Hepatitis C Is a Risk Factor for Death After Liver Retransplantation

Shawn J. Pelletier,[1] Douglas E. Schaubel,[2] Jeffrey D. Punch,[1] Robert A. Wolfe,[2] Friedrich K. Port,[3] and Robert M. Merion[1,3]

See Editorial on Page 382

Retransplantation for liver allograft failure associated with hepatitis C virus (HCV) has been increasing due to nearly universal posttransplant HCV recurrence and has been demonstrated to be associated with poor outcomes. We report on the risk factors for death after retransplantation among liver recipients with HCV. A retrospective cohort of liver transplant recipients who underwent retransplantation between January 1997 and December 2002 was identified in the Scientific Registry of Transplant Recipients database. Cox regression was used to assess the relative effect of HCV diagnosis on mortality risk after retransplantation and was adjusted for multiple covariates. Of 1,718 liver retransplantations during the study period, 464 (27%) were associated with a diagnosis of HCV infection. Based on Cox regression, retransplant recipients with HCV had a 30% higher covariate-adjusted mortality risk than those without HCV diagnosis (hazard ratio [HR], 1.30; 95% confidence interval [CI], 1.10-1.54; $P = 0.002$). Other covariates associated with significant relative risk of death after retransplantation included older recipient age, presence in an intensive care unit (ICU), serum creatinine, and donor age. Additional regression analysis revealed that the increase in mortality risk associated with HCV was concentrated between 3 and 24 months postretransplantation, among patients age 18 to 39 at retransplant, and in patients retransplanted during the years 2000 to 2002. In conclusion, HCV liver recipients account for a considerable proportion of all retransplantations performed. Surprisingly, younger age predicted a higher mortality for recipients with HCV undergoing liver retransplantation. This may reflect a willingness to retransplant younger patients with an increased severity of illness or a more virulent HCV infection in this population. Although HCV was predicted of an increased risk of death, consideration of other characteristics of HCV patients, including donor and recipient age and need for preoperative ICU care may identify those at significantly higher risk. (*Liver Transpl 2005;11: 434-440.*)

Cirrhosis from chronic infection with hepatitis C virus (HCV) is the leading diagnosis for patients undergoing orthotopic liver transplantation in the United States, accounting for more than 50% of all liver transplantations.[1] Although persistence of hepatitis C viremia is nearly universal after liver transplantation, the course of allograft liver damage is variable. While the majority of patients will have a benign posttransplant course, about 20% to 40% will experience progressive graft damage, leading to allograft cirrhosis in 5 to 10 years.[2-4] A small subset will develop cholestatic HCV-related pathology, an early, aggressive form associated with a high death rate.[5-10] Current therapies against HCV carry significant morbidity and inconsistent efficacy and, as such, make it difficult to justify universal application for all HCV recipients.[11-17] Despite published literature reporting equivalent patient survival outcomes in HCV and non-HCV liver transplant recipients,[18,19] it is well recognized that allograft damage from HCV occurs commonly after transplantation.[20-22]

Despite the high proportion of liver transplants done for HCV and the occurrence of HCV-induced allograft injury, recipients with HCV represent only about 25% of those undergoing retransplantation.[23] However, the fraction of liver retransplants in patients with HCV infection has increased from 7% in 1990 to 38% in 1995.[24] This increase may reflect more accurate testing for the virus and further underscores the role of HCV in allograft failure. Because antiviral therapy for HCV following liver transplantation has limited efficacy, retransplantation may be the best option for recipients with allograft failure due to HCV.

A recently published review of national data demonstrated significantly decreased 1-year and 5-year posttransplant survival for retransplantation for recipients with HCV compared to those without HCV (57% vs.

Abbreviations: HCV, hepatitis C virus; HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; non-HCV, subgroup without HCV infection.

From the [1]Department of Surgery, Division of Transplantation, [2]Department of Biostatistics, University of Michigan, Ann Arbor, MI; and [3]Scientific Registry of Transplant Recipients (SRTR) / University Renal Research and Education Association (URREA), Ann Arbor, MI.

