

# ORIGINAL ARTICLES—LIVER, PANCREAS, AND BILIARY TRACT

## Increased Risk of Death From Iron Overload Among 422 Treated Proband With *HFE* Hemochromatosis and Serum Levels of Ferritin Greater Than 1000 $\mu\text{g/L}$ at Diagnosis

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**BACKGROUND & AIMS:** We investigated the risk of death from iron overload among treated hemochromatosis probands who were homozygous for *HFE* C282Y and had serum levels of ferritin greater than 1000  $\mu\text{g/L}$  at diagnosis. **METHODS:** We compared serum levels of ferritin at diagnosis and other conditions with the rate of iron overload-associated death using data from 2 cohorts of probands with hemochromatosis who were homozygous for *HFE* C282Y (an Alabama cohort,  $n = 294$ , 63.9% men and an Ontario cohort,  $n = 128$ , 68.8% men). We defined iron overload-associated causes of death as cirrhosis (including hepatic failure and primary liver cancer) caused by iron deposition and cardiomyopathy caused by myocardial siderosis. All probands received phlebotomy and other appropriate therapy. **RESULTS:** The mean survival times after diagnosis were  $13.2 \pm 7.3$  y and  $12.5 \pm 8.3$  y in Alabama and Ontario probands, respectively. Serum levels of ferritin greater than 1000  $\mu\text{g/L}$  at diagnosis were observed in 30.1% and 47.7% of Alabama and Ontario probands, respectively. In logistic regressions of serum ferritin greater than 1000  $\mu\text{g/L}$ , there were significant positive associations with male sex and cirrhosis in Alabama probands and with age, male sex, increased levels of alanine and aspartate aminotransferases, and cirrhosis in Ontario probands. Of probands with serum levels of ferritin greater than 1000  $\mu\text{g/L}$  at diagnosis, 17.9% of those from Alabama and 14.8% of those from Ontario died of iron overload. Among probands with serum levels of ferritin greater than 1000  $\mu\text{g/L}$ , the relative risk of iron overload-associated death was 5.4 for the Alabama group (95% confidence interval [CI], 2.2–13.1;  $P = .0002$ ) and 4.9 for the Ontario group (95% CI, 1.1–22.0;  $P = .0359$ ). **CONCLUSIONS:** In hemochromatosis probands homozygous for *HFE* C282Y, serum levels of ferritin greater than 1000  $\mu\text{g/L}$  at diagnosis were positively associated with male sex and cirrhosis. Even with treatment, the relative risk of death from iron overload was 5-fold greater in probands with serum levels of ferritin greater than 1000  $\mu\text{g/L}$ .

**Keywords:** Liver Disease; Prognostic Factor; Mortality; Genetic.

Iron overload, especially if severe, can cause hepatic cirrhosis, primary liver cancer, diabetes mellitus, other endocrinopathy, arthropathy, and cardiomyopathy.<sup>3–5</sup> Cirrhosis caused by iron overload and its complications, including primary liver cancer, are major causes of death and decreased survival after diagnosis among *HFE* C282Y homozygotes.<sup>4,6</sup> It is widely acknowledged that early diagnosis and treatment with phlebotomy to achieve iron depletion can reduce or prevent target organ injury caused by iron overload and decrease mortality in persons with hemochromatosis.<sup>7–9</sup> Serum ferritin (SF) is the most widely used surrogate marker of storage iron in persons with hemochromatosis.<sup>7,10</sup> SF >1000  $\mu\text{g/L}$  at diagnosis is associated with increased risk for cirrhosis in patients with hemochromatosis phenotypes and *HFE* C282Y homozygosity in many studies.<sup>4,6,11–13</sup>

We sought to determine the predictors of SF >1000  $\mu\text{g/L}$  and the relative risks of death caused by iron overload in nonscreening hemochromatosis probands with *HFE* C282Y homozygosity who had SF >1000  $\mu\text{g/L}$ . We performed separate analyses of observations in cohorts from 2 referral practices (294 Alabama probands and 128 Ontario probands). Each proband was treated with phlebotomy to achieve iron depletion and other appropriate therapy.<sup>7</sup> Herein, we discuss risks for severe iron overload and death caused by sequelae of iron overload in C282Y homozygotes with SF >1000  $\mu\text{g/L}$  at diagnosis demonstrated by the present results and those of previous reports.

### Methods

#### Selection of Hemochromatosis Proband

The performance of this work was approved by the Institutional Review Boards of Brookwood Medical Center, the University of Alabama at Birmingham, and the University of Western Ontario. We conducted computerized and manual

**Abbreviations used in this paper:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAFLD, nonalcoholic fatty liver disease; SF, serum ferritin.

