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A new score to predict outcome after liver transplantation

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ABSTRACT

Background: An ideal liver allocation system should reduce waitlist mortality and also improve post-transplant survival. Aim: To identify a new scoring system that predicts recipient survival at 3 months following liver transplantation (LT) in the Romanian program.
Methods: We included into analysis 242 adult patients (183 patients within the training set and 59 in the validation cohort) with liver cirrhosis consecutively transplanted between January 2012 and June 2014.
Results: Post-transplant overall survival was 84.2% at 3 months. Independent risk factors for survival following LT were: recipient age >53 years (p=0.01), serum albumin <2.7g/dl (p=0.02), diabetes mellitus (p=0.14), hyponatremia <130mmol/L, presence of non-malignant portal vein thrombosis (p=0.01), retransplantation (p=0.0005) and donor resuscitation following cardiac arrest (p=0.03). AUROC of RoSOFT score is 0.86 in both training and validation set. Diagnostic accuracy of RoSOFT for predicting 3 months mortality is 89.6%. Recipients with HCC outside Milan criteria had a significantly lower MELD score at LT compared to patients inside Milan (p=0.008) and received a higher proportion of marginal organs (p=0.005), but survival did not differ (p=0.47).
Conclusions: Combined recipient and donor risk factors can accurately predict 3-months survival following LT in our National LT Program and can be used to improve donor-recipient matching.
Key words: liver transplantation, marginal donor, MELD, outcome, scoring system

INTRODUCTION AND AIM

The MELD (Model for End Stage Liver Disease) based scoring system revolved the allocation policy for liver transplantation (LT) in United States since 2002 [1] and in Eurotransplant since 2006 [2]. Although MELD eliminates subjective assessments and has shown accuracy for outcome prediction in patients with decompensated cirrhosis, it has several limitations, especially the lack of prediction of post-transplant survival [3-5]. MELD score is also not sensitive for all liver diseases as there are already well established MELD exceptions in all liver transplant (LT) Programs. There are extensive published analyses indicating no significant differences in survival between various MELD score categories [6, 7].

However, since the introduction of MELD-based allocation there are several reports of impaired postoperative survival in Germany. A single center analysis showed a 3 months post-LT survival of only 79.6% in the 2 years after MELD introduction compared to 88.6% before MELD era (p=0.03) [8]. Another German multicenter analysis showed a 1 year survival rate of only 53% in the group of high MELD recipients (≥30) [9]. The introduction of MELD score for organ prioritization in the USA has not reduced the short-term survival of patients after LT, but patients with MELD score of 30 or higher had a relatively poor outcome [10].

It was suggested that a liver benefit score, a score that is donor and recipient specific and is computed as the difference between 5-year predicted post-transplant lifetime and 5-year predicted future waiting list lifetime, would change substantially the ordering of the waitlisted patients [5]. When mortality of recipients on the waitlist is compared with the highest and the lowest MELD scores, there is a 300-fold difference, in contrast to the 2-fold difference in survival of patients after LT [11]. Survival after LT must be greater than survival on the waitlist to justify LT. Taking into account these considerations, the first model to fully consider the effect of graft selection, recipient factors and operative impact (18 risk factors) have been developed by Rana A et al [12] and was shown to accurately predict 3 months survival following LT. Recently, Rana A. devised also a scoring system that predicts 3 months recipient survival after pediatric liver transplantation with a c-statistic of 0.74 and includes 5 factors [13]. German authors found that certain pre-LT variables such as age, pre-LT creatinine and cholinesterase (SALT score) are predictors of short-term post-LT survival and may be helpful as a bedside score in pre-LT clinical management, outcome prediction and decision-making [14].

Given the particularities of our transplant program with cirrhotic patients showing a lower average MELD score at LT than abroad (mean MELD = 17.7 ± 3.5), the already demonstrated/published new risk scores proving a better prediction of mortality on the waiting list compared to MELD score [15], the high number of patients with hepatocellular carcinoma on the waiting list [16], the significant increase of the deceased grafts in the last 2 years, and a significant proportion of extended criteria donors, we aimed to identify a new scoring system that predicts recipient survival at 3 months following liver transplantation in the National Romanian Liver Transplant program. A better prediction of outcome would improve preoperative patient selection and management.

