Employment of meld score for the prediction of survival after liver transplantation

**Emprego do escore MELD para a predição da sobrevivência pós-transplante hepático**

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**ABSTRACT**

**Objective:** To assess the overall accuracy of the preoperative MELD score for predicting survival after liver transplantation (LT) and appraise medium-term (24 months) predictors of survival. **Methods:** We conducted a cross-sectional study including patients transplanted by the Department of General Surgery and Liver Transplantation of the Oswaldo Cruz University Hospital, University of Pernambuco, between July 15th, 2003 and July 14th, 2009. We used analysis of area under ROC (receiver operating characteristic) as a summary measure of the performance of the MELD score and assessed predictors of medium-term survival using univariate and multivariate analysis. **Results:** The cumulative survival of three, six, 12 and 24 months of the 208 patients studied was 85.1%, 79.3%, 74.5% and 71.1%, respectively. The preoperative MELD score showed a low discriminatory power for predicting survival after TH. By univariate analysis, we identified intraoperative transfusion of red blood cells (p <0.001) and platelets (p = 0.004) and type of venous hepatocaval anastomosis (p = 0.008) as significantly related to medium-term survival of the patients studied. However, by multivariate analysis only red blood cell transfusion was a significant independent predictor of outcome. **Conclusion:** The MELD score showed low overall accuracy for predicting post-transplant survival of patients studied, among which only intraoperative transfusion of red blood cells was identified as an independent predictor of survival in the medium term after TH.

**Key words:** Survival analysis. Patients. Organ transplantation. Liver transplantation. Mortality.

**INTRODUCTION**

Liver transplantation (LT) is currently the most effective treatment for patients with terminal chronic liver disease. However, the shortage of liver grafts persists as the main limiting factor for its development. In order to reduce the number of deaths on the waiting list and eliminate possible confounding factors related to the chronological system, a new policy for allocation of liver grafts, based on the MELD (Model for End-Stage Liver Disease) system has been adopted in Brazil since July 4, 2006.

Based on easily measurable laboratory data, the MELD score has been considered more transparent and objective for the ordination of liver disease on the waiting list for TH. Nevertheless, it has been validated as a predictor of mortality in the list, the role of this scoring system for predicting survival after HT remains controversial, which could suggest the need to readjust the graft allocation criteria for a model that also took into consideration the results of TH.

The objective of this study was to evaluate the accuracy of preoperative MELD score to predict survival after TH and also analyze factors predictive of medium-term survival (24 months).

**METHODS**

We conducted a cross-sectional cohort study of adult and adolescent patients (≤ 16 years) undergoing orthotopic liver transplantation (cadaver donor) in the Department of General Surgery and Liver Transplantation of the Oswaldo Cruz University Hospital, University of

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Pernambuco (HUOC / UPE) between July 15th 2003 and July 14th, 2009.

All transplant recipients were listed in the Transplant Center of Pernambuco and had their data collected from the database of the Service itself, considering the end date of preservation until June 15, 2011. Retransplanted patients were considered only in relation to the first procedure and we excluded patients transplanted for acute liver failure / fulminant liver failure and those undergoing transplantation of multiple organs, such as “split-liver” or “domino”. Similarly, we also excluded patients with incomplete data in their hospital records. The variables studied included data related to the donor, recipient and transplant center. For the “MELD” score we considered “pure” value recorded in the medical records at admission for transplantation or calculated with examinations collected on this occasion, without regard to the proposed correction to prioritize candidates in “special situations” (corrected MELD) 4.

For the preoperative diagnosis of hepatocellular carcinoma (HCC) we considered the criteria of the Barcelona Consensus5, confirmed by pathology of the explant. For the selection of patients with HCC candidates for TH, we used the “Milan criteria”. The diagnosis of viral hepatitis was based on the positivity of serological markers of each viral type. After TH, tacrolimus, mycophenolate (mofetil or sodium) and prednisone were used as immunosuppressive treatment, without changes in the protocols applied from 2003 to 2009.

Continuous variables were expressed as medians and interquartile range, while categorical variables were presented in absolute frequencies and percentages. The odds of post-HT survival were estimated by the Kaplan-Meier product-limit method.

The overall accuracy of the MELD score to predict survival after TH was evaluated using ROC (receiver operating characteristic) curve analysis. The area under the ROC curve (AUC) was used as a summary measure of the performance of the MELD score to predict this outcome. Additionally, stratified analyzes were conducted among patients with or without HCC.

