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Balancing donor and recipient risk factors in liver transplantation: the value of D-MELD with particular reference to HCV recipients.

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(Article begins on next page)

Title page

Title:

Balancing donor and recipient risk factors in liver transplantation. *The value of D-MELD* with particular reference to HCV recipients in Italy.

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ABSTRACT

Donor-recipient match is a matter of debate in liver transplantation. D-MELD (donor age x recipient biochemical MELD) and other factors were analyzed on a national Italian database recording 5946 liver transplants. Primary endpoint was to determine factors predictive of 3-year patient survival. D-MELD cutoff predictive of 5 year patient survival <50% (5rPS<50%) was investigated. A prognosis calculator was implemented (www.D-MELD.com). Differences among D-MELD deciles allowed their regrouping into three D-MELD classes (A <338, B 338-1628, C >1628). At 3 years, the odds ratio (OR) for death was 2.03 (95% confidence interval, [CI], 1.44-2.85) in D-MELD class C versus B. The OR was 0.40 (95%CI 0.24-0.66) in class A versus B. Other predictors were HCV (OR=1.42; 95%CI 1.11-1.81), HBV (OR=0.69; 95%CI 0.51-0.93), re-transplant (OR=1.82; 95%CI 1.16-2.87) and low-volume Center (OR=1.48; 95%CI 1.11-1.99). Cox regressions up to 90 months confirmed results. The hazard ratio (HR) was 1.97 (95%CI 1.59-2.43) for D-MELD class C versus B and 0.42 (95%CI 0.29-0.60) for D-MELD class A versus B. Recipient age, HCV, HBV, re-transplant were also significant. The 5yrPS<50% cutoff was identified only in HCV patients (D-MELD≥1750). The innovative approach offered by D-MELD and covariates is helpful in predicting outcome after liver transplantation, especially in HCV recipients.

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INTRODUCTION

Donor-recipient match is a matter of debate in liver transplantation.⁽¹⁻³⁾ The combination of donor-related and recipient-related risk factors may offer a new therapeutic strategy with important effects on survival. The variability in donor organ quality and in recipient liver disease severity explains the various types of match adopted.^(4,5) Although the match or mis-match is sometimes purely the result of chance, in most cases surgeons and hepatologists can take the opportunity to combine organ and recipient on the basis of specific risk assessment methods, and/or to respect general principles (sickest first, maximization of resources, utility).

Optimization of donor-recipient match is the ultimate goal for improving liver transplant results. Its importance was reported in a small clinical series in 2005⁽²⁾, and confirmed one year later in larger series.^(3,5) Models able to predict 3-month and 12-month mortality from donor and recipient parameters have been developed on the European ELTR database (1988-2003).⁽⁶⁾ However, the hypothesis that donor-recipient match may have an even greater intrinsic prognostic role than that of donor organ quality or severity of the recipient disease, has recently been supported by the introduction of the D-MELD formula .⁽⁷⁾ D-MELD, the arithmetical product of donor age and Model for End-stage Liver Disease (MELD) score⁽⁷⁾, was developed on the American UNOS-STAR database (2003-2006) to combine donor-related and recipient-related risks; it has not yet been investigated in Europe.

In Italy donor and recipient characteristics show several peculiarities. Donor age is higher than in the United States^(3,7,9,10) or elsewhere in Europe.^(6,11,12) Unlike in major north American studies,^(1,6,9,13,14) we used donor age instead of the Donor Risk Index (DRI)⁽¹⁰⁾ to represent donor quality, because DRI is not applicable to the Italian donor population owing to the Caucasian ethnicity, absence of donation after cardiac death (DCD), higher prevalence of stroke death, limited sharing area and better outcome of split grafts.⁽¹⁵⁾ Finally, in Italy HCC patients undergoing liver transplantation commonly show a lower degree of liver function decompensation as compared with HCV candidates.⁽¹⁶⁾

Primary endpoint of the present study was to derive prognostic models according to donorrecipient match in relation to 3-year patient survival, median follow-up being 36 months. Secondary endpoints were to derive prognostic models of: a) patient survival at 90 days and 1 year; b) graft survival at 90 days, 1 and 3 years; c) overall patient and graft survivals. As additional research D-MELD was investigated in terms of possible *survival cutoffs*, according to the principle that transplants with 5-year patient survival <50% (5yrPS<50%) should not be performed, so as to avoid organ wasting⁽¹⁷⁾.

PATIENTS and METHODS

Study population

A database was filled with records of liver transplants performed in Italy from July 1st 2002 to December 31^{st} 2009, merging data prospectively collected by 21 Centers for clinical purposes and outcome analyses. All donors were heart beating white Caucasians. Very few grafts (N=6, 0.1%) were harvested abroad. Of the initial 5946 consecutive records, 5265 were included in the study after the exclusion of pediatric cases, split, living donor and multiorgan transplants (Figure 1). Organ allocation and donor-recipient match of second and third transplants were not analyzed but the *re-transplant* status was included as an independent factor for the outcome of the first match.

Among the variables stored in each Center database, the following were selected on the basis of evidence from previous major studies evaluating donor and recipient prognostic factors: donor age, gender, Hepatitis B anti-core (HBcAb) status, recipient age, gender, etiology of liver disease, concomitant etiologies, previous abdominal surgery, pre-transplant patency of portal vein, renal failure

American Journal of Transplantation

(at least 1 dialysis during the week before transplantation), biochemical MELD score at transplant, cold ischemia time (CIT), dates of listing, transplant, re-transplant, death, last follow-up, reason for failure, and cause of death. Calculated data were D-MELD, donor-recipient gender match, donor-recipient gender concordance, listing months, patient survival, graft survival.

The outcome was expressed as patient and graft survival. Follow-up ranged from 7 to 90 months (median, 36.5 months). Because donor age, MELD score at transplant and match policies were subject to change over time, the study period was subdivided into different biennia (2002-2003, 2004-2005, 2006-2007, 2008-2009). Centers were classified in terciles as low volume (<100 transplants per biennium, N=11); medium volume (100-149 transplants, N=6); high volume (≥150 transplants, N=4). The biennium and the Center volume were included in models as dummy variables. Donor-recipient match modalities were not codified by rules. Organ allocation was MELD-oriented. Strictly for allocation purposes, stage-2 HCC patients were recoded as MELD 22 unless their biochemical MELD was higher. Since the study aimed to evaluate the effect on prognosis of impaired liver function and of its systemic effects, the biochemical MELD was utilized for the D-MELD calculation, without adding any further points. The HCC status was evaluated as a dichotomic variable.

