Survival of Liver Transplant Recipients With Hemochromatosis in the United States

LEI YU*,‡ and GEORGE N. IOANNOU*,‡

*Division of Gastroenterology, Department of Medicine Veterans Affairs Puget Sound Health Care System and University of Washington, Seattle Washington; ‡Research Enhancement Award Program Veterans Affairs Puget Sound Health Care System

Background & Aims: **Earlier studies have suggested that patients with hemochromatosis have poor post-transplantation survival. We aimed to compare patients with hemochromatosis to those with other causes of liver disease with regard to post-transplantation survival.** ***Methods:*** **We compared the post-transplant survival of patients with and without hemochromatosis using data provided by the United Network for Organ Sharing on 50,306 adult, cadaveric liver transplantations performed in the United States between January 1, 1990, and July 18, 2006.** ***Results:*** **During 1990–1996, the post-transplantation survival of patients with hemochromatosis (n = 177) at 1 year (79.1%), 3 years (71.8%), and 5 years (64.6%) was lower than the average 1-year (86.4%), 3-year (79.5%), and 5-year (73.8%) survival of all other transplant recipients (hazard ratio for death, 1.38; 95% confidence interval [CI], 1.12–1.71). In contrast, during 1997–2006, patients with hemochromatosis (n = 217) had excellent 1-year (86.1%), 3-year (80.8%), and 5-year (77.3%) post-transplantation survival, which was not different from the 1-year (88.4%), 3-year (80.3%), and 5-year (74.0%) post-transplantation survival of all other transplant recipients (hazard ratio for death, 0.89; 95% CI, 0.65–1.22). Adjustment for donor and recipient characteristics did not substantially change these results. Compared with recipients without hemochromatosis, those with hemochromatosis were more likely to die of cardiovascular diseases and less likely to die as a result of graft failure.** ***Conclusions:*** **The post-transplantation survival of patients with hemochromatosis, which was previously reported to be poor, has been excellent in the United States during the past 10 years.**

It has been suggested that patients who undergo liver transplantation for cirrhosis related to hemochromatosis have a higher than average post-transplantation mortality. Kilpe et al[1] reported that 1-year survival after liver transplantation for hemochromatosis between 1982 and 1991 in 37 US centers was 54% (30/56), whereas the 1-year post-transplantation survival of all patients was 80% (4092/5180). Kowdley et al[2] reported that among 37 patients with hemochromatosis-related cirrhosis who underwent liver transplantation in 5 US centers between 1988 and 1993, 1-year post-transplantation survival was 58%. More recently, Kowdley et al[3] reported that the 1-year post-transplantation survival of 25 patients with *HFE*-related hemochromatosis who underwent liver transplantation at 1 of 12 US centers before 1996 was 64% which was lower than the 1-year post-transplantation survival (84%) of all liver transplant recipients in these 12 centers before 1996.

Those studies may not accurately reflect the current post-transplantation survival of patients with hemochromatosis for a number of reasons. All those studies analyzed liver transplantations performed before 1996, and survival in patients with hemochromatosis may have improved since then (for instance, as a result of more aggressive iron depletion before and after transplantation or more careful patient selection).[4–6] Those studies included a relatively small number of patients because hemochromatosis is a rare indication for liver transplantation. As a result, none of the previous studies adequately adjusted for other predictors of post-transplantation survival, such as donor age, cold ischemia time, recipient age, and causes of liver disease,[7] or directly compared the post-transplantation survival of patients with hemochromatosis-related cirrhosis with the post-transplantation survival of patients with other causes of cirrhosis such as viral hepatitis, alcoholic liver disease, or primary biliary cirrhosis. Finally, it is possible that those studies included patients with hemochromatosis-related cirrhosis with worse survival than the average post-transplantation survival of all patients with hemochromatosis-related cirrhosis in the United States.

To resolve these issues, we compared the post-transplantation survival of patients with hemochromatosis to the post-transplantation survival of patients with other causes of liver disease with and without adjusting for predictors of post-transplantation survival using data reported to the United Network for Organ Sharing

Abbreviations used in this paper: BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; UNOS, United Network for Organ Sharing.

