A New Formula as a Predictive Score of Post–Liver Transplantation Outcome: Postoperative MELD-Lactate

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ABSTRACT

Introduction. Liver transplantation (OLT) involves a 5% to 10% 30-day mortality rate. Multiple scores have been used as predictors of early postoperative mortality, such as the original Model for End-stage Liver Disease (MELD) and MELD sodium. Investigations have been conducted over the last 5 years to find new predictors of early post-OLT mortality.

Objective. The aim of this study was to develop a new mathematical model to predict the individual chance of 30-day mortality after OLT.

Methods. The study was conducted on 58 patients submitted to OLT at the University Hospital, between October 2008 and March 2012. The 29 latest survivor and 29 latest nonsurvivor cases were selected. Arterial blood sodium, lactate, international normalized ratio, total bilirubin, and creatinine values were determined 1 hour after the end of surgery. The MELD original equation, MELD sodium, and new MELD lactate were also elaborated. The results were analyzed by the Mann-Whitney and Wilcoxon tests. The level of significance was set at .05.

Results. The new formula elaborated was as follows: MELD lactate = 5.68 \times \log_{10}(\text{lactate}) + 0.64 \times (\text{Original MELD}) + 2.68. The MELD lactate values were significantly higher than the MELD sodium and original MELD values (P < .05). The area under the receiver operating characteristic curve of MELD lactate in predicting the outcome of patients submitted to OLT was 0.80, as opposed to 0.71 for the original MELD and 0.72 for MELD sodium (P < .05).

Conclusion. The postoperative MELD lactate score proved to be more specific and sensitive than the original MELD and MELD sodium as a predictive model of the outcome of patients submitted to OLT.

THE MODEL FOR END-STAGE LIVER DISEASE (MELD) score, introduced in 2000 to predict the survival of patients with liver cirrhosis undergoing transjugular intrahepatic portosystemic shunt \cite{1}, has also been used as a graft allocator, based on hepatic disease severity, and as a predictor of mortality after orthotopic liver transplantation (OLT) in 2002 in the United States \cite{2} and in 2006 in Brazil \cite{3}.

OLT presents survival rates of approximately 80%, though with a wide variation from 65% to 90% within 3 years \cite{4}. Because of the complexity of the surgery, this major operation is not without risk and has a 5% to 10% 30-day mortality \cite{5}. The outcome of patients submitted to OLT basically depends on the quality of the donor’s liver and its clinical condition \cite{6-8} and on the quality of the surgery and of the immediate postoperative care \cite{9,10}. The role of the anesthesiologist in patient management, with proper treatment of the pulmonary and hepatic repercussions of the ischemia-reperfusion (I/R) injury to the transplanted liver, is also of
fundamental importance for the postoperative outcome after OLT [11].

Over the last few years, many studies have pointed out the potential limitations of the MELD score, indicating that it does not serve all patients well as either a graft allocator or as post-OLT prognostic index [12–14]. However, when comparing post-OLT MELD with other score systems, such as Acute Physiology and Chronic Health evaluation II, Child-Turcotte-Pugh, and Sequential Failure Assessment, MELD is more effective, even with some limitations, in predicting early mortality (up to 30 days) after OLT [15–18].

To improve the ability of MELD to predict postoperative OLT short-term complications, several studies have incorporated other objective variables into the model. The prognostic accuracy of the original MELD score may be improved by adding age, serum sodium [19], ascites, and hepatic venous pressure gradient [20,21]. Similarly, we have shown that perioperative lactate and base excess values significantly discriminated survivors and nonsurvivors after OLT [15].

In view of the above considerations, the aim of the present study is to develop a new mathematical model that could more accurately predict the chance of 30-day mortality after OLT.

