SURVIVAL TREE SCORE: A NOVEL APPROACH TO PREDICT MORTALITY IN CIRRHOTIC PATIENTS

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- ABSTRACT: Although Model for End-Stage Liver Disease (MELD) score is adopted worldwide for liver transplant allocation, but it has prognostic limitations. The aim of this study was to apply the survival tree analysis to evaluate interaction between variables related to mortality in cirrhotics patients enlisted for liver transplantation, and to develop a new mortality predictive score. Demographic, clinical and laboratory data of cirrhotic patients waiting for liver transplantation during a 12-year period were considered. Charts from 765 patients were reviewed. The interaction between prognostic covariates was obtained using a survival tree analysis. In order to develop the predictive score, Cox regression analysis was performed applying significant data obtained by the survival tree analysis. The prognostic covariates evaluated in the survival tree were MELD score, Child-Pugh score, serum sodium, viral disease etiology, hepatocellular carcinoma diagnosis and generated a coefficient for each. Based on the survival tree analysis, MELD = 15 was the primary root variable ($p<0.001$). The survival tree provided eight prognostic groups. The higher mortality hazard ratio (HR) risk was observed in the MELD >28 group (HR= 16.7). The new score (Survival Tree Score – STS) was obtained according to the coefficients provided. The STS prognostic performance was superior to MELD score (AUROC 0.713 vs 0.653, $p<0.001$). STS, could be a useful tool to accurately identify individual mortality risk in advanced liver disease.

- *KEYWORDS:* Cirrhosis; mortality; liver transplantation; prognostic score; survival tree analysis; Cox regression

1. Introduction

There is a worldwide deficit of liver organs compared to the number of patients enlisted for liver transplantation. This has led to a constant effort to identify sicker patients waiting for the surgery (HUO *et al.*, 2008; DUTKOWSKI *et al.*, 2011; NORTHUP *et al.*, 2015). MELD (Model for End-stage Liver Disease) score has been adopted to classify sicker patients for liver allocation in many countries.

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However, MELD score has several drawbacks, such as failure to predict mortality in up to 30% of patients (CHOLONGITAS *et al.*, 2006; GOTTHARDT *et al.*, 2009; KAMATH *et al.*, 2001; LUCA *et al.*, 2007). In addition, MELD score failures to consider several other variables that independently impact on patient mortality, such as serum sodium, ascites, encephalopathy and hepatocellular carcinoma diagnosis (HCC) (PUGLIESE *et al.*, 2014; KIM *et al.*, 2008; D'AMICO *et al.*, 2006). MELD score may not be enough to assist on clinical decisions regarding prognosis in cirrhotic patients awaiting for liver transplantation. Also, these clinical variables may interact in the same individual and provide different mortality prognosis for patients with the same MELD score value. Therefore, literature on the impact of multiple prognostic factors in cirrhosis is scarce.

A Survival Tree Analysis as implemented by Hothorn et al (2006), is an innovative statistical method seldom used in hepatology setting, and provides an straightforward and easy interpretation method that identifies interaction between multiple prognostic variables, and can be used to assess mortality risk (BOU-HAMAD *et al.*, 2011). It generates an intuitive flowchart resembling a tree, with primary branches identifying the most relevant variables its respective cuts-off. Also, it combines the variables to provide several groups with different survival curves.

The aim of this study was to apply a Survival Tree Analysis to identify the interaction between variables associated to mortality in cirrhotic patients enlisted for liver transplantation, and to develop a severity score based on this analysis.

2. Material and methods

Demographics, clinical and laboratory data were retrieved from charts of cirrhotic patients at the waiting list for liver transplantation at the Federal University of Rio de Janeiro from November 1998 to September 2012 were reviewed.

Disease etiology, HCC diagnosis, bilirubin (mg/dl), INR (International normalized ratio for prothrombin time), creatinine (mg/dl), serum sodium (mEq/L), MELD and Child-Pugh scores were recorded, within three months after liver transplantation list enrollment.