Still, using univariate and multivariate analysis, we assessed the variables as factors predictive of medium-term survival (24 months) after TH. Initially, the association of each variable with the outcome mentioned in univariate models was evaluated using the logrank and Cox proportional hazards test. Then, the variables whose association with post-HT survival showed a statistically significance lower than 20% were analyzed in multivariate Cox proportional hazards to identify independent predictors. This analysis was also adjusted according to the criteria for allocation (chronological vs. MELD) and the time of transplantation (quartiles).

The collected data were tabulated in duplicate and the level of statistical significance in all analyzes was 1% (p <0.01).

The study was registered at SISNEP - National Information System on Ethics in Research involving Human Subjects (CAAE - 0003.0.106.000/10) and approved by the Ethics in Human Research cCommittee of the Oswaldo Cruz University Hospital - Cardiac Emergency Room of Pernambuco, under protocol number 12/2010.

RESULTS

From July 15th 2003 to July 14th, 2009 298 HTs were performed in 288 patients by the Department of General Surgery and Liver Transplantation HUOC / UPE. Eighty patients were ineligible and were excluded from the study: 63 were younger than 16 years, ten were transplanted for acute liver failure / fulminant hepatitis, one underwent a domino transplant, one underwent a transplant of the “split-liver” and five cases had incomplete data in their hospital records. Descriptive statistics corresponding to the remaining cases included in the study (n = 208) is summarized in Table 1.

The proportional cumulative survival of patients at three, six, 12 and 24 months after HT was 85.1%, 79.3%, 74.5% and 71.1%, respectively (Figure 1). Throughout the 95.1 months of follow-up, 76 patients died (36.5%) and seven (3.4%) were subjected to a retransplant. The main causes of death were infection, tumor recurrence and liver failure / transplant rejection. The median of follow-up of the surviving patients was 42.7 months, ranging from 24.8 to 95.1 months.

Figure 2 shows the ROC curve of MELD score to predict the medium-term survival after HT. Its corresponding AUC is 0.504. AUCs of 0.476, 0.477 and 0.504 were observed for the prediction of survival of three, six and 12 months after HT, respectively. For the strata HCC and non-HCC, the corresponding values of AUC for the prediction of survival of 24 months were 0.594 and 0.514.

By univariate analysis, we identified transfusion of red blood cells (p <0.001) and platelets (p = 0.004) and type of hepatic venous reconstruction (p = 0.008) as significantly related to survival after HT. However, multivariate analysis showed that only red blood cell transfusion was an independent predictor of medium-term survival of transplant patients. In this study, each unit of RBCs transfused during surgery increased the relative risk of death within 24 months at 13.5%, which ranged from 12.1% to 13.5% after multivariate analysis (Table 2).

DISCUSSION

The MELD score was initially described by Malinchoc et al.16 as a mathematical model capable of predicting survival in the first three months of patients who underwent percutaneous placement of transjugular intrahepatic portosystemic shunts (TIPS). Later, the model
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was rigorously validated as a predictor of mortality for cirrhotic patients on waiting lists for transplants \(^6\,11-13\) and was eventually incorporated into a new criterion for the allocation of grafts for HT \(^4,14,15\).

Nevertheless, the role of the MELD score to predict survival after HT, which has been considered a matter of vital importance to the issue of liver transplantation \(^6\), remains controversial \(^3,6,8\). In a systematic review on the performance of the MELD score in this scenario, Cholongitas \(et\ al\). \(^6\) concluded that this score was not a good predictor of short-term mortality after TH and that further studies were needed to evaluate its performance in the medium and long term.

In this study, analysis of the area under the ROC curve (AUC) was used as a summary measure of the MELD’s performance for the prediction of survival after HT. Normally,