METHODS

Study population

We performed a retrospective analysis of all consecutive adult (≥ 18 years old) recipients of LT performed in Fundeni Clinical Institute between 1st January 2012 and 1st June 2014. Donor and recipients data were collected at the time of transplant. Follow-up information was collected at 3 and 12 months after transplantation. All patients were followed from the date of transplant until either death or the date of last known follow-up. We analyzed 242 recipients divided in 2 groups: 183 patients transplanted between 1st January 2012 and 31st December 2013 (training group used to determine the score predicting survival after LT) and 59 patients transplanted between 1st January 2014 and 1st June 2014 (validation group).

The MELD score was calculated using serum creatinine, bilirubin and the International Normalized (Prothrombin) Ratio (INR) [17] according to the following formula currently in use by UNOS [18]: MELD score = [9.57 x loge creatinine mg/dl + 3.78 x loge bilirubin mg/dl + 11.20 x loge INR + 6.43]. For each recipient also MELD-Na score and Donor-MELD score were calculated according to the following formulas: MELD-Na score = MELD Score - Na - 0.025*MELD*(140-Na) + 140 (where the serum sodium concentration is bound between 125 and 140 mmol/L) [19]. Donor-MELD (D-MELD) score is composed of donor age x MELD score [20].

Patients with malignancy were known to have hepatocellular carcinoma (HCC) prior to transplantation and did not reflect incidentally discovered cancer at time of transplantation. Marginal livers are used extensively in our liver transplant center especially for patients with HCC. Eurotransplant "marginal donor" is considered any donor for whom one of the following criteria apply: donor age >65 years, ICU stay with ventilation >7 days, BMI >30kg/m², steatotic liver >40%, serum sodium >165mmoL/L, serum ALT >105IU/L, serum AST >90IU/L, serum bilirubin >3mg/dL [21]. In addition, we included also grafts from anti-HBc positive donors as marginal. No donors with cardiac death were included in this cohort, as well as no donors with positive HBs antigen or anti-HCV antibodies.

This study complies with the standards of Declaration of Helsinki and current ethical guidelines. All patient signed a dedicated inform consent at inclusion on WL for LT and at the moment of transplant.

Statistical analysis

Continuous variables were reported as a mean ± standard deviation. Comparisons between training and

validation groups were made by chi-squared-test or Fisher's exact test (two-tailed) for qualitative variables; Mann–Whitney test was performed for quantitative variables. Results were considered significant at a p-value of <0.05. All reported p-values were two sided. The primary outcome measure was patient death. Time to death was assessed as time from the date of LT to the date of death. Kaplan-Meier analysis with log-rank test was used for time-to-event analysis. Logistic regression analysis determined the predictors of patient death at 3 months post-transplantation. Variables found to be significant in univariate analysis were then subject to multivariate analysis. We formulated a score to predict 3 months survival outcomes following LT (RoSOFT= Romanian survival outcome following transplantation) that includes both donor and recipient factors to evaluate the short-time outcome at the time of transplantation. Model discrimination was assessed using the area under the receiver operating characteristic (ROC) curve. A c-statistic (area under the curve) 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. Data were analyzed using SPSS 15 software.

RESULTS

The recipients and donor factors included in the analysis are summarized in *tables 1 (A and B)* and *2 (A and B)*. There was no statistical differences regarding the characteristics of the recipients in the training and validation groups. In the donor groups, there was a

Table IA - Demographic characteristics of recipients in the training (n=183) and validation set (n=59)

	Training set	Validation set	P value
Age (years)	50.8 ± 10.2	49.9 ± 12.5	0.59
% Female gender	41.5%	32.2%	0.26
BMI>30kg/m^2	15.3%	22.0%	0.31
Malnutrition	22.9%	30.5%	0.31
Diabetes mellitus	24.5%	22.0%	0.82
INR	2.6 ± 1.1	1.5 ± 0.4	0.55
Creatinine (mg/dL)	0.9 ± 0.3	0.9 ± 0.3	0.95
Na (mmol/L)	136.1 ± 5.8	137.0 ± 5.2	0.32
Total bilirubin (mg/dL)	5.3 ± 0.5	7.3 ± 1.1	0.08
Thrombocytes/mm^3	76158.4 ± 52556.8	91491.5 ± 69057.0	0.12
Serum albumin (g/dL)	3.0 ± 0.5	2.9 ± 0.4	0.3
Cholesterol (mg/dL)	97.1 ± 39.5	114.0 ± 65.5	0.06
MELD score	16.9 ± 5.5	16.5 ± 5.8	0.65
MELD-Na score	19.1 ± 6.0	18.3 ± 6.0	0.36
Donor-MELD score	718.6 ± 353.5	734.9 ± 389.2	0.76

