Use of the model for end-stage liver disease score for guiding clinical decision-making in the selection of patients for emergency cardiac transplantation

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Abstract

OBJECTIVES: The outcomes of emergency cardiac transplantation remain controversial, but recipient selection is essential for success. With a shortage of organs, it is essential to determine an objective method, such as a risk score, for choosing patients who are at too great a risk to undergo cardiac transplantation. In this study, we analysed the model for end-stage liver disease in terms of predicting operative mortality after emergency cardiac transplantation.

METHODS: We analysed the Nancy University database of heart transplantation and selected all patients who underwent emergency heart transplantation between January 2005 and January 2012. The calibration and discriminatory power were evaluated to determine the model for end-stage liver disease (MELD) score. Preoperative and peri-operative variables regarding the prediction of operative mortality were analysed by univariate and multivariate logistic regression models.

RESULTS: Forty-three patients underwent emergency cardiac transplantation. The operative mortality was 20.9% (n = 9). The Hosmer-Lemeshow test demonstrated a calibrated model for predicting operative mortality (P = 0.15), and the MELD score presented an excellent discrimination between survivors and non-survivors (AUC: 0.89 ± 0.05; 95% CI: 0.79–0.99). In the univariate analysis, an MELD score of ≥16 and bilirubin concentration were predictive markers of operative mortality. Multivariate logistic regression tested the contribution of the univariate risk predictors (P < 0.15) and confirmed that an MELD score of ≥16 was predictive of operative mortality.

CONCLUSIONS: The MELD score appears to be adequate for predicting operative mortality among patients who undergo heart transplantation. The MELD score could therefore be used to guide clinical decision-making for emergency transplantation.

Keywords: Heart transplantation • Score • Results

INTRODUCTION

The number of patients with advanced heart failure (HF) is increasing worldwide. Cardiac transplantation remains the ‘gold standard’ treatment for these patients [1]. Some patients are transplanted as a priority because their clinical situation has worsened, such as becoming dependent on inotropic support. In France, since 1 July 2004, patients are classed as a priority if they are in intensive care and dependent on inotropes and with a clinical state that is compatible with transplantation. However, the outcomes of these patients are controversial and recipient selection processes are essential to obtain the optimal results [2, 3]. Many patients in this situation present with changes in the functions of other organs. Renal dysfunction generally occurs as a consequence of reduced cardiac output and decreased renal perfusion, accompanied by sodium and water retention. Medical treatment can also contribute to worsening renal failure, as a consequence of the use of diuretics and ACE inhibitors. These patients can also develop varying degrees of hepatic dysfunction due to congestive hepatopathy and reduced hepatic blood flow. Importantly, liver dysfunction increases operative mortality in cardiac surgery [4–7].

During periods of organ shortages, it is essential to define objective methods that can select patients who are at too high a risk for heart transplantation, and are likely to die as a consequence of surgery. A risk score can be used for this purpose. Accordingly, we analysed the model for end-stage liver disease (MELD) scores in patients awaiting cardiac transplantation. This score was originally developed to assess the prognosis of cirrhotic patients undergoing transjugular, intrahepatic Porto systemic shunts [8]. Nowadays, the MELD score is used to prioritize organ allocation in patients awaiting liver transplantation [9]. Although the MELD score was developed from a different population, it reflects a multiorgan dysfunction state that can be found in patients with cardiogenic shock. Therefore, MELD scores may be able to reliably identify patients at higher risks from emergency
heart transplantation. On the basis of a single-centre experience, we assessed the relevance of the MELD score in terms of predicting operative mortality and long-term survival after emergency heart transplantation.

MATERIALS AND METHODS

We analysed the Nancy University database of heart transplantation and selected all patients who underwent emergency heart transplantation between January 2005 and January 2012 at the Department of Cardiovascular Surgery and Transplantation, CHU Nancy, France.

Data collection

Demographic, clinical, laboratory and postoperative data were collected prospectively. The last laboratory analysis data before transplantation were used for the calculation of the MELD score, which were recorded on the day of or the day before transplantation. No patients were taking oral anticoagulation at the time of blood sampling. Complete data for the MELD calculation were available for all patients. The MELD score was calculated retrospectively twice by the first and second authors, using the following website: www.mayoclinic.org/meld. The calculation was based on the following formula: $3.8 \times \log_2(\text{bilirubin \ mg/dl}) + 11.2 \times \log_2(\text{INR}) + 9.6 \log_2(\text{creatinine \ mg/dl})$. In the cases of discrepancy between the two results, the score was recalculated to eliminate errors.

Operative mortality was defined as any death that occurred during the first 30 postoperative days or during the same hospital stay. Before statistical analysis was conducted, preoperative risk factors of interest for the outcomes were identified and these are listed in Table 1.

