Liver Transplantation with the Meld System: A Prospective Study from a Single European Center


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The efficacy of the Meld system to allocate livers has never been investigated in European centers. The outcome of 339 patients with chronic liver disease listed according to their Meld score between 2003 and 2005 (Meld era) was compared to 224 patients listed during the previous 2 years according to their Child score (Child era). During the Meld era, hepatocellular carcinomas (HCCs) had a ‘modified’ Meld based on their real Meld, waiting time and tumor stage. The dropouts were deaths, tumor progressions and too sick patients. The rate of removals from the list due to deaths and tumor progressions was significantly lower in the Meld than in the Child era: 10% and 1.2% versus 16.1% and 4.9%, p < 0.05. The 1-year patient survival on the list was significantly higher in the Meld era (84% vs. 72%, p < 0.05). The prevalence of transplantation for HCC increased from 20.5% in the Child to 48.9% in the Meld era (p < 0.001), but between HCCs and non-HCCs of this latter era the dropouts were comparable (9.4% vs. 14.9%, p = n.s.) as was the 1-year patient survival on the list (83% vs. 84%, p = n.s.). The Meld allocation system improved the outcome of patients with or without HCC on the list.

Key words: Allocation, hepatocellular carcinoma, mortality, prognosis, survival, waiting lists

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Introduction

In the United States, deceased donor livers are allocated to patients with chronic liver disease with a priority based on the model for end-stage liver disease (Meld) (1). As demonstrated in the United States, the Meld score provides a better prediction of mortality while on the waiting list than the Child score (2,3) and it selects those patients with chronic liver disease better able to survive without liver transplantation (LT) during the waiting time. Due to the risk of dropout secondary to tumor progression (4), patients with hepatocellular carcinoma (HCC) had an adjusted Meld score according to tumor stage: a score of 24 for T1 (5) and 29 for T2. In the United States, these scores have subsequently been reduced to 20 and 24, respectively, in order to limit the high transplantation rate for HCC, after the first year of organ allocation based on the Meld policy (6).

Due to the significant increase in the number of patients listed for LT in recent years and in accordance with the data in the literature, our center changed the previous liver allocation system based on the Child classification toward the Meld score (7). Our purpose was to improve the selection of those recipients with the highest risk of being removed from the list.

Differently from the US Meld score, patients with HCC did not have a fixed adjusted-Meld. The score was instead calculated by considering their real Meld score, the waiting time with tumor and the tumor stage.

We report the 2 years experience of our center with the Meld system, comparing the results with a series of recipients listed in the previous 2 years, where patients were selected according to their Child score (7).

Patients and Methods

Study design and patient population

We prospectively evaluated all patients on the waiting list for LT for chronic liver disease at the University of Bologna, Bologna, Italy, from March 2003, when our center started to apply the Meld score, to March 2005 (Meld era).

The outcome of this study population was compared with those patients listed for chronic liver disease during the pre-Meld era, from March 2001 to March 2003, when recipients were selected for LT according to their Child score (Child era) and the dropout rate of patients with HCC was basically controlled with the use of marginal donors (7).

The minimum criteria for placing adults on the liver transplant waiting list were those reported by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases (8) in both eras.
During the Child era, apart from ABO and body size matching, our organ allocation priority was based on the following criteria: (1) clinical characteristics of patients classified according to the Child score, (2) match between donor age over 60 years and preoperative diagnosis of HCC (7).

During the Meld era, apart from ABO and body size matching, liver allocation priority was based on the real Meld score for patients without HCC and on the modified Meld score (Meld-H) for patients with HCC.

The Meld score was calculated using serum creatinine, serum total bilirubin and the INR according to the formula (9) currently in use by UNOS (http://www.unos.org), and it was measured at the time of dropout, LT and end of the follow-up (10).

The preoperative criteria of selection for HCC patients, the diagnostic work-up, the treatment while on the waiting list and the histological evaluation were fully presented and discussed in our previous studies (11,12).

The scores added to the HCC patients’ real Meld score to compute the Meld-H changed over the 2 years of Meld experience, due to a preliminary analysis, which is reported in the results section.

The Meld-H score was therefore calculated differently between the first and second year of the Meld system.

During the first year, the Meld-H score was computed in the following way:

Real Meld score + 5 points for T1, 8 points for T2 or 12 points for T3 + 1 point × months on the waiting list with a diagnosis of HCC.

During the second year, the Meld-H score was computed in the following way:

real Meld score + 3 points for T1 or 6 for T2/T3 + 0.5 for T1 or 1 for T2/T3 × months on the waiting list with a diagnosis of HCC.

