Comparative Analysis of Hepatitis C Recurrence and Fibrosis Progression Between Deceased-Donor and Living-Donor Liver Transplantation: 8-Year Longitudinal Follow-Up

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Background. Hepatitis C virus (HCV) recurrence is universal after liver transplantation (LT). Whether the progression of recurrent HCV is faster after live-donor LT (LDLT) compared with deceased-donor LT (DDLT) is debatable.
Methods and Results. We retrospectively examined 100 consecutive LTs (65 DDLTs and 35 LDLTs) performed between July 2000 and July 2003. A total of 147 liver biopsies were performed between 6 months post-LT and last follow-up. Mean donor age and model for end-stage liver disease (MELD) score were significantly lower in LDLT ($P<0.01$). On a mean follow-up of 86.6±6.8 months, overall patient and graft survivals were 61% (51% DDLT vs. 77.1% LDLT; $P=0.026$) and 56% (46.2% DDLT vs. 71.4% LDLT; $P=0.042$), respectively. Eight of 39 (20.5%) deaths (7 DDLT and 1 LDLT) and two of nine (22.2%) retransplants (one in each group) were related to recurrent HCV. Mean fibrosis scores for DDLT and LDLT were 1.9±1.7 and 1.6±1.4, respectively ($P=0.01$). When donor age less than 50 years and MELD score less than 25 were matched among 64 patients (32 DDLT and 32 LDLT), the overall patient and graft survivals were 73.4% (68.8% DDLT vs. 78.1% LDLT; $P=0.439$) and 71.9% (71.9% DDLT vs. 71.9% LDLT; $P=0.978$), respectively.
Conclusions. Long-term survival rates were better, and fibrosis scores were lower for LDLT. The survivals between LDLT and DDLT were comparable for patients with MELD score less than 25 and donor age less than 50 years.

Keywords: Deceased, Donor, Fibrosis, HCV, Liver, Living, Recurrence, Survival, Transplant.

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End-stage liver disease secondary to chronic hepatitis C virus (HCV) infection is the most common indication for liver transplantation (LT) in the United States and Europe (*1*, *2*). The number of HCV-positive patients waiting for LT has grown exponentially in the last decade; however, the donor pool has remained relatively static. Consequently, living-donor LT (LDLT) has been embraced as a viable alternative to increase the organ pool and address the needs of patients who cannot wait for deceased-donor LT (DDLT) (*3–5*). However, there were some concerns on the outcomes of LDLT in HCV patients, representing poorer graft outcome and an earlier and more aggressive HCV recurrence after LDLT compared with DDLT (*6–8*).

Several theories have been proposed to explain differences in HCV recurrence in LDLT vs. DDLT recipients. One proposed explanation is that the intense hepatocyte proliferation occurring in partial liver grafts may lead to increased viral translation and replication (*7*, *9–11*). An increased genetic donor-recipient similarity is another potential mechanism for more severe HCV recurrence (*12*). However, the impact of these proposed mechanisms for an altered natural history of HCV infection in recipients of LDLT remains speculative, as numerous studies have not been able to identify LDLT as a risk factor for more intense viral recurrence in HCV patients (*13–17*). Alternatively, because LDLT donors

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typically are younger and the ischemia times are shorter than with DDLT donors, outcomes may be better among recipients of LDLT than of DDLT. Additionally, most of these studies were lacking liver biopsy data and have reported a relatively short follow-up.

In past, we have published an impact of HCV infection in 100 consecutive LTs (65 DDLTs and 35 LDLTs) (*13*). On a mean follow-up of 25±6.9 months, we found no significant difference for patient survival, graft survival, rate of HCV recurrence, severity of HCV recurrence, graft loss from HCV, and interval for recurrence between DDLT and LDLT recipients. The same patient population was followed up for 8 years. The aim of this study is to examine and compare the survival outcome and fibrosis progression between the respective DDLT and LDLT recipients on long-term follow-up.

