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 $\geq F2$. 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.

Keywords: Hepatitis C, liver transplantation, donor risk index

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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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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 (OTTRTM), electronic and paper medical records, as well as the United Network for Organ Sharing (UNOS)/Organ

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 $\geq$ 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 ($\pm$ 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 retransplantation; and (3) histological progression—defined as the progression of fibrosis from F0/F1 to $\geq$ 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 ($\pm$ 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 $\geq$ 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 retransplants. 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).

Table 1 Selected Descriptive Characteristics of the Study Cohort (n = 312).

	Percent
Donor characteristic	
Male (%)	60
Race (%)	
African American	35.3
White	51.6
Other	13.1
Cause of death (%)	
Trauma	29.8
Stroke	45.9
Anoxia	20.3
Other	3.9
Age (years)	
<50	60.3
50–59	17
60–69	15
>70	7.7
Partial/split (%)	3.2
DCD criteria (%)	6.15
Expanded donor criteria (%)	33.8
Liver share (%)	
Local	88.3
Regional	7.8
National	3.9
Recipient characteristic	
Age (years)	
25–54 (%)	42.0
55 + (%)	58.0
Male (%)	73
Race (%)	
African American	32.4
White	44.6
Other	23.0
Smoking (%)	
Current	13.6
Former	51.0
None	35.4
Alcohol (%)	
Current	12.8
Former	61.7
None	25.5
Pre LT HTN	40.3
Pre LT DM	22.1
Pre LT HL	4.2
Post LT DM	45.5
Post LT HL	9.2
Post LT HTN	76.6

Table 1 (Continued)

	Percent
Donor-recipient race^a	
D-R: AA-AA	14.1
D-R: W-AA	13.1
D-R: AA-W	15.7
D-R: W-W	25
Donor-recipient gender	
D-R: F-F	12.2
D-R: M-F	15.0
D-R: F-M	27.6
D-R: M-M	45.2

LT, liver transplantation; DM, diabetes mellitus; HTN, hypertension; HL, hyperlipidemia; R, recipient; D, donor; AA, African American; W, white; O, other (race).

^aAll combinations not represented.

Patient Survival

83 individuals (26.6%) died over a median follow-up of 58.5 months (95% CI: 46.5–67.3), with a mean survival of 110.4 months.

On bivariate analysis, factors associated with death were DRI >1.5, female donor to female recipient pairing, and national share. Recipient characteristics associated with death were age >55 and former alcohol use. On multivariate analysis, DRI >1.5 was the only donor factor significantly associated with death (Table 2 and Figure 2). No significant association was noted between fibrosis progression and liver-related death ($P = 0.6$). The recipient characteristics associated with death were former alcohol use and gender match (female donor to female recipient pairing).

DISCUSSION

Our single center cohort study of HCV-infected recipients demonstrates the importance of donor characteristics, not only on patient and graft survival, but also on histological progression of recurrent HCV. While it is well-recognized that advanced donor age and high DRI impact graft outcomes, ours is the first systematic analysis of donor variables on histological progression.

Importantly, we found that fibrosis progression was hastened by even modest increments of donor age with a threshold donor age of 50 conferring a 3-fold risk of accelerated fibrosis. Other donor factors such as DCD also led to more rapid fibrosis. Interestingly, AA or non-white recipients appeared to have. A recent analysis of the UNOS database demonstrated that AA recipients with HCV were more likely to suffer graft loss from a non-AA donor, with an interaction noted between donor age and donor race. AA donor-recipient matched pairs appeared to attenuate

Table 2 Predictors of Fibrosis Progression/Patient and Graft Loss.

