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ORIGINAL ARTICLE

MELD score versus conventional UNOS status in predicting short-term mortality after liver transplantation*

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Summary

The Model for End-stage Liver Disease (MELD) provides a score able to predict short-term mortality in patients awaiting liver transplantation (LT). In the early 2002, United Network for Organ Sharing (UNOS) has proposed to replace the conventional statuses 3, 2B, and 2A with a modified MELD score. However, the accuracy of the MELD model to predict post-transplantation outcome is fairly elusive. In the present study we investigated the predictive value of the MELD score for short-term patient and graft mortality in comparison with conventional UNOS status. Sixty-nine patients listed at UNOS status 3 ($n = 5$), 2B ($n = 55$) or 2A ($n = 9$) who underwent LT were enrolled according to strict criteria. No donor-related parameters affected 3-month patient survival. Through univariate Cox regression, pretransplantation international normalized ratio ($P = 0.049$) and activated partial thromboplastin time ($P = 0.032$) were significantly associated with 3-month patient survival, although not in the subsequent multivariate analysis. The overall MELD score was 17 ± 6.63 (median: 16, range: 4–34), increasing from UNOS Status 3 to 2A ($r^2 = 0.171$, $P = 0.0001$). No significant difference occurred in the median MELD score between patients who underwent a second LT and those who did not ($P = 0.458$). The inter-rate agreement between UNOS status and MELD score after categorization for clinical urgency showed a fair agreement ($\kappa = 0.244$). The 3-month patient and graft mortality was 15.94% and 20.29% respectively. The concordance statistic did not find significance between UNOS status and MELD score for 3-month patient ($P = 0.283$) or graft mortality ($P = 0.957$), although the MELD score revealed a major sensitivity for short-term patient mortality (0.637; 95%CI: 0.513–0.75). These findings suggest the need to implement MELD model accuracy for both inter-rate agreement with UNOS Status and patient outcome.

Introduction

The number of patients awaiting liver transplantation (LT) has increased progressively in the past decade [1]. However, the shortage of cadaveric donors and the incremental death rate in the potential recipients has forced the transplant community to search for more effective strategies for expanding the graft pool [2,3]. Thus, suboptimal donors or grafts, split-liver transplantation (SLT) and living-related liver graft donation have contributed to enlarge the donor pool [3–5]. Recently, the point of view that waiting time for LT should be discontinued in favor of more equitable organ allocation strategies based on medical characteristics and disease prognoses has become attractive [1,6]. In 2000, a Model for End-Stage Liver Disease (MELD) was

developed at the Mayo Clinic as a continuous scale to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS) [7]. In 2001, the MELD score was extended as a potential disease severity score for patients with end-stage liver disease awaiting LT [8]. In the early 2002, the United Network for Organ Sharing (UNOS) has proposed to replace the conventional statuses 2A, 2B and 3 with a modified version of the original MELD score based upon a patient's risk for 3-month mortality on the waiting list [9]. The status 1 category, which utilized strict medical criteria, has been maintained in effect for the most urgently ill patients [9,10]. Although the MELD score was effective in the prediction of patient mortality awaiting LT, its predictive value for post-transplantation mortality remained fairly elusive, suggesting the need for further analyses [11]. In this retrospective study, the MELD score was compared with conventional UNOS status in order to evaluate its potential predictive value for short-term mortality after LT in both patients and grafts.