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Hemochromatosis caused by homozygosity for the C282Y mutation of the *HFE* gene on chromosome 6p21.3 occurs in 0.003–0.006 of persons of northwestern European descent.<sup>1,2</sup>

searches of medical records to identify all patients evaluated for hemochromatosis because they had elevated values of transferrin saturation or SF. Each person selected for this study was white and was the first in his/her family to be diagnosed to have hemochromatosis (proband). We included probands who (1) were diagnosed to have hemochromatosis during medical care; (2) had *HFE* C282Y homozygosity; (3) were treated to achieve iron depletion by phlebotomy if SF levels at diagnosis were elevated (men, >300 µg/L; women, >200 µg/L)<sup>3,14</sup>; and (4) resided in central Alabama or Ontario. Each proband was evaluated for complications associated with iron overload, as appropriate.<sup>15-17</sup>

### Laboratory Methods

SF levels were measured using automated clinical methods. *HFE* mutation analysis was performed as previously described.<sup>17</sup> Some analyses were performed using buffy coat or DNA specimens obtained from probands diagnosed to have hemochromatosis before the discovery of *HFE* in 1996.<sup>1</sup> Sections of liver biopsy specimens were stained by using hematoxylin and eosin, Masson trichrome, and Perls Prussian blue techniques. Intrahepatic iron was graded according to the method of Scheuer et al.<sup>18</sup> Routine methods were used to detect hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and hepatitis C antibody.

### Diagnosis of Liver Conditions

We defined 5 liver conditions as elevated serum level(s) of hepatic aminotransferase levels; nonalcoholic fatty liver disease (NAFLD); heavy ethanol consumption; chronic hepatitis B or C; and cirrhosis. Probands were classified as having elevated aminotransferase levels if either their serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level was higher than the respective upper reference limit (>2 standard deviations above mean). In Alabama probands, NAFLD was defined as steatosis or steatohepatitis detected on liver biopsy specimens or by typical increase of hepatic echogenicity detected by ultrasonography, in the absence of self-reports of heavy ethanol consumption. There were no observations regarding NAFLD in Ontario probands. Heavy ethanol consumption was defined as the self-reported consumption of ≥60 g/d for 5 or more years. Chronic hepatitis B or C was defined as positivity for hepatitis B surface antigen or hepatitis C antibody, respectively, in association with clinical or liver biopsy abnormalities consistent with chronic viral hepatitis.

Liver biopsy was typically performed in probands who had SF >1000 µg/L at diagnosis, or in whom there was evidence of unexplained liver disease, regardless of SF level.<sup>7</sup> Cirrhosis was defined by pathologists' interpretations of liver biopsy specimens.

### Treatment of Iron Overload Manifestations

Iron depletion therapy, defined as the periodic removal of blood to eliminate storage iron, was performed as described in detail elsewhere.<sup>3,7</sup> An attempt to achieve iron depletion by phlebotomy was made in each proband with elevated ferritin levels. Hepatic, cardiac, endocrinologic, and rheumatologic manifestations of iron overload were evaluated and treated as described previously.<sup>3,7</sup> Liver transplantation was performed in probands with cirrhosis or primary liver cancer, as appropriate.

### Deaths Caused by Iron Overload

We defined 2 causes of death as consequences of iron overload: (1) hepatic failure (including primary liver cancer) caused by severe iron deposition in hepatocytes, Kupffer cells, or both; and (2) cardiomyopathy caused by myocardial siderosis proven by microscopy examination of myocardium.<sup>19</sup>

### Statistics

One primary analytical dataset consisted of observations on 294 Alabama hemochromatosis probands with *HFE* C282Y homozygosity (188 men, 106 women). We compiled these general characteristics of each proband: age at diagnosis; sex; SF level at diagnosis; date of diagnosis; elevated serum level of ALT or AST; NAFLD; heavy ethanol consumption; chronic viral hepatitis; cirrhosis; diabetes; cardiomyopathy caused by siderosis proven by microscopy examination of myocardium; and occurrence, date, and cause of death. A separate dataset comprised observations on 128 Ontario hemochromatosis probands with *HFE* C282Y homozygosity (88 men, 40 women). This was analyzed separately in a manner similar to that described for Alabama probands, except that the variable NAFLD was not available.

All probands designated as alive were so confirmed on July 1, 2011. The dates of death of probands were confirmed by review of office and hospital records and by using the Social Security Death Index (<http://ssdi.rootsweb.ancestry.com/>). Causes of death were tabulated from office and hospital medical records, death certificates, and communications with referring physicians and family members of probands. Duration of survival after diagnosis was computed by using date of diagnosis and either July 1, 2011 (living probands) or date of death, as appropriate.