Statistical analysis

Statistical analysis was performed using SPSS, version 20 (SPSS, Inc., Chicago, IL, USA) and STATA, version 10 (StataCorp LP, College Station, TX, USA). Categorical variables were expressed as percentages. The $\chi^2$ test was used to evaluate categorical data in a univariate manner when the minimum number of observations in a category was greater than five; otherwise, Fisher’s exact test was used. Continuous variables were expressed as means ± standard deviation. Student’s t-test was used to analyse continuous variables that had a normal distribution, and the Wilcoxon rank test for variables that had a non-parametric distribution.

Variables identified by univariate analysis with a $P$-value of <0.15 were added to a multivariate logistic regression model. Significant biological values included in the MELD calculation were excluded. We performed exact logistic regression modelling, which has replaced standard logistic regression for analysing small, skewed or sparse datasets. For all analyses, $P < 0.05$ was considered to be statistically significant.

Table 1: Demographic variables

<table>
<thead>
<tr>
<th>Indication for transplant</th>
<th>Total (n = 43)</th>
<th>Survivors (n = 34)</th>
<th>Non-survivors (n = 9)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic cardiomyopathy</td>
<td>11 (25.5%)</td>
<td>9 (26.4%)</td>
<td>2 (22.2%)</td>
<td>1</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>29 (67.4%)</td>
<td>22 (64.7%)</td>
<td>7 (77.7%)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1 (2.3%)</td>
<td>1 (2.9%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4.6%)</td>
<td>2 (5.8%)</td>
<td>0 (0%)</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Donor</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Weight</td>
<td>73.7 ± 12</td>
<td>74.5 ± 12.2</td>
<td>71.1 ± 11.7</td>
<td>0.42</td>
</tr>
<tr>
<td>Donor age</td>
<td>43.5 ± 12.9</td>
<td>41.9 ± 13.9</td>
<td>49 ± 6.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>33 (76.7%)</td>
<td>27 (79.4%)</td>
<td>6 (66.7%)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

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<tr>
<th>Surgery</th>
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<tbody>
<tr>
<td>Redux</td>
<td></td>
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<tr>
<td>Ischaemia time (min)</td>
<td>189.4 ± 53.2</td>
<td>188.6 ± 49</td>
<td>192 ± 67</td>
<td>0.85</td>
</tr>
<tr>
<td>EC time (min)</td>
<td>122.9 ± 41.6</td>
<td>119.6 ± 36.4</td>
<td>133.8 ± 55.6</td>
<td>0.35</td>
</tr>
</tbody>
</table>

INR: International Normalized Ratio; ECMO: extracorporeal membrane oxygenation; EF: ejection fraction; MELD: model for end-stage liver disease; EC: extracorporeal circulation.
Calibration, comparing the observed score and predicted probabilities, was evaluated by the Hosmer–Lemeshow goodness-of-fit test. A Hosmer–Lemeshow *P*-value of >0.05 indicates a well-calibrated model for the study population. The discriminatory power was evaluated by receiver operating characteristic (ROC) curves that were created to assess the predictive value of scores for operative mortality, including the area under the curve (AUC). By applying ROC curves, we established an MELD score cut-off point associated with an elevated risk of operative mortality. Survival analysis was conducted according to the Kaplan–Meier method, and corresponding curves were built. Curves were compared by the log-rank statistical test.

**RESULTS**

During this period, 43 patients underwent an emergency cardiac transplantation. The pre-transplantation baseline clinical characteristics and perioperative data for all patients analysed in the study are shown in Table 1. Two patients underwent a second transplantation (4.6%). The mean waiting time for heart transplantation was 173.5 ± 84.1 days.

**Predictive value of the model for end-stage liver disease score**

The mean MELD score for operative death and survivors were 18.3 ± 3.2 and 11.9 ± 4, respectively (Fig. 1).

The MELD score cut-off point for distinguishing patients who died during the operative period was 16. The Hosmer–Lemeshow test demonstrated that this was a well-calibrated model for predicting operative mortality (*P* = 0.15). When evaluating the ability of the MELD score to predict the occurrence of operative mortality in patients undergoing emergency heart transplantation, we found that the MELD score was excellent, with an AUC of 0.89 ± 0.05 (95% CI: 0.79–0.99) (Fig. 2).

**Operative mortality and morbidity**

The overall in-hospital mortality rate was 20.9% (*n* = 9). The causes of death were pulmonary infection (*n* = 3), primary graft failure (*n* = 2), sepsis (*n* = 2), multisystem organ failure (*n* = 1) and haemorrhagic stroke (*n* = 1). The mean ventilation time was 19.8 ± 2.7 days. The mean duration of intensive care was 44.7 ± 51 days. In univariate analysis, an MELD score of ≥16 and concentration of bilirubin were predictive of operative mortality (Table 2). Multivariate exact logistic regression to test the contribution of the univariate risk predictors with *P* < 0.15 showed that an MELD score of ≥16 was predictive of operative mortality (*P* = 0.006) (Table 2).

