**LIVER DISEASE**

**MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: a European study**

F Botta, E Giannini, P Romagnoli, A Fasoli, F Malfatti, B Chiaronello, E Testa, D Risso, G Colla, R Testa

*Gut* 2003;52:134–139

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**Background:** Indices for predicting survival are essential for assessing prognosis and assigning priority for liver transplantation in patients with liver cirrhosis. The model for end stage liver disease (MELD) has been proposed as a tool to predict mortality risk in cirrhotic patients. However, this model has not been validated beyond its original setting.

**Aim:** To evaluate the short and medium term survival prognosis of a European series of cirrhotic patients by means of MELD compared with the Child-Pugh score. We also assessed correlations between the MELD scoring system and the degree of impairment of liver function, as evaluated by the monoethylglycinexylidide (MEGX) test.

**Patients and methods:** We retrospectively evaluated survival of a cohort of 129 cirrhotic patients with a follow up period of at least one year. The Child-Pugh score was calculated and the MELD score was computed according to the original formula for each patient. All patients had undergone a MEGX test. Multivariate analysis was performed on all variables to identify the parameters independently associated with one year and six month survival. MELD values were correlated with both Child-Pugh scores and MEGX test results.

**Results:** Thirty one patients died within the first year of follow up. Child-Pugh and MELD scores, and MEGX serum levels were significantly different among patients who survived and those who died. Serum creatinine, international normalised ratio, and MEGX60 were independently associated with six month mortality while the same variables and the presence of ascites were associated with one year mortality. MELD scores showed significant correlations with both MEGX values and Child-Pugh scores.

**Conclusions:** In a European series of cirrhotic patients the MELD score is an excellent predictor of both short and medium term survival, and performs at least as well as the Child-Pugh score. An increase in MELD score is associated with a decrease in residual liver function.

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There is an increasing discrepancy between the number of cirrhotic patients on waiting lists for orthotopic liver transplantation (OLT) and the number of available donor livers. The correct timing for surgery has an important impact on both mortality and morbidity of the patients. Indeed, late transplantation affects patient outcome while performing OLT in those with less urgent indications penalises patients who could benefit most from the procedure. Moreover, the economics, social burden, and ethical considerations of maintaining patients on waiting lists should also be taken into consideration.

Over the years, many clinical and biochemical parameters have been suggested in order to more accurately predict the prognosis of cirrhotic patients and correctly assess their short and medium term survival. The Child-Pugh score is still considered the cornerstone in the prognostic evaluation of cirrhotic patients although it was formulated more than 30 years ago. Nevertheless, it has some drawbacks such as subjectivity of clinical parameters and limited discriminant ability.

Child-Pugh class A patients usually show good medium term survival without OLT unless other events (for example, hepatocellular carcinoma, uncontrolled bleeding due to portal hypertension, etc) occur; while Child-Pugh class C patients are considered the conventional candidates for the procedure. Child-Pugh class B patients can be considered a heterogeneous group as their clinical condition may remain stable for more than a year or rapidly deteriorate.

Quantitative liver function tests that evaluate the clearance of exogenous substances have been studied and combined with the Child-Pugh classification or with other scoring systems to create composite prognostic scores in an attempt to improve prognostic accuracy.

The monoethylglycinexylidide (MEGX) test, which depends on liver blood flow and cytochrome P450 activity, is a quantitative liver function test related to the severity of liver disease, and shows good correlation with medium and short term survival prognosis of cirrhotic patients.

Recently, the model for end stage liver disease (MELD) was introduced as a tool to predict mortality risk and to assess disease severity in patients with liver cirrhosis so as to determine organ allocation priorities. Although previously formulated as a prognostic index for cirrhotic patients undergoing transjugular intrahepatic portosystemic shunt (TIPSS), it was validated by the same authors on a broad series of patients with liver disease of various aetiology and severity. Nevertheless, although the MELD score takes into consideration objective parameters (serum creatinine, INR, alanine aminotransferase (ALT), total bilirubin), it has been validated beyond its original setting.