Statistical analysis

Validity and completeness of data were first verified by data managers at transplant Centers. A subsequent audit process was performed at the coordinating Center. All records were checked (progressive number, ranges, consistency control for dates and multiple choice classification for death causes and failure reasons)⁽¹⁹⁾ and pending cases were solved by data managers. Donor age, MELD, recipient etiology, time of transplant and Center name are required fields in the patient listing process, and utilized for organ allocation. All records were then considered correctly filled. In accordance with

the guidelines for the identification and validation of prognostic models in liver transplantation, only parameters with at least 80% of data available were included in the analyses. Definitions were those routinely used in the national listing process. No interpolation to manage missing data was performed. An exploratory analysis in the whole study population was performed, plotting patient death against donor age, MELD and D-MELD to generate cumulative logistic probability plots, as proposed by Halldorson et al.⁽⁷⁾

According to Thuluvath et al.⁽²⁰⁾ and in conformity with statistical guidelines in organ transplantation,^(21,22) the overall dataset was randomly split into a training set (2/3 of the records), utilized to generate the main model, and a validation set (1/3). D-MELD was first investigated as a continuous variable able to predict outcome, then a D-MELD categorical model was developed. For this purpose, donor age, MELD and D-MELD were stratified into 10 decile groups.⁽²³⁾ To distinguish between low-extreme, intermediate and high-extreme D-MELD cases, Mantel-Cox and Breslow tests were applied to Kaplan-Meier analyses to assess the differences between deciles. Three D-MELD classes were identified in the training set and the derived cutoffs were confirmed in the validation set. Regrouping was therefore done, reclassifying D-MELD decile 1 as class A (D-MELD<338), D-MELD deciles 2-9 as class B (D-MELD 338-1628), and D-MELD decile 10 as class C (D-MELD >1628). D-MELD class B was used as reference for subsequent regression analyses.

Potential prognostic factors were studied in both sets by univariate analysis. Chi square and Mann-Whitney tests were used to study significant factors for survival at fixed times. Mantel-Cox test was used for survival curves. The prediction of mortality and failure was subsequently verified by binary logistics using fixed times, and by Cox regression statistics using the overall follow-up. All variables with a p-value <0.25 at univariate analyses entered the models. The results were expressed as Odds Ratios (OR) and Hazard Ratios (HR) with 95% confidence intervals (95%CI). Statistical evaluation of the model was also performed in order to avoid variable co-linearity. Adequacy of fit for

American Journal of Transplantation

both sets was investigated using C-statistics and Hosmer-Lemeshow tests.⁽²⁴⁾

According to the hypothesis that the discrimination power of D-MELD class C should apply even at high and extremely high values of donor age or MELD, all cases were split at the high (upper quartile) and extremely high (upper decile) values of both donor age and MELD. Kaplan-Meier subanalyses were then performed according to the D-MELD 1628 limit.

The significance level was set at p=0.05. Statistical analyses were performed with JMP ver. 9.0 and SPSS ver. 18.0.

A website was implemented with a prognosis calculator on the basis of D-MELD and covariates values (www.D-MELD.com, password: "D-MELD123").

RESULTS

Preliminary logistic probability analysis

Logistic probability plots confirmed the association of donor age, MELD, D-MELD with a progressively decreasing probability of survival. The strongest prognostic power was obtained by D-MELD (steeper curve, Figure 2).

Stratification in deciles and in classes

Overall median values for donor age, biochemical MELD, D-MELD were 57 (min 12, max

97), 15 (6-40) and 790 (66-3240), respectively. Donor age increased through the study period, leading

to a parallel increase in D-MELD until the 2006-2007 biennium (Figure S1).

Stratification of cases was performed according to D-MELD deciles and classes in terms of patient (Figure 3A-B) and graft survival (Figure 3C-D). Significant differences were found solely

between decile 1 versus deciles 2 to 10 and between deciles 1 to 9 versus decile 10 (Table S1). Patient characteristics in the three D-MELD classes are summarized in Table 1.

D-MELD stratified outcome better than either donor age or MELD alone (Figure 3 and Table S2). The prevalence of the two extreme match-modalities varied according to the Center volume (Figure 4). At higher volume Centers there was a shift towards a lower prevalence of low D-MELD and higher prevalence of high D-MELD classes. The effect was even stronger in non-HCC recipients.

Primary endpoint and related prognostic factors

Significant factors identified at univariate analyses (data not shown) were included in the logistic models to address the primary endpoint. At 3 years, the strongest predictor of death in terms of OR was D-MELD. Cases in D-MELD class C had an OR equal to 2.03 (95%CI 1.44-2.85) as compared to class B cases (Table 2). Conversely, cases in D-MELD class A had an OR equal to 0.40 (95%CI 0.24-0.66). Other significant predictive factors for death were HCV status (OR=1.42; 95%CI 1.11-1.81), and low-volume transplant Center (OR=1.48; 95%CI 1.11-1.99). Recipient age and re-transplant status resulted predictive in the training set only (OR=1.015; 95%CI 1.002-1.028 and OR=1.82; 95%CI 1.16-2.87, respectively). HBV status was predictive of a favorable outcome (OR=0.69; 95%CI 0.51-0.93) in the training set only. The continuous D-MELD model is reported in detail at the bottom of table 2.

Secondary endpoints and additional analyses

In terms of *risk of death* at 90 days, the OR was 2.65 (95%CI 1.81-3.89) in D-MELD class C versus class B (Table 2) and reached 2.32 (95%CI 1.68-3.21) at 1 year. Conversely, the OR at 90 days was 0.46 (95%CI 0.24-0.86) in D-MELD class A and reached 0.43 (95%CI 0.26-0.72) at 1 year.

In terms of risk of failure at 90 days, the OR was 2.16 (95%CI 1.54-3.03) in D-MELD class C

American Journal of Transplantation

versus class B (Table 2) and reached 2.05 (95%CI 1.52-2.77) at 1 year and 1.92 (95%CI 1.39-2.67) at 3 years. At 90 days, the OR was 0.41 (95%CI 0.24-0.72) in D-MELD class A; OR was 0.41 (95%CI 0.26-0.66) at 1 year and 0.42 (95%CI 0.27-0.67) at 3 years.

Cox regression models (Tables 2 and 3) confirmed the predictivity, in terms of overall mortality and failure, of D-MELD, HCV status, HBV status and re-transplant status in both sets (Table 3). Recipient age resulted significant in both sets in terms of mortality but only in the validation set in terms of failure. A low-volume Center was predictive of mortality in the training set only. See Table 3 for the continuous D-MELD model.

Hosmer-Lemeshow and C-statistics confirmed the adequacy of the logistics and Cox models in both sets (Tables 2-3, Table S4).

Stratification according to specific high-risk classes

At Kaplan-Meier survival analyses, stratification according to high (\geq 68, upper quartile) and extremely-high (\geq 75, upper decile) donor age and to high (\geq 21, upper quartile) and extremely-high (\geq 28, upper decile) MELD showed that D-MELD class C values (>1628, 10th decile) were predictive of poorer survival both in the overall population and in the high and extremely-high risk cases. Focusing on high and extremely-high cases for both donor age and MELD, D-MELD class C had worse survival than intermediate plus low-risk classes (B plus A, Figure S2).