Supported by the Scientific Registry of Transplant Recipients (231-00-0116), which is funded by the Department of Health and Human Services, Health Resources and Services Administration, Office of Special Programs, Division of Transplantation.

Address reprint requests to Shawn J. Pelletier, MD, 2926 Taubman Center, 1500 E. Medical Center Dr., Ann Arbor, MI 48109-0331. Telephone: 734-936-8363; FAX: 734-763-3187; E-mail: spelleti@umich.edu

Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/lt.20342

65% and 54% vs. 61%, respectively; $P = 0.004$). However, it was predicted that if a subset of patients without severe hyperbilirubinemia or renal insufficiency were retransplanted, better results might be achieved.[25] Another study identified HCV as an independent risk factor for mortality following retransplantation.[23] In contrast, Sheiner et al.[26,27] demonstrated that survival for HCV recipients undergoing an initial transplant was similar to those undergoing retransplantation, leading the authors to the conclusion that patients with HCV-induced allograft failure should be offered retransplantation in the event of graft failure.Others believe acceptable outcomes can be obtained in selected patients when retransplantation is performed early in the course of recurrent disease, before transplant recipients become critically ill.[28]

This variability in outcomes and recommendations has lead to considerable debate about which subgroups of HCV liver transplant recipients with allograft failure should receive a second transplant or if HCV recipients should be retransplanted at all. The present study reports on risk factors for death after retransplantation among recipients with HCV as the underlying cause of liver failure.

Patients and Methods

A retrospective cohort study of data obtained from the Scientific Registry of Transplant Recipients, as submitted by the members of the Organ Procurement and Transplantation Network, was performed to investigate risk factors for death after liver retransplantation in recipients with HCV. Mortality ascertainment was supplemented through the Social Security Death Master File.[29]

Prior liver transplant recipients who were retransplanted between January 1, 1997, and December 31, 2002, were eligible for inclusion in the study cohort. Recipients younger than 18 years old and those receiving multiorgan or living donor retransplants were excluded. Patients were followed from the date of retransplantation until death or the end of the observation period (June 30, 2003).

All univariate comparisons were unpaired and all tests of significance were 2-tailed. For univariate analysis, continuous variables were compared by Student's *t* test. Categorical data were compared using chi-square testing. All values are expressed as the mean ± standard error (continuous variables) or as a percentage of the group from which they were derived (categorical variables). Crude (unadjusted) mortality rates were computed as the number of deaths per 100 patient-years of postretransplant follow-up. Unadjusted patient survival following liver retransplantation was compared using Kaplan-Meier analysis with log-rank test to evaluate for significance. A Cox regression model was fitted to compute covariate-adjusted mortality hazard ratios (HR), adjusted for the following potentially confounding covariates: recipient age, gender, race, creatinine, intensive care (ICU) at retransplantation, time from first transplant to retransplantation, calendar year of retransplantation, retransplant cold ischemia time, and donor age. Recipients with diagnosis codes designated as alcoholic cirrhosis with hepatitis C (cirrhosis type C), and non-A non-B hepatitis were included within the HCV group. Retransplant recipients without HCV infection (non-HCV) comprised the reference group. Thus, each tabulated HR represents the ratio of death rates (HCV/non-HCV) among patients who are comparable with respect to the above set of covariates. In addition, Cox nonproportional hazards models were fitted in order to compare HCV and non-HCV covariate-adjusted mortality rates by postretransplant follow-up interval. Further subgroup analyses were performed based on recipient age group and by year of retransplantation.