**Abbreviations:** OLT, orthotopic liver transplantation; MEGX, monoethylglycinexylidide; MELD, model for end stage liver disease; TIPSS, transjugular intrahepatic portosystemic shunt; INR, international normalised ratio; HCV, hepatitis C virus; HBV, hepatitis B virus; HDV, hepatitis D virus; ROC, receiver operating characteristic; SS, sensitivity; SP, specificity; RR, relative risk.
The MELD score was calculated according to the original formula proposed by the Mayo Clinic group:

$$3.8 \times \log_2 (\text{bilirubin (mg/dl)}) + 11.2 \times \log_2 (\text{INR}) + 9.6 \times \log_2 (\text{creatinine (mg/dl)}) + 6.4 \times \text{etiology: 0 if cholestatic or alcoholic, 1 otherwise}.$$

Moreover, we computed the MELD score with or without aetiology of liver disease.

All patients had undergone the MEGX test as follows: lidocaine was injected into a forearm vein over approximately 2–3 minutes at a dose of 1 mg/kg body weight, and blood samples were then taken 15, 30, and 60 minutes after lidocaine injection (MEGXt, MEGXs, and MEGXc). MEGX serum concentration was measured at the three sampling times by means of the TDx fluorescence polarisation immunoassay system, and was calculated as follows: $\text{MEGX} = \text{MEGX}_0 \times \text{MEGX}_t$, where $\text{MEGX}_0$ is MEGX concentration at sampling time and $\text{MEGX}_0$ is MEGX concentration at baseline.

Both Child-Pugh and MELD scores were calculated on parameters obtained at referral. Biochemical evaluations were carried out by the same laboratory. Prothrombin expressed as per cent activity was converted to prothrombin time INR using internal standards of the laboratory and were assessed by a single operator (GC).

Statistical analysis was first performed on the whole group of 129 patients and then on the subgroup of 63 Child-Pugh class B patients, evaluating six month and one year survival. Comparisons between groups were performed using Fisher’s exact test and the Mann-Whitney U test. Results are expressed as median (range). The correlation between variables was evaluated by means of Spearman’s rank correlation test ($r$). Receiver operating characteristic (ROC) curves were used to determine the cut off values of MEGX serum concentrations, Child-Pugh score, and MELD, with the best sensitivity (SS) and specificity (SP) in discriminating between patients who survived and those who died. The validity of the models was measured by means of the concordance ($c$) statistic (equivalent to the area under the ROC curve). A $c$ value of 0.8–0.9 indicates excellent diagnostic accuracy; a model with a $c$ value >0.7 should be considered useful. Univariate survival curves were estimated using the Kaplan-Meier method. Stepwise survival analysis was performed by means of Cox regression to determine the variables independently associated with one year and six month mortality. For all analyses a $p$ value <0.05 was considered statistically significant. Data were analysed using the SPSS package for Windows (SPSS Inc., Chicago Illinois, USA).

### RESULTS

During the one year follow up, 31 patients died: five were Child-Pugh class A (12%), 16 were class B (25%), and 10 were class C (44%). The causes of death were all related to liver disease. Ninety eight patients survived more than one year: 38 were Child-Pugh class A (88%), 47 were class B (75%), and 13 were class C (56%).
MEGX60 showed the best SS in predicting six month survival. Among the various parameters of the 63 Child-Pugh class B patients, only MEGX$_{v}$ (16.4 ng/ml (2.9–63.3) vs 9.3 (0.58–13.3); p=0.02) and MEGX$_{s}$ (24.6 ng/ml (6.7–55.6) vs 13.9 (0.9–18.5); p=0.02) were significantly lower among patients who died in the short term (six months), while MEGX$_{s}$ (19 ng/ml (4–54) vs 11 (1–63); p=0.05) was lower among patients who died in the medium term (one year).