To explore potential clinical applications of D-MELD we searched for specific patients subgroups with a 5yrPS<50% predictable by D-MELD. The cutoff value predicting the 5yrPS<50% was identified in HCV patients only (D-MELD≥1750, Figure 5). The identification of a D-MELD cutoff in any other situation was precluded by the smaller number of cases with other etiologies and conditions, together with their better outcome.

DISCUSSION

Our study was performed on a national basis over an 8-year period. The wide spectrum of donor age and MELD makes the study population an ideal "match laboratory" because the variability in both donor quality and recipient disease severity facilitated the development of algorithms able to stratify the risk. We primarily evaluated D-MELD as a continuous variable according to Halldorson et al.⁽⁷⁾ and then stratified data in D-MELD deciles, obtaining a graphic representation of outcome in terms of graft and patient survival. The categorical approach, stratifying survival in deciles, was almost progressive, spanning a broader interval than previously reported.^(6,7,10,25) D-MELD predicted the outcome through the whole database and it maintained its prognostic power throughout the followup, with an intrinsically good performance at high and extremely-high values of donor age and MELD. In addition, although the arithmetical nature of D-MELD strengthens the weight of donor age and MELD particularly when both values are high, D-MELD remained predictive even at low values. According to the D-MELD approach, candidates previously judged as risky because of an extremelyhigh MELD showed a down-leveling of the risk when matched to a young donor (e.g. MELD=40, donor age=20->D-MELD=800) and likewise elderly grafts previously judged as risky because of an extremely-high donor age showed a down-leveling of the risk when a graft characterized by an extremely-high donor age was matched to a low-MELD candidate (e.g., donor age=80, MELD=10->D-MELD=800). On this basis, the prospective, intentional adoption of the D-MELD approach could prove beneficial in balancing donor and recipient risk factors. Further evidence to support this concept is derived from DCD studies showing an enhanced survival effect of donor quality.^(32,33) Patients with a low biochemical MELD could better sustain a complicated postoperative course after grafting with a high-risk organ but, from a justice perspective, we must ask ourselves whether and why it is fair to expect them to bear the extra risk of a complicated postoperative course.

Using logistic and Cox regression statistics, we identified additional independent determinants

Page 13 of 65

American Journal of Transplantation

of outcome according to different time endpoints: recipient age, HCV, HBV, pre-transplant portal thrombosis, re-transplant, biennium of transplantation and Center volume. As recently reported,⁽²⁶⁾ portal thrombosis resulted significant on 90-day and 1-year graft survival only and the effect of recipient age was significant on 1-year patient survival only. The outcome was impaired in cases of a high D-MELD combined with an old recipient, and even more so in an old recipient with portal thrombosis. As shown by other Authors, HCV typically entails an additional risk, while HBV has a protective effect, and the effect of the primary disease is generally more evident in the long run.^(11,13,27,28) However, the prognostic power of HCV, portal thrombosis and recipient age was less strong than that of D-MELD even if their role was relevant in cases with a D-MELD value close to the identified limit of 1628. We failed to demonstrate a prognostic effect of pre-transplant abdominal surgery, gender match, gender concordance, CIT, and HBcAb-positivity, although these factors were found significant by other Authors.^(6,9,13,19,29-31) Due to the peculiar donor characteristics, extreme attention was paid to keeping the CIT as short as possible. Moreover, the improvement in the D-MELD model we obtained with the introduction of other significant covariates did not reduce the power of D-MELD itself, whose major strength lies in its immediacy of calculation.

The high prevalence of HCC represents a peculiarity of our study population. Nevertheless, HCC was not recognized as an independent determinant of outcome. This is probably due to the fact that the majority of patients complied with Milan criteria, a condition that keeps down the risk of recurrence.^(16,34) Due to the common combination between cirrhosis and HCC, in our database we cannot differentiate patients *listed for* HCC from those *listed with* HCC. In D-MELD class B, which accounts for 80% of cases, donor age and MELD were matched at different levels of risk, while in D-MELD class C, donor age and MELD were matched at the corresponding level (young-donor to low-MELD and old-donor to high-MELD, respectively). This explains the low number of HCC patients in D-MELD class C, in which all patients, including those with HCC, were

Page 14 of 65

transplanted for decompensated cirrhosis.

Although our study design set the primary endpoint at 3 years, the peculiarity of the HCV population allowed Kaplan-Meier sub-analyses to be performed in order to identify the 5yrPS<50% cutoff. The concept of the 5yrPS<50% threshold was introduced in 1999 to avoid organ wasting^(17,35,36). A similar metric was also utilized when exploring an extension of Milan criteria for HCC.⁽³⁸⁾ However, in both approaches, the 50% value and its 5 year time-limit were arbitrarily set. As yet, stratification in relation to the 5yrPS<50% cutoff has not been done using a single quantitative parameter.^(38,39) Nor have different percentages and time-limits been identified according to etiology. In the present study HCV and HBV had a predictive role in several prognostic models. Since HBV patients had a more favorable outcome, the 5yrPS<50% cutoff could not be identified among them. Instead, we identified 7% of HCV patients (3% of all transplants) exceeding the cutoff. This is probably due to the fact that a strong contributing factor to the worse prognosis of HCV recipients is the negative effect of donor age, as repeatedly reported.^(11,28) In summary, while the D-MELD 1628 limit predicted poor prognosis in the overall dataset, an even poorer prognosis was predicted by the 5yrPS<50% cutoff (D-MELD≥1750) in HCV patients.

Using the 5yrPS<50% cutoff could be misleading since it is not evidence-based. However, it identifies a sub-group of HCV patients with a performance status below the currently defined minimal survival requirements. The 5yrPS equal to 50%, indeed, should be read as the minimal sustainable survival rate considering the competition within the waiting list for the same given graft: this is a potential operative limit depending on the characteristics of both donor and listing populations. It is well fitted to the Italian population in which organ shortage is critical. Organ availability is inevitably a key point. Assuming the same high D-MELD value, an organ from an elderly donor is likely to fail in an HCV but not in an HBV recipient. This depicts the shift from the 5yrPS<50% *transplant cutoff* towards a novel concept: the "*unsustainable match cutoff*". We should note that the recent

American Journal of Transplantation

introduction of the survival benefit approach is radically changing the modality of result reporting after liver transplantation. After stratification for MELD, this model was designed to quantify the survival gain between undergoing transplantation and staying on medical care.⁽⁴⁰⁾ The model denies a transplant to patients with a low biochemical MELD and absence of HCC nodules. We believe that the approach we suggest does not conflict with the clinical application of 2nd generation survival benefit models, that are eagerly awaited. They include MELD components, *survival with* and *without transplant*, donor age, recipient age, primary disease and other determinants of outcome.^(41,42,43) This type of modeling could better link prognosis to resource availability and be strictly tailored to different populations according to their donor and recipient characteristics. Hopefully, the next survival benefit studies will offer final answers to the problem of match in patients with low biochemical MELD.

