Serum Ferritin Concentration Predicts Mortality in Patients Awaiting Liver Transplantation

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Additional markers are required to identify patients on the orthotopic liver transplant (OLT) waiting list at increased risk of death and adverse clinical events. Serum ferritin concentration is a marker of varied pathophysiological events and is elevated with increased liver iron concentration, hepatic necroinflammation, and systemic illness, all of which may cause a deterioration in liver function and clinical status. The aim of this study was to determine whether serum ferritin concentration is an independent prognostic factor in subjects awaiting OLT. This is a dual-center retrospective study. The study cohort consisted of 191 consecutive adults with cirrhosis accepted by the Queensland (Australia) Liver Transplant Service between January 2000 and June 2006 and a validation cohort of 131 patients from University of California Los Angeles (UCLA) Transplant Center. In the study cohort, baseline serum ferritin greater than 200 μg/L was an independent factor predicting increased 180-day and 1-year waiting list mortality. This effect was independent of model for end-stage liver disease (MELD), hepatocellular carcinoma, age, and sex. Subjects with higher serum ferritin had increased frequency of liver-related clinical events. The relationship between serum ferritin and waiting list mortality was confirmed in the UCLA cohort; all deceased patients had serum ferritin greater than 400 μg/L. Serum ferritin greater than 500 μg/L and MELD were independent risk factors for death. Conclusion: Serum ferritin concentration is an independent predictor of mortality-related and liver-related clinical events. Baseline serum ferritin identifies a group of “higher-risk” patients awaiting OLT and should be investigated as an adjunct to MELD in organ allocation. (HEPATOLOGY 2010;00:000-000)

Orthotopic liver transplant (OLT) waiting list mortality remains of major concern despite the widespread use of the model for end-stage liver disease (MELD) to allocate deceased donor

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Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; MELD, model for end stage liver disease; OLT, orthotopic liver transplantation; ROC, receiver operating characteristic; SF, serum ferritin concentration; UCLA, University of California Los Angeles.

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livers.1-3 The absence of any major foreseeable therapeutic developments means that OLT will remain the only definitive therapy for patients with end-stage liver disease. It has been estimated that incident cases of liver failure and hepatocellular carcinoma (HCC) will double by 2020 in some parts of the world.4 Unless there is a commensurate increase in organ donation, the number of patients awaiting OLT and liver transplant waiting list mortality will increase. To manage liver transplant waiting lists in an optimal fashion, predictors of waiting list mortality—in addition to MELD—will be required.

Serum ferritin concentration (SF) is a widely available and easily measured biochemical parameter. SF is increased in patients with elevated body iron stores, hepatic necroinflammatory activity, and systemic inflammatory states.5,6 These causes of increased SF may be associated with an increased risk of clinical deterioration and progressive liver dysfunction. Therefore, we hypothesized that an elevated SF may be an important predictor of mortality in patients awaiting
OLT. In this study, we measured SF in patients awaiting OLT, and our results suggest that it is an important predictor of death on the liver transplantation waiting list—indeed of the baseline MELD score.

Patients and Methods

Study Design and Patient Population

Two hundred sixty-six adults were listed for OLT by The Queensland Liver Transplant Service between January 2000 and June 2006. Twelve retransplantations, 14 primary liver transplant recipients with fulminant liver failure, 48 subjects with noncirrhotic liver diseases, and a single subject with C282Y-related hemochromatosis were excluded from the analysis, resulting in a study population of 191 subjects. Patient demographics, cause of their cirrhosis, and indication for OLT were confirmed by review of patients’ medical records, relevant laboratory investigations, and explant histology. Patients were followed until their death, OLT, or the end of the study period (June 2007). Observations ended after any of these primary endpoints. The study was approved by the Princess Alexandra Hospital Research Ethics Committee and the University of California Los Angeles (UCLA) Research Ethics Review Board. No donor organs were obtained from executed prisoners or other institutionalized persons.