Table 1. Primary Causes of End-Stage Liver Disease for Liver Transplant Recipients Who Underwent Retransplantation Between January 1, 1997, and December 31, 2002 (N = 1,718)

Cause of liver disease	n (%)
Acute liver failure	205 (11.9)
Primary biliary cirrhosis	66 (3.8)
Primary sclerosing cholangitis	148 (8.6)
Other cholestatic liver disease	8 (0.5)
Alcoholic cirrhosis	119 (6.9)
Hepatitis B virus	75 (4.4)
Hepatitis C virus	464 (27.0)
Other noncholestatic liver disease	237 (13.8)
Other	396 (23.1)

Results

Between January 1, 1997, and December 31, 2002, 1,718 liver transplant recipients meeting the cohort inclusion criteria underwent retransplantation. A total of 27% of those undergoing retransplantation had HCV infection as the original recorded diagnosis leading to liver failure requiring transplantation (Table 1).

As described in Table 2, a significantly greater proportion of patients without HCV were in the youngest (18-39 years old; 22.8% vs. 6.5%; $P < 0.001$) and oldest age groups (≥60 years old; 13.5% vs. 9.5%; $P = 0.03$). In contrast, a greater proportion of patients with HCV were in the age group ranging from 40 to 49 years old (50.7% vs. 31.8%; $P < 0.001$). Compared with those with HCV undergoing retransplantation, recipients without HCV were more likely to be female (29.7% vs. 41.2%, respectively; $P < 0.001$). Other than an increased proportion of Asian retransplant recipients in those without HCV infection, there was

Table 2. Characteristics of Liver Transplant Recipients With or Without Hepatitis C Virus (HCV) Infection Who Underwent Retransplantation Between January 1, 1997, and December 31, 2002

	HCV negative	HCV positive	*P**
N	1,254 (73.0%)	464 (27.0%)	
Age at retransplant (years)			
18–39	286 (22.8%)	30 (6.5%)	<0.001
40–49	399 (31.8%)	235 (50.7%)	<0.001
50–59	400 (31.9%)	155 (33.4%)	0.59
≥60	169 (13.5%)	44 (9.5%)	0.03
Race			
African American	122 (9.7%)	47 (10.1%)	0.79
Asian	38 (3.0%)	5 (1.1%)	0.02
Caucasian	1,063 (84.8%)	401 (86.4%)	0.40
Other	31 (2.5%)	11 (2.4%)	0.99
Female	516 (41.2%)	138 (29.7%)	<0.001
Interval to retransplantation (months)	21.6 ± 1.0	27.5 ± 1.5	0.002

*Determined by chi square analysis.

no difference in race between the 2 groups. Comparison of the time from primary liver transplant to retransplantation demonstrated that those with HCV underwent retransplantation approximately 6 months later than those without HCV (27.5 ± 1.5 vs. 21.6 ± 1.0 months, respectively; $P = 0.002$).

Unadjusted mortality rates are listed in Table 3. In total, there were 685 deaths observed during 3,310 patient-years of follow-up, for an unadjusted mortality rate of 20.7 deaths per 100 patient-years. Retransplant recipients with HCV infection had a higher crude death rate when compared to non-HCV retransplant recipients (26.0 vs. 8.8 deaths / 100 patient-years, respectively). Furthermore, Kaplan-Meier survival analysis comparing unadjusted mortality demonstrated retransplant recipients with HCV infection had a significantly decreased survival compared with recipients without HCV infection (Fig. 1; 44.8% vs. 56.3% survival, respectively, at 5 years; $P < 0.001$).

Covariate-adjusted mortality hazard ratios with 95% confidence intervals (CIs) for all liver recipients undergoing retransplantation are listed in Table 4. Retransplant recipients with HCV had a 30% higher covariate-adjusted risk of death than those without HCV (HR, 1.30; 95% CI, 1.10-1.54; $P = 0.002$). In addition to HCV diagnosis, covariates associated with significantly increased relative risk of death after retransplantation included older recipient age (HR, 1.04/year; 95% CI, 1.01-1.06; $P = 0.001$), presence in an ICU vs. nonhospitalized retransplant recipients (HR, 1.25; 95% CI, 1.02-1.53; $P = 0.03$), higher serum creatinine (HR, 1.08/1 mg/dL; 95% CI, 1.04-1.13; $P < 0.001$), and donor age 60 years or older vs. 40-59 years (HR, 1.30; 95% CI, 1.03-1.64; $P = 0.02$). Retransplant recipients who received allografts from