While the effect of the biennium during the 8-year study period was not relevant there was, as expected,^(6,44,45) a predictive effect of low volume Center on 3-year mortality at logistic regressions. Interestingly, in terms of graft failure, the difference was not significant. It could be hypothesized that access to elective re-transplantation might be limited in some low-volume Centers. However, we should note that the larger the Center volume, the higher the prevalence of high D-MELD classes. This finding, that is more evident in non-HCC patients, implies that, in general, high and medium volume Centers do a bit better with high-risk match combinations.

There were three main reasons why we developed the prognosis calculator. Firstly, to provide a direct example of how donor and recipient factors interact in determining prognosis. Secondly, to help hepatologists, transplant surgeons and transplant coordinators in the everyday practice of matching donor and recipient factors when choosing the recipient. Lastly, to allow researchers from other countries to perform an external validation.

Some differences with respect to the American D-MELD study⁽⁷⁾ need to be highlighted. Firstly, the methodology adopted in our study (a larger number of factors evaluated, time-based endpoints, training set and validation set, decile method, logistic regressions) is coherent with the guidelines for statistical analysis in organ transplantation.^(21,22) Secondly, the data collection period, minimum and median follow-up are nearly twice as long. Nevertheless, our cutoff exceeds the American one by only 28 units, quite a small difference considering the older donor age and the higher prevalence of HCV in the study population. Moreover, our model identifies three match combinations with a potential clinical applicability. The 1628 limit has an obvious implication in capping the risk of death⁽⁷⁾, and the 338 limit identifies a pool of organs which could theoretically be reserved for the sickest patients. Finally, the identification of other predictive factors and the definition of the 5yrPS<50% cutoff in HCV recipients enrich our model.

Our study suffers from several limitations. Although based on prospectively filled Centerspecific databases, our analysis remains retrospective like all other large prognostic studies. Secondly, the high number of patients harboring HCC may represent a selection bias. That means that coefficients, analyses and conclusions obtained in this Italian study may not be directly applicable to countries with different donor and recipient populations. Thirdly, the intentional use of the D-MELD approach will narrow the donor pool for the sickest candidates who are in the greatest need of transplantation, while widening the donor pool for less ill candidates. We are aware that because few patients exceeded the D-MELD 1628 limit, and even fewer HCV patients exceeded the 5yrPS<50% cutoff, a meaningful evaluation of the accuracy of this approach could be performed only on huge continental databases. We are also in need of more complex models in HCV patients transplanted with HCC and in those transplanted for HCC, in whom neither the severity of liver disease nor its prognosis are correctly quantified by MELD. In this setting the outcome could be more strictly related to other factors (stage, time on list, bridging procedure, surgical or medical treatment of recurrences).

In conclusion, D-MELD, a simple numerical expression of the donor-recipient match, remains the main determinant of graft and patient survival after liver transplantation. The use of D-MELD and

covariates can support the intentional balancing of risk factors, limiting high risk donor-recipient matches especially when the primary disease is HCV cirrhosis.

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DISCLOSURE

All the authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Figure 1. Enrolment and outcomes through month 60.

[At_the_bottom_of_Figure_1_(Enrolment_and_outcomes)]

*Patients with acute liver failure (ALF) were included. MELD exception points for patients with hepatocellular carcinoma (HCC) were not considered. Patients with MELD scores >40 (N=62, 1.2%) were reclassified as MELD 40.

^{\sim}Exclusions were performed to avoid confusion with categorical variables characterized by a low number of cases. Although the match was not considered in cases of second transplants (N=270, 4.5%) and of third transplants (N=2, 0.04%), analysis was made of the follow-up of all patients (patient survival), including follow-up after re-transplant.

§Main indications for transplantation were reclassified according to Roberts.(18) Since in Italy there are fewer patients with primary sclerosing cholangitis and patients with primary biliary cirrhosis than in Northern Europe or in the United States, both categories (N=191, 3.6%) are included in the 'OTHER' group. Since the prevalence of concomitant etiologies was >20%, HCC, HCV, HBV status and/or alcohol abuse were treated in subsequent analyses as dichotomic variables.

\$Causes of failure/death were reclassified according to Adam.(19)

Figure 2. Performance of (A) donor age, (B) MELD, (C) D-MELD in the prediction of patient survival. All 3 curves are significant (p<0.0001). The D-MELD curve is steeper.

Figure 3. Stratification of D-MELD deciles (A-C) and of D-MELD classes (B-D) in terms of patient and graft survivals.

Figure 4. Prevalences of D-MELD class A and D-MELD class C in HCC and non-HCC patients according to the transplant volume of the Center (p<0.001). Variability of D-MELD reflects different policies concerning donor age limit and severity of recipient liver disease, in relation to different match modalities.

Figure 5. D-MELD cutoff identifying a population characterized by 5-year patient survival <50% (5yrPS<50%) among HCV positive patients (including those with HCC). The cutoff (unsustainable match cutoff) was identified at D-MELD value 1750 in the training set (5-year patient survival=44.2%, 95% CI 0.32-0.50), and validated in the validation set (5-year patient survival=43.7%, 95% CI 0.28-0.49, data not shown). Being aware of potential implications, we built the model keeping the upper limit of the confidence interval below 50% at 5 years in both sets.(PLEASE LEAVE THE ITALIC TYPING)

Figure S1. Histograms of donor age, MELD, and D-MELD according to the 4 study biennia. For each box the median values and the prevalences according to their upper quartile and to their upper decile are reported.

Figure S2. Overall patient survival for recipients (A) by donor age ≥ 68 (upper quartile), (B) by donor age ≥ 75 (upper decile), (C) by MELD ≥ 21 (upper quartile), and (D) by MELD ≥ 28 (upper decile). Subanalyses of patient survival for recipients (a) by donor age ≥ 68 (upper quartile), (b) by donor age ≥ 75 (upper decile), (c) by MELD ≥ 21 (upper quartile), and (d) by MELD ≥ 28 (upper decile) according to the extremely high D-MELD class (C vs A+B).

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Whole	Model	Test

X-Model	-LogKikelihood	DF	ChiSq	Prob>ChiSq
Difference Donor Age	26.9855	1	53.9710	<.0001
Difference MELD	26.3366	1	52.6732	<.0001
Difference D-MELD	46.8161	1	93.6323	<.0001

Figure 2







Figure 5



T.I.I. 1. D.	Am	erican Journal of Tra	nsplantation	
Table I. Descrij	ptive statistics accord	mg to the D-MELD	class in the	training set.