SF levels were converted to natural logarithms (ln) to normalize them for univariable comparisons and to a dichotomous variable (>1000 µg/L or ≤1000 µg/L) for logistic regression analyses. Mean SF results are displayed as anti-ln of mean ln SF (95% confidence interval). Descriptive statistics are displayed as enumerations, percentages, or mean ± 1 standard deviation. Comparisons of continuous data were made by using Student two-sided *t* test; percentages were compared by using Fisher exact or  $\chi^2$  test, as appropriate. We performed logistic regression analyses on SF >1000 µg/L (dependent variable) to identify significant predictors (positive or negative association). We computed relative risks (95% confidence interval) for death caused by iron overload in probands with SF >1000 µg/L by comparing these data with those of probands with SF ≤1000 µg/L. Values of *P* < .05 are defined as significant. Analyses were performed by using GB-Stat v. 8.0 (Dynamic Microsystems, Inc, Silver Spring, MD) and Microsoft Excel 2000 (Microsoft Corp, Redmond, WA).

## Results

### Characteristics of 294 Alabama Hemochromatosis Probands

These observations are summarized in Table 1. Cirrhosis in one proband with SF ≤1000 µg/L was attributed predominantly to hepatic sarcoid.<sup>20</sup> Three Alabama probands, all with SF >1000 µg/L and cirrhosis caused by iron overload, died of liver failure before iron depletion could be achieved. The

**Table 1.** Characteristics of 422 Hemochromatosis Proband With *HFE* C282Y Homozygosity

SF at diagnosis (n)	≤1000 µg/L	>1000 µg/L <sup>a</sup>	P value
Alabama probands (n = 294) <sup>a</sup>	n = 182	n = 112	
Men, %	54.4	79.5	<.0001
Mean age at diagnosis, y	48 ± 14	50 ± 13	.2086
Elevated ALT/AST, %	23.6	40.2	.0011
Cirrhosis, %	3.8	32.1	<.0001
Cardiomyopathy, %	0	4.5	.0076
Diabetes mellitus, %	12.1	29.5	.0002
Ontario probands (n = 128) <sup>b</sup>	n = 67	n = 61	
Men, %	53.7	85.2	.0001
Mean age at diagnosis, y	44 ± 18	53 ± 13	.0109
Elevated ALT/AST, %	20.9	67.2	<.0001
Cirrhosis, %	9.0	45.9	<.0001
Cardiomyopathy, %	0	3.3	.2251
Diabetes mellitus, %	18.0	31.1	.0494

<sup>a</sup>Heavy ethanol consumption was reported in 16.7% of probands. Prevalence of heavy ethanol consumption was greater in probands with SF >1000 µg/L (25.9% vs 11.0%; *P* = .0009). Chronic viral hepatitis was diagnosed in 14 probands (12 hepatitis C, 2 hepatitis B).

<sup>b</sup>Heavy ethanol consumption was reported in 5.5% of probands. Chronic viral hepatitis was not detected in any proband.

mean survival of 294 probands after diagnosis was 13.2 ± 7.3 years.

#### **Variables Associated With SF >1000 µg/L in 294 Alabama Proband**

We performed a logistic regression analysis on SF >1000 µg/L by using these independent variables: sex; age at diagnosis; elevated serum levels of ALT/AST; NAFLD; heavy ethanol consumption; chronic viral hepatitis; cirrhosis; diabetes; and cardiomyopathy caused by myocardial siderosis. Male sex and cirrhosis were positively associated with SF >1000 µg/L (*P* = .0008 and <.0001, respectively).

#### **Iron Overload Deaths in 294 Alabama Proband**

There were 66 deaths during the study interval. The proportion of iron overload deaths in probands with SF >1000 µg/L (20 of 35, 57.1%) was greater than that of probands with SF ≤1000 µg/L (6 of 31, 19.4%; *P* = .0001). The relative risk of death caused by iron overload during the study interval in probands with SF >1000 µg/L was 5.4 (2.2–13.1) (Table 2). Two probands with cirrhosis died of liver failure while awaiting liver transplantation.

#### **Characteristics of 128 Ontario Proband**

These observations are summarized in Table 1. The mean survival of 128 probands after diagnosis was 12.5 ± 8.3 years.