METHODS

The study was conducted on 58 adult patients who were referred to our transplant program for candidacy for cadaveric donor liver transplantation and submitted to OLT at the University Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo, from October 2008 to March 2012. Patients who underwent retransplantation and those who underwent transplantation for acute liver disease and familial amyloid polyneuropathy were excluded. Donors and recipients with probable diagnosis of infection or sepsis were excluded for transplant. The research protocol was approved by the research ethics committee of the hospital (Protocol 4206/2010). Among the 58 OLT procedures performed during this period that we selected, according to survival up to 30 post-transplantation days, the 29 latest survivor and 29 latest non-survivor cases were selected to develop a statistical model to predict patient survival and to find the best function that could predict whether the patient would survive after OLT. According to the protocol rigorously defined before the beginning of our liver transplantation program, this study was performed a posteriori, with the establishment of 2 study groups, survivors and nonsurvivors. The sample size was calculated according to Kelley and Maxwell [22]. All OLT procedures were performed by the piggyback technique without a portacaval shunt in the anhepatic phase [23].

Arterial blood sodium, lactate, international normalized ratio, total bilirubin, and creatinine values were determined 1 hour after the end of surgery. The MELD original equation, MELD sodium, and new MELD lactate were also elaborated in the same moment. The results were analyzed by the Mann-Whitney and Wilcoxon tests, and all P values < .05 were considered significant.

The postoperative MELD Na score was calculated as MELD Na = MELD + 1.59 (135 – Na) with a maximum and minimum sodium of 135 and 120 mEq/L, respectively, where all variables that are less than 1 are reported as 1.

The Postoperative MELD Lactate Score

Our aim was to find the best function that could predict whether the patient would survive after the operation. We have the outcome for each patient, which is Y = 1 for nonsurvivors and Y = 0 for survivors. We defined the original MELD and the natural logarithm of blood lactate concentrations as the inputs for this formula. We maintained the same logarithmic structure found in the original MELD equation.

Using logistic regression analysis, we fitted the outcome Y and the original MELD scores of each patient, and the results were a correlation of $R^2 = 0.13$ and a misclassification rate of 0.35 ($P < .001$). Then, we performed the logistic regression again but including the variable (lactate) of each patient, and the results were a correlation of $R^2 = 0.27$ and a misclassification rate of 0.26 ($P < .001$). Therefore, the inclusion of this new variable is significant since the correlation increased by twice and the misclassification rate was reduced by 9 basis points. The formula for the probability of 30-day mortality after OLT is given below:

$$P(Y = 1) = \frac{e^{-6.971 - 1.42 \log_{10} (\text{Lactate}) + 0.16 \text{(Original MELD)}}}{1 + e^{-6.971 - 1.42 \log_{10} (\text{Lactate}) + 0.16 \text{(Original MELD)}}}$$

The formula returns the probability of 30-day mortality after OLT given patient’s data as input, and therefore, it is a value from 0 to 1. If we were only looking for the probability of 30-day mortality after OLT for a given patient, then the equation would provide a satisfactory result. However, we were looking for an index with a scale similar to previous MELD scores, then a shifting adjustment was applied to the previous equation $P(Y = 1)$. The following MELD lactate score was obtained through function mapping using a monotone increasing function $f(p) = 4 \times \log_{10}(p/(1-p)) + 26.96$, where $p$ is the function $P(Y = 1)$ given above, which preserves the following characteristic: If the probability of 30-day mortality after OLT for patient 1 is greater than for patient 2, then MELD lactate for patient 1 is greater than MELD lactate for patient 2. The final solution is given by the following formula:

$$\text{MELD lactate} = 2.68 \times 5.68 \times \log_{10}(\text{lactate}) + 0.64 \times (\text{original MELD}),$$

where all variables that are less than 1 for lactate are reported as 1.

Statistical Analysis

Data are reported as means ± standard deviations or standard error of the means. The nonparametric Mann-Whitney test was used to compare differences in postoperative MELD scores between survivors and nonsurvivors. The capacity of each index to predict the outcome of OLT patients was described by receiver operating characteristic (ROC) curves. The area under the ROC curve (AUC) was used as a measure of overall index accuracy, and its significance was tested using the Wilcoxon test. The level of significance was set at .05. All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc, Cary, NC, United States).