	D-MELD	D-MELD	D-MELD	p-value
	Class A	Class B	Class C	
	(<338)	(338-1628)	(>1628)	
	N=332	N=2621	N=328	
D-MELD (N=3281; 100.0%)	250.0±60.3	834.3±325.7	2089.7±397.3	<0.001*
MELD (N=3281; 100.0%)	11.5 ± 4.3	16.1±6.2	30.5 ± 5.8	<0.001*
MELD in HCC+ (N=1380; 42.1%)	10.1±5.2	13.7±5.5	28.1±5.2	<0.001*
MELD in HCV+ (N=1570; 47.9%)	11.8±4.0	15.6±5.7	29.5±5.4	<0.001*
MELD in HCV+ HCC+ (N=789;24.1%)	10.5±3.2	13.9±5.3	27.5±4.8	<0.001*
MELD in HCV+ HCC- (N=781; 23.8%)	13.7±4.3	17.5±5.9	30.6±5.4	<0.001*
Recipient age (N=3260; 99.3%)	50.3±11.2	53.5±9.1	49.7±10.5	<0.001*
Recipient gender (N=3203; 97.6%)				
- Male	239 (74.0)	1976 (77.2)	224 (69.6)	<0.001
HCV status (N=3281; 100.0%)				
- Positive	138 (41.6)	1287 (49.1)	146 (44.5)	0.016
HBV status (N=3281; 100.0%)		~ /		
- Positive	85 (25.6)	670 (25.5)	76 (23.2)	0.643
Alcohol status (N=3281; 100.0%)	× /	× /	× /	
- Positive	48 (14.5)	494 (18.8)	45 (13.7)	0.017
Acute liver failure status (N=3281: 100.04	%)	- (-0.0)	- (••)	- · • — •
- Positive	3 (0.9)	41 (1.6)	37 (13.3)	<0.001
HCC (N=3281: 100.0%)		- ()	(10.0)	
- Positive	156 (47.0)	1151 (43.9)	76 (23.2)	<0.001
Pre-Tx abdominal surgery (N=2600.79.5	5%)			
- Yes	58 (21.6)	365 (18.8)	40 (16.5)	0.331
Dialysis (N=2546: 77.6%)		200 (10:0)		
- Yes	0(0,0)	8 (0.4)	9(36)	<0.001
Pre-Tx portal thrombosis $(N=2814\cdot 857)$	%)	0 (0,1)	> (0.0)	
- Yes	14 (5 0)	172 (7 7)	29 (10 1)	<0.001
Listing months $(N=3038\cdot 92.5\%)$	8 2+8 6	7 7+8 2	5 9+8 5	< 0.001*
Re-transplant $(N=3281 \cdot 100.0\%)$	0.2-0.0	,,,,.0.2	5.7-0.5	10001
- Yes	10 (3 0)	127 (4.8)	21(64)	0.125
Donor age $(N-3281 \cdot 100.0\%)$	24 3+10 1	54 6+16 3	69 3+10 0	<0.0123
Donor gender (N=3107.07.4%)	∠ ¬,J±10,1	57.0110.5	07.3±10.0	N0.001
- Male	230 (71.2)	1416 (55 5)	163 (50.8)	<0.001
Donor HBcAb (N=2070, 02.5%)	230 (71.2)	1+10 (33.3)	103 (30.0)	~0.001
- Vec	3/(11/4)	<i>A</i> 10 (16 7)	50 (18 7)	0 003
- 100 Donor-Recipient conder match (N-2100.	3+ (11.4) 07.2%)	410 (10.7)	37 (10.7)	0.003
- Female - Female	38 (11 8)	355 (12.0)	57 (17.8)	
- remain / remain	JO (11.0) 55 (17.0)	555 (15.9) 782 (20 7)	$\frac{31}{(11.0)}$	
- remain / Wale Mole - Econole	33(17.0)	103 (30.1)	74 (31.3) 11 (12 9)	
- $Male \rightarrow Felliale$	40 (14.2) 184 (57.0)	224 (0.0)	41(12.8) 122(27.0)	∠ ∩ ∩∩1
- widt 7 widt	104 (37.0)	1191 (40.0)	122 (37.9)	<0.001
Voc	N=319/; 9/.4%)	1517 (60 6)	170 (55 9)	0 002
- Its Cold Isohomia Time? At 2705, 02, 470	222 (08.7)	134/ (00.0)	1/9 (33.8)	U.UUJ 0.042*
Conditional fille $(N=2/05; 82.4\%)$	0.2±2.1	9.1±3.3	0.9±2.7	0.043*
DIEITITUITI (N=3281; 100.0%)	((10.0))	242 (12 1)	22(0.0)	
- 2002-2003	00 (19.9) 70 (22.0)	545 (13.1) 712 (27.2)	52 (9.8) 97 (9.6)	
- 2004-2005	79 (23.8) 06 (20.0)	/13 (27.2)	8/(26.5)	
- 2006-2007	96 (28.9)	/81 (29.8)	114 (34.7)	0.00-
- 2008-2009	91 (27.4)	786 (29.9)	95 (29.0)	0.005
Volume of the centre (N=3281; 100.0%)				
- Low	144 (43.4)	882 (33.7)	60 (18.3)	
- Medium	99 (29.8)	839 (32.0)	113 (34.5)	
- High	89 (26.8)	900 (34.3)	155 (47.3)	<0.001

Means and Standard Deviations are reported for continuous variables; absolute and relative frequencies are reported for categorical ones. *Kruskal-Wallis test; all the other p-values were setained or Chisusporter 34 964 4100

Page 31 of 65

American Journal of Transplantation

Table 2. Predictive factors of mortality and graft failure at 90 days. 1 and 3 years by Logistic Regression in the training set.