Laboratory Investigations

The patients in the study cohort were divided into three groups on the basis of their fasting SF measured at the time of their listing for OLT. Serum ferritin concentration was analyzed as a trichotomous variable, with preselected cutoff values of less than 200 µg/L, 200 to 400 µg/L, and more than 400 µg/L. The separation of patients into these three groups was based on local laboratory reference ranges for SF and represented normal, borderline-elevated, and increased SF levels, respectively. Explant hepatic iron grade was estimated according to the method of Searle et al.7

Prothrombin time, serum bilirubin, creatinine, albumin, and sodium levels were recorded at the time of liver transplant assessment and at monthly intervals thereafter. All laboratory tests designated as baseline results were taken within 28 days of the listing date and when all patients were considered to be clinically stable. MELD was used as a measure of liver disease severity.1 Each patient underwent an echocardiogram and measurement of the left ventricular ejection fraction at the time of evaluation.

Liver-related clinical events (see following definitions) were recorded at the time of listing and documented at monthly intervals for the duration of the study. Patients’ medical records were reviewed for clinical complications of liver disease before admission to the transplant waiting list and for documentation of liver-related clinical events while on the waiting list. A diagnosis of HCC was made using the radiological criteria proposed by the American Association for the Study of Liver Disease Practice Guidelines Committee8 and confirmed on explant histology. Hyponatremia was defined as greater than two consecutive serum sodium concentrations between 126 and 135 mmol/L and severe hyponatremia as less than 126 mmol/L.9 Hepatorenal syndrome, ascites, and spontaneous bacterial peritonitis were diagnosed using the criteria proposed by the International Ascites Club10 and American Association for the Study of Liver Disease, respectively.11 Variceal bleeding was confirmed by endoscopy within 24 hours of presentation. The presence of spur cell anemia was defined as (1) significant acanthocytosis (>20%) on peripheral blood film; (2) a serum hemoglobin level of less than 10.5 g/dL in the absence of any other identifiable cause of anemia12; and (3) need for at least monthly transfusions for at least 2 months before listing.

Validation Cohort

To further investigate our hypothesis that elevated SF is associated with an increased risk of liver transplant waiting list mortality, we studied 131 consecutive adult patients with cirrhosis undergoing OLT at the UCLA Liver Transplant Center, California. The inclusion criteria were identical to those applied to the Australian patients except that SF was measured within 120 days of admission to the waiting list and evaluated independently of the subject’s clinical status.

Statistical Methods

Normally distributed variables were expressed as mean ± standard deviation, and differences between groups were identified using analysis of variance. Nonparametric tests were used to compare the medians of continuous variables that were not normally distributed. Differences in categorical variables between groups were assessed using Pearson’s chi-squared and Fisher’s exact tests. Serum ferritin concentration was analyzed as a continuous and as a categorical variable with preselected cutoff values of less than 200, 200 to
400, and greater than 400 μg/L. Logarithmic transformation of laboratory measurements of SF and serum alanine transaminase was performed before assessment because of the skewed distribution of values. Cox proportional hazard ratios (HR), with 95% confidence intervals for death, were estimated for univariate models of baseline demographics and clinical variables as well as multivariate models using the biological MELD, serum sodium concentration, and SF at the time of listing. Testing of proportional hazards assumptions was performed. Area under the receiver operating characteristics (ROC) curves for biological MELD with and without SF and serum sodium concentration at listing as predictors of 180-day and 1-year mortality were assessed using nonparametric methods.¹³ Statistical significance was defined as a P value less than 0.05. All statistical analyses were performed using Stata, version 9.2 (Stata Corporation, College Station, TX).

