

## Liver Transplantation in Patients With Hepatic Iron Overload: Favorable or Unfavorable Outcome?

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Hepatic iron overload may be primary, most often caused by hereditary hemochromatosis (HHC), or secondary, related to transfusional iron loading, ineffective erythropoiesis or end-stage liver disease, particularly alcohol-induced liver disease, chronic hepatitis C, and  $\alpha_1$ -antitrypsin deficiency.<sup>1-4</sup> HHC is the most common genetic disease in Caucasians, with a typical prevalence rate of 5 per 1,000 in population surveys.<sup>1,2</sup> Based on previously known linkage of hereditary hemochromatosis to HLA-A3, Feder et al.<sup>5</sup> in 1996 identified the candidate gene through positional cloning in a cohort of patients with hemochromatosis and named it *HLA-H*, which was later renamed *HFE*.<sup>6</sup> Two missense mutations were identified, a substitution of tyrosine for cysteine at position 282 (C282Y) and a substitution of aspartate for histidine at position 63 (H63D). HHC is a disorder of iron metabolism characterized by inappropriate intestinal absorption of iron, progressive iron deposition in organ parenchymal cells, and eventual multiorgan failure in untreated individuals. The widely accepted criteria for the diagnosis of iron overload caused by HHC include 4 g or more of iron removed by phlebotomy (16 units of blood) before the onset of iron-limited erythropoiesis or at least one of the following results derived from liver biopsy: grade 3 or 4 stainable iron in hepatocytes, hepatic iron concentration greater than 80  $\mu\text{mol}$  (4,500  $\mu\text{g}$ ) per gram dry weight of liver tissue, and hepatic iron index (hepatic iron concentration divided by age) greater than 1.9.<sup>1,2</sup> The identification of specific mutations in the *HFE* gene of patients with HHC has permitted the introduction of genetic testing in the clinical setting. Most patients of Northern European descent with classic phenotypic HHC are homozygous for C282Y or, less commonly, compound C282Y/H63D heterozygotes.

The major target organs in patients with HHC include the liver, heart, pancreas, joints, and pituitary gland, putting untreated individuals at risk for cirrhosis and hepatocellular carcinoma, cardiomyopathy and cardiac arrhythmias, diabetes mellitus, arthropathy, and hypogonadotropic hypogonadism.<sup>1,2</sup> The risk of hepatocellular carcinoma in patients with HHC is substantial in patients who have progressed to advanced fibrosis or cirrhosis, with liver cancer causing up to 45% of deaths in patients with HHC.<sup>7,8</sup> Early diagnosis and

treatment of HHC with phlebotomy to remove excess iron is associated with a good prognosis.<sup>1,2,7</sup> For those patients who progress to end-stage liver disease, liver transplantation is the only available treatment option.

Secondary iron overload is increasingly recognized in patients with end-stage liver disease due to a number of different causes, although most often in patients with hepatocellular liver diseases such as alcohol-induced liver disease and chronic hepatitis but only occasionally in patients with chronic cholestatic liver diseases such as primary biliary cirrhosis or primary sclerosing cholangitis.<sup>3,4,9,10</sup> There is also emerging evidence that the majority of patients with end-stage liver disease and hepatic iron overload do not have the common *HFE* mutations.<sup>4,11-13</sup> Among 918 patients who had a liver transplantation at Mt. Sinai, 15 patients with miscellaneous liver diseases were identified as having hepatic iron overload and 4 patients had the clinical diagnosis of HHC.<sup>4</sup> Of the 15 patients with iron overload, 1 was homozygous for C282Y, 1 was a C282Y heterozygote, 6 were H63D heterozygotes, and 7 had neither mutation. Two of the 4 patients with suspected HHC were homozygous for C282Y, whereas the other 2 had neither mutation. In a review of 41 explants with a hepatic iron index greater than 1.9, only 4 (9.8%) were C282Y homozygotes.<sup>11</sup> A Canadian report showed that the prevalence of C282Y heterozygotes among transplant recipients, *i.e.*, 26 of 304 (8.6%) recipients, was not different from the prevalence rate in blood donors (8.4%).<sup>12</sup> In this study, stainable iron ( $\geq 2+$ ) was more frequent in C282Y heterozygotes (23%) than in patients with wild-type *HFE* (14%), but mean hepatic iron concentration was not significantly different. Data on 144 explants with moderately or severely increased hepatic iron from 22 liver transplant centers were submitted to the National Hemochromatosis Transplant Registry.<sup>13</sup> After excluding C282Y homozygotes and C282Y/H63D compound heterozygotes, the frequency of C282Y heterozygosity in livers with iron overload was 9 of 42 (21%), which approached statistical significance compared with the expected frequency in North America ( $P = .08$ ). The frequency of H63D heterozygosity was approximately 25%, which is the expected frequency in the general population. Thus, patients transplanted for end-stage liver disease associated with hepatic iron overload may have true HHC and be homozygous for C282Y, be heterozygous for either the C282Y or H63D mutation or, most commonly, have neither mutation.

The survival rate after liver transplantation in patients with hepatic iron overload and clinically suspected HHC appears to be decreased based on reports by a number of individual centers and by pooling data that have been compared with recipients transplanted for other conditions.<sup>11,14-19</sup> An analysis of 5,180 liver transplant recipients from 37 transplant centers reporting data to Medicare showed 1-year and 5-year survival rates of 79% and 69% overall, respectively, but only 54% and

Abbreviation: HHC, hereditary hemochromatosis.

