Laboratory Test Variability and Model for End-Stage Liver Disease Score Calculation: Effect on Liver Allocation and Proposal for Adjustment

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Background. The use of the Model for End-Stage Liver Disease (MELD) score to prioritize patients on liver waiting lists must take the bias of different laboratories into account.

Methods. We evaluated the outcome of 418 patients listed during 1 year whose MELD score was computed by two laboratories (lab 1 and lab 2). The two labs had different normality ranges for bilirubin (maximal normal value [Vmax]: 1.1 for lab 1 and 1.2 for lab 2) and creatinine (Vmax: 1.2 for lab 1 and 1.4 for lab 2). The outcome during the waiting time was evaluated by considering the liver transplantations and the dropouts, which included deaths on the list, tumor progression, and patients who were too sick.

Results. Although the clinical features of patients were similar between the two laboratories, 36 (13.1%) out of 275 were dropped from the list in lab 1, compared to 5 (3.5%) out of 143 in lab 2 ($P<0.01$). The differences were mainly due to the deaths on the list (8% lab 1 vs. 2.1% lab 2, $P<0.05$). The competing risk analysis confirmed the different risk of dropout between the two labs independently of the MELD score, blood group, and preoperative diagnosis. The bias on MELD calculation was considered and bilirubin and creatinine values were "normalized" to Vmax of lab 1 (corrected value=measured value×Vmax lab 1/Vmax lab 2). By comparing receiver operating characteristic curves, the ability of MELD to predict the 6-month dropouts significantly increased from an area under the curve of 0.703 to 0.716 after "normalization" ($P<0.05$).

Conclusions. Normalization of MELD is a correct and good compromise to avoid systematic bias due to different laboratory methods.

Keywords: Liver transplantation, Allocation, MELD, Waiting list, Dropout.

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The priority for liver transplantation (LT) based on the Model for End-Stage Liver Disease (MELD) score, according to the data from the United States, is the most effective system of reducing the dropouts from the waiting list (*1–8*). The advantages of MELD with respect to Child score (*9*) is due to two factors: 1) the introduction of the measurement of creatinine, which reflects renal function (*10*); and 2) the presence of objective variables, which are not dependent on the physician's evaluation.

The MELD score theoretically avoids subjective variations and appears the best tool to share organs between centers. On the other hand, it has been suggested that systematic variability due to different laboratory methods between liver transplant centers may cause bias on the assessment of the severity of illness (*11*).

We evaluated the impact of different laboratory methods on the dynamics of the waiting list after 1 year of using MELD scores to share livers between two transplant programs (University of Bologna and Modena) located in the Emilia-Romagna Region, Italy.

PATIENTS AND METHODS

Study Design and Patient Population

The study was approved by the local institutional review committee. We prospectively evaluated the outcome of 418 patients with chronic or acute liver disease listed for LT between April 2004 and April 2005 at the Emilia-Romagna Region Transplant Reference, Italy. Organs were shared between two liver transplant programs (University of Bologna and Modena) and blood tests came from the university hospital laboratories (lab 1 and lab 2).

Priority for LT was based on the MELD score, calculated using serum creatinine, serum total bilirubin, and the International Normalized Ratio (INR) according to the formula (*12*) currently in use by the United Network for Organ Sharing (http://www.unos.org), measured at the time of dropout, at liver transplantation, and at the end of the follow-up (*6*). The minimum criteria for listing patients were those reported by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases (*13*).

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Patients with hepatocellular carcinoma (HCC) had a modified MELD score obtained by adding a number of points to the calculated MELD score, taking into account the extent and duration of the HCC. In particular, 3 points were added for T1 plus 0.5 points for each month on the waiting list with a diagnosis of HCC (1 point if alfa-feto protein levels were >200 ng/ml), or 6 points for T2 plus 1 point for each month. Tumor stage T1 was a single HCC with a diameter ≤3 cm, whereas T2 was a single HCC with a diameter between 3 and 5 cm or multiple HCCs no more than 3 with a diameter ≤3 cm. The preoperative criteria of selection for HCC patients, the diagnostic workup, the treatment on the waiting list, and the histological evaluation were widely discussed in our previous studies (*14*, *15*).