Outcome variable	Bivariate analysis			Multivariate analysis		
	Predictor	HR	P value	Predictor	HR	P value
Fibrosis progression (n = 104)	Donor age ^a			Donor age ^a		
	>50	3.6	0.01	50–59	3.8	0.04
	>60	4.0	0.01	>60	5.4	0.04
	>70	9.0	0.001			
	DCD criteria	3.03	0.03	DCD criteria	2.8	0.06
	Expanded donor	1.65	0.05			
Graft failure (n = 312)	DRI >1.7	1.88	0.03	DRI >1.7	1.76	0.02
	Race mismatch D-R: W-AA	2.2	0.02	Recipient race (non-white)	1.7	0.04
	Donor age >60	2.5	0.01			
	DRI ^b	1.68	0.04	DRI >1.5	1.5	0.05
	Female donor D-R: F-F	2.1	0.0091			
	D-R: F-M	1.6	0.04			
Patient death (n = 312)	DRI >1.5	1.6	0.04	DRI >1.5	1.6	0.04
	National share	3.8	0.04			
	Gender match D-R: F-F	2.2	0.01			
	Recipient past alcohol use					

DCD: deceased donor criteria; R: recipient; D: donor; AA: African American; W: white; M: male; F: female; DRI: donor risk index.

^aReference age group 0–19 years.

^bContinuous variable.

the negative effect of increasing donor age on graft survival.⁸ The reasons behind such an interaction remain speculative and considerations include racial differences in immune response to hepatitis C. We did not demonstrate any relationship between race and graft loss, perhaps due to limited sample size, but could hypothesize that the fibrosis progression noted in a single center study such as ours when generalizable to a larger population may manifest as graft loss.

We also found that when both the donor and recipient were female, there was a greater likelihood of graft loss and death. While female-male discordance in LT has been shown to be associated with increased risk of graft loss

in one UNOS database analysis,⁹ other results have been contradictory.^{1,10,11} It is possible that female donor status is a surrogate for an as yet unidentified variable that influences graft survival. A recently published analysis sought to define the corrected donor age (CDA) for HCV-infected LT recipients. Graft failure was noted to be independently predicted by several of the same factors, namely DCD, donor-race recipient combinations (especially non AA donor and AA recipient) and female donor, identified in our study.¹²

A significant disparity continues to exist between the number of available donor livers and the number of patients in need of transplant nationwide.¹³ This

Figure 1 Fibrosis progression by donor risk index (DRI). **Figure 2** Patient survival by donor risk index (DRI).

discrepancy between donor liver supply and demand is exaggerated in certain geographic regions, prompting increased utilization of extended criteria donor livers, even in patients with more advanced liver disease at the time of transplant.¹⁴

Weighing the risk of suboptimal donor livers versus the risk of longer wait time and associated waitlist mortality is even more difficult in patients with HCV. Active HCV infection at the time of transplant recurs in all recipients, and the progression of fibrosis in post-transplant HCV occurs rapidly, with approximately one-third of patients developing cirrhosis within 5 years.^{3,15}

In order to make informed decisions regarding organ selection for listed patients with HCV, transplant professionals need to fully understand both the donor and recipient characteristics that contribute to post-LT fibrosis progression and eventual graft loss/patient mortality. Prior studies have indicated that advanced donor age contributes to impaired outcomes in patients transplanted for HCV.^{16–19} However, conflicting data exist regarding the impact of recipient age on post-LT outcome for HCV.^{20,21} In our series, we could find no relationship between recipient factors and outcomes.

It is important to note that new and potent combinations of direct-acting antiviral (DAA) agents have shown promise in terms of significantly increasing HCV eradication rates post-LT above what was traditionally observed with pegylated interferon, ribavirin, and first-generation protease inhibitors.^{22,23} However, these studies also demonstrate that HCV is more difficult to clear post-LT once advanced fibrosis and cirrhosis have developed, and re-transplant outcomes for recurrent HCV remain poor.²⁴

Our study has limitations inherent to a single center such as relatively small sample size and center specific histological interpretation. However, the availability of serial histologic data and the granularity of clinical data allow us to draw conclusions about donor and recipient interactions that would not be possible from a large database analysis.

In conclusion, we observe that higher DRI predicts fibrosis progression, allograft, and patient loss in LT patients with HCV infection. Furthermore, advanced donor age was predictive of fibrosis progression and graft survival. Taken together, these findings affirm and expound on a growing body of literature which demonstrate aggressive recurrence of HCV in suboptimal donor livers, especially those of advanced age.

AUTHOR CONTRIBUTIONS

Arun Jesudian: data analysis, draft article, critical revisions.

Sameer Desale: statistical analysis, data analysis.

Jonathan Julia, Elizabeth Landry, Christopher Maxwell: data gathering, abstraction and entry; draft article.