### Results

#### Patient Characteristics

The follow-up of patients in the study cohort concluded on June 30 2007, 12 months after the final patient was admitted to the study. During the study, 139 patients had received a liver transplant, 31 patients had died of liver failure (n = 26) or progressive HCC (n = 5), eight patients were still waiting, and 13 patients did not proceed to transplantation because of improvement of liver function (n = 7), relocation with transfer of care to another institution (n = 3), psychiatric issues (n = 2), and diagnosis of metastatic adenocarcinoma (n = 1).

The study cohort comprised 79% male subjects with a median age of 50.6 years (20-66) (Table 1). The cirrhosis was of hepatocellular origin in 84%, chronic viral hepatitis B and C infection in 51%, alcohol-induced liver disease in 20%, and miscellaneous causes in 12%. Sixteen percent of subjects had a cholestatic cause, including primary sclerosing cholangitis (8%), primary biliary cirrhosis (3%), overlap disease (3%), and other causes in 2%. The median SF at the time of listing for OLT was 264 μg/L (10-2210 μg/L), and the mean transferrin saturation was 50.1% (±28.3). The mean MELD at the time of listing was 15.4 (±5.1). Before listing for OLT, the following liver-related clinical events had been observed: ascites in 139 subjects (73%), hepatic encephalopathy in 70 (37%), variceal hemorrhage in 39 (20%), HCC in 38 (20%), spur cell anemia in 36 (19%), spontaneous bacterial peritonitis in 28 (15%), and hepatorenal syndrome in eight (4%).

#### Clinical Characteristics of Subjects in Relation to Baseline Serum Ferritin

Patients were divided into three groups according to baseline SF (Table 2). Group A (SF < 200 μg/L) was composed of 83 subjects, group B (SF 200-400 μg/L) was composed of 45 subjects, and group C (SF > 400 μg/L) was composed of 63 subjects.
of 45 subjects, and group C (SF > 400 µg/L) of 63 subjects. There were significant differences in sex distribution, mean transferrin saturation, MELD, and type of liver disease between the three groups (P = 0.05, P < 0.0001, P < 0.0001, and P = 0.035, respectively). Those patients with elevated baseline SF were more likely to have increased hepatic iron in their explanted liver. The mean hepatic iron grades of group A, B, and C patients who underwent OLT were 0.21, 0.81, and 1.80, respectively (P < 0.0001). There was a positive correlation between baseline serum alanine transaminase levels and SF in the study population (r = 0.36, P = 0.005). There was no difference in the mean left ventricular ejection fraction of the three groups; group A, 65.4 ± 4.1%; group B, 64.6% ± 4.8%; group C, 65.2% ± 4.9%.

Serum Ferritin Concentration as a Predictor of Waiting List Mortality: Cox Proportional Hazard Models

180-Day Mortality. In univariate analysis, SF, MELD, and serum sodium concentration at time of listing for OLT were independent factors predicting 180-day mortality (Table 3). Used as a categorical value, increasing SF was associated with an increased risk of death in patients in groups B and C (HR, 5.35; P = 0.015, and HR, 5.68; P = 0.008, respectively). Increasing MELD and decreasing serum sodium concentration as continuous variables were predictive of 180-day mortality (HR, 1.09; P = 0.017, and HR, 0.87; P < 0.001, respectively). Age, sex, and the presence of HCC at the time of listing for OLT did not predict death at 180 days. Multivariate analysis, including SF analyzed as a trichotomous variable showed increased mortality for subjects in group B (HR, 4.62; P = 0.03) with a strong trend observed in group C (HR, 3.54; P = 0.07). Serum sodium concentration when evaluated as a continuous variable was associated with a decreased risk of death (HR, 0.87; P = 0.002); in other words, patients with a higher serum sodium concentration had a lower mortality.