Preliminary evaluation of the data at the end of the study period revealed a different rate of dropout between the two transplant centers in the absence of differences in clinical and laboratory data (see below). For this reason, attention was paid to the possible role of systematic differences due to different laboratory methods.

Methods Used to Measure MELD and "Normalized" MELD Scores

The laboratories of the two centers (lab 1 and lab 2) adopted the same thromboplastin reagent for INR determination (Thromborel S, Dade Behring, Marburg) and the same methods for bilirubin (BIL-T, bilirubin DPD) and creatinine (CREA, creatinine Jaffè method, rate-blanked and compensated) both from the same company (Roche Diagnostics GmbH, Mannheim, Germany), the same instruments (Hitachi, Modular) and calibrators (calibrator for automated systems). The two laboratories had different normality ranges: bilirubin maximal normal value (Vmax) was 1.1 mg/dL for Bologna (lab 1) and 1.2 mg/dL for Modena (lab 2); creatinine Vmax was 1.2 mg/dL for lab 1 and 1.4 mg/dL for lab 2. Both laboratories participate in the same external quality evaluation program. The analysis of data related to the last two controls performed in 2004 and 2005 showed good alignment for bilirubin. An overestimation was found in creatinine levels of 11% in lab 2 results with respect to both the mean values of reference samples and to the mean results of lab 1 and was mainly due to the use of a different compensation factor for protein matrix (*16*, *17*). This led to differences in normality ranges, calculated from 2.5–97.5th percentiles of the measured creatinine concentration of reference samples. INR determinations showed no significant systematic differences.

Based on these findings bilirubin and creatinine values were "normalized" to Vmax of lab 1, which had a higher number of listed patients. The "normalized" values were calculated in the following way: measured value×Vmax lab 1/Vmax lab 2, and normalized MELD score recalculated.

Statistical Analysis and Criteria of Analysis

Statistical analyses were performed using Fisher's exact test, the Mann-Whitney test, or the chi-square test, as appropriate. For the analysis of dropout predictors, the approximated MELD score, as used for patient allocation, was considered. The exact numbers, with decimals, were used to calculate median values to describe patients' features.

The follow-up to evaluate the events (liver transplantation, dropout, still on the list) started in April 2004 and finished in April 2005. The dropouts included deaths, removals from the list due to tumor progression, and patients who were too sick.

The waiting time was calculated from the date of listing to the following events: liver transplantation, dropout, and end of follow-up. The MELD score included in the statistical analysis was the score detected at the time of liver transplantation, dropout, and end of follow-up if still on the waiting list.

The competing risk analysis was performed to compare the outcome of patients on the list between the two laboratories, as reported by Kim et al. (*18*). The competing outcomes while on the waiting list for liver transplantation included transplantation and dropouts due to death, withdrawal from the list for tumor progression, or patients who were too sick. Competing risk models were constructed based on the Cox proportional-hazard model, to simultaneously consider the blood group, the etiology, the MELD score, and the patient's laboratories on the risk of dropout during the waiting time.

The concordance statistic (c-statistic), which is the equivalent of the area under the receiver operating characteristic (ROC) curves, was calculated to assess the accuracy of MELD and normalized MELD scores as dropout predictors. The areas under the ROC curves were then statistically compared (*19*, *20*).

Differences were considered significant for P values <0.05. Statistical analysis was carried out with SPSS (SPSS Base 10.0; Application Guide, SPSS Inc., Chicago, IL) and STATA/SE 9.0 software (Stata Corporation, College Station, TX).

RESULTS

Clinical-pathological variables of the recipients on the waiting list were comparable between the two laboratories (Table 1) and the MELD score of patients did not differ: median value for lab 1 was 15.7 (mean 16.9±6.8) versus 15.2 for lab 2 (mean 17.5±7.7; P=NS).

Patient Outcome

During the study period, 108 patients underwent LT and they were equally distributed according to the number of listed patients of each lab: 73 (26.5%) from lab 1 and 35 (24.5%) from lab 2. At the time of liver transplantation the MELD score of patients was comparable between the two laboratories: the median value for lab 1 was 18.6 (mean 19.8±8.1) vs. 20.1 for lab 2 (mean 22.6±9.5; P=NS).