The criteria for including patients for liver transplantation was: Child-Pugh B or presence of ascites, previous digestive bleeding, presence of uncontrolled encephalopathy or the HCC diagnosis within the Milan criteria. During the study period, the criteria adopted for liver allocation was chronological until 2006, and from 2006 to 2012, MELD score was adopted.

Patients with acute liver failure, familial amyloid polyneuropathy, younger than 12 years or older than 70 years, waiting for re-transplantation, with HIV (Human immunodeficiency virus) and other diseases not leading to cirrhosis were excluded from the analysis.

The MELD score was calculated according to the modified UNOS (United Network for Organ Sharing) formula (ANGERMAYR *et al.* 2003), as follows:

$$MELD = 3.8 \log_e b + 11.2 \log_e INR + 9.6 \log_e cr + 6.4$$

where b is serum bilirubin (mg/dL); INR is the International Normalized Ratio for prothrombin time; and cr is serum creatinine (mg/dL).

Child Pugh Score original scoring system uses five clinical and laboratory criteria to categorize patients as shown in Table 1:

Table 1 - Child Pugh Score

Measure	1 point	2 points	3 points
Encephalopathy	None	Grade 1 and 2	Grade 3 and 4
Ascites	None	Slight	Moderate
Bilirubin	< 2 mg/ml	2 to 3 mg/ml	> 3 mg/ml
Albumin	> 3.5mg/ml	2.8 to 3.5mg/ml	< 2.8mg/ml
Prothrombin Time* (sec prolonged)	< 4 sec	4 to 6 sec	> 6 sec

The primary outcome for all the analysis was survival time, in days, from liver waiting list enrollment, until death, or censure. Withdrawal from the list, lost to follow up and liver transplantation were defined as censure. Patients lost to follow up were censored at the last date known to be alive and patients undergoing orthotropic liver transplantation were censored at the date of transplantation. The institutional ethic board approved this study.

Descriptive statistics were used to describe the study population: continuous variables are shown as mean and standard deviation (SD) and dichotomous variables are presented as percentages.

The survival tree analysis

Decision tree is a non-parametric technique used in data mining. The CART (Classification and Regression Trees) method introduced by BREIMAN *et al.* (1984) is an algorithm for recursive partitioning of the covariate space that results in a tree-structured model. These models are widely used in survival analysis, especially in biomedical applications.

A survival tree shows significant association between the covariates and the outcome and provide a survival function graph for each identified group. A single tree can naturally group subjects according to their survival behavior based on their covariates. Prognostic groups can therefore be derived easily from survival trees. Each node provided by the tree, categorizes a mortality group and yields a Bonferroni-adjusted P-value.

Also, it provides an interaction and categorization of several variables analyzed. The primary branch should provide the most prognostic significant covariate ant their respective cut-off. The secondary branches also provides the variables most associated with the primary outcome, and so on. The final branches can group the co-variates into statistically prognostic values and provides different Kaplan Meier graphs. NASCIMENTO *et al.* (2012) presented the theoretical framework for survival trees and an application with liver transplantation list enrollment data.

In order to obtain a rank of severity index for each of the patients, two Cox models were implemented with different sets of covariates. The first model, with five relevant variables identified from the survival tree, and the second using the groups obtained by the survival tree as independent variables. The coefficients (coefGr) of this second model combined with the coefficients of the first model yielded the Survival Tree Score (STS). In addition, the hazard ratio for each group was obtained by calculating exp (CoefGr).

To compare the accuracy of the two scores as predictors of survival within the overall casuistic, the area under the receiver operating characteristic curve (AUROC) was calculated.

The survival tree was implemented using the party package (HOTHORN *et al.*, 2006) of the R software (R CORE TEAM, 2020). The ROC curves and the AUROC calculations were performed using the pROC package (ROBIN *et al.*, 2011) of the R software (R CORE TEAM, 2020). A p value <0.05 were considered to indicate statistical significance.

3. Results

Data from 765 cirrhotic patients enlisted for liver transplantation at Federal University of Rio de Janeiro, from November 1998 to September 2012 were analyzed. In total, 62 patients were excluded from the study: 20 for fulminant hepatic failure, 23 for repeat liver transplant, and 16 for etiologies other than cirrhosis. Three patients were retrieved from the analysis due to death on the same day of waiting list enrollment.