Patients and methods

Liver recipient characteristics

In our department, 80 adult patients underwent 98 LT procedures between January 1, 2000 and December 31, 2001. Of these procedures, 70 were whole-liver transplantation (WLT) and 28 were *in situ* SLT. Sixty-nine patients who, at the time of the first LT, were listed at UNOS status 3, 2B or 2A were enrolled in this study. Exclusion criteria were patients listed at UNOS status 1, patients with an incomplete data set concerning laboratory parameters before LT, patients lost to follow-up, and no missing data with regard to matching donors. No regression model was used to predict the missing values by the raw data. Patients who underwent retransplantation ($n = 14$) were included because graft survival has been considered in the analysis [12]. The preoperative patient characteristics dealt in this study were recipient age, body mass index (BMI), diagnostic category, waiting time for LT, Child–Turcotte–Pugh (CTP) score, UNOS status and conventional biochemical parameters. These parameters were entered in univariate analyses, as were donor–recipient age ratio, sex mismatch, and standard liver volume (SLV) ratio, cold ischemia time (CIT), surgical procedure (WLT or SLT) and intraoperative transfusions. The CTP score was calculated as previously described [13,14], listing the patients in the corresponding CTP class (class A: CTP scores 5–6; B: 7–9; C: ≥10). SLV was calculated following the formula derived for the White population (1072.8 * body surface area−345.7) [15].

MELD calculation

The MELD score was calculated in each patient before anesthesia induction for LT according to the formula [0.957*$\log_e$(creatinine mg/dl) + 0.378*$\log_e$(total bilirubin mg/dl) + 1.12 $\log_e$(INR) + 0.643]*10 [8, 9]. The UNOS on-line calculator was used to MELD score calculation [16]. The minimal values of total bilirubin (TB) and creatinine were setting at 1 mg/dl [9, 17]. Prothrombin time (PT) was converted to international normalized ratio (INR) as described in *Biochemical assays*. The MELD score was stratified in agreement with the intervals proposed by the Mayo Clinic group (≤9, 10–19, 20–29, 30–39), where a higher MELD score indicates a worse degree of liver disease severity than a lower score [8]. Patients were also grouped according to median value of the MELD score, as well as for the MELD score after dichotomization based on the clinical urgency (MELD score ≥25) [11], presence/absence of virus C (HCV)-related disease or hepatocellular carcinoma (HCC) unrelated to HCV infection. As organ allocation was not originally founded on the MELD score, in this retrospective study no adjustment for malignancy was made [11]. The potential impact of body size on the MELD score was evaluated by patient stratification for body size and creatinine by age (<50 and ≥50 years old) and sex, as previously described [8].

Liver donor characteristics

Inclusion criteria for donor selection were: intensive care unit recovery ≤5 days; TB ≤2.5 mg/dl; alanine aminotransferase (ALT) ≤300 U/l; γ-glutamyltranspeptidase (γ-GT) ≤150 U/l; hemoglobin ≤10 g/dl; Na^+ <160 mmol/l; hemodynamic stability in the last 24 h; normality in the portal blood flow evaluated by Doppler ultrasonography. The organ procurement criteria applied to cadaveric donors for WLT included elderly donors (>60 years old) and/or suboptimal grafts (macrosteatosis ≤30% in the preperfusion frozen section biopsy). The donor parameters that were considered in this study were: donor age, TB, ALT, aspartate aminotransferase (AST), γ-GT, platelet count (PLT), PT, activated partial thromboplastin time (APTT), fibrinogen, creatinine, blood urea nitrogen (BUN), Na^+, and K^+.

Liver transplantation

Sixty-nine adult patients underwent 48 WLT and 21 SLT procedures. WLT was performed using piggyback technique [18]. Liver splitting was carried out in the heart-beating cadaveric donor before organ preservation, as previously described [4,19,20]. After the dissection had

been completed, two liver sections were separated each with its own vascular pedicles and biliary drainage. The right livers obtained with this procedure were transplanted into adult recipients in our department, whereas left livers were transplanted into pediatric recipients in other Italian and European Centers. Intraoperative transfusions of packed red cells (PRC), fresh frozen plasma (FFP) and PLT were supplied as previously described [20]. All adult recipients were informed about the details of the procedure and they consented to undergo LT at the time of acceptance, while they were on the waiting list. They repeated their consent when called for transplantation.