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(UNOS) for all liver transplantations performed in the United States from January 1, 1990, until July18, 2006.[8]

Materials and Methods

Data Collection

Transplantation centers and organ procurement organizations in the United States are required to submit to UNOS[8] standardized data collection forms, including the "Transplant Candidate Registration Form," which contains patient information at the time of listing for liver transplantation; the "Deceased Donor Registration Form," which contains information on all consented recovered and nonrecovered donors; the "Transplant Recipient Registration Form," which includes the patient status at discharge, clinical information before and after transplantation, as well as treatment data; and the "Transplant Recipient Follow-up Form," which is generated 6 months after transplantation and on each subsequent transplantation anniversary and includes patient status and clinical and treatment information. These forms are currently submitted to UNOS electronically, and the information is entered into a single Standard Transplant Analysis and Research file that includes one record per transplantation event and the most recent follow-up information on patient status as of the date the file was created. The Standard Transplant Analysis and Research file created by UNOS on July 18, 2006, was kindly provided to the authors for this study.

Study Population

Of 63,679 liver transplantations involving recipients >18 years of age which were performed in the United States between January 1, 1990, and July 18, 2006, we excluded patients who had donors <10 or >75 years of age (n = 1472), living donors (n = 2040), split-liver donors (n = 763), and non–heart-beating donors (n = 916). We also excluded patients with multiple simultaneous organ transplantations (n = 2278) or previous liver transplantation (n = 5904), leaving 50,306 participants in univariate analyses. We divided these patients into 2 time periods, 1990–1996 (n = 16,286) and 1997–2006 (n = 34,020) for more direct comparison with previous studies performed before 1996 and to look for any changes in the post-transplantation survival of patients with hemochromatosis in more recent years for which no data are currently available.

We additionally wanted to explore whether any difference in post-transplantation survival between patients with and without hemochromatosis could be explained by differences in donor or recipient characteristics. For these multivariate analyses, we excluded patients with missing information in donor characteristics, including cold ischemia time (n = 5206), and race (n = 353), and recipient characteristics, including age (n = 1), body mass index (BMI; calculated as the weight in kilograms divided by the square of height in meters [kg/m^2]; n = 1375), race (n = 281), serum albumin (n = 1509), bilirubin (n = 368), and creatinine (n = 67). Finally, we excluded 943 patients with "very abnormal" values of cold ischemia time, BMI, serum bilirubin, creatinine, and albumin, (because they might have been recorded erroneously) and 183 with "implausible" values for these variables (almost certainly recorded erroneously), leaving 40,020 patients in multivariate analyses, including 13,342 who received transplants in 1990–1996 and 26,678 in 1997–2006. ("Very abnormal" values were defined as follows: cold ischemia time, 0.5 to <1 hour or >24 to 48 hours; BMI, 10–15 or 55–65; serum creatinine, >0 to <0.1 or >15 to 20 mg/dL; serum total bilirubin, >0 to <0.1 or 45–100 mg/dL; and serum albumin, >0 to <0.5 or >6 to 10 g/dL. "Implausible" were values even more extreme than the abnormal values).

Definition of Hemochromatosis and Comparable Liver Diseases

The recipient's primary diagnosis leading to liver transplantation was identified by using the UNOS variable "diag." This variable describes the recipient's primary diagnosis that was derived from information at discharge from the hospital after the transplantation, that is, after the explanted liver was also available for analysis. If the recipient's primary diagnosis at the time of discharge was not recorded, then the diagnosis at transplantation was used, and, if that was not available, the diagnosis at listing. By using this variable, we divided liver transplant recipients into the following categories: hemochromatosis, hepatitis C virus (HCV; including HCV and alcoholic liver disease or hepatitis B virus), hepatitis B virus, alcoholic liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, cryptogenic cirrhosis and fatty liver or nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma, acute hepatic necrosis (excluding acute viral hepatitis B and C and acute alcoholic hepatitis), and others.

We attempted to identify if any of the patients with a diagnosis of hemochromatosis also had a diagnosis of hepatocellular carcinoma by looking at secondary diagnoses, which have been reported to UNOS only since April 1, 1994. In addition, since the introduction of the model for end-stage liver disease allocation system on February 27, 2002, an "exception" has been recorded for patients with hepatocellular carcinoma who receive a high priority score, and this was also used to identify patients with hemochromatosis who also had hepatocellular carcinoma.

Predictors of Post-Transplantation Survival

We wanted to investigate whether any observed difference in post-transplantation survival between patients with and without hemochromatosis was due to differences in the following donor and recipient characteristics that are predictors of post-transplantation sur-