Variables presented in database were: age, gender, disease etiology, viral disease, HCC diagnosis, Child-Pugh score, serum sodium, bilirubin, INR, creatinine, MELD score, date of inclusion in liver transplantation waiting list and date of transplantation, withdrawal or death. General data distribution was according to Table 2.

The survival tree (Figure 1) was plotted, considering all variables presented in database. The Survival tree yielded MELD score as primary root variable, with a cut-off for mortality prediction of 15 ($p<0.001$). The covariates: viral disease ($p=0.013$), HCC ($p=0.004$), Child-Pugh ($p<0.001$; $p=0.006$) and serum sodium ($p<0.001$) were significantly relevant. The variables and their respective cut-offs were: Child (≤ 10; >10) and MELD (≤ 28; > 28) were significant as secondary branches, followed by Child (≤ 7; >7) and sodium (≤ 139 mEq/L; >139mEq/L). Finally, viral disease and HCC diagnosis were also plotted as the terminal branches of the tree.

The leaves of the tree presented the survival function of 8 different groups according to the mortality risk. The highest survival was observed in the group: patients with MELD ≤ 15; Child-Pugh ≤ 10; and sodium > 139. Conversely, lowest survival was observed in MELD > 28 group. The hazard ratio between the groups were compared according to a baseline group (Group 1) with the higher survival (Table 3).

Table 2 - Demographic, clinical, and biochemical features in cirrhotic patients enlisted for liver transplantation (n=765)

Age (years)	
Mean (±SD)	58 (±12.3)
Min-max	19 - 78
Gender (%)	
Male	487 (62.5%)
Outcome (%)	
Death	353 (46.1%)
Transplant	182 (23.7%)
Follow up (Mean/days)	1051 (±931)
Disease Etiology (%)	
HCV	388 (50.7%)
Alcohol	103 (13.5%)
Criptogenic	69 (9.1%)
HBV	56 (7.1%)
Other	149 (19.6%)
HCC (%)	148 (19.3%)
Child-Pugh(%)	
Child A	106 (13.9%)
Child B	401 (52.4%)
Child C	258 (33.7%)
Sodium (mg/dl)	
Mean (±SD)	138 (±4.9)
Min-max	119 - 153
MELD	
Mean (±SD)	138 (±6.5)
Min - max	6 - 46
MELD ≤15	481 (62.9%)
15 < MELD £ 28	244 (31.8%)
MELD > 28	40 (5.3%)

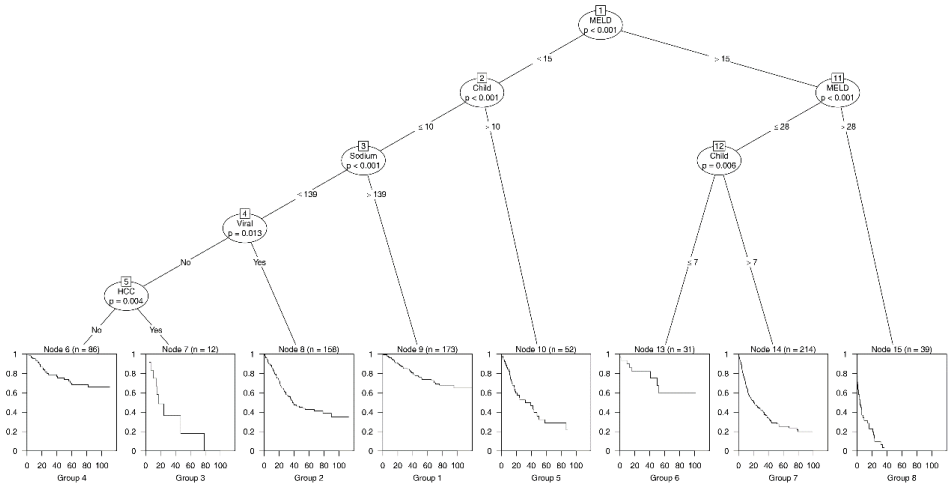

Figure 1 - Survival tree: Interaction between MELD score, Child-Pugh score, serum sodium, viral disease etiology and hepatocellular carcinoma.