Biochemical assays

All assays concerning liver recipients were performed at the Clinical Chemistry Laboratory of S. Martino University Hospital. Only parameters that were entered in the MELD formula were transformed to their natural logarithms [7]. The INR values were derived from calibrations of commercial thromboplastin reagents against the international reference preparation using the International Sensitivity Index (ISI) as follows [21]: INR = [patient PT (s)/normal PT (s)]^{ISI}. The INR was calculated in all patients by using the same lot of thromboplastin reagent and the equal reagent-instrument combination.

Biochemical assays concerning cadaveric donors were performed out of our Clinical Chemistry Laboratory in 53 cases (76.81%), and out of our regional district in 38 cases (55%). Considering that PT was not expressed in each donor as INR, while each donor-plasma clotting time was provided as a percentage of standard plasma pooled from normal subjects, the latter measurement was entered in the analyses involving donor-related parameters.

Follow-up

The mean follow-up was 9.99 ± 3.92 months (median: 12 months, range: 0.3–12 months). Overall 3-month survival in patients and grafts, assumed as the main outcome measure, was 84.06% and 79.71% respectively. Overall 1-year patient and graft survival was 75.36% and 72.46% respectively. The cause of patient death was multiorgan failure ($n = 8$), sepsis ($n = 5$), hepatic artery thrombosis ($n = 1$), hepatic necrosis ($n = 1$), cerebral edema ($n = 1$), and recurrence of original disease ($n = 1$).

Statistical analysis

The univariate association between cadaveric donor characteristics and liver recipient or graft survival was tested by a series of logistic regression models. Mann–Whitney test and one-way ANOVA were used for comparisons of continuous variables. Bartlett's test for equal variances, post-test for linear trend and Tukey's multiple comparison test were used when one-way ANOVA reached significance. The Spearman's ranked test was applied for correlations. Kaplan–Meier product-limit estimator and the log-rank test were used in the survival analysis. Univariate Cox proportional hazard regression was carried out to test the association of patient characteristics, MELD-related parameters, and surgery with post-transplant patient or graft survival. Variables that were significantly associated with survival were introduced into a multivariate Cox regression analysis. Cohen's κ value was calculated to assess the level of agreement between UNOS status and MELD model after their categorization for clinical urgency [22]. The mathematical measure to determine the validity of the UNOS status and MELD model for short-term mortality was the concordance (c)-statistic, equivalent to the area under receiver operating characteristic (ROC) curve [23]. The ROC curves were fitted with death of patients or grafts after LT (sensitivity) for patient or graft survival at the same times (1-specificity). The differences were assumed to be significant at $P < 0.05$ with a two-tailed null hypothesis. No adjustment was fixed to the nominal *P*-value that resulted from the analyses, in view of the retrospective nature of this study. Statistical analyses were performed by using the software packages STATISTICA 6.1 (StatSoft, Tulsa, OK, USA), Prism 3.02 (GraphPad Software, San Diego, CA, USA), MedCalc 6.16 (MedCalc Software, Mariakerke, Belgium), and a logistic regression calculator (by John Pezzullo, in http://members.aol.com/johnp71/javastat.html).

Results

The mean ± SD age of patients enrolled in this study was 48.68 ± 9.63 years, while male–female ratio was 2.13 (Table 1). Diagnostic categories were established according to European Liver Transplant Registry (Table 1). The logistic regression models that were used to test the univariate association of cadaveric liver donor characteristics with 3-month patient survival showed no statistical significance (Table 2). Univariate Cox proportional hazard regression was carried out to test the potential association between a set of variables related to patients and surgery with short-term patient survival after LT (Table 3). INR and APTT measured before LT were the only independent predictors of 3-month patient survival ($P = 0.049$ and $P = 0.032$, respectively), whereas surgical procedure (WLT or SLT) approached but did not reach statistical significance ($P = 0.063$). Univariate Cox proportional hazard regression applied to MELD-related laboratory parameters after their natural logarithmic transformation

Table 1. Patient characteristics.