RESULTS

Demographics and Baseline Characteristics

The demographics and baseline characteristics of the DDLT and LDLT recipients are summarized in Table 1. Of the 100 consecutive patients reviewed, 75 were men and 25 were women with a mean age of 50.3±7.0 (median=49.6, range=32.9–72.6) years at the time of transplant. Of these, 65 patients underwent primary whole DDLT, whereas the remaining 35 patients underwent right lobe LDLT consisting of hepatic segments V, VI, VII, and VIII as described previously (*3–5*). Forty-eight (85.7%) DDLT recipients and 28 (87.5%) LDLT recipients had HCV genotype 1. HCV genotype was not known in 12 patients (DDLT nine and LDLT three). The model for end-stage liver disease (MELD) score was calculated at the time of LT, without regard for exception points. The mean donor age and MELD score were significantly lower in LDLT compared with DDLT (Table 1). The mean cold ischemia time (CIT) of the deceased donor's grafts was 11±3.1 hr.

TABLE 1. Donor and recipient characteristics

	DDLT	LDLT
Number of patients	65	35
Male/female	52/13	23/12
Age (yr, mean±SD)	49.9±6.8	50.5±7.4
MELD score (mean±SD)[a]	16.8±7.3	14.5±3.9
Donor age (yr, mean±SD)[a]	47.2±19.8	34.3±9.3
Presence of hepatocellular carcinoma, n (%)	13 (20)	2 (5.7)
HCV genotype		
1	8	1
1a	20	17
1b	19	9
1a/1b	1	1
2b	3	1
3a	4	3
5a	1	0
Unknown	9	3
Cause of death		
Recurrent HCV	7	1
Sepsis	6	2
Cardiac arrest	4	2
Recurrent HCC	4	0
De novo carcinoma (lung, esophagus, and stomach)	1	3
Biliary cast syndrome	2	0
Postresection gangrenous bowel	0	1
Hemorrhage from accidental dialysis catheter dislodgement	1	0
Withdrawal of care	1	0
Intracranial hemorrhage	2	0
Portal vein thrombosis	1	0
Unknown	1	0
Causes of retransplant		
Primary nonfunction	3	0
Hepatic artery thrombosis	2	1[b]
Recurrent HCV	1	1[b]
Biliary complications	1	0

[a] *P* value <0.01.
[b] Same patient.

Patient Survival

With a mean follow-up of 86.6±6.8 months (median: 82.5 months, range: 73–97 months), the overall actuarial patient survival was 61%. The respective 1, 3, 5, and 7 years patient survival for DDLT was 90.8%, 76.9%, 64.6%, and 51% compared with 91.4%, 82.9%, 80%, and 77.1% for LDLT (*P*=0.026, Fig. 1). Thirty-nine (39%) patients died during the follow-up period, 30 (46.1%) in DDLT group and 9 (25.7%) in LDLT group. The distribution of causes of death is presented in Table 1. Seven (10.8%) patients in DDLT group and one (2.8%) patient in LDLT group died from recurrent HCV. The mean time to death from recurrent HCV was 53.1±31.2 months in DDLT group and 38 months in LDLT group.

The subanalysis of 64 patients (32 in DDLT and 32 in LDLT) adjusted for MELD score less than 25 and donor age less than 50 years showed an overall Kaplan-Meier patient survival of 73.4% (68.8% for DDLT vs. 78.1% for LDLT; *P*=0.439) (Fig. 2).

Graft Survival

Graft loss was considered as patients who either underwent retransplantation or died without retransplantation. The overall actuarial graft survival was 56%. The respective 1, 3, 5, and 7 years graft survival for DDLT was 90.8%, 75.4%, 61.5%, and 46.2% compared with 88.6%, 80%, 77.1%, and 71.4% for LDLT (*P*=0.042, Fig. 3). During the observed follow-up period, eight patients underwent nine retransplants, with one patient undergoing two retransplants in LDLT group (first retransplant for recurrent HCV and second for hepatic artery thrombosis). The indications for retransplants are presented in Table 1.

The subanalysis of 64 patients (32 in DDLT and 32 in LDLT) adjusted for MELD score less than 25 and donor age less than 50 years showed an overall Kaplan-Meier graft survival of 71.9% (71.9% for DDLT vs. 71.9% for LDLT; *P*=0.978) (Fig. 4).

