The Association Between Hepatitis C Infection and Survival After Orthotopic Liver Transplantation

LISA M. FORMAN,* JAMES D. LEWIS,* JESSE A. BERLIN,* HAROLD I. FELDMAN,* and MICHAEL R. LUCEY1

*From the Center for Clinical Epidemiology and Biostatistics and the Department of Biostatistics and Epidemiology; †Renal-Electrolyte and Hypertension Division; ‡Division of Gastroenterology, University of Pennsylvania, Philadelphia, Pennsylvania; and the §Section of Gastroenterology and Hepatology, University of Wisconsin-Madison School of Medicine, Madison, Wisconsin

See editorial on page 1162.

Background & Aims: The effect of hepatitis C viral (HCV) infection on patient and allograft survival after orthotopic liver transplantation is controversial. Hepatitis C recurrence after transplant is inevitable, but studies to date have not found a survival difference between recipients with and without HCV.

Methods: Using data from the United Network for Organ Sharing, we performed a retrospective cohort study of 11,036 patients who underwent 11,791 liver transplants between 1992 and 1998. The hazard rates of patient and allograft survival for patients who were HCV-positive as compared with patients who were HCV-negative were assessed by proportional-hazards analysis, with adjustment for potential confounding variables, including donor, recipient, and transplant center characteristics.

Results: Liver transplantation in HCV-positive recipients was associated with an increased rate of death (hazard ratio, 1.23; 95% confidence interval [CI], 1.12–1.35) and allograft failure (hazard ratio, 1.30; 95% CI, 1.21–1.39), as compared with transplantation in HCV-negative recipients. This reduction in survival persisted after adjusting for potential confounders. There was an interaction between HCV and sex ($P < 0.001$) with the effect of HCV on survival being most pronounced in female recipients (patient survival hazard ratio, 1.56; 95% CI, 1.35–1.81; allograft survival hazard ratio, 1.51; 95% CI, 1.34–1.70). Conclusions: HCV infection significantly impairs patient and allograft survival after liver transplantation.

Liver transplantation is the treatment of choice for many patients with end-stage liver disease. Cirrhosis secondary to hepatitis C viral (HCV) infection, alone or in combination with alcohol use, is the leading indication for liver transplantation among adults in the United States.1 After transplantation into an HCV-infected recipient, infection of the allograft by HCV is inevitable. HCV-induced allograft hepatitis and fibrosis/cirrhosis occur in 75%–80% and 10%–21% of recipients at 5 years, respectively.2,3 Furthermore, a syndrome called fibrosing cholestatic hepatitis occurs in up to 10% of patients infected with HCV and leads to accelerated allograft failure and death.4,5

Despite the high incidence of HCV-induced allograft injury, prior studies have not reported higher mortality rates in HCV-infected recipients.2,6–8 These studies have used data from single centers or small multicenter databases. The primary objective of this study was to compare patient and allograft survival after transplant in patients with and without HCV infection using a large national database.

Materials and Methods

Study Cohort

The study design was approved by the institutional review board of the University of Pennsylvania. We performed a retrospective cohort study using data from the United Network for Organ Sharing (UNOS) Scientific Registry for Liver Transplantation. Data was available for all adults age 18 or older who underwent whole organ orthotopic liver transplantation (OLT) between January 1992 and December 1998 with follow-up through December 1999. In accordance with our study design, patients who underwent simultaneous combined organ transplants, partial transplants, or whose initial transplant was before 1992 were excluded from the dataset provided by UNOS. The starting date of our cohort was selected to coincide with the advent of improved sensitivity and specificity of anti-HCV testing.9

HCV status was determined using results of HCV serological testing (enzyme immunoassay [EIA], recombinant immunoassay [RIBA], or RNA). Recipients with recorded positive HCV serologies were defined as having HCV infection.
and recipients with recorded negative HCV serologies were defined as being HCV-negative.