Table IB - Demographic characteristics of recipients in the training (n=183) and validation set (n=59)

	Training set	Validation set	P value
HCV related liver cirrhosis	27.3%	28.8%	0.95
HBV related liver cirrhosis	15.8%	13.5%	0.82
HBV/HDV related liver cirrhosis	30.0%	20.3%	0.19
Alcoholic related liver cirrhosis	17.4%	23.7%	0.38
Autoimmune related liver cirrhosis	2.2%	6.8%	0.19
Acute liver failure	3.8%	0%	0.28
Refractory ascites	38.2%	27.1%	0.16
Spontaneous bacterial peritonitis	16.9%	13.5%	0.68
Hepatocellular carcinoma	28.4%	28.8%	0.91
HCC – within Milan	63.4%	52.9%	0.62
TACE pre-LT	34.6%	58.8%	0.13
Upper digestive bleeding	21.3%	30.5%	0.20
Hepatic encephalopathy	40.9%	38.9%	0.90
Hepato-renal syndrome	20.2%	11.8%	0.21
Severe hyponatremia <130 mmol/L	44.8%	37.2%	0.38
Portal vein thrombosis	10.3%	10.1%	0.84

Table IIA - Demographic characteristics of donors in the training (n=183) and validation set (n=59)

	Training set	Validation set	P value
Age (years)	42.2 ± 15.2	44.5 ± 14.4	0.31
% Female Gender	39.9%	28.8%	0.16
Donor-recipient gender mismatch	54.1%	40.6%	0.10
BMI>30kg/m^2	8.2%	8.4%	0.87
Creatinine (mg/dL)	1.2 ± 0.8	1.2 ± 0.6	0.80
ALT (IU/L)	60.7 ± 8.9	58.6 ± 10.3	0.91
AST (IU/L)	77.8 ± 8.6	82.9 ± 10.9	0.77
Na (mmol/L)	148.5 ± 9.9	145.9 ± 10.1	0.15
Total bilirubin (mg/dL)	0.9 ± 0.8	0.7 ± 0.4	0.25
Hemoglobin (g/dL)	11.7 ± 2.3	11.6 ± 2.2	0.78
LDH (IU/L)	591.9 ± 531.9	618.0 ± 305.2	0.82

Table IIB - Demographic characteristics of donors in the training (n=183) and validation set (n=59)

	Training set	Validation set	P value
Living donor	15.8%	3.4%	0.02
Cause of death	27.4%	36%	0.31
Trauma	3.8%	8%	0.39
Ischemic CVA	39.8%	40%	0.87
Hemorrhagic CVA	13.2%	9.1%	0.56
Anoxia			
Hypotensive periods	9.8%	4.8%	0.49
Resuscitation following cardiac arrest	9.8%	15.2%	0.36
Marginal donor	33.8%	32.2%	0.74

significantly lower number of living donors in the validation group compared to the training group. No other donor characteristic differed in the 2 groups.