Multivariate analysis was performed on variables contained in both the Child-Pugh and MELD scores, and on all MEGX sampling times to identify parameters independently associated with six month and one year mortality. This analysis showed that INR (relative risk (RR) 4.282 (range 1.438–12.751); p<0.009), creatinine serum levels (RR 8.785 (0.213–36.186); p=0.03), and MEGX$_{v}$ (RR 0.920 (0.860–0.983); p=0.01) were the variables significantly associated with six month mortality, while the presence of ascites (RR 2.146 (1.203–3.895); p=0.01), creatinine serum levels (RR 1.473 (1.091–2.014); p=0.01), INR (RR 2.47 (1.056–5.863); p=0.04), and MEGX$_{s}$ (RR 0.969 (0.939–1); p=0.05) were significantly associated with one year mortality.

MELD scores showed a highly significant correlation with both MEGX serum levels (MELD$_{v}$, $r_{c}$=-0.545, p<0.0001; MELD$_{s}$, $r_{c}$=-0.542, p<0.0001) and Child-Pugh scores $(r_{c}=0.817, p<0.0001)$. Moreover, Child-Pugh scores were correlated with MEGX serum levels (MELD$_{v}$, $r_{c}$=-0.529, p<0.0001; MELD$_{s}$, $r_{c}$=-0.598, p<0.0001; MELD$_{v}$, $r_{c}$=-0.577, p<0.0001).

### Prognostic analysis of Child-Pugh class B patients

Among the various clinical, biochemical, and functional parameters of the 63 Child-Pugh class B patients, only MEGX$_{v}$ (16.4 ng/ml (2.9–63.3) vs 9.3 (0.58–13.3); p=0.02) and MEGX$_{s}$ (24.6 ng/ml (6.7–55.6) vs 13.9 (0.9–18.5); p=0.02) were significantly lower among patients who died in the short term (six months), while MEGX$_{s}$ (19 ng/ml (4–54) vs 11 (1–63); p=0.05) was lower among patients who died in the medium term (one year).

### Table 2 Clinical and biochemical characteristics of the 129 cirrhotic patients subdivided according to six month survival

<table>
<thead>
<tr>
<th></th>
<th>Survived patients</th>
<th>Deceased patients</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>86/31</td>
<td>9/3</td>
<td>NS</td>
</tr>
<tr>
<td>Age (y)</td>
<td>49 (22–75)</td>
<td>55 (35–71)</td>
<td>NS</td>
</tr>
<tr>
<td>Encephalopathy (yes/no)</td>
<td>10/107</td>
<td>1/11</td>
<td>NS</td>
</tr>
<tr>
<td>Ascites (yes/no)</td>
<td>44/73</td>
<td>9/3</td>
<td>0.03</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>1.7 (0.3–12)</td>
<td>3.1 (1.6–6.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.5 (2.4–5)</td>
<td>2.9 (2.3–4.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Prothrombin activity (%)</td>
<td>58 (31–100)</td>
<td>50 (30–85)</td>
<td>0.01</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>7 (5–12)</td>
<td>10 (6–14)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.9 (0.6–1.3)</td>
<td>1.0 (0.8–1.3)</td>
<td>NS</td>
</tr>
<tr>
<td>INR</td>
<td>1.6 (1.0–2.9)</td>
<td>1.9 (1.1–2.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>MELD scores</td>
<td>7 (5–17)</td>
<td>11 (6–19)</td>
<td>0.0007</td>
</tr>
<tr>
<td>MELD$_{v}$ score</td>
<td>7 (5–23)</td>
<td>16 (13–25)</td>
<td>0.0002</td>
</tr>
<tr>
<td>MEGX$_{v}$ (ng/ml)</td>
<td>13.8 (0–110.8)</td>
<td>7.2 (0–29.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>MEGX$_{s}$ (ng/ml)</td>
<td>20.2 (2.2–90.9)</td>
<td>9 (0.58–39)</td>
<td>0.0007</td>
</tr>
<tr>
<td>MEGX$_{c}$ (ng/ml)</td>
<td>26.1 (4.1–92.9)</td>
<td>14.3 (0.95–40)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are median (range).

INR, international normalised ratio; MELD, model for end stage liver disease; MELD$_{v}$, model for end stage liver disease computed including aetiology of liver disease; MEGX, monoethylglycinexylidide.