Subjects with UNOS codes indicating the diagnosis of HCV infection (4204 “HCV postnecrotic cirrhosis,” 4206 “postnecrotic cirrhosis, type B and C,” 4216 “Laennec’s cirrhosis and HCV”) but with negative HCV serological test results were excluded. Patients were also excluded if they underwent OLT for acute hepatic failure (N = 11,340), had absent or equivocal HCV serology (UNOS codes “cannot disclose, indeterminate, not done, unknown, missing”) (N = 7,373), or had absent follow-up data (N = 227). After all exclusions, 11,036 patients and 11,791 transplants were available for analysis.

Definitions

Primary endpoints were death and allograft failure. Patient survival was defined as time from initial transplant until date of death or last known follow-up. Allograft survival was defined as time from transplant until retransplantation or death, whichever came first. Patients with intact allografts at the end of study period were censored. Patients lost to follow-up were censored at the date last known to be alive for both analyses of patient and allograft survival.

Potential Confounders

Potential confounders included recipient, donor, and center variables. Recipient characteristics at the time of transplantation included age, sex, race, cytomegalovirus status, diabetes mellitus, hypertension, recipient location immediately before transplantation (intensive care unit [ICU], non-ICU hospital), use of life support (defined as inotropic for blood pressure support, mechanical ventilation, or the notation “on life support”), hepatic encephalopathy, spontaneous bacterial peritonitis, cachexia, ascites, variceal bleeding and preoperative serum total bilirubin, prothrombin time, albumin, and creatinine as recorded on the UNOS transplant or candidate registration forms. Owing to 2 changes in the definition of UNOS status during the study, we did not include it specifically as a variable, and instead used recipient location as its surrogate. Donor factors included age, sex, race, and cytomegalovirus status. Center factors included year of transplantation, number of transplants performed the previous year, and cold and warm ischemia times. We were unable to identify individual transplant centers.

Implausible Data

To maintain the integrity of the database, data were examined for outliers. Plausible ranges were defined as: creatinine (mg/dL) 0.1–15.0 (8.8–132.6 μmol/L); bilirubin (mg/dL) 0.1–45.0 (1.7–769.5 μmol/L); prothrombin time (seconds) 9.0–90.0; albumin (g/dL) 0.7–6.0 (7.0–60.0 g/L); warm ischemia (minutes) 1.0–90.0; and cold ischemia (hours) 1.0–20.0. Implausible data were excluded.

Data were missing on serum chemistries for 5.0% of transplants, on cold and warm ischemia times for 6.0% and 28%, respectively, on general medical factors (e.g., diabetes mellitus, hypertension) for 10.0%, and on liver-related factors (e.g., ascites, encephalopathy) for 0.02%–8.0%. Data on all potential confounders were available for 6,174 patients.

Statistical Analysis

The Student t test and the χ2 test were used for the statistical comparison of means and proportions between HCV-positive and HCV-negative groups. Variables not distributed normally were compared using the Wilcoxon rank sum test.

Unadjusted patient and allograft survival were estimated using the Kaplan–Meier method with comparison between groups performed using the log-rank test. The assumption of proportional hazards was tested by graphical and weighted residual methods and Cox proportional-hazards analysis was used to identify factors independently associated with patient and allograft survival. Each potential confounding variable was individually examined in a model containing only HCV and that variable. If inclusion of the given variable yielded an adjusted hazard ratio that differed from the crude hazard ratio for the association of HCV and survival by 10% or more, that variable was included in the final model. To assess for the potential influence of missing data, we assigned values to the missing observations for each potential confounding variable using the method of simple imputation based on all the other variables in the full proportional-hazards model (except for the outcome variable). The Cox model was also used to examine the potential interaction between HCV status and sex, race, age, and year of transplantation. Patients who were not infected with HCV were further subdivided into categories based on UNOS diagnostic codes and survival analyses comparing HCV-infected patients and these subgroups were performed.

For allograft survival, we performed an analysis, using robust variance estimation, where we adjusted for lack of statistical independence related to the inclusion of more than 1 allograft per patient.