### Table 1 - Variables studied.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Median (interquartil interval) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptor</strong></td>
<td></td>
</tr>
<tr>
<td>Age do receptor (years)</td>
<td>54 (44.5-60.5)</td>
</tr>
<tr>
<td>Score MELD</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>15 (12-19)</td>
</tr>
<tr>
<td>Non-hepatocellular carcinoma</td>
<td>13 (10-15)</td>
</tr>
<tr>
<td>Non-hepatocellular carcinoma</td>
<td>17 (13-20)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>137 (65.86)</td>
</tr>
<tr>
<td>Female</td>
<td>71 (34.13)</td>
</tr>
<tr>
<td>Blood type ABO</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>84 (40.38)</td>
</tr>
<tr>
<td>B</td>
<td>24 (11.53)</td>
</tr>
<tr>
<td>AB</td>
<td>11 (5.28)</td>
</tr>
<tr>
<td>O</td>
<td>89 (42.78)</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>53 (25.48)</td>
</tr>
<tr>
<td>B</td>
<td>94 (45.19)</td>
</tr>
<tr>
<td>C</td>
<td>61 (29.32)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic viral hepatitis</td>
<td>86 (41.34)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>61 (29.32)</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>53 (25.48)</td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td>25 (12.01)</td>
</tr>
<tr>
<td>Autoimmune chronic hepatitis</td>
<td>13 (6.25)</td>
</tr>
<tr>
<td>Cholestatic liver diseases (^2)</td>
<td>11 (5.28)</td>
</tr>
<tr>
<td>Miscellany</td>
<td>51 (24.51)</td>
</tr>
<tr>
<td><strong>Donor and transplant center</strong></td>
<td></td>
</tr>
<tr>
<td>Number of transplants / month</td>
<td>6 (4-8)</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>40.5 (25.5-51)</td>
</tr>
<tr>
<td>Cold ischemic time (hours)</td>
<td>6.8 (5.4-8.7)</td>
</tr>
<tr>
<td>Warm ischemia time (minutes)</td>
<td>47.5 (40-55)</td>
</tr>
<tr>
<td>Red blood cell transfusion (units)</td>
<td>3 (1-5)</td>
</tr>
<tr>
<td>Platelet transfusion (units)</td>
<td>0 (0-9)</td>
</tr>
<tr>
<td>Hepato-caval anastomosis</td>
<td></td>
</tr>
<tr>
<td>Conventional</td>
<td>127 (61.06)</td>
</tr>
<tr>
<td>Piggyback</td>
<td>81 (38.94)</td>
</tr>
<tr>
<td><strong>Periods of Transplantation (quartiles)</strong></td>
<td></td>
</tr>
<tr>
<td>First period (15/7/2003 – 22/9/2005)</td>
<td>52 (25)</td>
</tr>
<tr>
<td><strong>Allocation Criteria</strong></td>
<td></td>
</tr>
<tr>
<td>Chronological (15/7/2003 – 14/7/2006)</td>
<td>73 (35.10)</td>
</tr>
<tr>
<td>MELD (15/7/2006 – 14/7/2009)</td>
<td>135 (64.90)</td>
</tr>
</tbody>
</table>
Also, since the survival of transplanted patients with HCC is influenced by parameters related to the tumor, we performed analyses stratified between subgroups HCC and non-HCC. However, no statistically significant difference was found between the medium-term survival of these subgroups, and the MELD score had also low overall accuracy for predicting survival after HT in both strata. Although the MELD criteria have been adopted to prioritize the most severe patients on the waiting list, the majority of transplanted patients is still low MELD scores. Furthermore, it has been shown that the score does not display the same prognostic precision in milder forms of hepatic cirrhosis. Thus, the effect of hepatic dysfunction may not be evident in patients with MELD scores below 30, suggesting that only higher values would affect post-HT survival. In accordance with these reports, only 3.4% of transplant patients by the Service under review had MELD scores ≥ 30 (data not shown). This low proportion of patients with high scores likely contributed to minimize its overall accuracy for predicting survival after TH in this series.

Intraoperative transfusion of red blood cells has often been related to lower survival after liver transplantations, which can also be seen in this series, which identified a strong influence of the transfusion of blood components in the medium-term survival of transplant patients. This negative effect of blood transfusions probably stems from immunomodulation related to transfusions and changes of its components from storage process, which may increase the risk of nosocomial infections, acute lung injury and development of autoimmune diseases in the long term. Moreover, as emphasized by Mitchell et al., the need for blood transfusion may act only as a marker of severity of the patients undergoing HT, for whom lower survival rates are expected.

Given the current recommendations for the presentation of observational studies, we used a significance level of only 1% for the statistical analyzes in our work. In addition, we avoided the categorization of continuous variables in order to minimize losses in statistical power and the occurrence of residual confounding related to the dichotomization method. Similarly, stratified analyzes were performed according to the diagnosis of liver disease and multivariate analysis adjusted for temporal variables that could serve as confounding factors in interpreting the results, as the criterion for the allocation of grafts and the time of transplantation.