	morta	ulity at 90 days			mortality at 1 ye	ar	m	ortality at 3 yea	ars	gra	ft failure at 90 d	ays	gı	aft failure at 1 y	ear	gra	ft failure at 3 ye	ears
D-MELD ^{\$}	OR	(95% CI)	р	OR	(95% CI)	р	OR	(95% CI)	р	OR	(95% CI)	р	OR	(95% CI)	р	OR	(95% CI)	р
Class A vs B Class C vs B	0.46 2.65	(0.24-0.86) (1.81-3.89)	0.015 <0.001	0.43 2.32	(0.26-0.72) (1.68-3.21)	0.001 <0.001	0.40 2.03	(0.24-0.66) (1.44-2.85)	<0.001 <0.001	0.41 2.16	(0.24-0.72) (1.54-3.03)	0.002 <0.001	0.41 2.05	(0.26-0.66) (1.52-2.77)	<0.001 <0.001	0.42 1.92	(0.27-0.67) (1.39-2.67)	<0.001 <0.001
Recipient age	1.013	(0.997-1.029)	0.099	1.018	(1.005-1.031)	0.008	1.015	(1.002-1.028)	0.024*	1.007	(0.993-1.020)	0.32	1.01	(0.999-1.022)	0.079	1.008	(0.996- 1.020)	0.181
HCV status Positive vs negative	0.98	(0.72-1.33)	0.887	1.16	(0.90-1.48)	0.249	1.42	(1.11-1.81)	0.006	0.99	(0.77-1.29)	0.966	1.13	(0.91-1.41)	0.275	1.42	(1.12-1.79)	0.004*
HBV status Positive vs		((,	
negative	0.89	(0.62-1.26)	0.503	0.72	(0.53-0.96)	0.027	0.69	(0.51-0.93)	0.015*	0.86	(0.64-1.16)	0.328°	0.72	(0.55-0.94)	0.014	0.72	(0.54-0.95)	0.019
Pre-tx portal throm Yes vs no	oosis 1.9	(1.21-2.96)	0.005*	1.43	(0.97-2.11)	0.07	1.46	(0.97-2.20)	0.071	1.85	(1.26-2.71)	0.002	1.51	(1.06-2.15)	0.021	1.47	(0.99-2.17)	0.056
Re-transplant																		
Yes vs no	2.61	(1.62-4.22)	<0.001	2.73	(1.83-4.08)	<0.001	1.82	(1.16-2.87)	0.010*	-	-	-	-	-	-	-	-	-
Biennium																		
'02-'03 vs '08-'09 '04-'05 vs '08-'09 '06-'07 vs '08-'09	1.26 0.85 0.83	(0.83-1.91) (0.58-1.25) (0.57-1.19)	0.287 0.407 0.308	0.99 0.86 0.85	(0.69-1.41) (0.63-1.16) (0.63-1.14)	0.94 0.319 0.282	0.83 0.75	(0.61-1.13) (0.58-0.97) -	0.24 0.027* -	1.21 0.82 0.72	(0.84-1.74) (0.59-1.13) (0.53-0.99)	0.304 0.228 0.045*	0.99 0.81 0.78	(0.72-1.38) (0.61-1.07) (0.59-0.1.02)	0.959 0.135 0.068	0.92 0.72	(0.69-1.23) (0.57-0.92)	0.578 0.009* -
Volume of the centre																		
Low vs medium High vs medium	2.21 0.64	(1.56-3.12) (0.43-0.94)	<0.001 0.022*	1.91 0.83	(1.43-2.54) (0.62-1.12)	<0.001* 0.219°	1.48 0.85	(1.11-1.99) (0.64-1.13)	0.008 0.26	1.56 0.81	(1.15-2.12) (0.59-1.10)	0.004* 0.175°	1.57 0.95	(1.24-2.04) (0.73-1.23)	0.001* 0.705	1.27 0.91	(0.96-1.68) (0.70-1.19)	0.094 0.503
Hosmer Lemeshow (training s	set)	0.259			0.731			0.702			0.317			0.607			0.527
Hosmer Lemeshow (validation	n set)	0.444			0.31			0.643			0.9			0.132			0.862
°significant in th	e valida	ition se validation set																
C-statistic (train	ing set)	vanuation Set	0.690			0.664			0.667	7		0.640			0.624			0.633
C-statistic (valid	ation se	et)	0.733			0.698			0.672	2		0.687			0.668			0.662

^{\$}D-MELD was analysed also as a continuous variable. To comply with the 4 digit integers, D-MELD values were divided by 100 in order to achieve 2 digit decimals of Odd Ratio (OR). OR, 95% CI and significances at 90 days, 1 year, 3 years were 1.08 (1.05-1.11) p<0.001; 1.08 (1.05-1.09) p<0.001; 1.07 (1.05-1.09) p<0.001; for mortality and 1.07 (1.05-1.09) p<0.001; 1.06 (1.05-1.08) p<0.001; for graft failure. In other words, at 3 years for each 100 point D-MELD increment the relative risk increases of 1.07 for mortality and 1.06 for graft failure.

	overall 1	mortality (1 to 90 n	nonths)		overall graft failure (1 to 90 months)					
	HR	(95% CI)	p-value		HR	(95% CI)	p-value			
D-MELD ^{\$}										
Class A vs class B	0.42	(0.29-0.60)	<0.001		0.41	(0.29-0.58)	<0.001			
Class C vs class B	1.97	(1.59-2.43)	<0.001		1.86	(1.53-2.27)	<0.001			
Recipient age	1.015	(1.006-1.024)	0.001		1.008	(1.000-1.016)	0.047*			
HCV status										
Positive vs negative	1.43	(1.21-1.70)	<0.001		1.40	(1.20-1.64)	<0.001**			
HBV status										
Positive vs negative	0.72	(0.58-0.89)	0.002		0.75	(0.62-0.91)	0.004			
Re-transplant										
Yes vs no	2.21	(1.70-2.87)	<0.001		-	-	-			
Biennium										
2002-2003 vs 2008-2009	1.28	(0.99-1.65)	0.096		1.14	(1.07-1.71)	0.010*			
2004-2005 vs 2008-2009	1.06	(0.84-1.33)	0.627		1.03	(0.84-1.27)	0.784			
2006-2007 vs 2008-2009	1.28	(0.99-1.65)	0.056		1.09	(0.89-1.33)	0.416			
Volume of the centre										
Low vs medium	1.35	(1.11-1.65)	0.003*		1.19	(0.99-1.45)	0.059			
High vs medium	0.92	(0.76-1.12)	0.391		0.98	(0.82-1.17)	0.779			
C-statistics										
Training set				0.641				0.701		
Validation set				0.643				0.721		

Table 3. Predictive factors at the Cox regression in the training set.

* not significant in the validation set

** 0.051 in the validation set

^{\$}D-MELD was analysed also as a continuous variable. To comply with the 4 digit integers, D-MELD values were divided by 100 in order to achieve 2 digit decimals of Hazard Ratio (HR). HR (95% CI) and significances were 1.06 (1.04-1.07) p<0.001 for mortality and 1.06 (1.05-1.07) p<0.001 for graft failure. In other words, for each 100 point D-MELD increment the relative risk increases of 1.06 for mortality and 1.06 for graft failure.





Figure S2

Table S1. Kaplan Meier analysis p-value in the training set.