Table 3 - Mortality groups data distribution and mortality hazard risk analysis

	Survival tree groups	**n**	**Events**	**CoefGr**	**HR**
Group 1	MELD ≤15 & Child ≤10 & Sodium >139	17	40	0	1
Group 2	MELD ≤15 & Child ≤10 & Sodium ≤139 & Viral=1	15	75	1.009	2.742
Group 3	MELD ≤15 & Child ≤10 & Sodium ≤139 & Viral=0 & HCC=1	12	9	1.701	5.478
Group 4	MELD ≤15 & Child ≤10 & Sodium ≤139 & Viral=0 & HCC=0	86	24	0.111	1.118
Group 5	MELD ≤15 & Child >10	52	31	1.304	3.686
Group 6	MELD >15 & MELD ≤28 & Child ≤7	31	8	0.284	1.329
Group 7	MELD >15 & MELD ≤28 & Child >7	21	131	1.596	4.934
Group 8	MELD >28	39	35	2.815	16.691

Viral and HCC: 0 = Negative, 1=Positive; Events = Deaths; CoefGr = Group Coefficient; HR = Hazard Ratio.

On a second step, in order to develop a prognostic score, the relevant variables identified by the survival tree (MELD, viral disease, HCC, Child-Pugh and sodium) were analyzed with proportional Cox regression and included in a prognostic score. Then, a second Cox model was performed using the groups as the only independent variable. This second model provided coefficients related to the eight groups (CoefGr) that were combined to the results obtained with the first Cox model to achieve an equation.

This formula, denominated Survival Tree Score (STS) can be used to identify individual mortality risk. The resulting equation is, as follows:

$$STS = 10^3 exp(0.163v + 0.351hcc + 0.125CS - 0.039Na + 0.074 * Meld + CoefGr)$$

where v is viral disease etiology; hcc is hepatocellular carcinoma diagnosis; CS is the Child Pugh Score; Na is sodium; and CoefGr is the respective coefficient according to group provided in Table 3.

The viral etiology and HCC diagnosis are categorized: 1 for positive and 0 for negative. The final resulting number of STS were adjusted times 1000 to provide a resulting number above 1.

Finally, the STS equation prognostic ability was determined by an area under receiver operating characteristic curve (AUROC) and compared to MELD score in the overall sample (Figure 2). The respective AUROCS were: STS: 0.713 vs. MELD score: 0.653 ($p<0.001$). STS vs MELD AUROC comparison was then categorized for 3, 6, 12 and 24 months. The AUROCS comparison between STS and MELD was, respectively: 3 months 0.795 vs 0.791 ($p=0.87$); 6 months 0.777 vs 0.732 ($p=0.019$); 12 months 0.775 vs 0.732 ($p=0.003$) and 24 months 0.749 vs 0.690 ($p<0.001$).

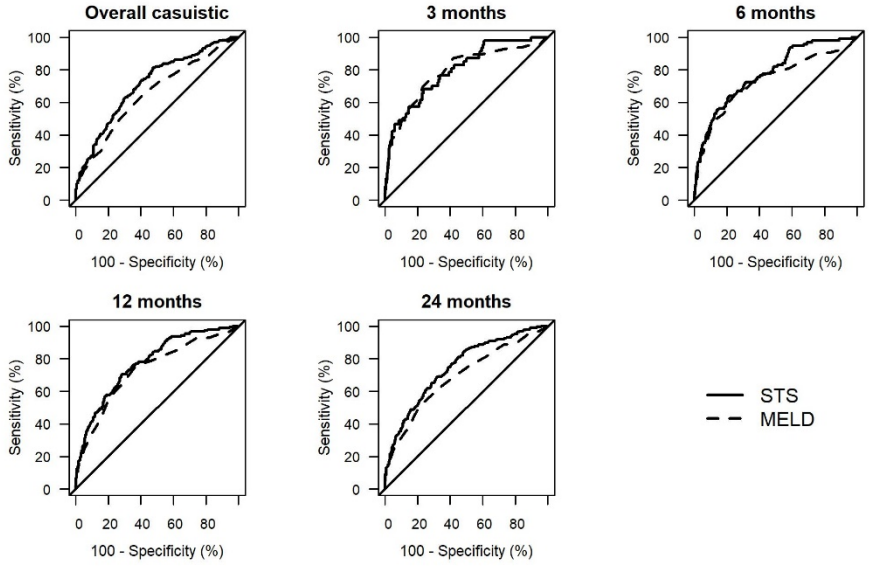

Figure 2 - ROC curve comparison between STS and MELD in overall casuistic and 3, 6, 12 and 24 months.