Table 3. Unadjusted Mortality Rates for Liver Transplant Recipients Undergoing Retransplantation With or Without HCV Infection Between January 1, 1997, and December 31, 2002

	Deaths	Patient-years (PY)	Rate per 100 PY
HCV negative	462	2,451	18.8
HCV positive	223	858	26.0
Total	685	3,310	20.7

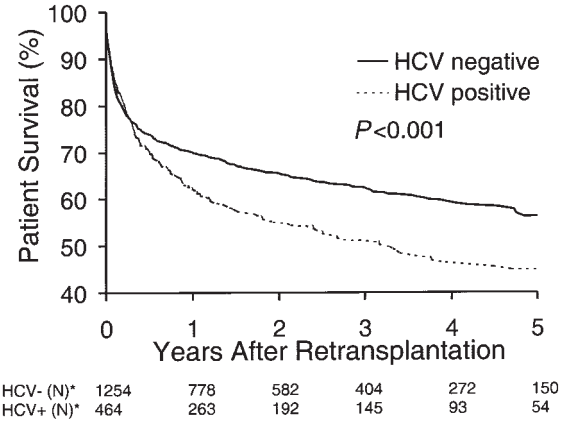

Figure 1. Kaplan-Meier curve comparing unadjusted mortality between HCV-positive and HCV-negative liver retransplant recipients. *Number of patients at risk at each corresponding time.

Table 4. Covariate-Adjusted Mortality Hazard Ratios (HR) ± 95% Confidence Interval (CI) for All Liver Recipients Undergoing Retransplantation

	HR	CI	*P*
Hepatitis C virus positive (vs. negative)	1.30	1.10-1.54	0.002
Age (per year)	1.04	1.01-1.06	0.001
Female (vs. male)	1.13	0.96-1.32	0.14
Time from liver transplant to retransplantation (per 6 months)	0.99	0.98-1.01	0.40
Total bilirubin (per 1 mg/dL)	1.06	1.00-1.13	0.06
Creatinine (per 1 mg/dL)	1.08	1.04-1.13	<0.001
Cold ischemic time (per hour)	1.01	1.00-1.03	0.16
Recipient race			
African American (vs. Caucasian)	0.93	0.71-1.22	0.60
Asian (vs. Caucasian)	1.05	0.66-1.67	0.83
Other race (vs. Caucasian)	1.46	0.93-2.30	0.10
Year of retransplantation			
1997 (vs. 2000-2002)	1.22	0.99-1.52	0.07
1998 (vs. 2000-2002)	1.06	0.86-1.32	0.61
1999 (vs. 2000-2002)	1.15	0.93-1.43	0.19
Recipient hospitalization status			
Hospitalized, not ICU* (vs. not hospitalized)	0.97	0.77-1.21	0.77
Hospitalized, ICU* (vs. not hospitalized)	1.25	1.02-1.53	0.03
Donor age (years)			
0-19 (vs. 40-59)	0.71	0.57-0.88	0.002
20-39 (vs. 40-59)	0.76	0.63-0.91	0.004
60+ (vs. 40-59)	1.30	1.03-1.64	0.02

*Intensive care unit.

donors younger than 40 years of age had significantly decreased relative risk of death (donor age 0-19 vs. 40-59 years old: HR, 0.70; 95% CI, 0.57-0.88; $P = 0.002$; donor age 20-39 vs. 40-59 years old: HR, 0.76; 95% CI, 0.63-0.91; $P = 0.004$). Recipient gender and race, hospitalization outside of an ICU, year of retransplantation, time from primary transplant to retransplantation, and cold ischemic time were not associated with significantly increased mortality risk.