### Table 3 Six month survival sensitivity, specificity, and $c$ index of the Child-Pugh score, MELD scores, and MEGX serum levels at each sampling time

<table>
<thead>
<tr>
<th></th>
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<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>$c$ index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh score</td>
<td>8</td>
<td>92</td>
<td>72</td>
<td>0.824</td>
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<tr>
<td>MELD score</td>
<td>8</td>
<td>75</td>
<td>68</td>
<td>0.796</td>
</tr>
<tr>
<td>MELD$_{v}$ score</td>
<td>14</td>
<td>75</td>
<td>72</td>
<td>0.823</td>
</tr>
<tr>
<td>MEGX$_{v}$ (ng/ml)</td>
<td>4</td>
<td>50</td>
<td>91</td>
<td>0.689</td>
</tr>
<tr>
<td>MEGX$_{s}$ (ng/ml)</td>
<td>15.2</td>
<td>92</td>
<td>63</td>
<td>0.799</td>
</tr>
<tr>
<td>MEGX$_{c}$ (ng/ml)</td>
<td>22.8</td>
<td>92</td>
<td>61</td>
<td>0.782</td>
</tr>
</tbody>
</table>

MELD, model for end stage liver disease; MELD$_{v}$, model for end stage liver disease computed including aetiology of liver disease; MEGX, monoethylglycinexylidide.

### Table 4 One year survival sensitivity, specificity, and $c$ index of the Child-Pugh score, MELD scores, and MEGX serum levels at each sampling time

<table>
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<tbody>
<tr>
<td>Child-Pugh score</td>
<td>8</td>
<td>61</td>
<td>75</td>
<td>0.691</td>
</tr>
<tr>
<td>MELD score</td>
<td>6</td>
<td>87</td>
<td>42</td>
<td>0.675</td>
</tr>
<tr>
<td>MELD$_{v}$ score</td>
<td>12</td>
<td>74</td>
<td>58</td>
<td>0.680</td>
</tr>
<tr>
<td>MEGX$_{v}$ (ng/ml)</td>
<td>11</td>
<td>74</td>
<td>63</td>
<td>0.676</td>
</tr>
<tr>
<td>MEGX$_{s}$ (ng/ml)</td>
<td>18</td>
<td>81</td>
<td>64</td>
<td>0.703</td>
</tr>
<tr>
<td>MEGX$_{c}$ (ng/ml)</td>
<td>26</td>
<td>77</td>
<td>54</td>
<td>0.657</td>
</tr>
</tbody>
</table>

MELD, model for end stage liver disease; MELD$_{v}$, model for end stage liver disease computed including aetiology of liver disease; MEGX, monoethylglycinexylidide.
application to patients with different stages of liver cirrhosis in order to evaluate their short term survival prognosis. Lastly, two independent studies performed in North American cirrhotic patients showed that the MELD score performed at least as well as the Child-Pugh score in predicting patient outcome following acute variceal bleeding and mortality in patients referred for OLT. Nevertheless, in Europe the MELD scoring system has been evaluated only in the prognostic assessment of patients undergoing TIPSS.

In this study our aim was to evaluate the short and medium term prognostic ability of the MELD scoring system compared with the Child-Pugh score in a European series of cirrhotic patients who were referred to a tertiary care medical centre and who were followed up for at least one year. Moreover, we assessed the correlations among these staging systems and the degree of liver functional impairment, as evaluated by means of the MEGX test. Lastly, we performed these analyses focusing on Child-Pugh class B patients due to the peculiar importance of the prognostic accuracy in this subgroup of patients.

Firstly, we observed that Child-Pugh and MELD scores, and MEGX could discriminate between deceased and surviving patients both in the short and medium term. Moreover, we showed that these parameters had high diagnostic accuracy for predicting six and 12 month mortality although none performed better than the others. Secondly, we found that among the clinical variables of the traditional score, the presence of ascites seemed to be significantly related to both short and medium term mortality as it was clinically detected more frequently among deceased patients. Lastly, multivariate analysis showed that signs of liver decompensation, such as the presence of ascites, subclinical decrease in renal function, INR, and impairment of liver metabolic activity (MEGX) were independently associated with both one year and six month mortality, although the presence of ascites was not associated with earlier death.