Demographic	
Age (years)	51 (20–65)
Sex (M/F)	47/22
ELTR diagnostic categories	
D4	18 (26)
D4E1	9 (13.03)
D1	8 (11.6)
D5	5 (7.24)
D3	4 (5.8)
D3E1	4 (5.8)
D5E1	3 (4.34)
C4	2 (2.9)
Other	16 (23.32)

Age is reported as median (range). For other enteries percentage values are given in parentheses.
ELTR, European Liver Transplant Registry; D4 virus C related cirrhosis; D1, alcoholic cirrhosis; D5, virus BD related cirrhosis; D3, virus B related cirrhosis; C4, congenital biliary disease; E1, hepatocellular carcinoma and cirrhosis.

Table 2. Univariate association between cadaveric liver donor characteristics and 3-month liver recipient survival.

Characteristic	Median	χ^2	OR	95% CI	*P*-value
Donor age (years)	43	0.126	1.0062	0.97–1.04	0.723
TB (mg/dl)	1.1	1.483	0.762	0.5–1.15	0.201
ALT (U/l)	25	0.169	1.000	0.99–1.00	0.729
AST (U/l)	35	0.348	1.002	0.99–1.01	0.639
γ-GT (U/l)	25	0.726	0.99	0.969–1.01	0.379
PLT ($\times 10^9$/l)	142	0.000	1.000	1.00–1.00	0.982
PT (%)	75	0.611	0.982	0.93–1.02	0.446
APTT (s)	38	0.641	0.984	0.947–1.00	0.411
Fibrinogen (mg/dl)	482	0.061	0.999	0.99–1.00	0.804
Creatinine (mg/dl)	1	0.859	1.37	0.55–3.37	0.489
BUN (mg/dl)	20	0.699	0.982	0.94–1.02	0.390
Na (mmol/l)	147.5	0.872	1.03	0.96–1.1	0.372
K (mmol/l)	3.8	0.240	1.22	0.53–2.79	0.627

OR, odds ratio; CI, confidence interval.

found significance only for INR $\log_e$ value ($P = 0.035$) (Table 3). Multivariate Cox regression analyses performed by introducing INR and APTT (first model) or INR $\log_e$ value and APTT (second model) did not show significant association with 3-month patient survival (first model: INR, $P = 0.351$; APTT, $P = 0.27$; second model: INR $\log_e$ value, $P = 0.394$; APTT, $P = 0.247$). An univariate Cox regression performed by entering the same parameters of the Table 3 for 3-month graft survival found no statistical significance (data not shown).

At the time of LT, the patients enrolled in this study were listed at UNOS status 3 ($n = 5$), 2B ($n = 55$) or 2A ($n = 9$). The median of CTP score for liver recipients in UNOS status 3, 2B, and 2A was 9, 10, and 11 respectively.

Table 3. Univariate Cox proportional hazard regression between patient/surgery characteristics and 3-month patient survival after liver transplantation.

Characteristic	Median	χ^2	β	β SE	*P*-value
Demographic					
Recipient age (years)	51	0.04	0.0065	0.032	0.841
Donor–recipient age ratio	0.84	0.5	–0.437	0.645	0.498
Sex mismatch	–	0.009	0.061	0.626	0.922
Clinical					
Diagnosis	–	0.176	0.015	0.036	0.669
BMI	24.2	1.356	–0.113	0.097	0.248
Waiting time (days)	163	0.748	0.001	0.001	0.356
CTP score	10	0.033	0.035	0.193	0.855
UNOS status	–	0.121	–0.003	0.01	0.713
Biochemical before LT					
ALT (U/l)	52	3.68	–0.014	0.009	0.126
AST (U/l)	57	2.285	–0.01	0.008	0.220
TB (mg/dl)	3.2	2.63	–0.11	0.104	0.254
TB ($\log_e$ value)	–	2.35	–0.501	0.336	0.136
γ-GT (U/l)	36	0.001	0.0002	0.005	0.964
PLT ($\times 10^9$/l)	60	0.358	0.0000	0.000	0.589
INR	1.64	5.67	–2.31	1.176	0.049
INR ($\log_e$ value)	–	5.28	–3.314	1.578	0.035
APTT (s)	46	5.98	–0.08	0.03	0.032
Fibrinogen (mg/dl)	182	0.634	0.002	0.002	0.395
Albumin (mg/dl)	3.3	1.758	0.494	0.325	0.128
BUN (mg/dl)	13	0.142	0.008	0.02	0.696
Creatinine (mg/dl)	0.9	1.246	0.133	0.099	0.179
Creatinine ($\log_e$ value)	–	1.007	0.477	0.423	0.259
Na (mmol/l)	137	0.283	–0.034	0.062	0.581
K (mmol/l)	4.1	0.026	0.073	0.442	0.868
Surgery					
Donor–recipient SLV ratio	1.02	0.99	1.794	1.753	0.306
CIT (min)	444	0.101	–0.0006	0.002	0.753
Procedure	–	3.38	1.125	0.605	0.063
Intraoperative transfusions					
PRCs (U)	10	1.95	0.062	0.042	0.139
FFP (U)	22	0.681	0.014	0.016	0.374
PLT (U)	2	0.221	0.238	0.493	0.628