The patients removed from the list due to death or clinical reasons were significantly higher for lab 1 compared to lab 2: 36 cases (13.1%) vs. 5 cases (3.5%) respectively ($P<0.01$; Table 2). Despite this, the MELD scores at the time of dropout were similar: the median value for lab 1 was 18.8 (mean 20.4±9.3) vs. 14.0 for lab 2 (mean 21.9±13.7; P=NS; Table 1). Consequently, the rate of patients still on the list at the end of the study period was significantly higher for lab 2 with respect to lab 1 (72% vs. 60.4%, $P<0.01$).

The different rates of dropout between the two laboratories were mainly due to the different rates of deaths on the list, which were 22 cases (8%) for lab 1 compared to 3 cases (2.1%) for lab 2 ($P<0.05$; Table 2).

The competing risk analysis confirmed the different risk of dropout on the list between the two laboratories, as reported in Figure 1A and B. With the Cox proportional-

TABLE 1. Clinicopathological variables of the patients listed

Variable	Total	Lab 1	Lab 2	*P* value
n	418	275 (65.8%)	143 (34.2%)	
Male	297 (71.1%)	197 (71.6%)	100 (69.9%)	NS
Age, mean years	52.3±10	52.6±9.8	51.9±10.3	NS
Median years	54.3	54.4	54.2	
Blood group				
A	153 (36.6%)	101 (36.7%)	52 (36.4%)	NS
O	201 (48.1%)	132 (48%)	69 (48.3%)	
B	50 (12%)	33 (12%)	17 (11.9%)	
AB	14 (3.3%)	9 (3.3%)	5 (3.5%)	
Preoperative diagnosis				
HCC	120 (28.7%)	74 (26.9%)	46 (32.2%)	NS
Postnecrotic	182 (43.5%)	113 (41.1%)	69 (48.3%)	
Acute liver failure	4 (1%)	2 (0.7%)	2 (1.4%)	
Re-OLT	12 (2.9%)	4 (2.8%)	8 (2.9%)	
Alcoholic	50 (12%)	39 (14.2%)	11 (7.7%)	
Other	50 (12%)	39 (14.2%)	11 (7.7%)	
MELD score				
All cases, median	15.5 (6–46)	15.7 (6–46)	15.2 (6–42)	NS
All cases, mean	17.1±7.1	16.9±6.8	17.5±7.7	
Transplanted, median	19.1 (7–43)	18.6 (7–43)	20.1 (8–42)	NS
Transplanted, mean	20.7±8.7	19.8±8.1	22.6±9.5	
Removed from the list, median	18.3 (6–46)	18.8 (6–46)	14.0 (11–42)	NS
Removed from the list, mean	20.5±9.7	20.4±9.3	21.9±13.7	
Still on the list, median	14.4 (6–40)	14.3 (7–28)	14.6 (6–40)	NS
Still on the list, mean	15.1±4.8	14.9±4.4	15.5±5.5	

TABLE 2. Outcome of patients listed

Variable	Total	Lab 1	Lab 2	*P* value
n	418	275 (65.8%)	143 (34.2%)	
Transplanted	108 (25.8%)	73 (26.5%)	35 (24.5%)	NS
Still on the list	269 (64.4%)	166 (60.4%)	103 (72%)	<0.05
Removed from the list	41 (9.8%)	36 (13.1%)	5 (3.5%)	<0.01
Died on the list	25 (6%)	22 (8%)	3 (2.1%)	<0.05
Too sick	9 (2.2%)	8 (2.9%)	1 (0.7%)	NS
Tumor progression	7 (1.6%)	6 (2.2%)	1 (0.7%)	NS

hazard model, lab 2 showed a lower risk of drop-out on the list compared to lab 1, while adjusting for the MELD score, the blood group, and the preoperative diagnosis (Table 3).