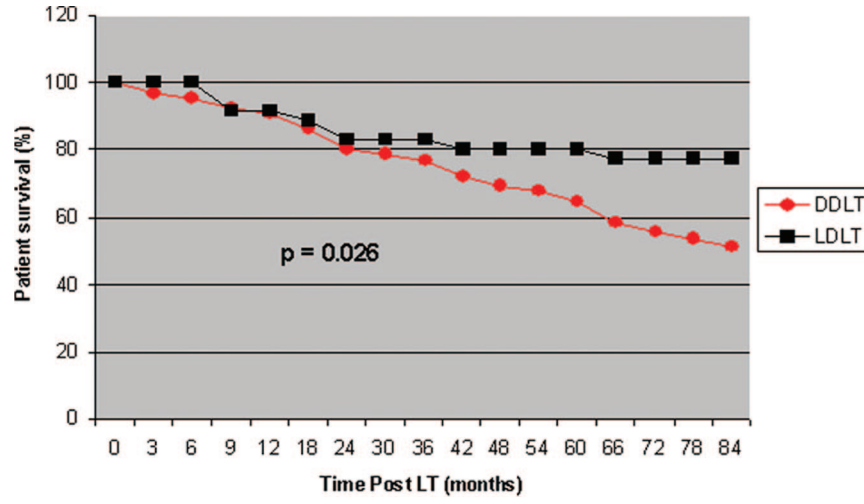

FIGURE 1. Patient survival by type of LT (n=100). LT, liver transplantation; DDLT, deceased donor liver transplantation; LDLT, live donor liver transplantation.

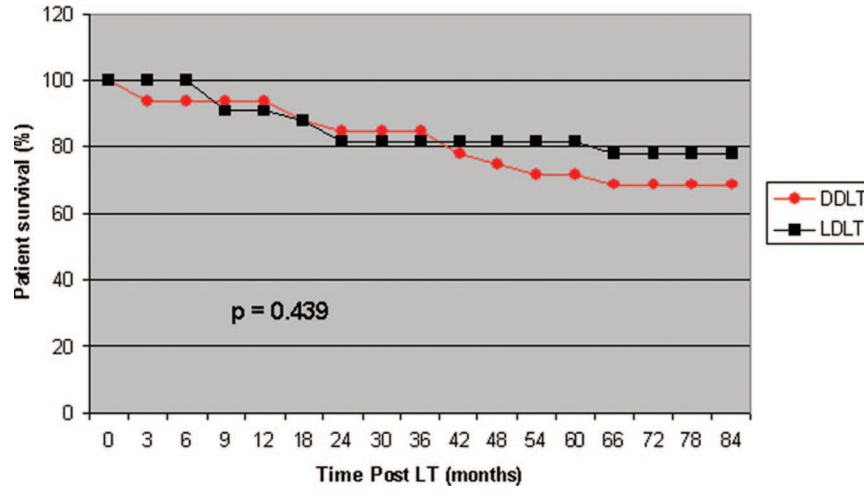

FIGURE 2. Patient survival by type of LT: adjusted for model for end-stage liver disease score and donor age (n=64). LT, liver transplantation; DDLT, deceased donor liver transplantation; LDLT, live donor liver transplantation.