Tumor stage T1 was a single HCC with a diameter ≤3 cm, while T2 was a single HCC with a diameter between 3 and 5 cm or multiple HCCs not more than 3 cm with a diameter ≤3 cm.

Patients with T3 stage had a single HCC with a diameter ≤8 cm or two HCCs with a diameter ≤5 cm or multiple HCCs ≤5 with a diameter ≤4 cm, which after preoperative treatments were downstaged to T2 at the time of listing.

Patients listed for re-LT or with a preoperative diagnosis of acute liver failure were excluded from the study, because they were placed on a national urgent waiting list and had a national priority as status 1. The principal aim of the study was to evaluate the efficacy of organ allocation based on the Meld score and on the Meld score modified for HCC, as proposed by our center.

The study was approved by the local institutional review committee.

**Statistical analysis and criteria of analysis**

Statistical analyses were performed using Fisher’s exact test, the Mann-Whitney test or the chi-square test, as appropriate.

The survival of patients on the list was calculated by the Kaplan-Meier method starting from the day when patients were listed to the day of dropout, LT and the end of the follow-up period if they were still on the list.

Dropouts included deaths while on the list, tumor progressions exceeding the transplant criteria and too sick cases, no longer suitable for transplantation.

The survival of patients after LT was calculated by the Kaplan-Meier method starting from the day of LT to the day of death or to the most recent follow-up visit.

The follow-up of patients in the Child era started in March 2001 and finished in March 2003 and for those in the Meld era it started in March 2003 and finished in March 2005.

Differences were compared by the log-rank test and variables were evaluated in the multivariate analysis using Cox’s proportional hazard model.

The waiting time was computed from the date when patients were listed to the date of one of the following events: LT, death, exclusion from the waiting list or the end of the follow-up period if they were still on the waiting list.

Among the dropouts from the list, the deaths while on the list and the removals from the list for tumor progression or because the patient was too sick were computed. When the dropout rate was calculated at 6 months, patients transplanted within 6 months were excluded from the analysis (13,14).

Logistic regression was used to assess the accuracy of variables as predictors of dropout. The concordance statistic (c-statistic), which is the equivalent of the area under the receiver operating characteristic (ROC) curves, was also calculated and the areas under the ROC curves were statistically compared (14–17).

Differences were considered significant for p values less than 0.05. Statistical analysis was performed with SPSS (SPSS Base 10.0; Application Guide, SPSS Inc., Chicago, USA, 1998).

**Results**

**Patient features and outcome on the list during the Child and the Meld era**

The mean age of patients (53.1 ± 8.9 years) and the sex (males 70.4%) was comparable between the two periods, while the prevalence of cases with the preoperative diagnosis of HCC was higher in the Meld than in the Child era (34.5% vs. 25.9%, p < 0.05).

Patient outcome on the list together with the respective preoperative diagnosis, waiting time, Child and Meld score are reported in Table 1.

At the time of transplantation the real median Meld score was significantly higher in the Meld than in the Child era (19 vs. 18, p < 0.05). Among transplanted patients (135 in the Meld era and 127 in the Child era), the prevalence of cases with a preoperative diagnosis of HCC was significantly higher in the Meld than in the Child era (48.9% vs. 20.5%, p < 0.001).

In the Child era patients had priority for LT according to their Child score (c-statistic = 0.601, p < 0.01), while during the
Table 1: Patient outcome on the list with the respective preoperative diagnosis, waiting time, Child and Meld scores