We chose a very specific definition of HCV infection based on serology. To test the possibility that our results may be biased by our strict definition of HCV infection, we performed a series of sensitivity analyses. In the first sensitivity analysis, we defined patients as having HCV if either HCV serology or UNOS diagnostic code indicated HCV infection was present (N = 6,795). All other patients were considered to be HCV-negative (N = 11,949). In an additional sensitivity analysis, we compared patients who had positive HCV serology (N = 4,439) to all others (N = 14,305).

All statistical analyses were performed with STATA 6.0 software (Stata Corporation, College Station, TX). All reported P values are 2-sided.

Results

Patient Characteristics at the Time of Transplantation

The study cohort included 11,036 patients who underwent 11,791 liver transplants (Figure 1). A total of 4,439 recipients were HCV-positive and 6,597 were
HCV-negative. Documentation of HCV infection included only RNA-positive in 4, only RIBA-positive in 162, only EIA-positive in 2749, both RNA and EIA-positive in 31, both RNA and RIBA-positive in 5, and both RIBA and EIA-positive in 1454. The characteristics of the HCV-positive and HCV-negative patients are summarized in Table 1. Statistically, all characteristics were different ($P < 0.0001$), except for recipient and donor race and history of diabetes mellitus, reflecting the cohort’s very large sample size. Clinically, the HCV-positive group had a greater percentage of male recipients (69.7% vs. 54.6%), a lower total bilirubin (4.8 vs. 6.6 mg/dL [82.1 vs. 112.9 µmol/L]), and a lower percentage of patients in the ICU and on life support at the time of transplant (12.3 vs. 14.2%, and 6.4 vs. 7.6%, respectively). The prevalence of HCV infection among patients receiving liver transplants increased from 20% in 1992 to 45.1% in 1998.

Patient Survival

HCV infection was associated with significantly shorter patient survival. Using the Kaplan–Meier method, patient survival rates with HCV infection were 86.4%, 77.8%, and 69.9% at 1, 3, and 5 years, respectively, as compared with 87.5%, 81.8%, and 76.6%, among patients without HCV infection ($P < 0.0001$, log-rank test) (Figure 2).

Univariate analysis yielded a hazard ratio of 1.23 (95% confidence interval [CI], 1.12–1.35; $P < 0.0001$) for HCV-positive compared with HCV-negative recipients. Adjusting individually for any of the potential confounding variables did not substantially change the HCV hazard ratio. Nonetheless, we wanted to verify that adjusting simultaneously for multiple potential confounders would not change our conclusion. Multivariable analysis on those patients with complete data (N = 6174) revealed a HCV hazard ratio of 1.17 (95% CI, 1.03–1.32; $P = 0.017$). To ensure that we were not introducing bias by excluding patients with incomplete data, a

![Figure 2. Kaplan–Meier estimates of patient survival according to hepatitis C status. The number of patients in each group at each time point is indicated.](image-url)
univariate analysis using these same 6174 patients was performed and revealed an unadjusted hazard ratio of 1.13 (95% CI, 1.00–1.28; P = 0.048). This suggests that the change in hazard ratios, after adjustment for covariates, from 1.23 to 1.17 was related to excluding patients with incomplete data and not caused by adjusting for confounding per se.

Imputation methods were also used to substitute for the missing data on confounders, and the final multivariable model using all patients (N = 11,036) yielded a HCV hazard ratio of 1.26 (95% CI, 1.15–1.39; P < 0.0001), nearly identical to the unadjusted value of 1.23 (Table 2).

The UNOS registry identified the causes of death in 42.4% of patients. Causes of death were similar in both the HCV-positive and HCV-negative groups and included infection (30.8% vs. 35.3%), cardiac complications (17.0% vs. 17.1%), graft failure (10.6% vs. 9.6%), and multi-organ failure (8.1% vs. 7.7%).