One-Year Mortality. In univariate analysis, SF, MELD, and serum sodium concentration at time of listing for OLT were independent factors predicting 1-year mortality (Table 4). Used as a categorical value, increasing SF was associated with an increased risk of death in patients in groups B and C (HR, 5.16; P = 0.008; and HR, 5.32; P = 0.004, respectively). Increasing MELD and decreasing serum sodium concentration as continuous variables were predictive of 1-year mortality (HR, 1.10; P = 0.006; and HR, 0.88; P < 0.001, respectively). Age, sex, and the presence of HCC at the time of listing for OLT did not predict death at 1 year. Multivariate analysis, including SF, serum sodium concentration, and MELD at listing showed that SF and serum sodium concentration were independent predictors of 1-year patient mortality. Serum ferritin concentration predicted increased mortality for subjects in groups B and C (HR, 4.69; P = 0.01; and HR, 3.49; P = 0.04, respectively). Serum sodium concentration evaluated as a continuous

Table 3. Variables Associated with 180 day Waiting List Mortality in the (A) Study Population and (B)Validation Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR [CI]</td>
<td>P Value</td>
</tr>
<tr>
<td>(A) Study Population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.01 [0.96–1.06]</td>
<td>0.67</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.61 [0.54–4.80]</td>
<td>0.39</td>
</tr>
<tr>
<td>MELD</td>
<td>1.09 [0.21–1.17]</td>
<td>0.017</td>
</tr>
<tr>
<td>Presence of HCC</td>
<td>1.72 [0.66–4.45]</td>
<td>0.27</td>
</tr>
<tr>
<td>SF &lt;200 µg/L</td>
<td>1.00</td>
<td>-</td>
</tr>
<tr>
<td>SF 200–400 µg/L</td>
<td>5.35 [1.38–20.81]</td>
<td>0.015</td>
</tr>
<tr>
<td>SF &gt;400 µg/L</td>
<td>5.68 [1.58–20.39]</td>
<td>0.008</td>
</tr>
<tr>
<td>Serum sodium</td>
<td>0.88 [0.82–0.94]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(B) Validation Population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1.003 [0.96–1.05]</td>
<td>0.90</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.81 [0.33–1.97]</td>
<td>0.64</td>
</tr>
<tr>
<td>MELD</td>
<td>1.15 [1.10–1.21]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Presence of HCC</td>
<td>0.43 [0.12–1.46]</td>
<td>0.17</td>
</tr>
<tr>
<td>SF &gt; 500 µg/L</td>
<td>8.07 [2.37–27.55]</td>
<td>0.0001</td>
</tr>
<tr>
<td>Serum sodium</td>
<td>&lt; 126 mmol/L</td>
<td>4.80 [1.54–15.02]</td>
</tr>
<tr>
<td></td>
<td>&lt; 131 mmol/L</td>
<td>3.75 [1.46–9.62]</td>
</tr>
</tbody>
</table>
A total of 181 new liver-related clinical events were recorded among all patients during follow-up. Sixty-three new clinical liver complications were recorded in group A, 43 in group B, and 75 in group C (Table 5). There was a significant increase in the total number of new clinical events observed during follow-up with increasing SF ($P = 0.017$). Episodes of spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy were reported more frequently in subjects in group C.

### Liver-Related Clinical Events According to Baseline Serum Ferritin

A total of 181 new liver-related clinical events were recorded among all patients during follow-up. Sixty-three new clinical liver complications were recorded in group A, 43 in group B, and 75 in group C (Table 5). There was a significant increase in the total number of new clinical events observed during follow-up with increasing SF ($P = 0.017$). Episodes of spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy were reported more frequently in subjects in group C.

**Fig. 1.** Kaplan-Meier survival curve at 1 year according to baseline SF, adjusted for MELD and serum sodium concentration.
Validation of Findings in a Separate Cohort

Patients in the validation cohort were predominantly male (65.6%), with a median age of 54.5 years. The most common causes of cirrhosis were chronic hepatitis C infection (56%), alcohol-induced liver disease (13%), and nonalcoholic fatty liver disease (8%). The median SF at entry to the study was 314 µg/L (12-3224 µg/L), and the mean MELD was 19.2 ± 8.8. The patients in the UCLA cohort were older (54.5 versus 50.6, \( P = 0.002 \)) and had a higher mean MELD (19.2 ± 8.8 versus 15.4 ± 5.1, \( P = 0.003 \)) than in the study cohort (Table 1).

