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ORIGINAL ARTICLE

Predictors of death on the waiting list for liver transplantation characterized by a long waiting time

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Summary

The number of patients dying while on the liver transplantation (LT) waiting list (WL) has continued to increase in recent years as a result of severe shortage of organs. Therefore, it is important to evaluate the existing models that predict death on the WL and to determine the independent predictors of death. The study cohort comprised 152 adult patients listed for LT in our centre over a period of 2 years (January 2001 to January 2003). The 12-month survival rate has been calculated by Kaplan–Meier method. The survival analysis performed by Cox proportional hazard model has evaluated the three parameters which compose the model for end-stage liver disease (MELD) score. Forty-four patients (28.9%) died while listed for LT. The survival rate was 92% at 3 months, 80% at 6 months and 69% at 12 months. Median survival was not reached. MELD score was found to be an excellent predictor of death at 12 months on our WL – c-statistic (area under curve) 0.84. In our survival analysis, only international normalized (prothrombin) ratio (INR) and serum creatinine were identified as an independent predictors of death ($P < 0.0001$). A new simplified version of the MELD score, which does not include serum bilirubin, is proposed and its c-statistic as predictor for death on the WL at 12 months is 0.86, as good as the original MELD score, when evaluated on our list. There is a fourfold increase in mortality on our WL for LT between 3 and 12 months after the inclusion. A simplified version of the MELD score, using only serum creatinine and INR might be taken into account when predicting 12 months mortality on WL with longer waiting time, but it has to be confirmed by other prospective studies.

Introduction and Aim

With the overwhelming success of liver transplantation (LT), the demand for this intervention has progressively increased over the past years in the setting of a relatively fixed cadaveric organ supply. As a consequence, an increasing percentage of listed patients are dying while on waitlists and an additional number of listed candidates are disqualified as they become too sick for transplantation [1]. This disparity between organ demand and supply has led to extraordinary pressure on organ allocation programmes, which in turn has generated tremendous interest and continuous reassessment of listing and priority criteria for cadaveric liver allocation [2].

Liver allocation policy in the USA was changed in February 2002 to a continuous scale of disease severity based on the model for end-stage liver disease (MELD) score for adults [3] and pediatric end-stage liver disease (PELD) score for pediatric population [4]. The goal of the new allocation MELD/PELD system (MPS) was to use more objective criteria of disease severity and immediate need of transplantation, given minimal weight to waiting time in an effort to prioritize patients at highest risk of short-term pretransplant mortality [5]. As MPS scores have

been well validated in several large cohorts to accurately predict short-term mortality, the architects of the new liver allocation system defined the need for LT as the risk of death from liver disease within a 3-month period [6–8]. The major advantage of MELD score is that, it only requires three objective routine laboratory tests – serum creatinine, bilirubin, and international normalized (prothrombin) ratio (INR) – incorporated into an equation [3]. The new United Network for Organ Sharing (UNOS) policy for cadaver livers allocation has been an important shift towards an objective evidence-based approach in the field of organ allocation [9].

In this study, we have evaluated the predictive value of MELD score for the death on the WL for LT in a cohort of 152 adult candidates with chronic liver disease included on the WL between January 2001 and April 2003 at the single LT centre in Romania where this procedure is performed – Fundeni Clinical Institute. We also tried to evaluate in a survival analysis, the three MELD score components.

Material and methods

Study population

The cohort of patients used for the survival analysis included 152 consecutive adult patients with chronic liver disease (2B or 3 UNOS status) listed for cadaveric LT at the referral centre between January 2001 and April 2003. All patients had complete data required for MELD calculation at the time of listing. Survival analysis was conducted 1 year after the inclusion of the last patient in the study, in April 2004. The date of the death while on waitlist (WL), the date of the last contact with our centre and the date of the LT have been registered. Transplanted patients during the study interval and patients still alive at the moment of the survival analysis were considered censored cases.

The MELD score for each patient was computed at the time of listing using the method of Malinchoc *et al.* [10]. To avoid negative scores, laboratory values such as serum creatinine levels that were <1 mg/dl were rounded off to 1. The MELD equation used to calculate the severity score was as follows: MELD score = $(9.57 \times \log_e$ creatinine mg/dl + $3.78 \times \log_e$ bilirubin mg/dl + $11.20 \times \log_e$ INR + 6.43).