β regression coefficient; SE, standard error; CIT, cold ischemia time.

Within UNOS status 2B, the percentage of patients in CTP class A, B, and C was 4.64%, 25.64%, and 69.29% respectively. The overall MELD score calculated in liver recipients before LT was 17 ± 6.63 (median: 16, range: 4–34). In both genders, no significant correlation between BMI and MELD score occurred (men: $r = –0.10$; $P = 0.496$; women: $r = 0.13$; $P = 0.6$). Following the original MELD strata, the patients were listed at MELD interval ≤9 ($n = 7$), 10–19 (n = 42), 20–29 ($n = 16$), and 30–39 ($n = 4$). No statistically significant difference was found between median MELD score in patients who underwent a second LT versus those who did not ($P = 0.458$), as well as after patient dichotomization for the presence/absence of HCV-related liver diseases ($P = 0.781$) or HCC unrelated to HCV ($P = 0.752$).

Table 4. MELD score calculated before liver transplantation in patients listed according to conventional UNOS statuses.

Patients	UNOS Status	MELD Score	Median	Range	95% CI
5	3	11.6 ± 5.59	9	6–19	4.65–18.54
55	2B	16.5 ± 5.95	15	4–30	14.9–18.11
9	2A	23 ± 7.71	20	15–34	17–28.92

The MELD score calculated in each UNOS status (Table 4) exhibited a linear trend to increase from status 3 to 2A ($r^2 = 0.171$, $P = 0.0001$). The Spearman's ranked test showed a better correlation for MELD versus UNOS ($P = 0.018$) than for MELD versus CTP ($P = 0.05$). Comparison by one-way ANOVA of the MELD score calculated in the three UNOS groups reached significance ($P = 0.0005$), without significant differences for variances ($P = 0.527$). Tukey's multiple comparison test showed significance for MELD score in the UNOS status 3 versus 2B ($P < 0.01$), and 3 versus 2A ($P < 0.001$). Conversely, no significant difference for MELD score in the UNOS Status 2B versus 2A occurred ($P > 0.05$). Patients listed at UNOS status 3 fell into the MELD strata ≤9 (with respect to total: 4.35%, with respect to UNOS status: 60%) and 10–19 (2.9%, 40%), while patients in UNOS status 2B were in MELD strata ≤9 (5.8%, 7.27%), 10–19 (53.62%, 67.27%), 20–29 (18.64%, 23.64%) and 30–39 (1.45%, 1.82%). Patients listed at UNOS status 2A were into MELD strata 10–19 (5.8%, 44.44%), 20–29 (2.9%, 22.22%), and 30–39 (4.35%, 33.33%). After categorization of UNOS status and MELD score for clinical urgency (sick 2B and 2A, MELD score ≥25), the inter-rate agreement measured by the Cohen's κ was 0.244 ($SE = 0.125$; 95% CI from 0 to 0.488).