Survival following LT in the training group

Overall patient survival following LT was 84.2% at 3 months and 79.2% at 12 months (*figure 1*). Median survival was not reached. The mean follow-up interval was 12.6 months. Three months survival following LT, according to MELD categories were as follow: 82.4% for a MELD score <17 at LT, 88.4% for a MELD score between 17 and 25 and 75% for a MELD score >25 (log rank test p value = 0.71). When consider patients with HCC, overall 3 months and respectively 12 months survival did not differ compared to patients without HCC (log rank test p value = 0.38). Patients with HCC matching Milan criteria had a 3 and 12 months survival of 90.6% and 87.9% respectively in comparison to patients with HCC outside Milan criteria with a survival of 85.2% and 80.8% (p=0.74). MELD score at LT was significantly lower in patients with HCC outside Milan criteria compared to patients inside Milan (14.6 ± 3.9 vs 17.1 ± 5.1, p=0.008). Other significant differences between patients with HCC outside and inside Milan criteria were: higher percentage of male recipients (80.7% vs 53.4%, p=0.04) and higher proportion of marginal grafts (65.4% vs 27.9%, p=0.005) used in patients beyond Milan. Living related liver transplantations were performed in 23.2% of patients with HCC inside Milan criteria compared to 3.8% of patients with HCC outside Milan (p=0.07). Older donor age reached only marginal level of significance in the subgroup of patients with HCC outside Milan (47.8 ± 16.4 years vs

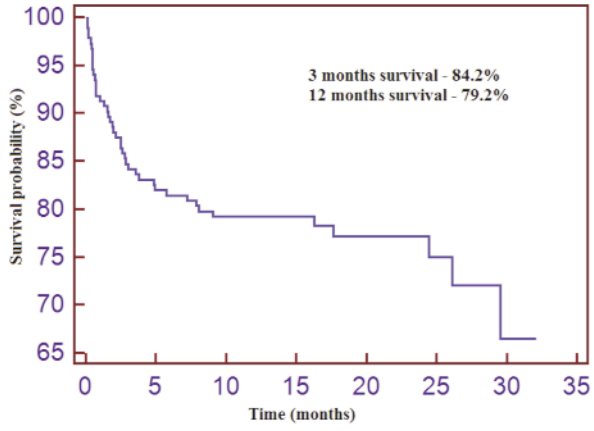

Figure 1 - Kaplan –Meier curve for overall survival following LT in the training set (n=183 patients)

40.7 ± 13.9 years, p=0.06). However, although D-MELD score as slightly higher in the group with HCC outside Milan, statistical significance was not reached (640.6 ± 64.6 vs 591.7 ± 56.6, p=0.58).

There was no difference regarding bridging therapies such as trans-arterial chemoembolization before LT between patients within vs outside Milan (p = 0.97). Patients with HCC receiving marginal livers had a similar 3 months survival compared to patients with HCC receiving good grafts (78.3% vs 89.7%, p = 0.42).

Univariate and multivariate analysis

Tables 1(A/B) and 2 (A/B) list all risk factors that were considered for univariate analysis in the training group. The following recipient-related risk factors have been shown to be significant in univariate analysis for predicting 3 months mortality after LT: serum albumin <2.7 g/dL at LT (OR = 3.20, 95%CI = 1.38-7.39, p = 0.006), serum creatinine >0.9 mg/dL at LT (OR = 2.92, 95%CI = 1.24-6.87, p = 0.01), recipient diabetes mellitus (OR = 4.00, 95%CI = 1.72-9.25, p = 0.001), pre-LT severe hyponatremia <130mmol/L (OR=4.62, 95%CI = 1.85-11.53, p = 0.001), recipient age >53 years old (OR = 2.56, 95%CI = 1.09-6.02, p = 0.03), malnutrition (OR = 3.12, 95%CI = 1.33-7.29, p = 0.008), presence of non-malignant portal vein thrombosis at LT (OR = 2.97, 95%CI = 1.02-8.65, p = 0.03), re-transplantation (one previous LT) (OR=25.66, 95%CI = 2.75-59.45, p = 0.004) and only one donor factor – donor resuscitation following cardiac arrest (OR = 3.25, 95%CI = 1.10-9.55, p = 0.03). The independent risk factors identified in the multivariate analysis are presented in *table 3*. Value of MELD score at LT was not identified as a predictor of 3 months post-LT survival.