Model for end-stage liver disease (MELD) score was recalculated for each patient according to the accepted standards. For patients with MELD score <10, we have recalculated the score after 1 year, for scores between 11 and 18 after 90 days, for scores between 19 and 24 after 30 days and for scores over 25 we have recalculated the score weekly.

In patients with hepatocellular carcinoma (HCC), LT was recommended if it fulfilled the Milano criteria: one nodule <5 cm or two to three nodules with maximum diameter <3 cm. Conventionally for patients with one HCC nodule, a MELD score of 20 was allocated and for patients with two or three nodules, a MELD score of 24 was considered.

In our cohort of patients only two were listed for LT because of impaired quality of life (pruritus etc.) Their position on the WL was established according to their MELD score also.

Patients characteristics are given in Table 1.

Statistical analysis

The primary goal was the evaluation of the 12-month survivorship using the Kaplan–Meier method. To assess the MELD score ability to correctly rank order patients according to risk of death while on the WL, our analysis was performed by measuring the concordance (c-statistic) equivalent to the area under the receiver-operating characteristic curve (ROC). The outcome we assessed was the occurrence of death within 12 months while waiting on the list. A c-statistic between 0.8 and 0.9 indicates excellent diagnostic accuracy and a parameter with a c-statistic over 0.7 should be considered clinically useful.

Table 1. Patients characteristics.

Parameter	Value
Male:female ratio	1.49:1
Age	42.8 ± 10.59
Blood type	
O	47 (30.9%)
A	61 (40.1%)
B	32 (21.1%)
AB	12 (7.9%)
Aetiology of liver disease	
Hepatitis B virus	26 (17.1%)
Hepatitis C virus	34 (22.3%)
Hepatitis B and C co-infection	8 (5.2%)
Hepatitis B and D co-infection	33 (21.7%)
Alcoholic liver disease	7 (4.6%)
Hepatocellular carcinoma eligible for LTx	5 (3.2%)
Wilson's disease	10 (6.5%)
Autoimmune cirrhosis	6 (3.9%)
Primary biliary cirrhosis	7 (4.6%)
Secondary biliary cirrhosis	2 (1.3%)
Primary sclerosing cholangitis	5 (3.2%)
Overlap syndromes	3 (1.9%)
Others	6 (3.9%)
INR	1.62 ± 0.53 (range 0.9–4.17)
Total bilirubin (mg/dl)	4.58 ± 4.61 (range 1.2–22.5 mg/dl)
Serum creatinine (mg/dl)	1.13 ± 0.8 (range 0.6–6.5 mg/dl)
MELD score	17.09 ± 6.6 (range 9–38)
Child–Pugh Score	9.04 ± 1.92 (range 7–13)

MELD score components were included in a multivariate survival analysis conducted by Cox proportional hazards model, at 12 months after the inclusion of the last patient. The parameters identified as independent predictors of death were used in a logistic regression equation to form a new, simplified model to predict 12-month mortality on our WL for LT. The new simplified model was retrospectively evaluated and its ability to predict death on the WL was compared by c-statistic with the classical MELD score. Two-tailed *P*-values <0.05 were considered statistically significant.

Results

Forty-four patients (28.9%) died while on the WL for LT. Three-month survival rate was 92%, 6-month survival rate 80% and 12-month survival rate was only 69%. Median survival was not reached during the follow-up. The mean follow-up interval was 18.2 months (Fig. 1).

In the multivariate survival analysis performed by Cox proportional hazards model, only INR and creatinine were found as independent predictors of death on our WL ($P < 0.0001$ for both variables). The level of serum bilirubin at the moment of listing was not a significant variable in the survival analysis ($P = 0.06$; Table 2).