The comparison of the MELD score in patients grouped as survivors and nonsurvivors did not find statistical significance at 1 month ($P = 0.488$) and 3 months ($P = 0.138$) after LT. When we dichotomized MELD score at the median value (<16, ≥16), the patient survival at 1 month for the group MELD <16 or MELD ≥16 was 93.75% and 91.89% ($P = 0.799$), whereas survival at 3 months was 81.15% and 86.49% ($P = 0.57$) respectively. The ratio between 3-month nonsurvivors and survivors in the UNOS status 3, 2B, and 2A was 1/4 (0.25), 9/46 (0.19), and 1/8 (0.125) respectively. The same ratio in the MELD stratum ≤9, 10–19, and 20–29 was 2/5 (0.4), 8/34 (0.23), and 1/15 (0.06) respectively. No death occurred within the first 3 months after LT in the four patients with a MELD score that was within the 30–39 interval. Log-rank test performed for 3-month patient survival using the UNOS status 3 or MELD ≤9 as reference group did not show significant difference by comparison with status 2B ($P = 0.857$) and 2A ($P = 0.866$), or with the MELD interval 10–19 ($P = 0.381$) and 20–29 ($P = 0.175$) respectively. No statistical significance for 3-month graft survival occurred (data not shown). The ratio between 1-year nonsurvivors and survivors in the UNOS status 3, 2B, and 2A was 1/4 (0.25), 12/43 (0.279), and 4/5 (0.8), respectively, while the same ratio in the MELD strata ≤9, 10–19, 20–29, and 30–39 was 3/4 (0.75), 11/31 (0.354), 2/14 (0.142), and 1/3 (0.33) respectively. Following the same approach describe above, UNOS status 3 or MELD ≤9 did not show significant differences at log-rank test when compared respectively with the other UNOS statuses or MELD intervals for 1-year survival in both patients and grafts (data not shown).

Table 5. Comparison of UNOS status and MELD score in predicting mortality of patients and grafts after liver transplantation. Values are reported as the area under receiver operating characteristic curve in the concordance statistic (95% CI).

	UNOS	MELD	*P*-value
Patients			
1-week mortality	–	–	–
1-month mortality	0.525 (0.401–0.647)	0.577 (0.452–0.695)	0.726
3-month mortality	0.531 (0.407–0.653)	0.637 (0.513–0.75)	0.283
6-month mortality	0.511 (0.388–0.633)	0.57 (0.445–0.689)	0.531
1-year mortality	0.613 (0.488–0.728)	0.543 (0.419–0.644)	0.419
Grafts			
1-week mortality	0.631 (0.507–0.744)	0.614 (0.489–0.728)	0.898
1-month mortality	0.532 (0.408–0.653)	0.515 (0.392–0.637)	0.871
3-month mortality	0.534 (0.41–0.655)	0.529 (0.405–0.65)	0.957
6-month mortality	0.505 (0.382–0.628)	0.519 (0.396–0.641)	0.897
1-year mortality	0.563 (0.438–0.682)	0.532 (0.408–0.653)	0.709

The patient short-term mortality after LT measured at 1 week, 1 month, and 3 months was 1.45%, 7.25%, and 15.94% respectively. The patient mortality at 6 months and 1 year was 18.84% and 24.64% respectively. Graft mortality at 1 week, 1 month, 3 months, 6 months, and 1 year was 4.35%, 17.39%, 20.29%, 21.74%, and 27.54% respectively. Comparison of UNOS status and MELD score in predicting post-transplant mortality of patients and grafts by using the (c)-statistic did not find significance at each time point (Table 5).