Risk score (RoSOFT)

The independent predictors of death at 3 months after LT have been included in a logistic regression equation in order to develop a new prognostic score. The following new risk score (RoSOFT) for short-term death after LT was calculated as following:

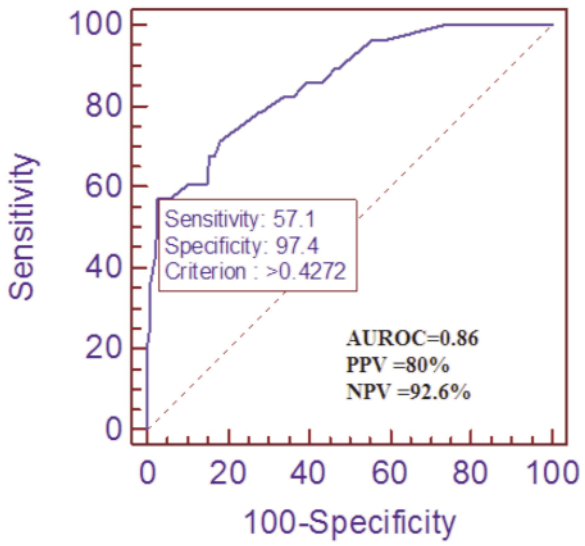

Figure 2 - Receiver operating characteristic curve for the new predictive score of short-term death after LT (training set)

RoSOFT score = 1/ (1 + EXP {- [-5 + (1.32 x (serum albumin <2.7g/dL)) + (0.77 x recipient diabetes mellitus) + (1.77 x (serum Na<130mmol/L)) + (4.53 x re-transplantation) + (1.68 x portal vein thrombosis) + (1.46 x (recipient age >53years)) + (1.47 x donor resuscitated cardiac arrest)]}).

This model includes values between 0 and 1 and comprises each variable as a categorical parameter. The area under the receiver operating characteristic curve for this model was 0.86 (*figure 2*). A cut-off value of 0.42 for the new score had a sensitivity of 57.1%, a specificity of 97.4%, a positive predictive value (PPV) of 80%, a negative predictive value (NPV) of 92.6% and a diagnostic accuracy of 89.6% for predicting 3 months death following LT. This new score was validated on a cohort of 59 recipients, obtaining the same AUROC curve of 0.86 for predicting 3 months death after LT (*figure 3*).

MELD score, MELD-Na score, D-MELD at LT and new RoSOFT score were investigated as predictors of death at 3 months after LT based on the c-statistic (ROC curve).

Table 3 - Significant adjusted risk factors for predicting 3 months mortality after LT in multivariate logistic regression analysis

Variable	Odds ratio	95%CI	P
LT serum albumin <2.7 g/dL	3.77	1.23 - 11.59	0.0202
Recipient diabetes mellitus	2.17	0.76 - 6.17	0.1461
Pre-LT severe hyponatremia <130 mmol/L	5.87	1.90 - 18.06	0.0020
Retransplantation	93.15	7.37 - 1177.42	0.0005
Presence of non-malignant portal vein thrombosis at LT	5.40	1.38 - 21.07	0.0150
Recipient age >53 years	4.32	1.32 - 14.16	0.0154
Donor resuscitation following cardiac arrest	4.36	1.07 - 17.72	0.0390

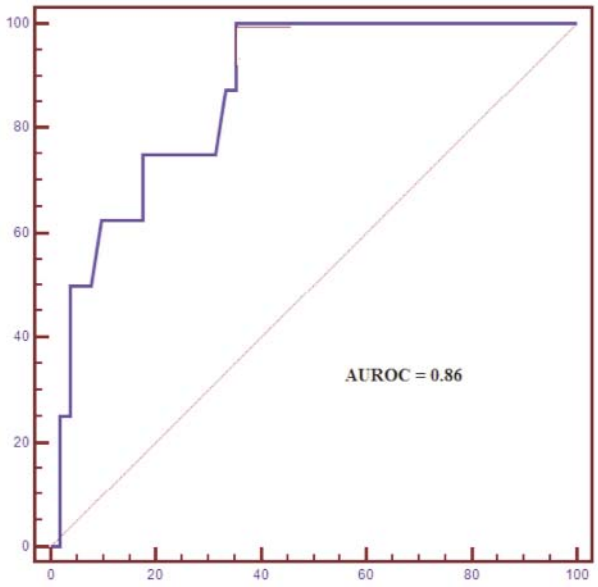

Figure 3 - Receiver operating characteristic curve for the new predictive score of short-term death after LT (validation set)

RoSOFT score with a c-statistic of 0.86 was found to be an excellent tool to predict 3 months mortality after LT, while MELD (AUROC=0.50), MELD-Na (AUROC=0.53) and D-MELD (AUROC=0.51) scores had no clinical usefullness in predicting short term death after LT ($p<0.0001$).