#### **Variables Associated With SF >1000 µg/L in 128 Ontario Proband**

We performed a logistic regression analysis on SF >1000 µg/L by using these independent variables: sex; age at diagnosis; presence or absence of elevated serum levels of ALT/AST; heavy ethanol consumption; cirrhosis, diabetes; and cardiomyopathy caused by myocardial siderosis. SF >1000 µg/L was positively associated with age, male sex, elevated ALT/AST levels, and cirrhosis (*P* = .0010, .0007, .0118, and .0006, respectively).

#### **Iron Overload Deaths in 128 Ontario Proband**

There were 15 deaths during the study interval. The proportion of all iron overload deaths in probands with SF >1000 µg/L was greater than that of probands with SF ≤1000 µg/L (*P* = .0177) (Table 2). The relative risk of death

**Table 2.** Iron Overload Deaths in 422 Hemochromatosis Proband With *HFE* C282Y Homozygosity

SF at diagnosis (n)	≤1000 µg/L	>1000 µg/L	P value
Alabama probands (n = 294)	n = 182	n = 112	
Cirrhosis deaths, prevalence, % (n)	3.3 (6) <sup>a</sup>	17.0 (19) <sup>b</sup>	<.0001
Cardiomyopathy deaths, prevalence, % (n)	0	0.9 (1)	.3810
Relative risk of iron overload death, (95% CI)	—	5.4 (2.2–13.1)	.0002
Ontario probands (n = 128)	n = 67	n = 61	
Cirrhosis deaths, prevalence, % (n)	3.0 (2) <sup>c</sup>	13.1 (8) <sup>d</sup>	.0342
Cardiomyopathy deaths, prevalence, % (n)	0	1.6 (1)	.4766
Relative risk of iron overload death, (95% CI)	—	4.9 (1.1–22.0)	.0359

CI, confidence interval.

<sup>a</sup>Two of 6 cirrhosis deaths were due to primary liver cancer.

<sup>b</sup>Five of 19 cirrhosis deaths were due to primary liver cancer.

<sup>c</sup>One of 2 cirrhosis deaths was due to primary liver cancer.

<sup>d</sup>Five of 8 cirrhosis deaths were due to primary liver cancer.

caused by iron overload consequences in probands with SF >1000 µg/L was 4.9 (1.1–22.0) (Table 2). One proband with cirrhosis and primary liver cancer died after undergoing liver transplantation.

## Discussion

In the present study, male sex and cirrhosis were independent variables that were positively associated with SF >1000 µg/L at diagnosis in both Alabama and Ontario hemochromatosis probands. Relative risks for iron overload deaths in probands with SF >1000 µg/L were approximately 5-fold higher than in probands with SF ≤1000 µg/L in both proband cohorts. In previous reports, the survival of hemochromatosis probands with SF >1000 µg/L from the present Alabama and Ontario referral practices determined by Kaplan–Meier analyses was significantly decreased.<sup>21–23</sup> In the present and in previous studies,<sup>21–23</sup> the predominant cause of death because of iron overload was cirrhosis and complications thereof. Taken together, these observations demonstrate that risk of death caused by iron overload is significantly greater in hemochromatosis probands with *HFE* C282Y homozygosity and SF >1000 µg/L at diagnosis than in probands with SF ≤1000 µg/L, even when all probands are treated with phlebotomy and other appropriate therapy.

We observed some differences between the 2 present cohorts that might be due to genetic and cultural differences in 2 respective European populations and customary medical practice and referral habits in the respective geographic areas. These differences include the older mean age of probands with SF >1000 µg/L in Ontario probands, the higher percentage of Ontario probands who had SF >1000 µg/L, and the higher prevalence of heavy ethanol consumption and chronic viral hepatitis in Alabama probands.

Reports of heavy ethanol consumption were more than 2-fold higher in Alabama probands with SF >1000 µg/L at diagnosis. In *HFE* C282Y homozygotes, excessive alcohol consumption accentuates risk for cirrhosis, but increased dietary iron content and iron absorption are unlikely explanations.<sup>24</sup> The added cofactor effect of iron and alcohol, both of which cause oxidative stress, hepatic stellate cell activation, and hepatic fibrogenesis, could explain the increased cirrhosis risk.<sup>24</sup> In another report, excessive alcohol consumption in persons with *HFE* hemochromatosis was likewise associated with increased risk for liver fibrosis or cirrhosis.<sup>25</sup>

Chronic viral hepatitis increases the risk of fibrosis or cirrhosis in patients with hemochromatosis and *HFE* C282Y homozygosity,<sup>25</sup> and patients with hepatitis might be more sensitive to iron hepatotoxicity than patients with hemochromatosis.<sup>26</sup> Although we were unable to identify reports of serum hepcidin levels in persons with both C282Y homozygosity and hepatitis C, the suppression of hepcidin typical of C282Y homozygotes<sup>27,28</sup> and of persons with chronic hepatitis C<sup>28</sup> could act in concert to promote liver iron accumulation in persons with both conditions.