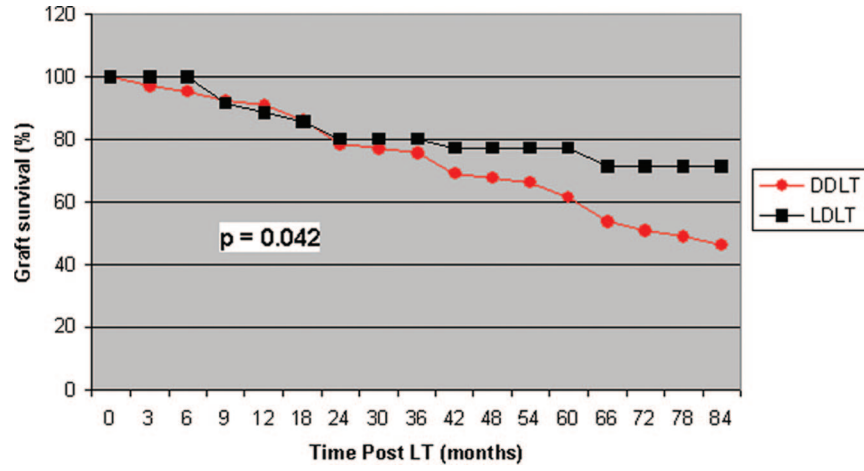

FIGURE 3. Graft survival by type of LT (n=100). LT, liver transplantation; DDLT, deceased donor liver transplantation; LDLT, live donor liver transplantation.

Histological Findings

A total of 147 liver biopsies (94 in DDLT group and 53 in LDLT group) were performed in 82 patients (56 in the DDLT group and 26 in the LDLT group); 6 months after LT to last follow-up. The mean times to biopsy were 34.3±21.6 (median, 30.8) months and 43.4±24.3 (median, 39) months for the DDLT and LDLT groups, respectively. The fibrosis scores for DDLT (●) and LDLT (■) are depicted in Figure 5. The overall mean fibrosis scores for DDLT and LDLT were 1.9±1.7 and 1.6±1.4 (P=0.01), respectively. The mean fibro-

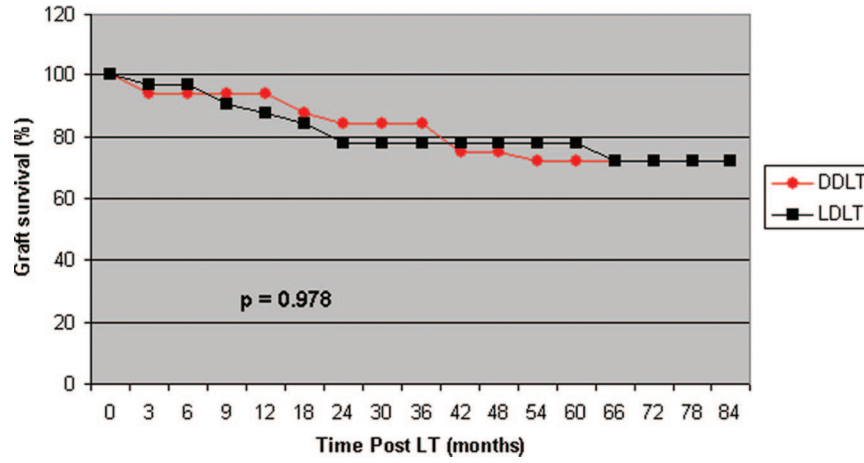

FIGURE 4. Graft survival by type of LT: adjusted for model for end-stage liver disease score and donor age (n=64). LT, liver transplantation; DDLT, deceased donor liver transplantation; LDLT, live donor liver transplantation.

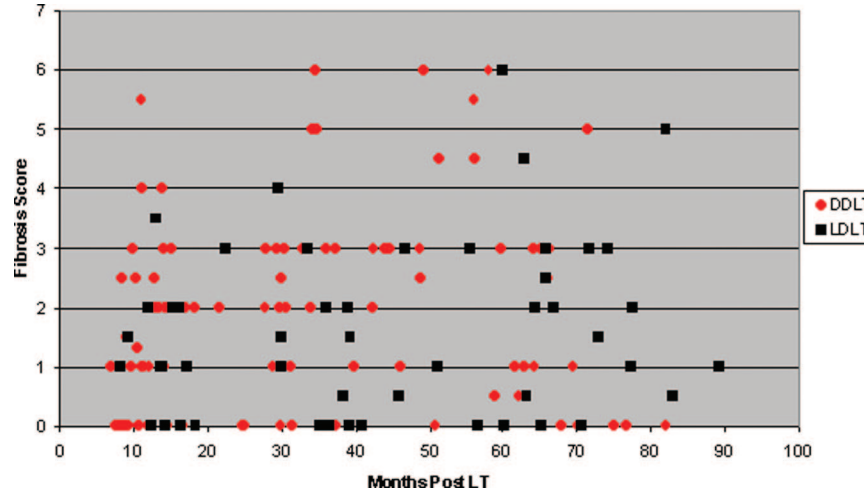

FIGURE 5. Fibrosis score of all liver biopsies by type of LT. LT, liver transplantation; DDLT, deceased donor liver transplantation; LDLT, live donor liver transplantation.