Allograft Survival

HCV infection was associated with significantly shorter allograft survival. Using the Kaplan–Meier method, allograft survival rates with HCV infection were 76.9%, 66.4%, and 56.8% at 1, 3, and 5 years, respectively as compared with 80.1%, 73.3%, and 67.7%, among patients without HCV infection (P < 0.0001, log-rank test) (Figure 3).

Univariate analysis yielded a hazard ratio of 1.30 (95% CI, 1.21–1.39) for HCV-positive compared with HCV-negative recipients. None of the potential confounding variables individually changed the HCV crude hazard ratio by more than 10%.

Multivariable analysis with all potential confounders on those patients with complete data yielded a hazard ratio of 1.28 (95% CI, 1.15–1.40; P < 0.0001) for HCV-positive compared with HCV-negative recipients. None of the potential confounding variables individually changed the HCV hazard ratio after multivariable analysis.

Multivariable analysis of only the patients with complete data revealed an unadjusted hazard ratio of 1.29 (95% CI, 1.17–1.42; P < 0.0001). Multivariable analysis after imputation using all patients demonstrated a HCV hazard ratio of 1.29 (95% CI, 1.21–1.39; P < 0.0001) (Table 2). The results did not change after adjusting for multiple allografts per patient.

Sensitivity Analysis

When survival analyses were performed on the entire cohort (before excluding those with absent or equivocal serology), both patient and allograft survival was reduced in the HCV-positive recipients. Both sensitivity analyses (see Materials and Methods) yielded similar results. For example, when using the least stringent definition of HCV infection to include either a UNOS diagnosis code indicating HCV or a positive HCV serology, the hazard ratios for patient and allograft survival were 1.16 (95% CI, 1.09–1.24; P < 0.0001) and 1.19 (95% CI, 1.13–1.25; P < 0.0001), respectively, again very similar to the results using serology alone to define HCV positivity.

Effect Modification

A statistical interaction was identified between HCV status and sex (P < 0.001) for patient and allograft survival, but not with age, race, or year of transplantation. Female recipients with HCV infection had significantly worse patient and allograft survival rates than female recipients without HCV infection; the hazard ratios were 1.16 (95% CI,1.09–1.24; P < 0.0001) and 1.19 (95% CI, 1.13–1.25; P < 0.0001), respectively, whereas the association with HCV was weaker for males. This difference persisted when sex was analyzed as a function of donor and recipient matching/mismatching (Table 3). To examine whether the interaction was re-
Table 3. The Effect of Interaction Between HCV Status and Sex on Survival

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient survival hazard ratio (95% CI)</th>
<th>Allograft survival hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV+</td>
<td>1.23 (1.12–1.35)</td>
<td>1.30 (1.21–1.39)</td>
</tr>
<tr>
<td>Female</td>
<td>1.56 (1.35–1.81)</td>
<td>1.51 (1.34–1.70)</td>
</tr>
<tr>
<td>Male</td>
<td>1.06 (0.95–1.19)</td>
<td>1.18 (1.08–1.29)</td>
</tr>
<tr>
<td>DM → RM</td>
<td>1.12 (0.97–1.29)</td>
<td>1.24 (1.11–1.39)</td>
</tr>
<tr>
<td>DM → RF</td>
<td>1.54 (1.26–1.89)</td>
<td>1.46 (1.23–1.72)</td>
</tr>
<tr>
<td>DF → RM</td>
<td>0.98 (0.81–1.19)</td>
<td>1.09 (0.95–1.26)</td>
</tr>
<tr>
<td>DF → RF</td>
<td>1.58 (1.28–1.96)</td>
<td>1.56 (1.32–1.85)</td>
</tr>
</tbody>
</table>

Excluding cholestatics:

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient survival hazard ratio (95% CI)</th>
<th>Allograft survival hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.38 (1.18–1.62)</td>
<td>1.37 (1.21–1.56)</td>
</tr>
<tr>
<td>Male</td>
<td>0.96 (0.85–1.08)</td>
<td>1.14 (1.03–1.25)</td>
</tr>
</tbody>
</table>

NOTE. The hazard ratio is for survival of HCV-positive compared with HCV-negative recipients. CI, confidence interval; DM, donor male; RM, recipient male; RF, donor female; DF, recipient female.