HCV retransplant recipients had significantly increased mortality risk in the postoperative period between 3 and 24 months (Table 5). Although HCV retransplant recipients were not at increased risk of death in the first 3 postretransplant months compared to non-HCV patients (HR, 0.98; 95% CI, 0.77-1.23; $P = 0.83$), significantly increased covariate-adjusted mortality risk was observed during the postretransplant follow-up periods of 3 to 6 months (HR, 2.04; 95% CI, 1.31-3.18; $P = 0.002$), 6 to 12 months (HR, 2.19; 95% CI, 1.38-3.46; $P < 0.001$), and 1 to 2 years (HR, 1.81; 95% CI, 1.08-3.03; $P = 0.03$). After the first 2 postretransplant years, the relative mortality risk for HCV recipients was higher, but not statistically significant, compared with non-HCV recipients (HR, 1.25; 95% CI, 0.76-2.07; $P = 0.38$).

Mortality HRs by age group are presented in Table 6. When compared with non-HCV retransplant recipients, significantly increased risk of death for HCV recipients was observed only for those younger than 40 years of age (18-29 years: HR, 4.30; 95% CI, 1.83-10.11; $P < 0.001$; 30-39 years: HR, 2.49; 95% CI, 1.38-4.49; $P = 0.003$).

Because higher rates of allograft injury associated with HCV have been demonstrated in more recent

Table 5. Covariate-Adjusted Mortality Hazard Ratios (HRs) ± 95% Confidence Interval (CI) by Postoperative Time Intervals Following Retransplantation of Hepatitis C Virus Recipients*

Posttransplant period (months)	HR	CI	*P*
0-3	0.98	0.77-1.23	0.83
3-6	2.04	1.31-3.18	0.002
6-12	2.12	1.38-3.46	<0.001
12-24	1.81	1.08-3.03	0.03
>24	1.25	0.76-2.07	0.78

*Compared with hepatitis C virus–negative recipients.

years,[3] the adjusted relative mortality risk for HCV retransplant recipients was compared to non-HCV recipients by year of retransplantation (Table 7). While mortality risk was similar for HCV and non-HCV recipients who underwent retransplantation between 1997 and 1999, HCV recipients who underwent retransplantation between 2000 and 2002 had significantly higher risk of death (HR, 1.57; 95% CI, 1.22-2.01; $P < 0.001$).

Table 7. Covariate-Adjusted Mortality Hazard Ratios (HRs) ± 95% Confidence Interval (CI) by Year of Retransplantation for Hepatitis C Virus Recipients*

Year	HR	CI	*P*
1997	1.04	0.73-1.49	0.81
1998	1.25	0.84-1.86	0.26
1999	1.11	0.75-1.65	0.59
2000-2002	1.57	1.22-2.01	<0.001

*Compared with hepatitis C virus–negative recipients.

Discussion

Compared with primary transplantation, liver retransplantation results in significantly decreased patient and graft survival.[30] As corroborated in the present study, HCV infection in those undergoing retransplantation independently predicts an increased risk of death.[23] The 30% increase in mortality for HCV retransplant recipients demonstrated in the present study was considerably increased compared with the 20% increase for HCV recipients at 5 years that was previously demonstrated for primary transplant.[31] To potentially improve utilization of the limited supply of donor livers, some authors have questioned liver retransplantation in some settings, including recipients with HCV.[25-28,32-34] The present study set out to identify risk factors for mortality in HCV retransplant recipients in order to guide more optimal patient and donor selection and to improve outcomes.

Surprisingly, younger age was associated with higher mortality for recipients with HCV undergoing liver retransplantation when compared with those of similar age without HCV. This may reflect a willingness to retransplant younger patients with higher severity of illness or more virulent HCV infection in this population.

When compared with those without HCV infection, the present study demonstrated that retransplant recipients with HCV had a significantly increased risk for mortality from 3 to 24 months after retransplantation. Roayaie et al.[34] reported nearly 50% mortality within the first 6 months after retransplantation for HCV-induced primary graft failure. A total of two thirds of these deaths were associated with infection, with peritonitis and pneumonia as the most common.[34] Although the increased mortality risk during the early postoperative retransplant period in HCV recipients appears to be infection related,[34] the exact mechanism underlying this connection remains poorly understood. Possible contributors include an immunomodulatory effect of the HCV virus itself or the generally debilitated state of the recipient. Careful screening of potential recipients for sources of bacterial or fungal pathogens should be considered prior to and during the early period following retransplantation.