In the UCLA cohort, there were 27 deaths while awaiting OLT, and all of these deaths were reported in patients with an SF greater than 400 µg/L. The survival curves for Australian and UCLA patients with an SF greater than 400 µg/L are shown in Fig. 4. Because all deaths in the validation cohort occurred in patients with SF greater than 400 µg/L, calculation of a HR based on investigating SF as a trichotomous variable (as in the study cohort) could not be performed. Thus, we evaluated effects of SF using a cut-point of 500 µg/L, as well as increments of 50 and 100 µg/L. An increment in SF of 50 µg/L was associated with a 4% (USA patients) and 8% (Australian patients) increased risk of death on the waiting list. Similarly, an increment of 100 µg/L in SF was associated with a 9% (USA patients) and 16% (Australian patients) increased risk of death on the liver transplant waiting list.

In univariate analysis, the following factors were associated with 180-day mortality: SF greater than 500 µg/L (HR 8.07 [2.37-27.55], \( P = 0.001 \)), MELD (HR 1.15 [1.10-1.21], \( P < 0.0001 \)), serum sodium concentration less than 126 µM (HR 4.80 [1.54-15.02], \( P = 0.007 \)) and serum sodium concentration less than 131 µM (HR 3.75 [1.46-9.62], \( P = 0.006 \)). After multivariate analysis, only MELD (HR 1.19 [1.12-1.27], \( P < 0.0001 \)) and SF greater than 500 µg/L (HR 10.52 [2.88-38.43], \( P < 0.0001 \)) were associated with increased 180-day mortality (Table 3).

In univariate analysis, the following factors were associated with 1-year mortality: SF greater than 500 µg/L (HR 11.05 [3.33-36.7], \( P < 0.0001 \)), MELD (HR 1.15 [1.10-1.21], \( P < 0.0001 \)), serum sodium concentration less than 126 µmol/L (HR 4.80 [1.54-15.02], \( P = 0.007 \)), and serum sodium concentration less than 131 µmol/L (HR 2.81 [1.16-6.80], \( P = 0.02 \)). After multivariate analysis, MELD (HR 1.20

Table 5. Frequency of New Liver-Related Clinical Events During Follow-up in the Study Population

<table>
<thead>
<tr>
<th>Clinical Event (n, %)</th>
<th>Group A SF &lt; 200 (n = 83)</th>
<th>Group B SF 200-400 (n = 45)</th>
<th>Group C SF &gt; 400 (n = 63)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites—new</td>
<td>4 (4.8)</td>
<td>4 (8.9)</td>
<td>8 (12.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Ascites—worsening</td>
<td>20 (24.1)</td>
<td>9 (20)</td>
<td>14 (22.2)</td>
<td>0.87</td>
</tr>
<tr>
<td>SBP</td>
<td>5 (6)</td>
<td>4 (8.9)</td>
<td>8 (12.7)</td>
<td>0.16</td>
</tr>
<tr>
<td>Variceal bleed</td>
<td>3 (3.6)</td>
<td>5 (11.1)</td>
<td>2 (3.2)</td>
<td>0.15</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>20 (24.1)</td>
<td>11 (24.1)</td>
<td>22 (34.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>Spur cell anemia</td>
<td>7 (8.4)</td>
<td>6 (13.3)</td>
<td>9 (14.3)</td>
<td>0.5</td>
</tr>
<tr>
<td>HRS</td>
<td>4 (4.8)</td>
<td>3 (6.7)</td>
<td>10 (15.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>Total events</td>
<td>63 (75.9)</td>
<td>43 (95.6)</td>
<td>75 (119)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Abbreviations: SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome.
P < 0.0001) and SF greater than 500 μg/L (HR 14.39 [4.10-50.47], P < 0.0001) were associated with increased 1-year mortality (Table 4).