*P < 0.05.

*aCholestatics refers to patients with primary sclerosing cholangitis or primary biliary cirrhosis.

Patient Survival of HCV-Positive vs. Subgroups of HCV-Negative Recipients

Survival analyses were also performed comparing HCV-positive recipients and subgroups of HCV-negative recipients (Tables 4 and 5). Patient survival of recipients with HCV infection was better than those transplanted for malignancy, worse than those transplanted for cholestatic or metabolic diseases, and comparable to those transplanted for hepatitis B infection, autoimmune hepatitis, cryptogenic cirrhosis, and alcoholic liver disease. Allograft survival was significantly worse in recipients with HCV infection compared with all other diagnostic subgroups except malignancy.

Discussion

HCV-associated cirrhosis has become the most common indication for OLT. Unlike previous studies, which reported similar patient and allograft survival rates when compared with uninfected controls, we found that HCV infection was associated with a 23% increased mortality rate and a 30% increased allograft failure rate. This effect persisted after adjustment for extensive clinical and biochemical parameters. These data were collected before attempts to reduce HCV viral load after transplantation, and therefore, represent the natural history of HCV after liver transplantation.

The design of our study differed from prior studies in several ways. Our study used nationally representative data and used stringent criteria for HCV-infectivity. Additionally, prior studies each had relatively small cohorts, the largest including 1075 patients. By comparison, our study, with a nearly 11-fold increase in sample size, is better powered to detect a survival difference.

This reduction in patient and allograft survival is not surprising. HCV infection of the allograft is inevitable, leading to allograft hepatitis in 50%–80% at 2 years and fibrosis/cirrhosis in 21% of patients at 5 years. HCV-related disease progression is accelerated in the posttransplant immunocompromised patient as compared with the pretransplant patient. Once cirrhosis occurs, decomposition and death are common.

Although HCV infection is associated with decreased patient and allograft survival in this study, patient survival is comparable to those transplanted for hepatitis B infection, autoimmune hepatitis, cryptogenic cirrhosis, and alcoholic liver disease.
infection, autoimmune hepatitis, cryptogenic cirrhosis, and alcohol-related liver disease. These findings are similar to those of Charlton et al. using the NIH Liver Transplantation Database. The HBV-positive 1 and 5-year patient survival of 87.4% and 78.6%, respectively, is somewhat higher than reported in prior studies. This discrepancy, however, can be explained by the recent use of hepatitis B immunoglobulin and lamivudine posttransplantation, particularly given the fact that 88.4% of the HBV infected patients were transplanted between 1995 and 1998. However, importantly allograft survival in HCV-positive patients is worse than in patients with all other indications except malignancy.

We found that the effect of HCV on survival is modified by recipient sex. Female recipients with HCV infection have 56% and 51% lower rates of patient and allograft survival compared with female recipients without HCV. This reduction in survival persists after excluding patients with cholestatic liver disease. This finding has not previously been shown and was unexpected. Perhaps the combination of the restored female hormone milieu, immunosuppression, and HCV posttransplant accounts for such a survival difference. This interaction needs to be examined further and confirmed using another large database, for example, the European Liver Transplantation Registry. The effect of HCV on survival was not modified by year of transplantation, suggesting that despite the higher rate of posttransplant fibrosis in HCV-positive patients transplanted most recently, as demonstrated by Berenguer et al., patient and allograft survival do not yet appear to be affected.