<table>
<thead>
<tr>
<th></th>
<th>Child 224 patients</th>
<th>Meld 339 patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTs</td>
<td>127 (56.7%)</td>
<td>135 (39.8%)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>On the list</td>
<td>47 (21%)</td>
<td>160 (47.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dropouts</td>
<td>51 (22.8%)</td>
<td>44 (13%)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Deaths</td>
<td>36 (16.1%)</td>
<td>34 (10%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Too sick</td>
<td>4 (1.8%)</td>
<td>6 (1.8%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Tumor progressions</td>
<td>11 (4.9%)</td>
<td>4 (1.2%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LTs Median waiting time days</td>
<td>159</td>
<td>103</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Median Child</td>
<td>11</td>
<td>11</td>
<td>N.S.</td>
</tr>
<tr>
<td>Median Meld</td>
<td>18</td>
<td>19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HCC prevalence</td>
<td>26 (20.5%)</td>
<td>66 (48.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dropouts Median waiting time days</td>
<td>109</td>
<td>94</td>
<td>N.S.</td>
</tr>
<tr>
<td>Median Child</td>
<td>10</td>
<td>11</td>
<td>N.S.</td>
</tr>
<tr>
<td>Median Meld</td>
<td>18</td>
<td>21</td>
<td>N.S.</td>
</tr>
<tr>
<td>HCC prevalence</td>
<td>17 (34%)</td>
<td>11 (25%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>On the list Median waiting time days</td>
<td>253</td>
<td>267</td>
<td>N.S.</td>
</tr>
<tr>
<td>Median Child</td>
<td>10</td>
<td>9</td>
<td>N.S.</td>
</tr>
<tr>
<td>Median Meld</td>
<td>17</td>
<td>14</td>
<td>0.089</td>
</tr>
<tr>
<td>HCC prevalence</td>
<td>15 (31.9%)</td>
<td>40 (25%)</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Meld era patients had priority for LT according to their Meld score (c-statistic = 0.689, p < 0.001).

**Patient survival on the list during the Child and the Meld eras and risk of dropout**

The survival rate of patients on the list was significantly higher in the Meld than in the Child era, as reported in Figure 1 and the risk of dropout per patient day on the waiting list was 1.75 times higher in the Child than in the Meld era; confidence intervals (CI) 1.17–2.63, p < 0.01.

The risk of dropout divided per period and per category of Meld score is reported in Table 2.

The 6-month dropout rate was significantly higher in the Child than in the Meld era (22.3% vs. 12.5%, respectively, p < 0.05). Among HCC patients the 6-month dropout rate was 25.8% in the Child era and 9.1% in the Meld era (p < 0.05) and among non-HCC patients the 6-month dropout rate was 21.2% in the Child era and 13.9% in the Meld era (p < 0.05).

**Score for HCC in the Meld era and comparison with the policy during the Child era**

During the Meld era, HCC patients had a score based on their real Meld score, waiting time with tumor and tumor stage, as previously reported. Due to this correction, their real Meld score increased from a median value of 15 (mean 16 ± 6, range 6–42) to 25 (mean 27 ± 8, range 13–58). The median score added for the waiting time with tumor was 4 points and 6 points for the tumor stage. The scores added were significantly related to the risk of being removed from the list for tumor progression (c-statistic = 0.714, p < 0.01).

During the first 6 months of Meld experience with this policy, we observed a high rate of transplantation for HCC (64.7%) and no case of tumor progression for HCC; according to these data the scores added to the HCC patients were reduced as reported in the methods section.

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**Meld era: survival and dropouts on the list between HCC and non-HCC patients**

During the Meld era, the dropout rate was comparable between HCC and non-HCC patients: 9.4% and 14.9%, p = n.s. Among the 117 recipients listed with a preoperative diagnosis...
Table 2: The risk of dropout divided per period and per category of Meld score

<table>
<thead>
<tr>
<th></th>
<th>Child era survival on the list</th>
<th>Meld era survival on the list</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-months</td>
<td>6-months</td>
</tr>
<tr>
<td>All cases</td>
<td>89%</td>
<td>84%</td>
</tr>
<tr>
<td>No. patients at risk 563</td>
<td>159</td>
<td>104</td>
</tr>
<tr>
<td>Meld ≤20</td>
<td>93%</td>
<td>89%</td>
</tr>
<tr>
<td>No. patients at risk 380</td>
<td>109</td>
<td>78</td>
</tr>
<tr>
<td>Meld 21–30</td>
<td>88%</td>
<td>84%</td>
</tr>
<tr>
<td>No. patients at risk 155</td>
<td>47</td>
<td>27</td>
</tr>
<tr>
<td>Meld &gt;30</td>
<td>45%</td>
<td>23%</td>
</tr>
<tr>
<td>No. patients at risk 28</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

HR = hazard ratio; CI = confidence intervals.

Figure 2: Kaplan-Meier estimation of overall patient survival while on the waiting list during the Meld era according to the preoperative diagnosis of HCC (□) and non-HCC (■).

The c-statistics of the ROC curves predict that the dropouts were 0.579 for Child, 0.637 for Meld and 0.644 for Meld-H, as reported in Figure 3. The statistical comparison of the areas under the ROC curves showed: Child versus Meld, \( p < 0.05 \); Child versus Meld-H, \( p < 0.05 \); Meld versus Meld-H, \( p = \text{n.s.} \).

Meld era: survival after liver transplant

During the Meld era, the 1- and 2-year patient survival rates after LT were 91.8% and 85%, respectively. The survival rates were comparable between HCC and non-HCC patients.