TABLE 2. Follow-up HAI and fibrosis scores (n=100)

	HAI score				Fibrosis score			
Type of LT	Year 1	Year 3	Year 5	Last FU	Year 1	Year 3	Year 5	Last FU
DDLT (n=65)								
Mean	4.5	5.7	5.1	3.6	1.5	2.3	2.5	1.4
SD	3.3	2.8	2.2	2.5	1.4	1.7	1.9	1.5
LDLT (n=35)								
Mean	5.0	5.4	3.5	4.6	1.2	1.6	1.5	1.9
SD	3.7	2.1	2.8	2.5	1.0	1.5	1.8	1.5
P	0.01	0.01	0.001	0.01	0.001	0.012	0.014	0.001

LT, liver transplant; DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; SD, standard deviation; HAI, hepatitis activity index; FU, follow-up.

sis scores at 1, 3, 5 years, and at last follow-up were 1.5±1.4, 2.3±1.7, 2.5±1.9, and 1.4±1.5 for DDLT and 1.2±1.0, 1.6±1.5, 1.6±1.8, and 1.9±1.5 LDLT (Table 2), respectively. The mean fibrosis scores among patients adjusted for MELD score less than 25 and donor age less than 50 years were at 1, 3, 5 years, and at last follow-up were 1.3±1.3, 1.6±1.5, 1.6±1.1, and 2.0±2.1 for DDLT and 1.0±0.9, 1.1±1.3, 1.5±1.4, and 1.4±0.9 LDLT, respectively.

Similarly, the overall mean hepatitis activity index (HAI) scores for DDLT and LDLT were 4.8±2.9 and 4.6±2.9, respectively (P=0.01). The mean HAI scores at 1, 3, 5 years, and at last follow-up were 4.5±3.3, 5.7±2.8, 5.1±2.2, and 3.6±2.5 for DDLT and 5.0±3.7, 5.0±2.1, 3.5±2.8, and 4.6±2.5 LDLT (Table 2), respectively. All differences overall and at all time points examined were significantly better for LDLT compared with DDLT.

Biochemical Profile

Biochemical profiles indicative of liver allograft function were examined at the last follow-up. Total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma glutamyltransferase values were analyzed. No significant difference was identified between the two groups.

Maintenance Immunosuppression

At the last follow-up, the mean tacrolimus dose and trough concentrations were 3.6±2.4 mg/day and 6.8±3.2 ng/mL in the DDLT and 3±1.7 mg/day and 5.7±2 ng/mL in the LDLT, respectively. Because of the tacrolimus neurotoxicity, three patients in DDLT group and four patients in LDLT were switched to microemulsion formulations of cyclosporine, whereas two patients in DDLT group received rapamycin because of calcineurin inhibitors induced nephrotoxicity. Weaning of steroid was initiated at 2 to 6 weeks after transplant with efforts directed toward achieving patients on tacrolimus alone by 9 to 12 months. At the last follow-up, six recipients were receiving prednisone (four in DDLT group and two in LDLT group); five recipients were on 5 mg/day and one LDLT recipient was on 10 mg/day.

Antiviral Therapy

In both the groups, antiviral therapy was commenced when there were biochemical alterations in liver functions with biopsy-proven HCV recurrence (HAI ≥5 and/or fibrosis score ≥1). During the follow-up, 37 recipients (57%) in the DDLT group and 17 (49%) in the LDLT group were treated with pegylated interferon and ribavirin combination antiviral therapy. The timing of interferon therapy after transplant was 1.64±1.07 years in DDLT vs. 1.5±0.86 years in LDLT recipients. Seventeen (46%) of 37 patients in DDLT and 8 (47%) of 17 patients in LDLT achieved end of treatment response. The rates of sustained virologic response were also similar in DDLT (9/37, 24%) and in LDLT (5/17, 29%) recipients. None of the patient had acute rejection while receiving antiviral therapy for recurrent HCV.