Table 6. Covariate-Adjusted Mortality Hazard Ratios (HRs) ± 95% Confidence Interval (CI) by Age Group for Hepatitis C Virus Retransplant Recipients*

Recipient age (years)	HR	CI	*P*
18-29	4.30	1.83-10.12	<0.001
30-39	2.49	1.38-4.49	0.003
40-49	1.17	0.91-1.52	0.23
50-59	1.22	0.91-1.64	0.18
≥60	1.20	0.77-1.86	0.43

*Compared with hepatitis C virus–negative recipients.

While the incidence of retransplantation in HCV recipients appears to be increasing,[24] the present study also demonstrates a significant increase in the adjusted risk of mortality for HCV retransplant recipients between the years of 2000 to 2002, when compared with non-HCV recipients. These findings parallel those of Berenguer et al.,[3] who demonstrated a progressive increase in the rate of HCV-induced allograft injury for those recently transplanted compared to those transplanted in prior years.

While the use of older donors is associated with acceptable outcomes for liver transplantation in general,[35] the present study demonstrated that the use of donors 50 years and older was associated with a significantly increased risk for death in HCV retransplant recipients. However, the trend toward the use of older donors does not explain the increased mortality risk for HCV retransplant recipients in more recent years,[36] since the calendar time trend was adjusted for donor age. Possible explanations may include changes in immunosuppression or an increased virulence of the hepatitis C virus itself.

Prior studies have led some authors to recommend that retransplantation in HCV recipients should be avoided in those with elevated serum creatinine and bilirubin.[24] This is contrary to the current model for end-stage liver disease–based organ allocation system, in which higher priority is given to patients with higher serum creatinine and bilirubin levels, on the basis of higher predicted risk of pretransplant death. However, the current liver allocation system is not specifically designed to offer organs to patients with the best chance of long-term survival. Berenguer et al.[37] demonstrated that 42% of recipients with HCV-induced allograft cirrhosis had at least 1 episode of decompensation, which was associated with a 10% 3-year survival.While the present and prior studies suggest that better outcomes may be achieved after retransplantation in HCV recipients if performed at a lesser acuity of illness, the current model for end-stage liver disease allocation system's conceptual basis is antithetical to this concept. Although survival following retransplantation of HCV recipients may be inferior to others, we hypothesize that the poor 3-year survival without transplant makes it likely that HCV recipients may accrue a quantifiable survival benefit with retransplantation.

Several studies have been published evaluating the risk of death following liver retransplantation for hepatitis C recipients.[5,23,26,28,30,34] However, unlike the present study of 1,718 recipients, most have been single-center studies evaluating a relatively small number of patients. A prior study by Yoo et al.[23] also evaluated outcomes in a similar population using the United Network for Organ Sharing database. Unlike our study, this publication did not include further analysis investigating which characteristics or groups of HCV liver recipients were at the greatest risk of mortality. Our study is the first to demonstrate the continuing increased risk of mortality in recent retransplant recipients (those who underwent retransplantation between the years 2000-2002), a more detailed analysis of the effects of donor age, and the surprising result that younger retransplant recipients have an increased relative risk for death. Overall, the higher mortality risk for HCV retransplant recipients has been clearly demonstrated when compared to those with other etiologies of liver disease. Attention to other risk factors may help lower the death rate in this group of patients. While an increased serum creatinine and bilirubin will often be a functional requirement for retransplantation under the model for end-stage liver disease–based allocation system, attention to other risk factors, such as donor and recipient age and requirement for ICU care preoperatively, may help improve outcomes.