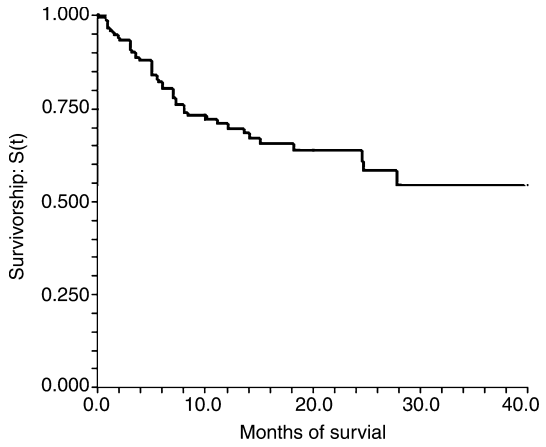

Figure 1 Kaplan–Meier survival curve of patients on the WL for LTx.

Table 2. Results of the multivariate survival analysis.

Variable	Regression coefficient (B)	Standard error	Exp(B)	*P*-value
INR	1.332	0.20	3.79	<0.0001
Serum bilirubin	0.066	0.034	1.06	0.06
Serum creatinine	0.45	0.099	1.57	<0.0001

Table 3. Results of the multivariate logistic regression analysis.

Variable	Regression coefficient (β)	Standard error	Chi-square (β = 0)	*P*-value
Intercept	9.9	0.53	36.8	<0.0001
INR	10.3	0.88	15.1	<0.0001
Serum creatinine	11.2	0.93	16.3	<0.0001

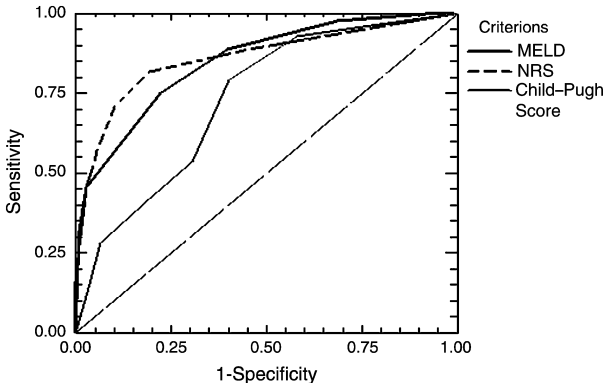

Figure 2 ROC Curves for MELD score, the new risk score (NRS), and Child–Pugh score as predictors of death on our WL for LTx.

The natural logarithms of INR and serum creatinine were included in a logistic regression analysis, and the dependent variable was considered the death within 12 months on the WL for LT. Results of the analysis are given in Table 3.

Based on the logistic regression equation, a new predictive model was created, which included only the INR and serum creatinine, variables that were identified by the multivariate survival analysis as independent predictors for survival on our WL. The new model allows the calculation of death risk score on the WL for LT using the following formula: new risk score $= 9.9 + 10.3 \times \ln$ INR $+ 11.2 \times \ln$ creat.

MELD score was found to be an excellent predictor of death within 12 months on our WL – c-statistic (area under curve) 0.84 (Fig. 2). The area under curve for the new predictive score was 0.86, so its predictive value for death within 12 months on our WL is at least as good as for the MELD score. Both scores predict better the occurrence of death within 12 months on the WL than the traditional Child–Pugh score, for which the area under curve was only 0.73 (Fig. 2).

Discussion

LT is the treatment of choice for patients with end-stage chronic liver disease, fulminant hepatic failure and certain metabolic diseases for which no effective therapy is available. Survival at 1 and 3 years after LT approaches

90% and 80%, respectively, at most leading centres for LT [1]. In addition to longer survival, many liver transplant recipients are now experiencing an improved quality of life, including resumption of active employment and reproductive capacity [1]. This successful outcome of LT in terms of survival and quality of life requires careful selection of potential recipients and optimal allocation of scarce resources. Over the past decade, this has become one of the most critical issue in the field, raising tremendous interest within transplantation programmes, facing reduced availability of cadaveric organs and long waiting time. Since LT programme successfully began in Romania at our institution in January 2000, the annual rate of deceased liver donors did not exceed 1 per million, highlighting the problem of optimal liver allocation policy.