DISCUSSION

Reinfection of allograft with HCV after LT is an important issue; virtually universal in patients undergoing LT with measurable viral RNA. Variables associated with graft and patient survival after LT for HCV patients include donor age, pretransplant HCV viral load, the degree and specific type of immunosuppression, the development of acute graft rejection, and the therapy used to treat it (*18–26*). Presence of hepatitis B virus or human immunodeficiency virus coinfection and the development of cytomegalovirus infection also reported to hasten the progression of allograft injury (*27–29*).

There has been concern for early and more severe recurrence after LDLT than DDLT (*6–8*). Several theories have been proposed to explain these findings. The rapid hepatic regeneration occurring in the early posttransplant period in living donor allografts may act as a stimulus for viral replication and may alter early virologic or immunologic events and thereby affect the risk of progressive liver disease (*7*, *9–11*). This hypothesis was based on several in vitro observations as follows: HCV appears to enter young and rapidly dividing hepatocytes more readily than older nonreplicating cells (*30*); HCV enters cells at least in part through the low-density lipoprotein receptor (*31*); the production of low-density lipoprotein receptor seems to be up-regulated by hepatocyte growth factor (*32*), and this and many other cytokines seem to stimulate hepatic regeneration (*33*). However, there are no data to suggest that the uptake of HCV into hepatocytes is enhanced after LDLT and leads to more severe form of recurrent HCV. Everson and Trotter (*12*) suggested that increased genetic donor-recipient similarity represents another potential mechanism for more severe HCV recurrence. Live-donor recipients are more likely than deceased donor recipients to share human leukocyte antigens (*34*).

This is the first study to report the long-term clinical and histological follow-up on consecutive DDLT and LDLT in HCV-positive patients. In this study, the mean donor age and MELD score were significantly lower in LDLT compared with DDLT. Donor age has been previously found to be associated with the progression of HCV recurrence after LT (*18–22*, *28*). Thus, increased rates of fibrosis progression have been reported for recurrent hepatitis C in grafts from deceased donors older than 49 (*19*), 55 (*20*), and 60 years (*29*). Our study showed significantly better overall patient and graft survival in LDLT compared with DDLT. Graft loss (death or retransplant) related to recurrent hepatitis C was more than twofold higher in DDLT (8/65, 12.3%) than in LDLT (2/35, 5.7%). The observed difference in liver-related mortality is compatible with donor age affecting both histologic disease progression and survival outcome as the patient and graft survivals among 64 patients (32 in DDLT and 32 in LDLT) adjusted for donor age less than 50 years and MELD score less than 25 were comparable. This raises the question of whether (and with which age cutoff) it remains justified to use older donors when HCV-positive recipients are transplanted.

Various studies have been performed regarding patient and graft survival and fibrosis progression in the first years after LT; however, results have been contrasting and somewhat contradictory. Table 3 illustrates the literature review on pattern of survival and histological recurrence of HCV between DDLT and LDLT recipients. Overall, 920 LDLT recipients were compared with 5372 DDLT recipients in 14 published studies. Garcia-Retortillo et al. and Gaglio et al. (*6*, *7*) reported early and more severe recurrence after LDLT than DDLT, whereas other 11 studies with variable follow-up varying from 12 to 72 months showed no significant difference for patient and graft survival and intensity of HCV recurrence between recipients of LDLT and DDLT (*13–17*, *35–40*). All these studies have reported similar patient and graft survivals on short-to-intermediate follow-up with three studies reporting a 5-year follow-up (*17*, *39*, *40*). However, most of these studies did not report the details of degree of histologic injury secondary to recurrent HCV.