Dropout Rate According to MELD and "Normalized" MELD Scores

As expected, due to the rules of MELD calculation, normalization had no effect when bilirubin was <1 mg/dL and creatinine was >4 mg/dL. After normalization, the median MELD score of patient listed by lab 2 dropped from 15.2 to 14.6.

On the whole, 90 (62.9%) out of 143 patients from lab 2 had an overestimated MELD score and the impact on the waiting list of 418 patients (lab 1 plus lab 2) was 2 points in 45 cases (10.8%) and 1 point in 45 (10.8%). As expected, the effect of laboratory test variability was more frequent in sick patients at the very top of the list. Among the 113 patients (72 from lab 1 and 41 from lab 2) with MELD scores ≥20, a total of 28 cases (24.8%) had an overestimated MELD score by 2 points and 8 cases (7.1%) by 1 point.

Overestimated MELD values were differently distributed among patients who had LT and those who dropped out: 27 (25%) out of the 108 transplanted cases had "undue" MELD points (2 of 17 and 1 of 10 patients), whereas only 3 (7.3%) of 41 dropouts had 1 undue additional point ($P<0.05$).

Considering all patients, by comparing ROC curves, the ability of MELD scores to predict the overall dropouts significantly increased from an area under the curve (AUC) of 0.605 to 0.622 after normalization of creatinine and bilirubin values ($P<0.005$), as reported in Figure 2. The results were

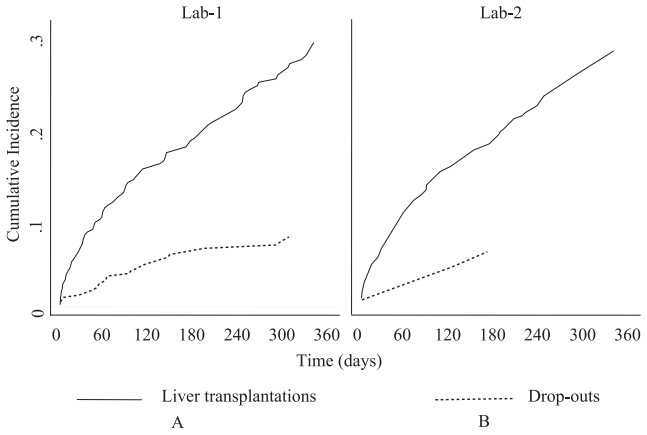

FIGURE 1. Cumulative incidence curves comparing risk of dropout by laboratory. The difference in the risk of dropout (dotted line) during the waiting time was significantly lower for lab 2 (B) compared to lab 1 (A; $P<0.001$).

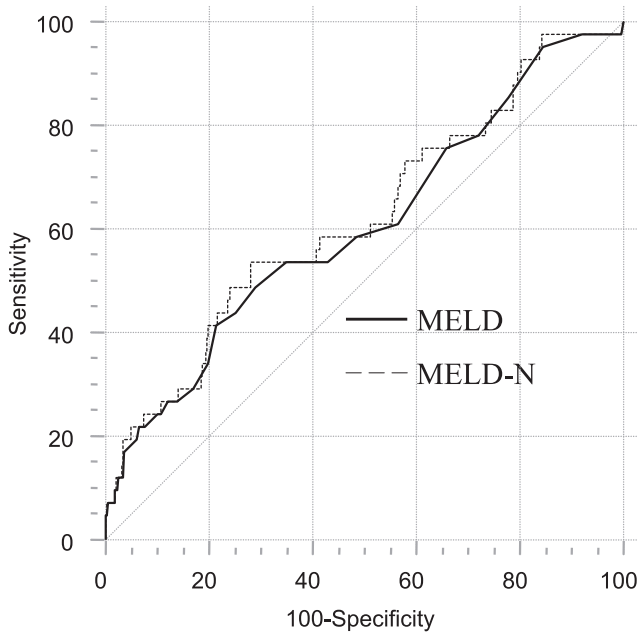

FIGURE 2. ROC curve analysis on the ability of MELD score and "normalized" MELD (MELD-N) score to predict dropouts.

confirmed when the dropout rate at 6 months on the waiting list was evaluated; the AUC was 0.703 for the MELD scores and 0.716 for the modified MELD scores ($P<0.05$; Fig. 3). To avoid any bias related to possible different causes of dropout (death, too sick, and tumor progression) and to the preoperative diagnosis of HCC, the ROC curves were also performed considering only the deaths on the list and excluding the cases with HCC.