References

1. 2003 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1993-2002. Rockville, MD: HHS/HRSA/SPB/DOT; UNOS; URREA.
2. Gane EJ, Portmann BC, Naoumov NV, Smith HM, Underhill JA, Donaldson PT, et al. Long-term outcome of hepatitis C infection after liver transplantation. N Engl J Med 1996;334:815-820.
3. Berenguer M, Ferrell L, Watson J, Prieto M, Kim M, Rayon M, et al. HCV-related fibrosis progression following liver transplantation: increase in recent years. J Hepatol 2000;32:673-684.
4. Berenguer M. Natural history of recurrent hepatitis C. Liver Transpl 2002;8:S14-S18.
5. Berenguer M, Prieto M, Palau A, Rayon JM, Carrasco D, Juan FS, et al. Severe recurrent hepatitis C after liver retransplantation for hepatitis C virus-related graft cirrhosis. Liver Transpl 2003;9:228-235.
6. Dickson RC, Caldwell SH, Ishitani MB, Lau JY, Driscoll CJ, Stevenson WC, et al. Clinical and histologic patterns of early graft failure due to recurrent hepatitis C in four patients after liver transplantation. Transplantation 1996;61:701-705.
7. Doughty AL, Spencer JD, Cossart YE, McCaughan GW. Cholestatic hepatitis after liver transplantation is associated with persistently high serum hepatitis C virus RNA levels. Liver Transpl Surg 1998;4:15-21.
8. Schluger LK, Sheiner PA, Thung SN, Lau JY, Min A, Wolf DC, et al. Severe recurrent cholestatic hepatitis C following orthotopic liver transplantation. Hepatology 1996;23:971-976.
9. Taga SA, Washington MK, Terrault N, Wright TL, Somberg KA, Ferrell LD. Cholestatic hepatitis C in liver allografts. Liver Transpl Surg 1998;4:304-310.
10. Pelletier SJ, Iezzoni JC, Crabtree TD, Hahn YS, Sawyer RG, Pruett TL. Prediction of liver allograft fibrosis after transplantation for hepatitis C virus: persistent elevation of serum transaminase levels versus necroinflammatory activity. Liver Transpl 2000;6:44-53.
11. Jain A, Demetris AJ, Manez R, Tsamanadas AC, Van Thiel D, Rakela J, et al. Incidence and severity of acute allograft rejection in liver transplant recipients treated with alfa interferon. Liver Transpl Surg 1998;4:197-203.
12. Singh N, Gayowski T, Wannstedt CF, Shakil AO, Wagener MM, Fung JJ, Marino IR. Interferon-alpha for prophylaxis of recurrent viral hepatitis C in liver transplant recipients: a prospective, randomized, controlled trial. Transplantation 1998;65:82-86.
13. Bizollon T, Palazzo U, Ducerf C, Chevallier M, Elliott M, Baulieux J, et al. Pilot study of the combination of interferon alfa and ribavirin as therapy of recurrent hepatitis C after liver transplantation. Hepatology 1997;26:500-504.
14. Feray C, Samuel D, Gigou M, Paradis V, David MF, Lemonnier C, et al. An open trial of interferon alfa recombinant for hepatitis C after liver transplantation: antiviral effects and risk of rejection. Hepatology 1995;22:1084-1089.
15. Sheiner PA, Boros P, Klion FM, Thung SN, Schluger LK, Lau JY, et al. The efficacy of prophylactic interferon alfa-2b in preventing recurrent hepatitis C after liver transplantation. Hepatology 1998;28:831-838.
16. Ahmad J, Dodson SF, Demetris AJ, Fung JJ, Shakil AO. Recurrent hepatitis C after liver transplantation: a nonrandomized trial