Patient survival

	D-MELD decile	1	2	3	4	5	6	7	8	9
		р	р	р	р	р	р	р	р	р
Mantel Cox	1									
	2	.022								
	3	.000	.127							
	4	.013	.872	.169						
	5	.000	.014	.363	.023					
	6	.000	.002	.127	.004	.530				
	7	.000	.015	.350	.021	.980	.525			
	8	.000	.007	.245	.010	.769	.721	.798		
	9	.000	.005	.199	.007	.699	.847	.698	.889	
	10	.000	.000	.000	.000	.002	.013	.001	.004	.005
Breslow	1									
	2	.022								
	3	.000	.109							
	4	.019	.961	.118						
	5	.000	.031	.623	.037					
	6	.000	.003	.174	.004	.340				
	7	.000	.029	.577	.033	.927	.387			
	8	.000	.009	.332	.010	.574	.680	.652		
	9	.000	.008	.314	.009	.568	.718	.648	.976	
	10	.000	.000	.000	.000	.000	.010	.000	.002	.002

Graft survival

	-									
Graft surv	ival									
Gruit Sur V	D-MELD decile	1	2	3	4	5	6	7	8	9
	L	р	р	р	р	р	р	р	р	р
Mantel Cox	1	1					1		1	1
	2	.019								
	3	.000	.068							
	4	.005	.663	.158						
	5	.000	.002	.223	.009					
	6	.000	.000	.053	.001	.476				
	7	.000	.010	.422	.028	.623	.237			
	8	.000	.003	.250	.010	.958	.430	.707		
	9	.000	.001	.146	.004	.818	.664	.481	.747	
	10	.000	.000	.000	.000	.003	.022	.000	.002	.005
Breslow	1									
	2	.027								
	3	.000	.065							
	4	.012	.774	.114						
	5	.000	.004	.314	.010					
	6	.000	.000	.068	.001	.388				
	7	.000	.023	.669	.044	.539	.141			
	8	.000	.004	.317	.009	.987	.390	.541		
	9	.000	.002	.208	.004	.788	.567	.383	.792	
	10	.000	.000	.000	.000	.002	.027	.000	.002	.004

Table S2. Kaplan Meier curves in the trangetigan Journal of Transplantation

Page 36 of 65

	12	24	% Pa 36	atien 48	t sui 60	rviva 72	ul mo P	12	24	% G 36	raft 48	sur 60	vival 72	mo P
D-MELD Class A (66, 226)	05	<u>-</u>	02	00	00	00		02	01	80	00	00	07	into 1
- Class B (338-1628) Class B (338-1628)	88 77	84 72	80 60	90 78	69 76	00 74	-0.001	95 85 72	80	69 77 65	75	00 73	87 71	-0.001
Donor age	//	12	09	00	03	01	<0.001	/3	08	00	02	38	30	<0.001
- 1 decile (12-24) - 2 decile (24-35)	89 93	88 91	87 89	86 86	85 86	84 86		89 91	87 89	86 86	85 84	84 84	84 84	
- 3 decile (35-44) - 4 decile (44-51)	87 87	83 83	82 79	80 77	79 75	79 71		84 84	80 80	78 76	76 75	76 73	76 69	
- 5 decile (51-56) - 6 decile (56-60)	87 87	86 82	82 79	81 75	78 73	77 69		84 83	82 79	77 75	76 72	74 69	74 66	
- 7 decile (60-66) - 8 decile (66-70)	87 85	81 81	78 78	77 75	74 73	70 72		83 83	79 79	74 77	71 73	69 71	66 70	
- 9 decile (70-76) - 10 decile (76-97)	85 87	79 79	73 77	69 73	63 70	62 63	<0.001	82 80	75 73	70 71	66 68	61 65	60 58	<0.001
MELD - 1 decile (6-8)	94	90	86	85	83	83	101001	91	86	82	82	80	80	101001
- 2 decile (9-10) 3 decile (11, 12)	90 93	88	85	81 81	77	75		88	85 83	81 70	78 78	74	72 76	
- 4 decile (13-13)	87 87	82 82	78	76	75	73 76		81	77	74 78	72	70	69 72	
- 5 decile (14-15) - 6 decile (16-17)	90	86	80 82	78 78	73	70		87 87	81	78 78	73	69 74	68	
- 7 decile (18-19) - 8 decile (20-22)	88 82	84 80	81 80	78 78	76 74	70 72		86 81	81 79	78 79	77	74 73	67 71	
- 9 decile (23-28) - 10 decile (29-41)	84 77	82 72	78 70	74 70	72 70	72 69	<0.001	80 74	70	73 67	70 67	68 67	68 65	<0.001
Recipient age $- \ge 60$ years	85	80	77	74	72	69		83	78	75	72	70	68	
- < 60 years Peripient gender	88	84	81	80	77	75	0.002	85	81	77	76	74	72	0.048
- Male	88	84	80	78	75	73	0 506	85	81	78 75	74	72	70	0 624
- Female HCV status	85	81	19	77	/0	74	0.590	82	77	75	74	15	12	0.024
- Positive - Negative	86 87	80 86	76 84	83	69 82	81	<0.001	82 86	83	73 81	70 80	66 79	64 78	<0.001
- Positive	91	88	86	85	83	83	0.001	88	85	83	82	81	80	0.001
- Negative Alcohol status	87	82	78	15	73	70	<0.001	83	78	75	72	70	68	<0.001
- Positive - Negative	87 87	85 83	81 80	79 78	77 76	75 74	0.672	84 84	81 80	77 77	75 75	74 73	72 71	0.895
Acute liver failure status - Positive	75	73	73	71	71	71		75	73	71	69	69	69	
- Negative HCC status	87	84	80	78	76	74	0.044*	85	80	77	75	73	71	0.161
- Positive - Negative	89 86	84 83	80 80	78 78	75 75	73 73	0.703	87 82	82 80	77 77	75 75	72 73	71 71	0.271
Pre-Tx abdominal surgery - Yes	86	82	80	78	76	76		82	78	76	73	72	72	
- No Pre-Tx portal thrombosis	87	83	80	77	75	72	0.796	84	80	77	74	73	70	0.621
- Yes - No	82 87	80 83	77 80	74 78	74 75	72 73	0.306	78 84	75 80	72 76	69 74	69 72	67 70	0.103
Dialysis - Ves	65	65	58	58	58	58		71	64	57	57	57	57	
- No	88	84	81	79	76	74	0.007	85	81	78	75	73	71	0.042*
- ≥90	86	83	80	77	76	73		82	77	74	73	70	70	
- <90 Re-transplant	88	84	81	79	77	74	0.286	85	80	77	75	73	71	0.352
- Yes - No	74 88	69 84	65 81	59 79	55 77	50 75	<0.001							
Donor age - > 60 years	85	80	76	73	70	67		82	76	72	69	66	64	
- < 60 years	88	86	83	81	80	78	<0.001	86	83	80	78	77	76	<0.001
- Male	87	83	80	76	75	74	0.001	84	80	76	74	72	71	0.004
Donor HBcAb	87	83	80	78	15	74	0.981	84	80	11	15	73	/0	0.894
- Positive - Negative	87 88	83 83	80 80	78 77	76 75	73 74	0.971	84 84	80 80	76 77	76 75	70 73	69 71	0.524
- Female->Male	88	84	80	78	76	73		85	81	77	75	73	70	
- Female->Female - Male->Female	85 85	81 81	80 79	78 76	76 76	74 75		82 82	77 78	76 76	74 74	73 73	71 72	
- Male->Male Donor-recipient gender concordance	87	84	80	77	75	73	0.972	84	81	77	74	72	70	0.928
- Yes - No	87 87	83 83	80 80	77 78	75 76	73 74	0.835	84 85	80 80	76 77	74 75	72 73	70 71	0.608
Cold ischemia time	86	82	70	76	75	73	-	83	80	76	75	74	73	-
- < 8 hours	87	84	81	78	76	, s 74	0.641	84	81	78	76	75	74	0.721
- 2002-2003	86	83	80	78	74	71		82	78	75	73	70	68	
- 2004-2005 - 2006-2007	87 87	82 83	80 80	78 77	77 76	/5	0 == :	84 85	80 81	78 76	75 74	74 73	73	0.4.**
- 2008-2009 Centre volume	88	85					0.274	85	82					0.107
- Low - Medium	84 88	81 84	78 80	76 79	74 76	70 76		82 85	79 80	76 77	74 75	73 73	69 72	
- High	89	85	82	79	77	75	0.016*	85	81	78	75	73	72	0.394