DISCUSSION

There are some particularities regarding the Romanian National Program that should be emphasized: one single liver transplant center up to 2014 (Fundeni Clinical Institute) with no regional allocation; marked increase in the number of donors in the last 2 years, particularly marginal donors; increasing number of patients with HCC on the waiting list for LT and also HCV-related end-stage liver disease, as mentioned in previous papers by our group [16, 22], similar to Western Europe; reduced number of living donors willing to donate due to the popularization of the increasing availability of deceased donors; significant reduction of wait list mortality after 2008; no score available in our country for evaluating the outcomes after LT taking into account the transplant survival benefit, considering that there is an increase of the recipients age/ HCC and HCV for which no new antivirals are available yet in Romania.

It is to note that a second LT Center opened in 2014 is located also in Bucharest and supports only a small number of procedures per year (10-15 out of >120 LT) performed under the supervision of the Chief of the Transplant Surgery Center from Fundeni Clinical Institute. That is why National Waiting List is unique under the coordination of the Chief of the Hepatology Department from Fundeni Clinical Institute. The current allocation policy in Romania is based on the decision of a Board Committee including a Surgeon, a Transplant Hepatologist and an Anesthesiologist that decide the best recipient based on the combination of factors: MELD/MELD-sodium scores, points given for complications that are underweighted by MELD score (hepatic encephalopathy, refractory ascites, hepatorenal syndrome), hepatocellular carcinoma (HCC), other MELD exceptions (eg. Hepatic polycystic disease, Budd Chiari syndrome, recurrent cholangitis), gender and weight matching between donor and recipient, donor age (young donors preferred for HCV etiology). In this way, patients within the same MELD category can be prioritized according to a worse prognosis given by associated cirrhosis complications or comorbidities.

Short-term (3 months) survival rates after LT in Romania are similar to other countries (88.6-79.6% in Germany [14] or 87.2% in Eurotransplant experience [23]). MELD score alone did not prove a good predictive value for short-term death on our waiting list [15] and this was true also for death after LT as demonstrated in the present study. This is in accordance to other previous articles demonstrating that MELD score is a poor predictor of 3 months mortality after LT (AUROC=0.54) [24]. On the contrary, same authors [24] found that a model based on four pretransplant variables (recipient age, mechanical ventilation, dialysis, and retransplantation) had a better ability to predict outcome compared to MELD score. As mentioned above, SALT score designed by German authors [14], including also only recipient pre-LT factors, identified a high risk and a low risk group for 12 months death after LT. Factors related only to donors, such as those incorporated in donor risk index (DRI) developed by Feng et al [25] showed also a poor predictive value with AUROC of 0.53. The newer Eurotransplant DRI created by Braat et al [26] showed a higher predictive value (AUROC=0.62) for outcome prediction after LT. SOFT score (Survival outcome following liver transplantation) was the first to implement both donor, surgical and recipient pre-LT factors in outcome prediction after LT [12]. Our group [27] already indicated in 2010 that the original SOFT score had a good clinical utility (AUROC=0.73) for predicting mortality after LT in our Transplant Program compared to MELD score (AUROC=0.50). Another recent study [28] indicated that all scores (SOFT score, pre-transplant-SOFT score, SALT score and labMELD score ≥30) are unable to discriminate short-term survivors from non-survivors in a

collective of high-risk LT recipients in order to guide clinical decision making in the current German transplant situation with decreasing numbers of deceased liver donors, decreasing donor organ quality and increasingly sick transplant candidates.

A score for predicting LT outcome adapted to Romanian allocation policy and strategy with single center allocation and a cold ischemia time that is in 90% of cases <6 hours, was warranted. The newly developed RoSOFT score includes mainly recipient variables and only one donor factor. Although, in a recent review [29], survival rates of kidneys, livers, hearts and intestines retrieved from donors brain dead after being resuscitated from cardiac arrest were not significantly different from that of organs transplanted from that of patients and organs retrieved from donors brain dead not due to cardiac arrest, in our study this impacted short term patient survival. Hypoperfusion of the liver during cardiac arrest may assign the graft within the extended criteria livers and thus affecting short term graft outcome.

