-saving therapy in advanced cirrhosis. However, inadequate availability of deceased donor livers has led to a significant shortage of suitable organs for transplantation. This disparity between organ availability and demand contributes significantly to waitlist mortality and has thereby led to increased utilization of marginal or extended criteria donor allografts. The donor risk index (DRI) predicts the likelihood of allograft loss by incorporating donor factors that have been associated with decreased graft survival.[1]

Chronic infection with hepatitis C virus (HCV) is the most common indication for LT in the US, and patients who are transplanted with active HCV infection invariably develop recurrent HCV in the allograft.[2] Recurrent HCV and other associated factors lead to compromised patient and graft survival compared to patients transplanted for other indications.[3,4] The contribution of donor factors to post-LT fibrosis progression in HCV patients remains to be fully elucidated. We therefore conducted this study to assess the impact of DRI and other donor characteristics on fibrosis progression, graft and patient survival in a cohort of HCV-infected LT recipients.

PATIENTS AND METHODS

Study Population and Clinical Variables

Adults who had undergone LT at our center between 1998 and 2013 for HCV were included in this study. Patients were excluded for concomitant human immunodeficiency virus (HIV) or hepatitis B virus (HBV) infections, post-LT follow-up less than 4 months, prior LT, or undetectable HCV RNA post-LT. Institutional Review Board approval was obtained. Data sources included a prospectively maintained center-specific organ transplant tracking record (OTTR™), electronic and paper medical records, as well as the United Network for Organ Sharing (UNOS)/Organ

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Abbreviations: AA: African-American; CDA: corrected donor age; CI: confidence interval; CIT: cold ischemic time; DCD: donation after cardiac death; DM: diabetes mellitus; DRI: donor risk index; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HL: hyperlipidemia; HTN: hypertension; LBx: liver biopsy; LT: liver transplantation; MMF: mycophenolate mofetil; OPTN: Organ Procurement and Transplantation Network; OTTR: organ transplant tracking record; REDCap: Research Database Capture; TAC: tacrolimus; UNOS: United Network for Organ Sharing
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Procurement and Transplantation Network (OPTN) database.

All eligible patients were included in survival analysis. Those who had at least two post-LT protocol liver biopsy (LBx) specimens available were considered for histological analysis. Biopsy samples were reviewed by a single pathologist for presence of rejection using the Banff scoring system.[5] Fibrosis stage and inflammatory grade were determined by utilizing the METAVIR scoring system.[6] For this study, significant fibrosis was defined as a METAVIR stage F2 or greater (range F0–F4) and progression of fibrosis was defined as development of ≥F2 fibrosis on subsequent biopsies if the baseline biopsy showed F0 or F1 fibrosis. Data were abstracted and entered into a prospectively maintained web-based database (Research Database Capture (REDCap) electronic data capture tools hosted at Georgetown University).

Donor variables were obtained from UNOS/OPTN data sources and DRI was calculated based on previously published formulae.[1] Extended criteria donors (by kidney criteria) were designated as per standard UNOS/OPTN criteria.[7] The presence of recipient diabetes mellitus (DM), hypertension (HTN), and hyperlipidemia (HL) were determined by retrospective chart reviews. These were deemed present prior to LT if chart documentation of the conditions themselves or medications used to treat these conditions existed prior to LT. These conditions were denoted to have developed following LT if review of the clinic visit at 4 months post-LT (±2 weeks) provided similar documentation that was new compared to pre-LT records. Immunosuppression information was compiled from chart reviews. Standard immunosuppression regimens at our center consist of tacrolimus (TAC), mycophenolate mofetil (MMF), and prednisone. TAC target levels were 8–12 ng/dL in the first 3 months, and 6–8 ng/dL thereafter. MMF doses were gradually tapered and stopped by 6 months post-LT. Prednisone was tapered and stopped by 3 months post-LT. Sirolimus was used in patients who were at risk of renal dysfunction, and cyclosporine in combination with MMF in patients intolerant of TAC.

Clinical outcomes included the following: (1) mortality—defined as the occurrence of death during follow-up; (2) graft failure—defined as the occurrence of death or re-transplantation; and (3) histological progression—defined as the progression of fibrosis from F0/F1 to ≥F2 fibrosis on subsequent LBx.

Statistical Analysis

Categorical variables were analyzed using the chi-square or Fisher's exact test. Continuous variables were compared with the Wilcoxon rank-sum test. Hazard ratio for bivariate analysis was computed using Cox proportional hazard regression analysis.

RESULTS

Recipient Characteristics

A total of 312 LT recipients were included in the overall analysis: 73% male, 32% African American (AA), and with a median age of 55 years (range 28–75 years). Forty percent had pre-LT HTN, 22% DM, and 4% had HL. At 4 months following LT, 77% were noted to have HTN, 46% DM, and 9% HL. Median recipient height was 170.8 ± 16.2 cm, weight pre-LT was 89.9 ± 35.1 kg, and post-LT weight was 80.3 ± 17.4 kg (Table 1).

Donor Characteristics

60% of donors were male and 35% were AA. Stroke was the main cause of death (46%). Forty percent of donors were age 50 or greater, with 22.7% aged over 60. Six percent met donation after cardiac death (DCD) criteria, and 33.8% met expanded donor criteria. The mean DRI (±SD) was 1.6 ± 0.4. Mean height was 170.9 ± 11.0 cm, mean donor age was 43.6 ± 18.4 years, and mean cold ischemic time (CIT) in hours was 6.3 ± 3.2. These results are summarized in Table 1.

Predictors of Fibrosis Progression

118 patients had a total of 417 liver biopsies performed (range per patient: 2–8). Fourteen patients had ≥F2 fibrosis on the index biopsy and were not analyzed further. The remaining 104 patients who underwent 385 total biopsies were utilized for fibrosis progression analyses. Of these, 70 patients (67.3%) showed progression of fibrosis, with a median time of progression from LT of 31.3 months (median follow-up 81.5 months). On bivariate analysis, donor age >50, DRI >1.7, donor meeting either DCD or expanded donor criteria, and race mismatch (white donor-African American recipient) were significantly associated with fibrosis progression (Table 2; Figure 1). On multivariate Cox proportional hazard regression analysis, donor age >50 and DRI >1.7 correlated with fibrosis progression. In addition, recipient age >55 years and recipient race (non-white) were associated with increased fibrosis progression. While not clinically significant, there was a trend towards DCD donors hastening the progression of fibrosis post-LT ($P = 0.06$) (Table 2). All multivariate models were adjusted for age, gender, and race of recipient (if significant in bivariate model).

Survival Analysis

Graft Survival

96 individuals (30.7%) had graft failure, with 14 total re-transplants. Mean time to graft failure was 84.3 months. The following donor factors were associated with graft failure on bivariate analysis: female gender, age >60, and DRI as a continuous variable. On multivariate analysis, DRI >1.5 was significantly associated with graft failure (Table 2).