For the first time, we found a significant correlation between MELD score and the degree of metabolic liver functional impairment, as well as confirmation of the relationship between MELD and Child-Pugh score. Lastly, Child-Pugh class B patients were then analysed separately as this subgroup of patients displays a prognosis that may be difficult to evaluate. Indeed, we found that correlations between MELD and degree of liver functional impairment were maintained even in this subgroup of patients, although only MEGX values were significantly lower in deceased patients than in survivors. While impaired liver function (MEGX) seemed to be the only parameter independently associated with six month mortality, multivariate analysis was unable to identify any variable associated with one year mortality, thus emphasising the complexity of medium term prognostic assessment of this group of patients.

In this study, we confirmed the prognostic ability and accuracy of the MELD scoring system in a setting which was different from that where the score was formulated (for example, ethnic background, features of disease, etc). In fact, the MELD score showed discriminant ability between patients who survived and those who died both at six and 12 months of follow up. Moreover, it showed excellent diagnostic accuracy in predicting short and medium term survival, at least comparable with the Child-Pugh score. Lastly, for the first time we showed that the MELD scoring system, which is simple, reproducible, and contains variables with important physiopathological connotations, correlated significantly with the degree of liver functional impairment.

Our findings are further strengthened by the results of multivariate analysis. Indeed, multivariate analysis showed that parameters contained in the MELD score (INR and...
serum creatinine levels) and the MEGX test results (MEGX_{60}) were independently associated with six month mortality, and that signs of liver decompensation such as the presence of ascites was an important parameter predicting one year mortality. These results seem to confirm the complementary role of clinical and functional assessment in the prognostic evaluation of cirrhotic patients. Moreover, they indicate the importance of both Child-Pugh and MELD scoring systems. Lastly, they underscore the importance of some parameters that are pathophysiologically inter-related, and that contribute to worsening of the patient’s condition, such as the subclinical decrease in renal function and the presence of ascites. Furthermore, these results are in keeping with those of recent studies showing that the presence of ascites as well as renal function impairment represents one of the most important prognostic variables in cirrhotic patients. 31, 32

The correlation between the MELD scoring system and the degree of liver functional impairment that we observed in the whole group was confirmed even in the subgroup of Child-Pugh class B patients, although in this group the MELD score was unable to discriminate between deceased and surviving patients, either in the short or medium term. It is likely that in this subgroup of patients evaluation of dynamic changes in the MELD score would help identify patients at higher risk of death. 33 Nevertheless, functional evaluation seemed to be the best tool for predicting one year (MEGX_{30}) and six month (MEGX_{60}) mortality in Child-Pugh class B patients. 34

The fact that the various analyses identified different MEGX sampling times as variables associated with medium and short term prognosis has a sound physiopharmacological basis. In fact, MEGX_{60} most likely represents comprehensive functional reserve in cirrhotic patients and reflects the combination of both impaired blood flow and metabolic activity. 35 MEGX_{30} is predominantly influenced by hepatic blood flow and probably represents a “load stress test” while MEGX_{oa} is more an expression of residual metabolic capacity. 36, 37

In conclusion, in this study we have confirmed the prognostic ability of the MELD scoring system for both short and medium term survival, even in a European series of cirrhotic patients. Moreover, for the first time we have shown that the MELD scoring system is correlated with the degree of liver functional impairment. As both the MELD and Child-Pugh scores showed similar accuracy, we feel that they should be considered complementary tools in evaluating the progressive worsening of the clinical condition of cirrhotic patients. Furthermore, particular attention should be paid to the presence of ascites and creatinine serum levels as clinical signs of derangement of more complex activities and markers of a higher risk of death. Lastly, among Child-Pugh class B patients, evaluation of liver functional reserve has an important role in assessing their short term prognosis.

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Gut 2003 52: 134-139
doi: 10.1136/gut.52.1.134

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