There are several potential limitations to this study. Studies using electronic databases are prone to misclassification bias. We took several steps to ensure that this was not a problem in our study. We classified patients according to recorded HCV serologies, not coded diagnoses. We excluded patients whose serologies were missing, equivocal, or were inconsistent with the UNOS code diagnosis. To ensure that exclusion of these patients did not bias our results, we performed sensitivity analyses using varying definitions of HCV infection. All sensitivity analyses showed similarly decreased survival in the HCV-infected group. Furthermore, although we used a strict definition of HCV-positivity, it is still difficult to accurately characterize the HCV status; the vast majority of patients lacked HCV-PCR testing and were instead diagnosed as having HCV infection with only a positive EIA. The minority of patients had supplementary confirmatory assays. Despite this, we believe our results are still valid for several reasons. Firstly, the positive predictive value of a positive EIA in the transplant population is high. Furthermore, it is unlikely that many patients undergoing transplant with a positive EIA have had successful treatment of their infection or have spontaneous clearance of the virus. Finally, and perhaps most importantly, even if we have misclassified uninfected patients as infected (and infected patients as uninfected), such information bias would bias the results to the null. Even with this potential misclassification, we still showed a survival difference.

Many patients were excluded in the multivariable analyses because of missing data. However, none of the confounders changed the HCV hazard ratio by 10% or more in bivariate analysis. Therefore, the unadjusted hazard ratio should be appropriate. Moreover, imputation methods showed similar results.

Although the study spans 8 years, the mean follow-up time was only 2.10 ± 1.48 years. However, the loss to follow-up was nondifferential and, therefore, should not bias the results. At year 4, there still remains a substantial 1500 patients available for analysis. Furthermore,
despite the mean survival time of approximately 2 years, a survival difference (both patient and allograft) is already demonstrated and it is likely that with longer and more complete follow-up, the differences in survival will become more apparent.

These data are derived from multiple centers. However, we were unable to account for center effects in our statistical analyses. If patient or allograft survival varies across centers, but the proportion of HCV-positive patients does not, our results could be biased. This problem would require adjustment to the estimated variance of the hazard ratios, using a “design effect” to account for the potential clustering by center. Given the unadjusted result we observed, it would require a design effect of close to 5 to move the observed effect from being statistically significant to being nonsignificant. Although this would represent a large design effect, we have no way of ruling it out.

If centers with relatively poor survival also had higher proportions of HCV-positive patients, then the associations we observed could potentially be caused by some unmeasured confounding characteristic of centers, rather than of individual patients within those centers. We believe this confounding is unlikely, because we performed analyses adjusted for several potentially important center characteristics (i.e., center size, year of transplant) and the adjustment had no effect on the estimated association between HCV and survival.

Although HCV-induced allograft injury has been shown to be possibly associated with factors such as genotype, pretransplant viral load, viral heterogeneity, and immunosuppression and rejection, the association between HCV and survival. Indeed, many recipient, donor, and center characteristics did affect outcome; however, none of the potentially confounding variables substantially changed the HCV hazard ratio. HCV infection was associated with significantly shorter patient and allograft survival, even after adjusting for confounders.

In conclusion, using nationally representative data, we found that HCV infection, the most common indication for OLT in the United States, is associated with decreased patient and allograft survival after OLT. The effect of HCV on survival is more pronounced in female HCV-infected patients represents an important focus for further research. Additional studies are needed to further explore the mechanisms underlying the reduction in survival and to identify which HCV-positive individuals are at greatest risk for poor survival.

References


Received June 29, 2001. Accepted December 31, 2001.
Address requests for reprints to: Lisa M. Forman, M.D., M.S.C.E., University of Pennsylvania, Division of Gastroenterology, 34th & Spruce Streets, 3 Ravdin, Philadelphia, Pennsylvania 19104. e-mail: formanl@mail.med.upenn.edu; fax: (215) 349-5915.
Supported in part by a training grant (DK-07740) and a center grant (K30-HL04134) from the National Institutes of Health and from a FDHN/AGA AstraZeneca LP Fellowship/Faculty Transition Award.
The authors thank John Holmes, Ph.D., and Kindra Wright, B.S., for their technical expertise and assistance as well as Erick Edwards, Ph.D., and Christine Tolleris, M.P.A., for providing us with the UNOS data.