4. Discussions

Since liver transplantation was introduced as a non experimental therapy in the 1980`s decade, there has been a growing mismatch between the number of patients waiting for an organ and the donation supply (AUSTIN *et al.*, 2007). MELD score has been proved as a reliable and reproducible score, and since its implementation in United States in 2002 for liver allocation policy, liver waiting list mortality showed a little decrease. However, MELD score still fails to accurately predict mortality in a significant number of patients (BAMBHA and BIGGINS, 2008). Also, it is an important tool to predict mortality and to allocate livers in the waiting list, but in the daily clinical practice, there are several different clinical variables that impact on prognostic in each patient and can help to assist on crucial clinical decisions such as to offer a liver transplant, or to postpone an non urgent surgery.

There are several clinical variables independently associated with mortality in cirrhosis, however, their potential interaction is not well described in the literature. In this study, we assessed multiple variables considered significant in the literature to predict mortality in cirrhotic patients awaiting for liver transplantation. We applied an innovative statistical tool, the survival tree analysis, that simulates the biological interaction among different variables that occurs in an individual patient (BOU-HAMAD *et al.*, 2011). The survival tree analysis provides an easy to interpret and visual information, that can assist the clinician in order to assess the severity of disease in an individual patient. In addition, based on the results of the survival tree analysis, a score (STS- Survival tree score) was developed. The STS provided a higher prognostic accuracy for mortality prediction compared to the MELD score alone.

The survival tree analysis is a straightforward and easy to interpret regression analysis method (HOTHORN *et al.*, 2006; BOU-HAMAD *et al.*, 2011). This method has been seldom used in medicine (BANERJEE *et al.*, 2014; GOTO *et al.*, 2014; HOTHORN and JUNG, 2014; LOFARO *et al.*, 2016) and has been recently demonstrated to perform adequately in liver cirrhotic patients (NASCIMENTO *et al.*, 2012). It generates a graph resembling branches in a tree with the primary branch providing the most statistically significant variables and the secondary and tertiary branches providing the following co-variates.

In the present study, the results obtained by the survival tree analysis showed some interesting information and clinical association with the daily practice, as follows: MELD score was the root variable. As a primary variable, it emphasizes the prognostic impact of this score. The MELD mortality primary cutting point of 15, identified by the survival tree analysis, is a well-known threshold, described by Merion *et al.* (2005). In their study, a higher mortality risk was observed for patients with MELD below 15, when submitted to a liver transplant, when compared the mortality in the waiting list. Our results identify the same classic prognostic threshold of 15 for MELD as previously described, but demonstrates that certain subgroups of patients with lower MELD might have a worse prognosis, and thus, might be considered for liver transplantation. In the present study, it is clearly demonstrated that patients with MELD below 15 and with HCC, or with MELD below 15 and Child-Pugh above 10 group had a significantly worse prognostic than the group with MELD < 15 only.

Child-Pugh score is a classic score described more than 40 years ago to assess prognosis of chronic liver disease, primarily cirrhosis, and it is widely used until now. It is determined by scoring five clinical measures of liver disease: total bilirrubin, serum albumin, prothrombin time, the presence of ascites and hepatic encephalopathy. Some of these measures are considered subjective, such as ascites and encephalopathy. Therefore, the Child-Pugh score is not considered appropriated to allocate livers for liver transplant. MELD score is based on result of lab tests and is considered reproducible and it is universally adopted to allocate liver organs for liver transplantation. Both scores are well known accepted tools to assess prognosis in patients with chronic liver disease and cirrhosis.