Discussion

The MELD score, originally developed as a continuous scale to predict early death in patients undergoing TIPS [7], has been proposed by UNOS in a slightly modified version to replace the conventional statuses 2A, 2B and 3 in order to better prioritize patients with end-stage liver disease awaiting LT [9]. The MELD score is calculated by using readily available laboratory parameters such as serum creatinine, TB and INR, making it easy to employ [8]. Although this score has revealed to be effective in the prediction of short-term mortality in patients awaiting LT

[8,10], suggesting its application to allocate donor livers [24], and ideal model should be able to predict also post-transplant outcome in both patients and grafts [12,17]. Recently, two large series have found a correlation between the pretransplantation MELD score and 1-year liver recipient survival [11, 17]. However, other series did not find significant differences between MELD score and other models when compared for post-transplantation patient mortality [25,26]. Moreover, the MELD score failed to predict patient or graft survival in living donor liver transplant recipients [12], and it did not correlate with the severity of patients affected by cancer or metabolic disorders [27], or with the degree of encephalopathy and ascites [28]. Finally, recent studies carried out in patients undergoing TIPS, the original source of the MELD score, found that MELD model and CTP can be used with equal accuracy for prognostic assessing [29,30], and that in patients with refractory ascites the mortality was unpredictable on the basis of pretransplant variables [31].

In Italy, where there is no formal priority score for patients in the waiting list [32], precedence for LT was assigned conventionally according to UNOS statuses. In view of the fact that the specifications for MELD usage were established by UNOS Policy 3.6, released on February 2002 [9], the MELD model came into use because of a growing number of Italian transplantation centers side by side with UNOS statuses only in the second half of 2002. For this reason, the MELD score was not included in the parameters meanwhile adopted by the Italian Ministry of Health (IMH) to evaluate retrospectively the quality of the national liver transplantation activity referred to the previous two-year period [33].

This retrospective study was performed with the aim to assess the potential predictive value of the MELD score for short-term mortality in both patients and grafts after LT. Our analysis has been focused on the period 2000–2001 for several reasons. First, it represents the main reference time in the retrospective analyses conducted by the IMH [33]. Secondly, at the beginning of year 2000, a new informative system was introduced in our department for a more reliable data management and recovery, especially with reference to cadaveric donors. Finally, in the same period a new generation of automated analyzer with accompanying kits for coagulation assays was adopted by the clinical chemistry laboratory of our hospital. In this analysis, special efforts were made to apply strict criteria for patient selection and data mining. Thus, only patients with a full data set concerning laboratory parameters before transplantation were enrolled, and differently from Malinchoc *et al.* [7] no regression model was performed to predict the missing values for the parameters that would be entered in the MELD formula. Furthermore, only parameters necessary for MELD calculation were transformed to their natural logarithms [7,8], avoiding applying this procedure to MELD-unrelated continuous variables. In particular, univariate analysis for short-term survival was performed by entering the MELD-related parameters as both the row values and their natural logarithms. This strategy was adopted for a comprehensive evaluation of INR, considering that this parameters is derived by a conversion process [21]. In addition, the potential impact of body size on the MELD score was also evaluated because of the fact that the MELD model may potentially underestimate the degree of liver disease in patients with a small body size [8]. Finally, a wide set of cadaveric donor-related variables was analyzed to evaluate its potential impact on patient survival.

In our series, patients were in diagnostic categories mainly associated with hepatitis viruses or malignancy (Table 1). However, several patients had a combination of at least two causes, such as hepatitis viruses–HCC or alcohol abuse–other liver disease, making it difficult for determining the primary cause of liver disease and suggesting its exclusion from the modified MELD formula [8,9]. Cadaveric donor-related variables were not associated with short-term patient survival (Table 2), as well as patient diagnostic category, UNOS Status, CTP score or waiting time for LT (Table 3). INR raw value, INR $\log_e$ value and APTT measured before LT were the only independent predictors for short-term patient survival, although no significance was found in the subsequent multivariate models. Focusing on the univariate Cox analysis performed for the MELD-related parameters, INR $\log_e$ value was significant for short-term patient survival with a negative β, while TB $\log_e$ value and creatinine $\log_e$ value did not reach significance (Table 3), differently from the analysis carried out in the development of original MELD model, where all parameters reached significance with a positive β [7]. In the largest series analyzed to date with a special emphasis on the correlation between MELD score and mortality after LT, no univariate analysis including the MELD-related parameters was proposed [11], making it unreliable for comparison with our series.