The results showed the same tendency previously reported: the modified MELD score gave a better prediction of the deaths on the list with or without HCC (AUC of 0.722 and 0.721) than the MELD score (AUC of 0.709 for both; $P<0.05$ for each comparison).

Effect on Patients at the End of the Period

On April 1, 2005, 269 patients were still on the waiting list. Considering patients regardless of their blood group, 60 had a lowered MELD score: 2 points in 28 cases (10.4%) and 1 point in 32 (11.9%). Among these patients, the median MELD score decreased from 18.1 to 16.3 after normalization. As previously reported, the overestimated MELD points were more relevant among the 43 patients with MELD scores ≥20: 2 points in 15 cases (34.9%) and 1 point in 3 cases (7%).

DISCUSSION

In an ideal health care system, it would be advisable for different laboratories to adopt methods and instruments to examine blood samples yielding the same numerical results for the same samples, thus abolishing interlab variations. Currently, each laboratory defines a specific normality range for each blood test based on a local "normal" population sample. If population samples are similar, different normality ranges usually reflect different methods. This means that a single patient with a creatinine level equal to the upper normal range value of 1.2 in one laboratory is expected, when tested by a different laboratory having, for example, a maximal normal value of 1.4, to display a value of 1.4. This has little clinical relevance for the physician who knows that both results are within the normal range but it does have a great impact on MELD calculation (1 to 2 points). This bias is well known in hepatology for liver enzyme evaluation or immunoglobulins levels, which are often expressed in scores not as numbers but as multiples of the upper normal range (*21*), merely to avoid laboratory range variability. The same could apply to creatinine and bilirubin levels when used to calculate MELD score.

The present study confirms the significant bias in the calculation of the MELD score by different laboratories reported previously by Trotter (*11*). We also show that this statistical bias may affect patient outcome and we suggest that normalization of bilirubin and creatinine values from different laboratories with different normal values to a unique upper normal laboratory value increased the accuracy in predicting dropout in our series.

TABLE 3. Multivariate analysis examining the effect of the laboratory on the risk of dropout during the waiting time, while adjusting for the blood group, the preoperative diagnosis, and the MELD score

Variables	Hazard ratio	SE	*P* value	95% CI
Lab 1 vs. Lab 2	2.327	0.462	<0.001	1.578–3.433
Preoperative diagnosis	—	—	NS	—
Blood group	—	—	NS	—
MELD score	3.604	1.154	<0.001	1.923–6.751

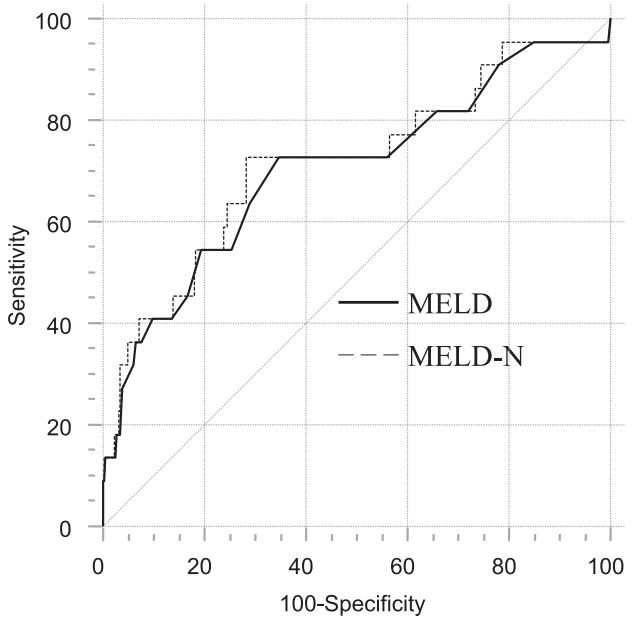

FIGURE 3. ROC curve analysis on the ability of MELD score and "normalized" MELD (MELD-N) score to predict the dropout rate at 6 months on the waiting list.