ROC curve analysis of mortality in the UCLA cohort showed the addition of SF to MELD increased the area under the ROC curve for 180-day and 1-year mortality by 21.4% (0.7-0.86, P = 0.001) and 40.3% (0.63-0.87, P < 0.0001), respectively. In contrast to the study population, there was no increase in the area under the ROC curve for 180-day and 1-year mortality when serum sodium was added to MELD and SF.

Discussion

Within two decades, liver transplantation has evolved from a novel treatment option conducted in a few major centers to a widely available and highly successful therapy for advanced liver disease. Simultaneous with the development of OLT, there has been a dramatic increase in the burden of liver disease in the community largely because of hepatitis C and obesity epidemics. Epidemiological studies predicting the future burden of liver disease suggest that incident cases of liver failure and HCC will double by 2020. Therefore, the number of patients requiring OLT is likely to increase. Unless there is a commensurate increase in organ donation, the number of patients on liver transplant waiting lists and waiting list mortality will rise, as is already occurring in some parts of the world. A further effect of increased number of patients on waiting lists is that many prospective recipients will have an identical MELD and organ allocation in this circumstance may return to decisions based on subjective criteria. Thus, it is important to identify objective prognostic markers that can be used in conjunction with MELD to maintain appropriate strategies for liver allocation and minimize deaths on the liver transplant waiting list.

Serum ferritin concentration is a widely available and objective laboratory parameter. In this study, we showed that SF provided important prognostic information—indeed, the presence of HCC—in predicting 180-day and 1-year OLT waiting list mortality in adult patients with cirrhosis. This relationship between SF and liver transplant waiting list mortality was identified in a study cohort of Australian patients, and these findings were confirmed in an analysis of patients from UCLA Transplant Center, California. Consistent with these observations, we also demonstrated an increased frequency of liver-related complications during follow-up in patients with a higher SF in our study cohort of Australian patients. The measurement of SF in normal patients and patients with hereditary hemochromatosis is a reliable reflection of body iron stores and hepatic iron concentration. However, SF is often increased in liver disease per se, probably because of release of ferritin molecules and reduced clearance of ferritin from the circulation. Thus, in many patients with liver disease, SF simply reflects hepatic necroinflammatory activity rather than increased body iron stores. Serum ferritin concentration is also frequently increased in infection, systemic inflammatory conditions, and malignancy.

The exact pathophysiological mechanism in end-stage liver disease that explains the relationship between SF and OLT waiting list mortality is uncertain. It is important to consider whether this relationship is attributable to increased liver iron stores promoting further hepatocyte injury. Approximately 30% of patients with advanced cirrhosis attributable to hepatocellular forms of liver disease have increased hepatic iron concentration independent of the HFE mutations. Serum ferritin concentration is usually increased in these subjects. Although controversial, some studies suggest that these patients have increased pretransplantation and posttransplantation mortality as well as an increased risk of HCC. Difficulty in obtaining liver tissue for the measurement of hepatic iron concentration has precluded large prospective studies addressing the effect of increased liver iron on the natural history of end-stage liver disease. However, magnetic resonance imaging technology to accurately measure hepatic iron concentration (FerriScan) using noninvasive techniques provides a method for studying patients with cirrhosis.
Increased hepatic necroinflammatory activity accompanied by worsening liver function is a possible explanation of the relationship between SF and waiting list mortality. This possibility is supported by the positive correlation between serum alanine transaminase levels and SF in this cohort. However, the correlation coefficient describing this relationship suggests that important factors in addition to serum alanine transferase concentration (and necroinflammation) also contribute to the elevated SF in advanced liver disease. Recently, Ruddell et al. proposed that ferritin functions as a proinflammatory cytokine, and this may have relevance to the findings of this study. Subjects with active or recent infection (within the previous month) were excluded from the Australian study cohort. Therefore, the relationship between mortality and SF is unlikely to be explained by an intercurrent infection. Similarly, the effect of SF on mortality was independent of the presence of HCC and other malignancies.