In addition to the socio-economic peculiarities concerning the study population, this series has special importance for the study of the predictive value of MELD score for post-HT survival in view of the divergent results found in Pernambuco after the adoption of the MELD criteria. Unlike the observed in other Brazilian states, in Pernambuco we observed a significant reduction in mortality on the waiting list and better post-HT survival after the adoption of this model, probably as a result of increasing governmental encouragements to transplantation of organs and tissues. On the other hand, the inclusion of more donor-related variables could add relevant information to
Table 2 - Univariate and multivariate predictors of medium-term survival (24 months) after liver transplantation.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate ¹</th>
<th>Non-adjusted</th>
<th>Allocation Criteria</th>
<th>Period of transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic categories¹</td>
<td>0.361</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Blood ABO rating</td>
<td>0.070</td>
<td>0.373</td>
<td>0.463</td>
<td>0.527</td>
</tr>
<tr>
<td>Receptor’s gender</td>
<td>0.667</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age of the recipient</td>
<td>0.924</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MELD score</td>
<td>0.867</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>0.360</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age of the donor</td>
<td>0.150</td>
<td>0.193</td>
<td>0.259</td>
<td>0.323</td>
</tr>
<tr>
<td>Cold ischemia time</td>
<td>0.062</td>
<td>0.306</td>
<td>0.287</td>
<td>0.221</td>
</tr>
<tr>
<td>Time of warm ischemia</td>
<td>0.125</td>
<td>0.251</td>
<td>0.384</td>
<td>0.775</td>
</tr>
<tr>
<td>Red blood cell transfusion</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>0.004</td>
<td>0.389</td>
<td>0.486</td>
<td>0.639</td>
</tr>
<tr>
<td>Number of transplants / month</td>
<td>0.649</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hepato-caval anastomosis</td>
<td>0.008</td>
<td>0.070</td>
<td>0.062</td>
<td>0.033</td>
</tr>
</tbody>
</table>

1. Univariate analysis using logrank tests and proportional hazards model of Cox; 2. Multivariate analysis using proportional hazards model of Cox. This analysis was adjusted for the allocation criterion (Chronological vs. MELD) and the time of transplantation (quartiles); 3. Categories Hepatocellular carcinoma versus Non-hepatocellular carcinoma.

this analysis, especially due to the considerable number of marginal donors employed by the Service in the study. ¹,²,³

It therefore follows that the MELD score was not accurate for predicting survival after HT in the Department of General Surgery and Liver Transplantation HUOC / UPE where only intraoperative transfusion of red blood cells was identified as an independent predictive factor of medium-term survival after HT.

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RESUMO

Objetivo: Analisar a acurácia geral do escore MELD pré-operatório para a predição da sobrevivência pós-transplante hepático (TH) e explorar fatores preditivos da sobrevivência de médio prazo (24 meses). Métodos: Estudo de corte transversal incluindo pacientes transplantados pelo Serviço de Cirurgia Geral e Transplante Hepático do Hospital Universitário Oswaldo Cruz, Universidade de Pernambuco, entre 15 de julho de 2003 e 14 de julho de 2009. Utilizou-se análise do área sob curva ROC (receiver operating characteristic) como medida-resumo do desempenho do escore MELD e se exploraram fatores preditivos da sobrevivência de médio prazo utilizando análise uni e multivariada.Resultados: A sobrevivência cumulativa de três, seis, 12 e 24 meses dos 208 pacientes estudados foi 85,1%, 79,3%, 74,5% e 71,1%, respectivamente. O escore MELD pré-operatório apresentou baixo poder discriminatório para a predição da sobrevivência pós-TH. Por análise univariada, identificaram-se a transfusão intraoperatória de hemácias (p<0,001) e plaquetas (p=0,004) e o tipo de anastomose venosa hepatocaval (p=0,008) como significativamente relacionados à sobrevivência de médio prazo dos pacientes estudados. No entanto, por análise multivariada, observou-se que apenas a transfusão de hemácias foi um fator preditivo independente deste desfecho. Conclusão: O escore MELD apresentou baixa acurácia geral para a predição da sobrevivência pós-transplante dos pacientes estudados, entre os quais, apenas a transfusão intraoperatória de hemácias foi identificada como fator preditivo independente da sobrevivência de médio prazo após o TH.


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