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43%, respectively, for 56 patients with the clinical diagnosis of hemochromatosis.<sup>14</sup> This was a heterogeneous population of patients, including some pediatric cases, and it is likely that many of these patients did not have HHC. However, the 1-year survival rate from the Medicare data of patients with hepatic iron overload was remarkably similar in two institutional reports published at about the same time. In a report from the University of Pittsburgh, the 1-year survival of 21 patients undergoing liver transplantation for hemochromatosis was 52%,<sup>15</sup> whereas 9 patients transplanted at California Pacific Medical Center for hemochromatosis had an actuarial survival rate of 53%.<sup>16</sup> The excess mortality in these earlier reports was attributed to cardiac, infectious, and malignant complications after liver transplantation, including hepatocellular carcinoma. It was speculated that recognition of HHC pretransplantation and treatment with phlebotomy or chelation might reduce the cardiac complications posttransplantation.<sup>16</sup> In fact, an earlier preliminary report from the University of Pittsburgh described a good outcome in 6 patients with the clinical diagnosis of HHC.<sup>17</sup> Five of 6 (83%) survived, and all patients had prolonged pretransplantation phlebotomy and/or desferoxamine, which may have favorably influenced survival. Finally, in a more recent report from the Mayo Clinic of 456 consecutive liver transplants, 41 explants with a hepatic iron index of greater than 1.9 were matched to 41 cases without increased hepatic iron.<sup>11</sup> Of the 41 patients, only 4 were C282Y homozygotes. The 5-year actuarial survival was significantly lower in recipients with hepatic iron overload compared with matched controls (48% vs. 77%), and the reduced survival was attributed mainly to bacterial and fungal infections.<sup>11</sup>

The heterogeneity of patients in the earlier report by Kilpe et al.<sup>14</sup> and from individual centers<sup>15-17</sup> was the stimulus to pool data from 5 centers on a more uniform group of patients documented as having severe hepatic iron overload.<sup>18,19</sup> The initial report noted that the diagnosis of HHC was not suspected pretransplantation in 35% of patients, and primary liver cancers, including 8 hepatocellular carcinomas and 2 cholangiocarcinomas, were found in the explant livers of 10 of 37 patients, with only 7 cases suspected pretransplantation.<sup>18</sup> The 1-year survival rate posttransplantation was 58%. A longer follow-up of this same cohort of patients with hepatic iron overload was later reported, and the 5-year survival rate after liver transplantation was 40% compared with an overall survival rate of 62% reported from the United Network for Organ Sharing (UNOS) registry.<sup>19</sup> Sepsis was the cause of 53% of all deaths in the first year, whereas cardiac complications accounted for 50% of the late mortality. These initial efforts at pooling data led to the establishment of the National Hemochromatosis Transplant Registry and expanded collection of data from patients with hepatic iron overload undergoing liver transplantation. Preliminary data from 9 liver transplant centers that submitted information to the National Hemochromatosis Transplant Registry were reported on 110 transplant recipients with hepatic iron overload.<sup>20</sup> The overall 1-year survival rate was 73%, which was less but not significantly different from the 1-year UNOS survival rate of 80% over the same time period. The confidence intervals were wide, and it is possible that the accumulation of further data in this ongoing study may make these differences significant. However, the 1-year posttransplantation survival rate in pa-

tients with genetically confirmed HHC (C282Y homozygotes,  $n = 11$ ; compound C282Y/H63D heterozygotes,  $n = 2$ ) was only 60%, which is significantly reduced.

The report by Stuart et al. in this issue of HEPATOLOGY questions whether increased hepatic iron *per se* is associated with an adverse outcome after liver transplantation.<sup>21</sup> In 282 consecutive adult patients with cirrhosis undergoing primary liver transplantation, 104 (37%) had stainable iron, with 27 having grade 3 or 4 iron. Patients with hepatocellular disease were much more likely than patients with cholestatic liver disease to have stainable hepatic iron. Iron concentration in explant livers was also assessed quantitatively using standard methods. Increased hepatic iron was associated with higher Child-Pugh scores, male gender, and hepatocellular disease. Child-Pugh was the only independent variable affecting survival. As had been reported and reviewed above, *HFE* mutations were uncommon in the 79 patients tested, with only 4 homozygotes and 7 heterozygotes for the C282Y mutation. The actuarial survival was not different among patients with no hepatic iron, mild iron accumulation, or severe hepatic iron. The investigators concluded that only Child-Pugh score, *i.e.*, disease severity, and not hepatic iron content, was a determinant of patient survival in these different groups.

What might account for differences in this current study compared with previous reports of an unfavorable outcome after liver transplantation in patients with end-stage liver disease and increased hepatic iron? The mean age of patients in the study of Stuart et al.<sup>21</sup> was 43 to 47 years of age in the 3 groups, which is lower than the mean age of 54 years in the earlier pooled outcomes data on patients transplanted for end-stage liver disease associated with increased hepatic iron.<sup>18</sup> In addition, patient selection factors for liver transplantation may vary and have changed over time. For example, patients may have been transplanted somewhat earlier in the Australian study than is common in the United States, based on the reported Child-Pugh scores (21%, 35%, and 44% were Child's class A, B, and C, respectively).<sup>21</sup> Finally, other factors such as the use of immunosuppression, which might influence rates of posttransplantation infection in iron loaded patients already at risk, have evolved over time and often vary in different centers.

The majority of prior studies substantiate decreased survival in patients with hepatic iron overload undergoing liver transplantation. The study by Stuart et al. finds no association between hepatic iron content and posttransplantation survival, and suggests that hepatic iron content may be a surrogate for disease severity rather than directly related to increased mortality.<sup>21</sup> The establishment of the National Hemochromatosis Transplant Registry in the United States provides the opportunity to definitely answer the question of whether hepatic iron *per se* or disease severity is the critical factor leading to decreased survival, and to better define posttransplantation outcomes in patients with confirmed HHC, patients with other end-stage liver diseases and increased hepatic iron, and patients with liver disease and normal iron stores.

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