RESULTS

The demographic, clinical, and surgical characteristics of 58 patients submitted to OLT and included in the study (survivors and nonsurvivors) are shown in Table 1. Sex distribution was similar in each group, with a predominance of
male sex. The groups were also similar regarding age, original pre-OLT MELD values, time of hypothermic and warm ischemia, diuresis volume, and permanence in the intensive care unit (ICU; \( P > .05 \)). The survivor group had a longer hospital stay than the nonsurvivor group (\( P < .005 \)).

The parameters used to calculate MELD lactate are shown in Table 2.

Using the proposed formula described previously, a statistically significant difference (\( P < .05 \)) in the individual distribution of the values between survivors and nonsurvivors was detected, with higher values in the nonsurvivor group. The MELD lactate value was higher than the original MELD and MELD sodium values (\( P < .05 \)).

Evaluation of the ROC curves for postoperative original MELD, MELD sodium, and MELD lactate in the immediate postoperative period of OLT showed that the AUC of MELD lactate was 0.80 with a cutoff of 26.3, with \( P < .05 \), when compared to the AUC of the original postoperative MELD score (0.71) and the AUC of the postoperative MELD sodium score (0.72; Fig 1).

A scatter diagram of MELD lactate score for individuals in both groups, nonsurvivors (median = 26.6) and survivors (median = 22.1), is shown in Fig 2.

**DISCUSSION**

In recent years, OLT has evolved as an effective therapeutic modality for patients with end-stage chronic liver disease. Early graft function after liver transplantation is an important prognostic marker for individual outcome \(^ {24} \), and initial poor graft function may be related not only to quality of the donor organ but also to secondary complications such as renal failure, severe bleeding, and septic infections, resulting in a negative effect on long-term patient health and employment \(^ {25} \).

I/R disorders caused by reperfusion after implantation are the end product that determines the nature of the postoperative evolution of OLT \(^ {26} \). Tissue injury occurs as a result of the initial ischemic insult, which is determined primarily by the magnitude and duration of the interruption of the blood supply, and the subsequent damage induced by reperfusion of the new liver in the recipient \(^ {26,27} \). The pathologic events induced by I/R orchestrate the opening of mitochondrial permeability transition pores, which appears to represent a common end-effector of the pathologic events initiated by I/R.

In addition, the implications of I/R injury can be aggravated by the characteristics of the donor liver, such as steatosis of various causes, liver fibrosis, and others, which are not always diagnosed with precision at the time of donor surgery. In the present study based on our own previous experimental and clinical studies with laser-induced fluorescence spectroscopy, liver grafts with high levels of steatosis or poorly perfused were not recovered for transplant \(^ {28,29} \).

In addition to these, the medical status of the recipient and surgical complications \(^ {9,10,26} \) can cause pulmonary and hemodynamic repercussions that may influence the outcomes of transplanted patients.

Studies have been conducted over the last 5 years to find a new way of using the MELD equation to find a mathematical model that can predict the individual chance of survival after elective OLT. In these studies, new indicators were added to the formula to increase the efficacy of the calculation of the severity of liver disease and thus allocate grafts for transplant in a more rational manner \(^ {2,3,19,20,30,31} \).

Recent studies have linked impaired liver function to high blood lactate concentrations \(^ {15,31,32} \), leading us to believe that early lactate clearance is a good indicator for post-OLT prognosis.

This substrate, the final product of glucose degradation in the absence of oxygen, is produced by the reduction of
pyruvate. The anaerobic metabolism of glucose produces lactate, adenosine triphosphate (ATP), and water, with acidosis occurring when ATP is transformed to ADP and inorganic phosphate, a reaction that releases 1 hydrogen ion. Thus, there is a reduction of blood pH and the occurrence of metabolic acidosis [24].