The pathological data in the present analyses ascertained significantly higher grades of inflammation and fibrosis in DDLT than in LDLT at all time points examined. This may be partly related to donor age as the mean fibrosis scores among patients matched for donor age and MELD score were not significantly different. Donor age greater than 45 to 50 years has been reported to carry a relative risk for developing severe fibrosis of approximately 3.5 (*22*, *29*). A recent study reported that donor age more than 45 years carried a relative

TABLE 3. Literature review on the pattern of histological recurrence and survival between DDLT and LDLT

Authors	n	LDLT/ DDLT	Follow-up (mo)	HAI LDLT/DDLT	Fibrosis LDLT/DDLT	Patient survival LDLT/DDLT (%)	Graft survival DDLT/DDLT (%)	Comments
Gaglio et al. (*7*)	68	23/45	24	—	—	87/89	87/85	Increased cholestatic hepatitis in LDLT
Garcia-Retortillo et al. (*6*)	117	22/95	22	—	F3-F4 in 30 patients (10/20)	—	—	Severe recurrence in LDLT
Van Vlierberghe et al. (*35*)	43	17/26	12	—	1/1	—	—	No difference in outcome
Bozorgzadeh et al. (*13*)	100	35/65	39	6.2±2.8/5.4±2.4	1.5±1.3/1.8±1.4	88.6/75	82.9/64.3	No difference in outcome
Russo et al. (*14*)	4234	279/3955	24	—	—	83/81	72/75	No difference in short-term outcome
Shiffman et al. (*15*)	76	23/53	36	6.2/7	0.9/1.9	79/82	76/82	No difference in outcome
Thuluvath and Yoo (*8*)	619	207/412	24	—	—	79/80.7	64.4/73.3	Lower graft survival in LDLT
Schiano et al. (*36*)	26	11/15	24	—	—	73/80	73/80	Similar survival rates
Maluf et al. (*39*)	126	29/97	72	—	—	67.1/70.6	64.2/68.9	No difference in survival, more rejection in DDLT and biliary complications in LDLT
Humar et al. (*16*)	51	12/39	28.3	0.33/1.31	0.22/0.96	92/90	—	No difference in outcome
Guo et al. (*38*)	67	15/52	24	—	1.4/1.2	93/96	87/94	No difference in outcome
Schmeding et al. (*17*)	289	20/269	60	2.2±0.84/1.27±0.74	2.76/2.02	—	—	LDLT does not increase the risk and severity of HCV recurrence
Terrault et al. (*38*)	275	181/94	3	—	—	74/82	68/80	No significant difference in graft survival at experienced LDLT centers
Selzner et al. (*40*)	201	46/155	60	—	—	84/78	76/74	Donor age, rather than transplant approach, affects the progression of recurrent HCV

DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation.

risk of 8.17 for reaching fibrosis stage 3 or 4 at 2 years post-LT (*40*). In our study, the fibrosis scores were lower in both DDLT and LDLT at the last follow-up compared with at 5-year follow-up. This was due to loss of 10 grafts in DDLT and two grafts in LDLT with higher fibrosis scores after 5 years post-LT as reflected in patient and graft survival.

Besides donor age, immunosuppressive strategy is another factor (*41*, *42*). The development of acute cellular rejection and use of steroid boluses are known to have detrimental effect on HCV recurrence (*23–25*). In this study, there was no difference for immunosuppression drugs, level of immunosuppression, or steroid weaning protocol be-

tween the DDLT and LDLT group. We have been using tacrolimus, intravenous mycophenolate mofetil, and steroid based triple-immunosuppression-drug regimen in both the groups (*43*, *44*). With this regimen, the event rate of acute cellular rejection (and consequently of bolus steroid use) was low, and our analysis failed to detect immunosuppression as independent variable for the progression of recurrent HCV.

The proportions of patients receiving antiviral therapy were similar in DDLT and LDLT recipients, and the rates of sustained virological response were virtually identical in the two groups. Analyzing DDLT and LDLT recipients separately according to their therapy response is beyond the scope of this article but would unlikely affect the overall results, given the similar proportions of patient's treated/clearing the virus.