In this study, we observed no statistical difference for short-term survival after patient dichotomization at the median MELD score value. However, Onaca *et al.* found only minimal differences in survival rates between patients with a MELD score <15 and those with a score of 15–24 [11]. As expected, the MELD score showed an increasing trend from UNOS status 3 to 2A (Table 4), reaching significance in the comparison of UNOS status 3 with statuses 2B or 2A. Conversely, no significant difference was found between the MELD scores of patients listed in statuses 2B and 2A. On the contrary, in our series

many patients listed at UNOS status 2B were in a sick 2B next to be shifted toward status 2A, as pointed by the prevalence of patients in CTP class C. The κ measured for inter-rate agreement between UNOS status and MELD score after their categorization for clinical urgency showed a fair agreement. The ratio between nonsurvivors and survivors showed a more linear trend in the UNOS statuses than in MELD strata, in particular at 1-year after LT. However, the median MELD score was slightly higher in the nonsurvivors than in the survivors within each MELD stratum but not within each UNOS status (data not shown). The assessment of more reliable MELD strata for patient survival is critical, considering that in the largest series analyzed until at present, the hazard ratio in patients with an MELD score of 11 to 18 was higher than in patients with an MELD score of 19–24 [17], and that survival of patients with an MELD score of 25–29 was worse than that of patients with an MELD score of 30 and higher [11]. In our series, although donor parameters did not affect short-term patient survival (Table 2), we found the tendency for which patients in UNOS status 3 or less sick 2B were matched with donors that showed a relatively suboptimal biochemical and clotting pattern, whereas patients in UNOS status sick 2B or 2A were matched preferentially with optimal donors. This tendency was maintained after patient grouping for MELD strata, suggesting that matching less ill patients with suboptimal donors might negatively counterbalance a low pretransplantation MELD score.

To assess the validity of MELD model in determining short-term mortality in patients and grafts we used the (c)-statistic [7,8,23]. In this series, an increasing area under the ROC curve for MELD score was calculated in predicting patient mortality within the first 3 months after LT, while decreasing values at 6 months and 1 year occurred (Table 5). Conversely, UNOS status showed a slightly better (c)-statistic than MELD model for 1-year patient mortality, confirming the hypothesis that MELD model loses its accuracy the longer the patients are followed [7]. In any case, (c)-statistic did not find any significant difference between UNOS status and MELD score for patient mortality, although the area under ROC curve calculated in the MELD score for 3-month patient mortality reached a major value. Moreover, the (c)-statistic did not find significant differences for post-transplant mortality between UNOS status and MELD model after patient stratification for HCV-related liver diseases or HCC unrelated to HCV (data not shown). Finally, we tested the accuracy of the MELD model also for graft mortality, without finding any significant difference after comparison with UNOS status (Table 5). Considering that in our series the MELD score showed a lower specificity for graft mortality than UNOS status, and that it does not predict survival in living donor liver transplant recipients [12], MELD model might be poorly accurate in predicting graft outcome.

This retrospective study was performed with the aim to assess the potential predictive value of the MELD model for short-term patient and graft mortality in comparison with conventional UNOS status. Our analysis has revealed a linear increase in the MELD score from UNOS status 3 to 2A, although mortality did not increase linearly by arising through the MELD strata, in agreement with larger series [11,17]. In addition, no significant difference for patient or graft survival was observed in UNOS status or MELD strata by intragroup comparison. Moreover, inter-rate comparison between MELD score and UNOS status has revealed a fair agreement for clinical urgency. Finally, the (c)-statistic has found better results in the MELD score than UNOS status concerning short-term patient mortality, but not 1-year patient mortality or graft mortality, and without reaching significance in any comparison. These findings suggest the need of larger studies to implement MELD model-driven allocation process for both inter-rate agreement with UNOS status and patient outcome.

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