The return of pH to normal values requires a correction of the processes that produced the disorder, which occurs through 3 mechanisms: intra- and extracellular buffer, adjustments of PCO₂ by respiration, and adjustment of effective renal acid excretion. In the buffer system, HCO₃⁻ is consumed to neutralize the increased acid. For the adjustment of PCO₂, the bulbar respiratory center is activated, and in an attempt to normalize the pH, it uses hyperventilation to eliminate excess CO₂. Finally, the kidneys act on HCO₃⁻ reabsorption and H⁺ excretion through the nephrons, a fact that also contributes to the return of pH to normal values. In this study, the ventilation of the patients remained constant; thus, it was not a possible error factor when the acid-base balance was analyzed. Additionally, the intraoperative diuresis was similar for the survivor and nonsurvivor groups, as is illustrated in Table 1.

Under normal conditions, the liver and kidneys are great consumers of lactate, being able to utilize as much as 60% of the lactate available, thereby regulating its cellular levels [33]. However, in situations of hypermetabolism, stress, and ischemia, as occur during OLT, lactate levels increase due to the involvement of the liver, with a consequent reduction of lactate clearance, because the liver begins producing this substrate [34–36].

In a series of previous investigations, it has been shown that a joint analysis of the original postoperative MELD score, base excess, and blood lactate can be used as an index of the severity of the postoperative course of patients submitted to liver transplantation [15,37]. In this study, significantly higher blood lactate levels were observed after surgery in nonsurvivors compared to survivors, a fact that demonstrates the cause-effect relationship with the postoperative course of transplanted patients. However, the dispersal of lactate levels was very high in the nonsurvivor group (7.28 ± 5.91 mmol/L), a fact that may impair its use as a predictive index of the type of postoperative evolution in OLT. This wide dispersal of values was already observed in a study previously published by our group [15,37].

On this basis, in the present investigation we maintained the same logarithmic structure found in the MELD equation and introduced a new variable (lactate). Using logistic regression technique, we searched for the coefficients that minimized the error in the new model, shifted it using a monotone increasing function, and the final solution was given below by the following formula: MELD lactate = 2.68 + 5.68 × logₑ (lactate) + 0.64 × (original MELD), where all variables that are less than 1 for lactate are reported as 1.

The postoperative MELD lactate values were significantly higher in the nonsurvivor group compared to the survivor group, as shown in Table 2. In addition, MELD lactate
values were superior to the postoperative values of classic MELD and MELD sodium in terms of discriminating between survivors and nonsurvivors (Table 2).

The introduction of lactate in the structure of the original MELD formula, in association with international normalized ratio, total bilirubin, and creatinine, increased the sensitivity of this indicator as a predictive factor of 30-day mortality of patients submitted to OLT, which was higher than that of the original MELD and MELD sodium, as shown in Table 2. The idea was not simply to create a new formula using lactate because of the characteristics of this compound related to ischemic changes of the liver, but rather to utilize the properties of the components of the original MELD related to the severity of liver disease and to add lactate to increase the accuracy of the score in terms of predicting the outcome of patients submitted to OLT. In this study, most nonsurviving patients died in the ICU a few days after surgery, a fact suggesting a strong cause-and-effect relationship with the surgical act.

The aim of the equation developed in this study was to produce an index that could predict the risk of 30-day mortality of patients submitted to OLT and to alert surgeons and intensivists to patients who would require special attention. It is important to remember that a prognostic index does not change the initial clinical actions and does not interfere with special treatments or with admission to the ICU but can optimize the postoperative care with the use of more rational and effective measures. Additionally, the MELD lactate formula calculated immediately after surgery can become an objective and sensitive tool for the assessment of the clinical status of the recipient and could be used in a legal situation.

The postoperative MELD lactate score has been already employed as part of the protocol in the 31 latest transplantations performed in our liver transplant unit and seems to confirm the results obtained in this study. However, a future larger prospective cohort study at the national level should be conducted before any definitive proposal can be made.

In conclusion, the new mathematical model proposed in our investigation, which incorporated blood lactate level into the original MELD equation, improved the predictive accuracy of the outcome (survivors vs nonsurvivors) of patients submitted to OLT.

REFERENCES