Uncertainties in the present study include lack of cause of death data in 29% of Alabama probands. Diabetes mellitus is associated with decreased survival of hemochromatosis patients by Kaplan–Meier analyses in the Alabama and Ontario referral practices,<sup>21,22</sup> although we did not define diabetes as a potentially fatal complication of iron overload in the present study. Thus, our estimates of deaths caused by iron overload sequelae are probably conservative. Although observations regarding

NAFLD were not available in Ontario probands, this liver condition was not a significant predictor of SF >1000 µg/L in Alabama probands. SF levels are the best predictors of body iron stores, and the positive correlation of SF and blood removed by phlebotomy to achieve iron depletion is significant.<sup>29,30</sup> Regardless, this correlation is not especially strong, even in C282Y homozygotes.<sup>29</sup> Therefore, there is probably some error in grouping patients according to levels of this surrogate marker of iron overload severity.

A major goal of early diagnosis and iron depletion therapy of patients with hemochromatosis is to prevent cirrhosis. Hepatocellular carcinoma occurs predominantly in hemochromatosis patients who have SF >1000 µg/L and cirrhosis, and thus it is likely that preventing cirrhosis would also reduce the risk of hepatocellular carcinoma. Hepatic fibrosis can be reversed by phlebotomy therapy in some patients.<sup>6,8,31</sup> Whether this also decreases the risk for subsequent development of primary liver cancer is unknown. Liver transplantation is an option for a small proportion of patients with hemochromatosis and cirrhosis or primary liver cancer, but survival after transplantation might be lower than for nonhemochromatosis transplant recipients.<sup>32</sup> Diagnosis of hepatic iron overload, *HFE* mutation analysis, and iron depletion before liver transplantation might improve survival.<sup>32</sup> Liver and cardiac function sometimes improves after iron depletion.<sup>7,8</sup> Across all C282Y homozygotes, survival benefits of iron depletion, if any, have been difficult to demonstrate because a small minority of *HFE* C282Y homozygotes have or will ever develop cirrhosis. Maximal benefits of therapy also require cessation of heavy ethanol consumption and successful treatment of viral hepatitis C, as appropriate. Consistent with the present observations, cirrhosis in some persons with hemochromatosis is not related to iron overload and would not be ameliorated by treatment to achieve iron depletion.

Observations in a California health appraisal screening program for hemochromatosis led to a proposal in 2008 that screen-positive participants (SF >1000 µg/L) would undergo *HFE* mutation analyses and other evaluations to refine their diagnoses and guide management, and that excluding participants with SF ≤1000 µg/L should not result in missed opportunities for early treatment of patients who could benefit.<sup>10</sup> The prevalence of cirrhosis in California study participants with *HFE* C282Y homozygosity and initial screening with SF >1000 µg/L was much lower than that in the present Alabama and Ontario probands with SF >1000 µg/L (5% vs 32% and 46%, respectively).<sup>10</sup> We typically performed liver biopsies in referred Alabama and Ontario probands with either SF >1000 µg/L or evidence of unexplained liver disease. In California screening study participants, performing liver biopsies was not routine.<sup>10,33</sup> Thus, it is possible that “silent” hepatic fibrosis or cirrhosis<sup>23,33</sup> was present in other C282Y homozygous participants in the California study.<sup>10</sup> In the Alabama and Ontario cohorts, cardiomyopathy caused by myocardial siderosis occurred almost exclusively in probands with SF >1000 µg/L and accounted for a small proportion of iron overload deaths. In the California study, cardiomyopathy caused by myocardial siderosis was not included as a serious manifestation of iron overload.<sup>10</sup> There are no published long-term outcomes of C282Y homozygotes from the California study. Taken together with the increased risk of iron overload deaths we documented in the present probands with SF >1000 µg/L, it would be unfavorable to withhold

iron depletion therapy of C282Y homozygotes in referral practices until SF levels are  $>1000 \mu\text{g/L}$ .

We conclude that in 2 cohorts of hemochromatosis probands with *HFE* C282Y homozygosity, SF  $>1000 \mu\text{g/L}$  at diagnosis was positively associated with male sex and cirrhosis. Even with treatment, the relative risk of death because of iron overload was 5-fold greater in probands with SF  $>1000 \mu\text{g/L}$ . Non-iron overload conditions probably contributed to liver injury and death in some probands.

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The authors disclose no conflicts.

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