Other markers of advanced liver disease have described to assess mortality risk in cirrhosis. Decompensated cirrhosis is associated with dilutional hyponatremia and low serum sodium is a strong independent predictor of mortality in cirrhosis. (BIGGINS *et al.*, 2005; CHOLONGITAS *et al.*, 2010; HINZ *et al.*, 2013; JENQ *et al.*, 2010)

It is well described, by several authors, that the predictive power of several variables as serum sodium, ascites and Child-Pugh score are stronger in patients with lower MELD scores (RIPOLL *et al.*, 2005; HEUMAN *et al.*, 2004; WANG *et al.*, 2007). In accordingly, another recurrent observation is that MELD score prognostic accuracy is lower in the earlier stages of cirrhosis (CHOLONGITAS *et al.*, 2006; HUO *et al.*, 2005). D'Amico *et al.* (2006), in a systematic review of 118 studies evaluating 174 different prognostic markers in cirrhosis also demonstrated that these prognostic indicators varied according to the stage of cirrhosis. The results obtained from the survival tree emphasizes the association of prognostic variables with the MELD score throughout the spectrum of hepatic disease. Thus, significant variables as sodium, viral disease, HCC and Child-Pugh had impact mainly in the lower MELD group. Conversely, in the highest MELD group (MELD >28), the MELD alone had a good prognostic value, with no associated covariates. In the intermediate MELD group (MELD 15-28), only Child-Pugh score yielded association with mortality (Figure 1).

The interaction between Child-Pugh and MELD scores was evaluated in this study, providing a better understanding of the association between these classic scores. The tree survival analysis demonstrated that patients with the same MELD score showed different mortality depending on the Child-Pugh score. For example, patients with MELD score between 15 and 28 and Child-Pugh score lower than 7 had a mortality hazard ratio 3 times lower than patients within the same MELD score range, and Child-Pugh higher than 7 (HR=1.3 vs HR=4.9; group 6 and group 7, respectively (Table 3). This result highlights these two scores as complimentary tools, suggesting that both should be used in clinical practice.

In this study, serum sodium was another secondary significative variable in patients with lower MELD score (Figure 1). In this study, serum sodium cut-off below 139 mEq/L was related to mortality. Others authors described clinical prognostic impact of lower sodium levels even if within the classical described normal range (KIM *et al.*, 2008).

Regarding the impact of HCC on mortality, we found that the higher the MELD, the lower is the impact of HCC, and the disease severity had a stronger impact on prognosis. HCC showed impact on mortality only in patients simultaneously with MELD ≤15, Child ≤10, sodium ≤139mEq/ml and non-viral etiology. It suggests that the prognostic impact of tumor diagnosis in cirrhotic patients enlisted for liver transplantation could be reweighed.

HCC often arises in patients with well preserved function. Initially, in several countries, HCC diagnosis within the Milan criteria, was assigned a MELD score of 29. This generated an overestimation of transplant rates for HCC. In USA, this MELD was then adjusted downward to 24, and then to 22. Even after this downsizing, many authors observe HCC patients are still being overrated (BITTERMANN *et al.*, 2014; WASHBURN *et al.*, 2010; GOLDBERG *et al.*, 2013). This value was based on the median MELD needed to reach transplant. However, these extra MELD points attributed to HCC were empirical. Based on our results, a suggested strategy would be to allocate granted exception points primarily to selected patients with MELD below 15.

The tree ramification for viral disease enforces the findings of some authors that viral disease might have a worse prognosis than others, and herein is once again identified as a relevant variable related to prognosis (ANGERMAYR *et al.*, 2009). Etiology of disease was once included in the original MELD formula, and then, retrieved (MALINCHOC *et al.*, 2000). Angermayr *et al.* (2003) demonstrated that with waiting time longer than three months for liver transplantation, viral disease had impact on liver disease prognosis. The current study findings, with a long median waiting time, reinforces Angermayr's findings, and suggests that viral disease etiology, as a prognostic variable, could be reconsidered.