Bhaskar Kallakury: pathologic review, data analysis.

Jacqueline Laurin and Kirti Shetty: data analysis, critical revisions, approval and concept design.

CONFLICTS OF INTEREST

The authors have none to declare.

REFERENCES

- Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant.* 2006;6(4):783–790.
- Shiffman ML, Stravitz RT, Contos MJ, et al. Histologic recurrence of chronic hepatitis C virus in patients after living donor and deceased donor liver transplantation. *Liver Transpl.* 2004;10:1248–1255.
- Gane E. The natural history and outcome of liver transplantation in hepatitis C-virus infected recipients. *Liver Transpl.* 2003;9: S28–S34.
- Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology.* 2002;122:889–896.
- Anonymous. Banff schema for grading liver allograft rejection: an international consensus document. *Hepatology.* 1997;24:658–663.
- Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology.* 1996;24:289–293.
- Metzger RA, Delmonico FL, Feng S, et al. Expanded criteria donors for kidney transplantation. *Am J Transplant.* 2003;3(suppl 4):114–125.
- Shore NJ, Dodge JL, Feng S, Terrault NA. Donor risk index for African American liver transplant recipients with hepatitis C virus. *Hepatology.* 2013;58:1263–1269.
- Rustgi VK, Marino G, Halpern MT, et al. Role of gender and race mismatch and graft failure in patients undergoing liver transplantation. *Liver Transpl.* 2002;8:514–518.
- Lai JC, Feng S, Roberts JP, Terrault NA. Gender differences in liver donor quality are predictive of graft loss. *Am J Transplant.* 2011;11: 296–302.
- Zeier M, Dohler B, Opelz G, Ritz E. The effect of donor gender on graft survival. *J Am Soc Nephrol.* 2002;13:2570–2576.
- Dirchwolf M, Dodge JL, Gralla J, et al. The corrected donor age for HCV-infected liver transplant recipients. *Liver Transpl.* 2015; 21:1022–1030.
- Organ Procurement and Transplant Network. Available at: <http://www.optn.transplant.hrsa.gov/>; 2015.
- Workgroup NYSDOH. Workgroup on expanded criteria organs for liver transplantation. *Liver Transpl.* 2005;11(10):1184–1192.
- Neuman UP, Berg T, Bahra M, et al. Fibrosis progression after liver transplantation in patients with recurrent hepatitis C. *J Hepatol.* 2004;41:830–836.
- Machicao VI, Bonatti H, Krishna M, et al. Donor age affects fibrosis progression and graft survival after liver transplantation for hepatitis C. *Transplantation.* 2004;77:84.
- Lake JR, Shorr JS, Steffen BJ, et al. Differential effects of donor age in liver transplant recipients infected with hepatitis B, hepatitis C and without viral hepatitis. *Am J Transplant.* 2005;5:549–557.
- Rayhill SC, Wu YK, Katz DA, et al. Older donor livers show early severe histological activity and graft failure after liver transplantation for hepatitis C. *Transplantation.* 2007;84:331–339.
- Uemura T, Nikkel LE, Hollenbeak CS, et al. How can we utilize livers from advanced aged donors for liver transplantation for hepatitis C? *Transpl Int.* 2012;25(6):671–679.

20. Condron SL, Heneghan MA, Patek K, et al. Effect of donor age on survival of liver transplant recipients with hepatitis C virus infection. *Transplantation*. 2005;80:145.
21. Maluf DG, Edwards EB, Stravitz T, et al. Impact of the donor risk index on the outcome of hepatitis C virus-positive liver transplant recipients. *Liver Transpl*. 2009;15:592–599.
22. Kwo PY, Mantry PS, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med*. 2014;371(25):2375–2382.
23. Reddy KR, Everson GT, Flamm SL, et al. Ledipasvir/Sofosbuvir with ribavirin for the treatment of HCV in patients with post-transplant recurrence: preliminary results of a prospective, multicenter study. In: *65th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD)*. November 7–11, Boston, MA 2014 [Abstract 8].
24. McCashland T, Watt K, Lyden E, et al. Retransplantation for hepatitis C: results of a U.S. multicenter retransplant study. *Liver Transpl*. 2007;13(9):1246–1253.