We evaluated whether the addition of SF to MELD increased the accuracy in predicting liver transplant waiting list mortality as assessed by ROC analysis. In the Australian study cohort, the addition of SF to MELD increased the area under the ROC curve by 7.6% and 7.5% for 180-day and 1-year survival, respectively; however, these differences did not reach statistical significance (P = 0.10, P = 0.10, respectively). Thus, in this cohort, our findings are similar to that described by Biggins et al., who evaluated the role of serum sodium concentration in predicting liver transplant waiting list mortality. In that study, the investigators showed that a low serum sodium concentration was a significant, independent factor predicting increased mortality and that the addition of sodium to MELD increased the area under the ROC curve at each time point studied. However, akin to our study, the differences failed to reach statistical significance. A complete understanding of the value of adding sodium concentration to MELD in predicting waiting list mortality was provided when Kim et al. evaluated 2000 patients registered with the Organ Procurement and Transplantation Network. In the current study, we provide further evidence in a validation cohort of USA patients undergoing OLT in a center in the United States that SF increases the accuracy in predicting liver transplant waiting list mortality. The addition of SF to MELD increases the area under the ROC curve for 180-day and 1-year mortality by 21.4% and 40.3%, respectively, for patients in the study cohort. These increases were greater than in the Australian cohort and were highly statistically significant (P = 0.001, P < 0.00001, respectively).

Further evidence of the importance of SF was demonstrated by our observation that increments in SF of 50 µg/L and 100 µg/L were associated with an increased risk of death on the waiting list for both Australian and USA patients. Moreover, an SF greater than 500 µg/L and MELD were the only factors associated with increased mortality in multivariate analysis in the validation cohort. We propose on the basis of the results presented in this study that a multicenter study evaluating the role of SF similar to that conducted by Kim et al. in relation to serum sodium concentration is now clearly required.

In the univariate analysis of the study population, MELD was significantly associated with an adverse outcome for 180-day and 1-year survival, although the HRs were modestly increased at 1.09 and 1.10, respectively. It is curious that MELD did not remain an independent predictor of mortality in the multivariate analysis for 180-day and 1-year survival in the Australian cohort. In contrast, MELD was identified as an important predictor of mortality by multivariate analysis in the USA cohort for 180-day and 1-year survival. This is an interesting observation that requires careful consideration and is possibly explained by differences between the two populations. The mean MELD of the study population (15.4) was significantly lower than in the USA cohort (19.2), and when one examines the relative risk of death versus MELD, the relative risk at a MELD of 15 is approximately 1.0, which is consistent with our observations. There are other caveats when using MELD that need to be considered; for example, MELD was created and validated in a cohort of USA patients who were undergoing transjugular intrahepatic porto-systemic shunt surgery rather than OLT, and the discriminative ability of MELD may not be directly applicable to an Australian population undergoing OLT.

To make the study findings more universal, we used the biological MELD when considering patients with HCC. We also ensured that in the study population, MELD was calculated on blood samples taken at the same times as the SF was measured. Thirdly, all patients in the study cohort were clinically stable at the time of evaluation without acute complications of liver disease within the previous 28 days. The retrospective design of the study has limitations, and referral bias may be operative because of the interest of the investigators in disorders of iron overload. Nevertheless, our results show the independent effect of SF in multivariate analysis in both populations, and the direction of shift of the ROC curve was consistent across all analyses. We consider it important that multicenter prospective studies are performed to confirm...
and extend these novel observations as well as to determine whether the effect is attributable to increased liver iron concentration, because this may have potential therapeutic implications.

References