Since April 2004, the Emilia-Romagna Region Transplant Reference, Italy, has applied the MELD score to prioritize patients of two transplant centers (University of Bologna and Modena) on a single waiting list for liver transplantation.

After 1 year, we noted a significant difference in dropouts between recipients from the two liver transplant programs, which calculate the MELD score adopting data from two different laboratories. This difference was present, despite the clinical-pathological features between the two laboratories being comparable, such as the MELD scores calculated at the time of liver transplantation, at dropout, and at the end of follow-up (Table 1).

The differences in dropouts between the two laboratories were mainly due to the deaths on the list, excluding any confounding factors, such as tumor progression in HCC patients or a "too sick" condition (Table 2). Furthermore, the competing risk analysis and the Cox proportional-hazard model confirmed the different risk of dropout on the list between the two laboratories, independently of the MELD score, the blood group, and the preoperative diagnosis (Fig. 1A and B, Table 3).

We suspect that the different methods of measuring bilirubin and creatinine level could have an effect on the rate of removals from the list due to death. Bilirubin and creatinine values were therefore normalized to the maximal normal value of lab 1 (with the higher number of listed patients) and the MELD score was recalculated. According to this processing, a number of patients from lab 2 had a MELD value possibly overestimated by 1 or 2 points, thus receiving liver transplantation "in advance" and dropping out from the list less frequently. This possibility was supported by the ROC analysis, which showed an improved accuracy in predicting dropouts with the normalized MELD with respect to the original score (Fig. 2). The data was also confirmed considering the deaths on the list and excluding cases with HCC from the analysis. This was expected since in our setting laboratory MELD values were the main component of the final MELD score of HCC patients.

The expression of prothrombin time as INR reached high standardization between different methods in monitoring anticoagulant treatment in patients with healthy livers. This is not the case in liver patients displaying a more complex coagulation deficiency. Our study did not analyze the differences in the MELD score attributed to the differences in the INR, reported as the principal bias by Trotter et al. (*11*), because the same thromboplastin reagent was used in both laboratories and systematic differences were not observed in reference samples and were not expected in liver patient samples. Nevertheless, multicenter control quality analysis using listed patient samples, including INR determination, is needed to optimize MELD reliability.

In addition, our study considered only 1 year of experience and, as reported by other authors (*22*), a longer follow-up may show a different transplant benefit for some categories of MELD score. On the other hand, this problem is common among the studies on the MELD system, which is a recent allocation system, particularly in Europe (*23*).

Our data suggest that laboratory dependent variability has also to be taken into consideration when comparing outcomes based on pretransplant MELD scores and suggest that normalization to a single upper normal value has to be considered an appropriate procedure to avoid systematic errors due to "false" high or low bilirubin and creatinine values, when blood tests are performed in different laboratories. This is clearly a compromise solution with respect to standardizing the labs to each other by using standard calibration, but it might represent a readily available improvement of MELD efficacy, without additional costs, in multicentric settings.

Even if it cannot be definitely proven that laboratory differences were the sole cause of different dropout rates at the two centers, corrected MELD scores worked better and we thus concluded that laboratory variability could have a role in our setting, and we adopted a readily available compromise solution. The policy to normalize bilirubin and creatinine values obtained in laboratories with different upper normal values was adopted by the Emilia-Romagna Region Transplant Reference on July 1, 2005 as a temporary solution, waiting for the results of a prospective quality control study, including INR and using reference patient samples.

Applying this modified MELD score since July 1, 2005, we observed a redistribution of dropouts between the two laboratories, which in the following 6 months had a comparable rate of deaths on the list, as reported in the 6-month interim analysis by the Emilia-Romagna Region Transplant Reference (report of the activity in the year 2005, data not reported in the manuscript).

In conclusion, the normalization of MELD score is a simple procedure to improve the MELD calculation and subsequently the allocation process, possibly reducing unequal dropouts among patients having blood tests in different laboratories. A multicenter study would be advisable to confirm this suggestion.

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