Hepatologists worldwide continuously revised organ allocation and distribution policy in an attempt to balance the ethical principles of medical justice and utility. The principle of justice advocates for the sickest patient who has been waiting for the longest time, whereas utility favours the patient with the highest likelihood of achieving successful outcome [11]. Prior to February 2002, candidates waiting for deceased liver donors were prioritized based on the well-established Child–Turcotte–Pugh (CTP) score for liver disease [12,13] and by waiting time. The major criticisms of CTP score consisted in the limited number of medical urgency categories (classes A, B, C) and the subjectivity of some parameters such as hepatic encephalopathy and ascites [14]. Within the CTP categories for disease severity, waiting patients were ordered according to time on the WL. As the number of patients on WL grew, the severity of their disease became much more heterogeneous within these limited categories. Consequently, waiting time became the major discriminator for patients in these large categories and diminished the role of medical status in determining priority on the list [15].

In February 2002, UNOS proposed to replace the current status 2A, 2B and 3 by a modified version of the original MELD score [10] based on patient risk for 3-month mortality on the WL [3]. MELD was proven as an objective, reliable and clinically useful model for assessing disease severity and predicting survival in patients with chronic liver disease [16]. Unlike the CTP score used in previous allocation policy, the MELD score has been rigorously tested and validated as a good predictor of mortality in different groups of patients with various types and degrees of chronic liver disease [7,17–21]. Independent studies performed in the USA and Europe showed that the MELD score performed at least as well as CTP score in predicting patient outcome following acute variceal bleeding [17], mortality in LT candidates [7,18], short- and medium-term survival in an European series of cirrhotic patients referred to a tertiary care centre [19] and mortality in patients with primary sclerosing cholangitis [20]. In the study of Wiesner *et al.* [7] the MELD score was superior to the CTP score in ranking patients according to severity of their liver disease and risk of dying at 3 months (MELD area under curve = 0.83, CTP area = 0.76).

In our study, MELD score was evaluated by predicting mortality on the WL in 152 UNOS 2B and 3 patients. Given to the long waiting time on the list which is characterizing our programme of LT (mean waiting time of 22 months) [22] we considered appropriate to evaluate the medium-long term (12 months) survival of patients listed for LT. The ROC analysis performed for MELD score revealed an excellent predictive value also for death at 12 months (MELD area = 0.84).

Although the mortality rate at 3 months in our study (patients in UNOS 2B or 3 status) was similar to that found in Wiesner's study for patients UNOS 2B (8% vs. 9.2%) [8], there was a fourfold increase in mortality on our WL for LT between 3 and 12 months after the inclusion. We suppose that the prolongation of waiting time for deceased donor livers, considerably increase the risk for intercurrent life-threatening complications such as variceal hemorrhage, hepatic encephalopathy and infections in otherwise stable populations (UNOS 2B or 3 patients) because of the progression of portal hypertension. According to these findings, concerted efforts should be taken to decrease the waiting time by increasing the number of deceased liver donors, using split livers and adult living donors.

In the multivariate survival analysis performed on individual components of MELD score by Cox proportional hazards model, the independent predictors of death on our waitlist were INR and creatinine, while serum bilirubin was not identified as a statistically significant predictor of survival. The independent value of these two components was already emphasized by other authors. INR was identified as the strongest component of the original MELD score [3]. Serum creatinine and INR were independently associated with 6- and 12-month mortality in a recent European series of cirrhotic patients [20]. On the contrary, a recent publication reviewing prognostic studies that use multivariate analysis in cirrhosis (57 identified so far), found that bilirubin is the parameter that most frequently appeared among the first five statistically significant predictors of survival, followed by INR [16]. Similarly, another recent study indicates that only bilirubin and creatinine have a significant contribution to the predictive value of MELD score [23].

Our study suggests the fact that serum bilirubin might be not an independent predictor of death on WL which include mainly patients in UNOS 2B and 3 status and which are characterized by a long waiting time. We can hypothesize that serum bilirubin is an independent

predictor of death only when assessing short-term survival (3 months) on the WL, as suggested by other studies [2], but it has limited value as a long-term (12 months) survival predictor in cirrhotic patients.

A new predictive model including only the INR and the serum creatinine was generated in order to simplify the evaluation of 12-month death risk on our WL for LT. The area under curve for the new predictive score, when retrospectively evaluated on our series, was 0.86, so its predictive value for death on the WL is at least as good as for the MELD score. This new score is only useful when evaluating long-term survival (12 months) and cannot substitute the original MELD score when evaluating 3 months risk of death on WL with a short waiting time. It has to be validated prospectively by other studies.