Discussion

The present study provides validation of the prognostic value of the Meld score, previously reported in the United States (6,10,14,18–20), in predicting the dropout rate from the waiting list in a European series. Furthermore the LT priority for HCC according to the modified Meld score, proposed by our center, proved to be a means of measuring the medical urgency for liver allocation in HCC patients, without increasing the removals from the list in the non-HCC group.
In accordance with the data reported in the literature and due to the increasing number of patients on the waiting list, our center changed its previous liver allocation system. In the preMeld era, we selected recipients for LT on the basis of their Child score and the HCC dropouts were controlled by offering them marginal grafts more often (7).

Since March 2003, recipients were placed on the waiting list according to their Meld score and HCC patients had a special score depending on their tumor stage, waiting time with tumor and real Meld score.

We supposed that HCC patients with the same tumor stage, but with a different liver function and a different waiting time, had a different dropout risk. We therefore introduced a modified Meld score for them, based on the combination of these three variables. Due to the absence of previous experience, our model was empiric and to avoid any disadvantage to non-HCC patients, the data obtained by following this policy were frequently analyzed and the scores for HCC were changed according to the results. We believe this method is the only way to manage the removals from the list, which change over the years according to the number of patients listed and their clinical status.

In some European centers the Meld score was found to be related to the prognosis of patients with liver cirrhosis (21,22), but no study has been published concerning the efficacy of the Meld score in the selection of recipients on the waiting list. Therefore, to assay the efficacy of our prospective experience with Meld scores, we compared the data of 2 years of prospective experience with the data of patients listed in the two previous years.

The comparison of these two periods showed that we were able to improve the survival of patients on the list during the Meld era (Figure 1) and this was more relevant for patients with high Meld scores (Table 2). This result was due to a lower rate of removals from the list for deaths and tumor progressions.

Our allocation policy completely changed the fate of patients with HCC: in the Child era their dropouts were managed by offering them marginal grafts more often, while in the Meld era they had a modified Meld score, which assigned priority according to their tumor stage, waiting time and real Meld score.

The first consequence of this policy was the increased rate of transplantation for HCCs, as described in the initial American experiences (6,20). Due to this result, present after the first 6 months of our activity in the Meld era, we reduced the scores added to the HCC patients according to their tumor stage and waiting time with tumor, as reported in the methods section. By following this policy, we maintained a comparable dropout rate between HCC and non-HCC patients and consequently their survival on the list was similar.

The purpose of our score applied to HCC patients was to prevent the deaths due to liver failure and the removals for tumor progression. The real Meld score worked well for HCC patients and for non-HCC patients in predicting the deaths on the list, and our additional score was well related to the prediction of tumor progressions. Patients with cancer on the list have an addition risk of being removed due to tumor progression, but at the same time they may die due to liver failure like non-HCC patients.

We therefore believe it correct to maintain a common score for these two types of recipients, which predicts the deaths on the list (the real Meld score), and to add additional points to HCC patients to predict the additional risk of dropout related to the presence of tumor. The mathematical formula to calculate this score is probably impossible to compile, because the removals from the list depend on the number of patients listed, on the donors available and on the clinical status of the recipients. Our policy was to adapt the additional scores for HCC patients, according to the yearly dropout results, in order to maintain a similar risk of being removed from the list between patients with and without a tumor. This solution seemed to be the best way to manage the removals from the list in our single center experience.

The last issue to consider was the potentially worse outcome after LT in recipients selected with the highest Meld scores, reported by some authors and contradicted by others (23–28). The results of the Meld era showed no relationship between the outcome after LT and the Meld score of recipients, but the analysis was performed with only 135 cases and further liver transplants are therefore needed to confirm these data.

In conclusion, this European series confirmed that the Meld score was an effective parameter for predicting the deaths on the list of patients with and without HCC and it should be applied in the liver allocation system of European transplant centers.

Our proposal of adding additional points to the real Meld score of HCC patients, according to their tumor stage and waiting time with tumor, was effective in our experience in controlling the dropouts for tumor progression and it could be a reasonable working method for other centers.

Further prospective multicentric European studies will be needed to confirm our findings, which had the statistical bias of a single center experience.

References

1. Freeman RB, Wiesner RH, Harper A et al. UNOS/OPTN Liver Disease Severity Score, UNOS/OPTN Liver and Intestine, and UNOS/OPTN Pediatric Transplantation Committees. The new liver

Liver transplantation and MELD