of interferon alfa alone versus interferon alfa and ribavirin. Liver Transpl 2001;7:863-869.
17. Mukherjee S, Rogge J, Weaver L, Schafer DF. Pilot study of pegylated interferon alfa-2b and ribavirin for recurrent hepatitis C after liver transplantation. Transplant Proc 2003;35:3042-3044.
18. Shuhart MC, Bronner MP, Gretch DR, Thomassen LV, Wartelle CF, Tateyama H, et al. Histological and clinical outcome after liver transplantation for hepatitis C. Hepatology 1997;26:1646-1652.
19. Ghobrial RM, Farmer DG, Baquerizo A, Colquhoun S, Rosen HR, Yersiz H, et al. Orthotopic liver transplantation for hepatitis C: outcome, effect of immunosuppression, and causes of retransplantation during an 8-year single-center experience. Ann Surg 1999;229:824-831.
20. Charlton M, Seaberg E, Wiesner R, Everhart J, Zetterman R, Lake J, et al. Predictors of patient and graft survival following liver transplantation for hepatitis C. Hepatology 1998;28:823-830.
21. Casavilla A, Mateo R, Rakela J, Irish W, Demetris AJ, Starzl TE. Impact of hepatitis C viral infection on survival following primary liver transplantation under FK506 (Prograft) [Abstract]. Hepatology 1994;20:133A.
22. Maor-Kendler Y, Batts KP, Burgart LJ, Wiesner RH, Krom RA, Rosen CB, Charlton MR. Comparative allograft histology after liver transplantation for cryptogenic cirrhosis, alcohol, hepatitis C, and cholestatic liver diseases. Transplantation 2000;70:292-297.
23. Yoo HY, Maheshwari A, Thuluvath PJ. Retransplantation of liver: primary graft nonfunction and hepatitis C virus are associated with worse outcome. Liver Transpl 2003;9:897-904.
24. Rosen HR, Martin P. Hepatitis C infection in patients undergoing liver retransplantation. Transplantation 1998;66:1612-1616.
25. Rosen HR. Retransplantation for hepatitis C: implications of different policies. Liver Transpl 2000;6(Suppl 2):S41-S46.
26. Sheiner PA, Schluger LK, Emre S, Thung SN, Lau JY, Guy SR, et al. Retransplantation for recurrent hepatitis C. Liver Transpl Surg 1997;3:130-136.
27. Sheiner PA. Retransplantation for hepatitis C: should it be performed? Yes. Liver Transpl Surg 1997;3(Suppl 1):S18-S19.
28. Ghobrial RM. Retransplantation for recurrent hepatitis C. Liver Transpl 2002;8:S38-S43.
29. Social Security Administration Death Master File. Springfield, VA: Federal Computer Products Center, National Technical Information Service, U.S. Department of Commerce.
30. Facciuto M, Heidt D, Guarrera J, Bodian CA, Miller CM, Emre S, et al. Retransplantation for late liver graft failure: predictors of mortality. Liver Transpl 2000;6:174-179.
31. Velidedeoglu E, Mange KC, Frank A, Abt P, Desai NM, Markmann JW, et al. Factors differentially correlated with the outcome of liver transplantation in hcv+ and HCV- recipients. Transplantation 2004;77:1834-1842.
32. Biggins SW, Terrault NA. Should HCV-related cirrhosis be a contraindication for retransplantation? Liver Transpl 2003;9:236-238.
33. Forman LM. To transplant or not to transplant recurrent hepatitis C and liver failure. Clin Liver Dis 2003;7:615-629.
34. Roayaie S, Schiano TD, Thung SN, Emre SH, Fishbein TM, Miller CM, Schwartz ME. Results of retransplantation for recurrent hepatitis C. Hepatology 2003;38:1428-1436.
35. Oh CK, Sanfey HA, Pelletier SJ, Sawyer RG, McCullough CS, Pruett TL. Implication of advanced donor age on the outcome of liver transplantation. Clin Transplant 2000;14:386-390.
36. Berenguer M, Prieto M, San Juan F, Rayon JM, Martinez F, Carrasco D, et al. Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipients. Hepatology 2002;36:202-210.
37. Berenguer M, Prieto M, Rayon JM, Mora J, Pastor M, Ortiz V, et al. Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. Hepatology 2000;32:852-858.