In summary, by taking into account the 12-month survival, our analysis gives a better picture of what happens with the dynamics of the WL in case of programmes with longer waiting time. The simplified MELD score might be used when evaluating 12 months mortality because in this case, serum bilirubin seems not to be an independent predictor of death.

References

1. U.S. Organ Procurement and Transplantation Network and the Scientific Registry for Transplant Recipients. *2001 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry for Transplant Recipients: Transplant Data 1991–2000*. Rockville, MD: Dept of Health and Human Services Administration, Office of Special Programs, Division of Transplantation; Richmond, VA: United Network for Organ Sharing; and Ann Arbor, MI: University Renal Research and Education Association, 2001.
2. Wiesner RH, Rakela J, Ishitani MB, *et al.* Recent advances in liver transplantation. *Mayo Clin Proc* 2003; **78**: 197.
3. Kamath PS, Wiesner RH, Malinchoc M, *et al.* A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464.
4. McDiarmid SV, Anand R, Lindblad AS. Development of a pediatric end-stage liver disease score to predict poor outcome in children awaiting liver transplantation. *Transplantation* 2002; **74**: 173.
5. Freeman RB. Mortality risk versus other endpoints: who should come first on the liver transplant waiting list? *Liver Transpl* 2004; **10**: 675.
6. United Network for Organ Sharing. *Organ distribution: Allocation of Livers.* Policy 3.6. United Network for Organ Sharing Web page. Available at: http://www.unos.org accessed May 2004.
7. Wiesner RH, McDiarmid SV, Kamath PS, *et al.* MELD and PELD: application of survival models to liver allocation. *Liver Transpl* 2001; **7**: 567.
8. Wiesner R, Edwards E, Freeman R, *et al.* United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91.
9. Freeman RB, Wiesner RH, Harper A, *et al.* The new liver allocation system: Moving toward evidence-based transplantation policy. *Liver Transpl* 2002; **8**: 851.
10. Malinchoc M, Kamath PS, Gordon FD, *et al.* A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864.
11. Yu AS, Keefe EB. Patient selection criteria for liver transplantation. *Minerva Chir* 2003; **58**: 635.
12. Child CG, Turcotte JG. Surgery in portal hypertension. In: Child CG, ed. *The Liver and Portal Hypertension*. Philadelphia, PA: Saunders, 1964: 50–64.
13. Pugh RNH, Murray-Lyon IM, Dawson JJ, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646.
14. Forman LM, Lucey MR. Predicting the prognosis of chronic liver disease: an evolution from Child to MELD. *Hepatology* 2001; **33**: 473.
15. Freeman RB, Wiesner RH, Edwards E, *et al.* Results of the first year of the new liver allocation plan. *Liver Transpl* 2004; **10**: 7.
16. Pagliaro L. MELD: the end of Child-Pugh classification? *J Hepatol* 2002; **36**: 141.
17. Chalasani N, Kahi CJ, Francois F, *et al.* Mayo clinic end-stage liver disease model (MELD) for predicting patient outcomes following acute variceal bleeding. *Hepatology* 2001; **34**: 345A.
18. Abouassi SG, Mihas AA, Williams LM, *et al.* MELD and CTP scores are equivalent predictors of mortality in cirrhotic veterans reffered for orthotopic liver transplantation (OLT). *Hepatology* 2001; **34**: 207A.
19. Botta F, Giannini E, Romagnoli P, *et al.* MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: an European study. *Gut* 2003; **52**: 134.
20. Brandsaeter B, Friman S, Broome U. Outcome following liver transplantation for primary sclerosing cholangitis in Nordic countries. *Scand J Gastroenterol* 2003; **38**: 1176.
21. Jeong EM, Hwang SG, Park HH, *et al.* The anaylsis of mortality rate according to CTP score and MELD score in patients with liver cirrhosis. *Taehan Kan Hakhoe Chi* 2003; **9**: 98.
22. Gheorghe L, Iacob S, Iacob R, Gheorghe C, Stoicescu A, Popescu I. Predictors of death on a waiting list for liver transplantation in Romania. *Gut* 2003; **52**: 160.
23. de Rave S. EMERALD – better than MELD? *J Hepatol* 2004; **40**: 9.