Recipient age, low albumin level at LT, presence of portal vein thrombosis and a previous liver transplant negatively impact short term survival after LT, similar to American SOFT score [12].

Pre-transplant hyponatremia is associated with an altered LT survival benefit in our study and the same was recently proven by Sharma P et al. [30]. The LT survival benefit increased significantly with decreasing serum sodium values when the MELD scores were >11 [30]. Our study showed a significant association between MELD score >11 and serum sodium <130mmol/L ($p<0.0001$, data not shown).

Pre-LT presence of diabetes mellitus lowers post-transplant survival in our analysis similar to a recent report by Wong [31]. Another recent paper proved as single independent predictors of recipient mortality, presence of pre-transplant and developing of post-transplant diabetes. Also donor's history of diabetes was independently associated with higher mortality and an increased the risk of liver graft failure [22, 32]. Obesity is reported with different conflicting results as a negative factor for post-transplant survival [31, 33], however malnutrition is for sure a negative prognostic factor due to the increased mortality rate through sepsis [34, 35].

In concordance to US, Europe, and Brazil, there was an increased percentage of patients with HCC on the waitlist and a shorter time to LT for patients with HCC, although they had a rather low MELD score at LT after 2008 [16, 22, 36, 37]. In our previous paper [16], in patients with HCC outside Milan criteria there were used more marginal grafts between 2008 and 2011 (11.2%) compared to 2% before 2008. In the years 2012-2014, with the greatest increase in the number of brain dead donors, the number of marginal grafts also increased up to 32.2-33.8% in the present paper. This figure is lower compared to Eurotransplant area where more than 50% of the transplanted organs had deficiencies corresponding to at least one extended donor criteria (between years 2003-2007) [38]. In Germany, 30% of the transplanted organs in 2011 already fulfilled extended donor criteria status only based on donor age irrespective of further medical details [39]. In Romania, advanced donor age is not yet the major problem as shown in present paper (D-MELD score has no major impact on survival), other criteria being of importance for defining marginal grafts. This can be still an advantage for our Program, having the possibility to choose young donors for HCV infected recipients. However, there are contradictory results regarding the use of these grafts and of MELD allocation system in relation to the short-time survival after LT (Italy/Switzerland vs Germany) [8, 40, 41]. Analysis of US data showed a significantly higher mortality in lower-MELD recipients matched with high-risk donor grafts, whereas all recipients with MELD ≥ 20 had a significant benefit from transplantation even when receiving high-risk donor grafts [42]. In our Center, the policy is to allocate marginal livers to HCC recipients that have usually low MED scores and survival on the waiting list is impacted by the progression of the tumor especially in patients beyond Milan criteria. Allocation of a marginal liver did not affect overall short-term patient survival in the present cohort as well as reported by an American center [43]. There are studies [44, 45] showing that patients with HCC within or outside Milan receiving extended criteria donors have good 3 and 5 years survival rates (79% and respectively 74%). However, the risk- benefit ratio in these instances should be evaluated on a case-by-case basis as it is in our Board that decide each recipient for each available graft.

As a strength of our study, we consider the validation of the new RoSOFT score in an independent cohort of LT recipients. Whereas one drawback of our study is that RoSOFT score was not validated also on the National Waiting List as predictor of 3 months mortality, but is the object of a new ongoing study.

Prognostic models that evaluate both mortality on waiting list and post-LT survival and include both recipient and donor factors are currently not used and should be developed, validated and further introduced in order to better allocate the available low number of organs and to achieve the best patient survival after LT. In countries with a scarcity of organs, where more and

more donors have extended criteria, marginal livers should be used in HCC recipients where risk of drop out, especially in patients outside Milan, overweight the risk of a decreased post-LT survival due to graft dysfunction. MELD score is not predictive of post-LT outcome and should not be the only criteria considered when a liver graft is allocated to a certain recipient. Continuous adaptation of the allocation system in countries like US, Eurotransplant or countries with a single Center LT Program is imperative and will remain a challenge.

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