Being a retrospective analysis, our study has several limitations. Though the study lacks the data for CIT for living donors; there must be an unavoidable difference between the two groups for CIT. The study also lacks the data on allograft steatosis. All the living donors in our program had a liver biopsy before donation; however, not all deceased donors were biopsied. Usually, living donor with macrosteatosis more than 10% was not used; however, deceased donors with macrosteatosis up to 20% to 30% were used depending on donor age. Furthermore, the apparent random (nonprotocol) nature of the biopsies constitutes an additional limitation. Also, although the follow-up period of up to 8 years is fairly long, there were on average only about two biopsies per allograft, which may not provide an optimal longitudinal follow-up for individual liver grafts.

CONCLUSIONS

On the basis of our data, we suppose that live donor liver allograft is not detrimental to progression of HCV recurrence. Overall patient and graft survivals were better for LDLT compared with DDLT. The rate and severity of HCV recurrence, graft loss, or death from HCV recurrence were lower in LDLT. Furthermore, benefit of LT with MELD score less than 25 and donor age less than 50 years is observed for both LDLT and DDLT. Considering the ongoing shortage of young deceased donor organs and on the basis of our findings, we strongly recommend LDLT for HCV-positive patients wherever there is an opportunity. Further prospective multicenter attempts should be continued to monitor all the clinical variables and their impact on HCV recurrence.

MATERIALS AND METHODS

With an approval of institutional review board, we retrospectively reviewed the 100 consecutive HCV seropositive adults (age >18 years) that underwent LT at our institution between July 2000 and July 2003. Data were obtained from a prospectively collected transplant database. All recipients were HCV-RNA positive at the time of transplant, and none of them was positive for HBs Ag, hepatitis B virus-DNA, or human immunodeficiency virus. Recipient and donor demographics and HCV genotype were described before (*13*) and given in Table 1. All patients were followed up until August 2008. Patient and graft survival were compared between DDLT and LDLT for entire group. Also, 64 patients (32 DDLT and 32 LDLT) adjusted for MELD score less than 25 and donor age less than 50 years were examined separately.

Liver Biopsy

Percutaneous liver biopsy was performed as clinically indicated when biochemical data indicates hepatic dysfunction without any evidence of vascular or biliary complications. Liver biopsy was also performed before commencing the interferon therapy. Sixty-nine liver biopsies that were performed within 6 months after LT (included in earlier report) are omitted from the present analyses to eliminate the overlap of rejection and hepatitis. Subsequent biopsies were scored for HAI and fibrosis score as per ISHAK scoring system (*45*) by an experienced pathologist who was blinded to the type of hepatic allograft. Findings were compared between DDLT and LDLT groups. For the analysis purposes, we have grouped the biopsies at 1 year (6–18 months), 3 years (19–36 months), 5 years (37–60 months), and at the last follow-up.

Immunosuppression Protocol

All patients received triple-agent–based immunosuppression consisting of tacrolimus, mycophenolate mofetil, and steroids. Tacrolimus was orally administered at 0.05 mg/kg/day with a target whole-blood trough concentration of 8 to 10 ng/mL in first 3 months. Mycophenolate mofetil was administered as 1 g twice per day. One gram of methylprednisolone was given during anhepatic phase before reperfusion of the allograft, followed by a steroid taper totaling 600 mg during the next 5 days. By day 6, all patients were receiving 20 mg prednisone daily. Subsequent steroid weaning was same for both DDLT and LDLT group. Prednisone was reduced to 15 mg/day by postoperative week 2 to 3; to 10 mg/day by weeks 6 to 8; and to 5 mg/day by 6 months. All patients were off steroids between 6 to 9 months. Immunosuppressive adjustments were based on the individual's clinical course considering the presence of rejection, drug toxicity, or infection.

Statistical Analysis

Values are presented as mean±standard deviation. Kaplan-Meier analysis (SPSS Window version 18; SPSS Inc., Chicago IL) was used to estimate the patient and graft survival. Log-rank method was used to estimate the difference between survivals. Differences in mean were compared by Student's *t* test. The *P* value of less than 0.05 was considered statistically significant.

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