**Long-term survival**

Long-term survival for all patients, including in-hospital mortality, was 76.7 ± 6.4% at 1 year, 68.1 ± 7.4% at 3 years, and 60.3 ± 8.3% at 5 years (Fig. 3a). The 1-year survival rates, including in-hospital mortality, for MELD scores <16 and ≥16 were 90.3 ± 5.31% and 41.6 ± 14.2%, respectively; 3-year survival rates were 82.4% ± 7.2% and 33.3 ± 13.6%, respectively, and 5-year survival rates were 76.5% ± 8.8% and 22.2% ± 12.8%, respectively (Fig. 3b).

**DISCUSSION**

In the present study, we analysed the in-hospital outcomes and long-term survival rates of patients with end-stage HF who...
underwent cardiac transplantation as an emergency. We determined whether preoperative risk factors enable the determination of operative mortality. We also assessed whether the MELD score is useful in predicting operative mortality and also in distinguishing patients who might benefit most from emergency heart transplantation. We also evaluated the long-term survival outcomes between patients with low and high MELD scores.

Patients on the priority transplantation list often present with changes in hepatic and renal function. The MELD score is an objective numerical score obtained by inserting the values of serum total bilirubin, INR and serum creatinine into a logarithmic formula. It presents advantages over simple common laboratory values, and is accessible in a clinical setting as it can be rapidly calculated on several websites. It was initially developed to assess the mortality of cirrhotic patients who underwent transjugular, intrahepatic Porto systemic shunt procedures [8]. MELD scores are also used to prioritize organ allocation in patients awaiting liver transplantation, and can also predict operative mortality in patients undergoing non-cardiac and cardiac surgery [4, 6, 7, 10, 11]. The MELD score reflects changes in hepatic and renal function, which can occur during cardiogenic shock.

In our study, the MELD score was found to be well calibrated and had an excellent level of discrimination (AUC: 0.89) in terms of predicting operative mortality in patients who underwent emergency heart transplantation.

Chokshi et al. [12] retrospectively reviewed 780 adults undergoing elective orthotopic heart transplantation. He showed that elevated MELD scores pre-transplantation were associated with increasing morbidity and mortality, and concluded that pre-transplant liver dysfunction plays an important role in the long-term survival of patients undergoing heart transplantation. This population differ from ours as transplantation was conducted in an emergency setting, but their study emphasizes the importance of the MELD score in terms of its prognostic value. The 1-year survival was 91.4% in patients with an MELD score of 14 compared with 85.5% in patients with an MELD score of 20. The 5-year survival was 83.2% in patients with an MELD score of 14 and only 70.1% in patients with an MELD score of 20.

In our study, we found that a cut-off value of the MELD score of ≥16 was predictive of operative mortality after emergency heart transplantation, but this was also predictive of long-term survival. In patients with a high surgical risk, it is important to optimize the medical treatment of shock, but sometimes the restoration of an adequate cardiac output and improving hepatorenal function is insufficient to alter overall outcomes. In this condition, end-stage heart failure patients with evidence of hepatic and renal dysfunction are reasonable candidates for the implantation of ventricular assistance devices (VADs), especially given that liver and renal function will improve in many of these patients while on VAD support. However, such patients present with higher levels of operative risk. Yang et al. [13] showed that the MELD scores were predictive of operative mortality after VAD implantation. They determined that a cut-off value that was similar to ours (MELD score: 17) predicted operative mortality in patients undergoing LVAD. Patients at a high risk for transplantation are also at a high risk for LVAD, but in the periods of organ shortages, optimization with cardiac assistance can be justified despite the high surgical risk. Russel et al. [14] showed that both renal and hepatic function are restored to normal values with the Heartmate 2 continuous-flow LVAD in patients awaiting heart transplantation within 1 to 2 months of device implantation.

The use of extracorporeal artificial liver support which can mimic the detoxifying functions of hepatocytes may improve the treatment of hepatic failure due to cardiogenic shock, but further studies are required in this field [15, 16].

Study limitations

This study was limited by its retrospective design and a limited number of patients who underwent emergency heart transplantation during the study period. Moreover, the present study was performed at a single centre, and our findings may not be generalizable to all centres worldwide.

CONCLUSIONS

The MELD score appears to be adequate for predicting operative mortality among patients who subsequently underwent heart transplantation. This result indicates that the MELD score could be used to guide clinical decision-making for selecting patients for emergency cardiac transplantation in periods of organ shortage. Larger independent prospective series are necessary to confirm these findings.
Conflict of interest: none declared.

REFERENCES