In order to increase applicability of survival tree findings, and to assess mortality risk individually in daily clinical practice, an equation was proposed. It includes MELD score, but also considers the influence of other variables that have prognostic impact, such as HCC, Child-Pugh score, serum sodium and viral etiology. The predictive ability of the STS, compared to MELD score, was significantly better, especially for prognostic assessment beyond six months. This score can be a useful tool to evaluate mortality risk in cirrhotic enlisted for liver transplantation. It also provides a wide resulting range of categories, minimizing the risk of tie between patients.

This study has some drawbacks. It was based on a retrospective, single center data, and need to be validated on large cohorts of multi centric data. In addition, the decision to utilize Child-Pugh score to the analysis might add criticism to the results. Child-Pugh score has been widely validated to assess prognosis in cirrhosis, with a prognostic ability considered equal to MELD score by many authors or slightly worse by others (CHOLONGITAS *et al.*, 2006; ANGERMAYR *et al.*, 2003; BOURSIER *et al.*, 2009). However, it has shortcomings, such as subjective variables as ascites and encephalopathy (PUGLIESE *et al.*, 2014; D'AMICO *et al.*, 2006; STEWART *et al.*, 2007). Thus, reproducibility of the STS score that incorporates Child-Pugh as a covariate could be diminished, nevertheless, it adds significant prognostic information to the score.

The prognostic power for original MELD in our cohort was lower than that observed by some investigators (MARRONI *et al.*, 2012; MYERS *et al.*, 2013) but similar to that reported by others (ANGERMAYR *et al.*, 2003; SHARMA *et al.*, 2008). The longer the follow up, the performance of MELD score tends to decrease (ISHIGAMI *et al.*, 2008; SALERNO *et al.*, 2002). The casuistic of this study had a high median waiting time in liver transplantation list, and STS showed a better prognostic performance in this setting.

The survival tree analysis provided an original and intuitive assessment of multiple prognostic factors in cirrhotic patients enlisted for liver transplantation. It helps to understand the relationship between clinically relevant variables as MELD, Child-Pugh, HCC, sodium and viral disease in a biological fashion and categorized different groups

regarding mortality. The STS, derived from the survival tree analysis along with the Cox regression, could be a potential tool to estimate mortality prognosis in cirrhotic patients.

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BASTO, S. T., NASCIMENTO, E. M., PEREIRA, B. B., RIBEIRO FILHO, J., PEREZ, R. M., NOGUEIRA, C. A. V. Escore da árvore de sobrevida: uma nova abordagem para predizer a mortalidade em pacientes cirróticos. *Rev. Bras. Biom*. Lavras, v.38, n.4, p.506-520, 2020.

- *RESUMO: Embora o escore MELD seja adotado mundialmente para alocação de transplante de fígado, há algumas limitações. O objetivo deste estudo foi aplicar a análise da árvore de sobrevida para avaliar a interação entre variáveis relacionadas à mortalidade em pacientes cirróticos na fila para transplante de fígado e desenvolver um novo escore preditivo de mortalidade. Foram considerados dados demográficos, clínicos e laboratoriais de pacientes cirróticos na fila para transplante de fígado durante um período de 12 anos. A interação entre covariáveis foi analisada usando a árvore de sobrevida. Para desenvolver o escore preditivo, o modelo de regressão de Cox foi usado com os dados significativos obtidos na árvore de sobrevida. Gráficos de 765 pacientes foram revisados. A árvore de sobrevida identificou MELD = 15 como variável primária (p <0,001). A árvore forneceu oito grupos prognósticos. O maior risco de mortalidade (HR) foi observado no grupo de MELD> 28 (HR = 16,7). O novo escore (Escore da árvore de sobrevida - STS) incluiu MELD, Child-Pugh, sódio, doença viral, diagnóstico de CHC e coeficiente para cada grupo prognóstico. O desempenho prognóstico do STS foi superior ao MELD (AUROC 0,713 vs 0,653, p <0,001). O STS, procedente desta análise, pode ser uma ferramenta útil para identificar com precisão o risco de mortalidade individual nesse cenário.*

- *PALAVRAS-CHAVE: Cirrose; mortalidade; transplante de fígado; escore prognóstico; árvore de sobrevida; regressão de Cox*

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