*Not significant in the validation set.

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Page 37 of Table S3. Kaplan Meier curves in the valuation Journal of Transplantation

	-		(% Pa	atien	t su	rviva	al					% G	Fraft	sur	viva	
1		12	24	36	48	60	72	m	o P		12	24	36	48	60	72	mo P
2	D-MELD Class A (66, 226)	06	02	00	00	00	07				04	00	00	07	07	96	
2	- Class A (00-550) - Class B (338-1628)	90 88	92 83	80	00 77	80 75	87 73				94 84	90 79	00 76	73	72	70	
4	- Class C (1632-3240)	71	68	67	63	61	61	<0).001		64	62	61	58	58	58	<0.001
5	- 1 decile (12-24)	90	87	84	82	82	82				88	84	81	80	80	80	
6	-2 decile (24-35)	88	84	83	81	79	74				85	82	81	79	77	74	
7	- 3 decile (35-44) - 4 decile (44-51)	90 89	87	85 82	82 80	79	81 79				89 86	83 83	82 80	80 78	79	75	
8	- 5 decile (51-56)	89	84	80	79	78	75				86	80	77	76	75	71	
9	- 6 decile (56-60) - 7 decile (60-66)	88 88	84 83	80	72 80	/1 78	/1 75				88 85	83 79	75 77	73 76	70 75	70	
10	- 8 decile (66-70)	83	76	74	72	72	70				80	72	72	68	68	66	
11	-9 decile (70-76) - 10 decile (76-97)	87	85	69 80	64 69	57 68	54 68	<().001		72 79	66 78	62 73	58 64	55 61	52 61	<0.001
12	MELD		0.0		=0		= 0				0.0						
13	-1 decile (6-8) - 2 decile (9-10)	92 93	88 88	83	78	81	73				90 89	84 85	80 81	75 78	73	70	
14	- 3 decile (11-12)	<u>93</u>	91	88	84	84	84				90	87	84	80	80	80	
15	- 4 decile (13-13) - 5 decile (14-15)	87 91	81	79	77	73	70				83	78	75	75	75	69 76	
16	- 6 decile (16-17)	89	82	79	79	77	72				85	78	75	74	73	68	
17	- 7 decile (18-19) - 8 decile (20-22)	85 87	80	77 81	74	71	67 73				81	76	73	70	67 67	64 65	
18	- 9 decile (23-28)	81	77	75	75	75	73				78	74	72	72^{1}	72	70	
19	- 10 decile (29-41)	69	67	63	62	60	60	<().001		65	63	60	60	60	60	<0.001
20	- > 60 years	83	77	74	72	69	65				80	75	72	70	68	64	
21	- < 60 years	89	84	81	78	77	75	<0	•001		85	80	77	75	73	72	0.017
22	Recipient gender	07	02	80	77	75	72				Q /	80	77	74	70	70	
23	- Female	85	80	77	75	74	72	0.	.102		81	⁸⁰ 76	73	71	71	69	0.289
24	HCV status	05	70	75	71	70	67				01	76	70	60	"	61	
25	- Positive	83 89	79 86	75 84	82	80	07 78	<().001		82 85	70 82	80	08 78	00 77	64 76	<0.001
26	HBV status	00	0.0	00	0.4	0.2	00				00	07	05	0.7	00	0.1	
27	- Positive - Negative	92 85	88 80	86 77	84 74	83 72	82 70	<().001		90 82	87 76	85 73	83 70	82 69	81 66	<0.001
28	Alcohol status	00	0.4		00						0.2	70			- 4	70	
29	- Positive - Negative	88 87	84 82	82 79	80 76	74	$\frac{7}{72}$	0.	.198		83 84	79 79	76	73 73	74 72	70	0.626
30	Acute liver failure status										<i>.</i>						
31	- Positive - Negative	75 87	75	75	71	71	71	0	.264		69 84	69 79	69 76	65 74	65 72	65 70	0.124
32	HCC status	07														10	0.121
33	- Positive	89 85	84 81	80 79	76	73	71 74	0	859		88 81	82 77	78 75	74 73	71	68 71	0 202
34	Pre-Tx abdominal surgery	0.5	01					0	.007		01					/1	0.202
35	- Yes - No	86 86	83	81 78	76 75	74 74	72	0	727		84 83	80 78	78 75	75 72	75	70	0 424
30	Pre-Tx portal thrombosis	00	02	70	15	/ 4	15	U	., 2,		05	70	15	12	/1	10	0.424
30	- Yes - No	82 87	74	70	70	70 74	70	0	133		78	70	66 76	66 73	66 71	66 70	0 129
30	Dialysis	07	05		10	/ 4	15	U	.155		05	1)	10	15	/1	10	0.127
39 40	- Yes	58	58 84	58	58	58 75	58 74	0	018		58	58	58	58 73	58	58 71	0.061
40 /1	Listing days	00	04	80	//	15	/4	U	.010		85	80	70	15	12	/1	0.001
41	- ≥90	88	84	81	78	76	74				85	80	78	75	73	72	
42	- <90 Be transplant	86	81	78	75	74	72	0.	.163		82	77	73	72	70	68	0.091
43	- Yes	67	61	61	55	53	50										
44 45	- No	88	84	80	80	76	75	<().001								
46	- > 60 years	84	79	76	72	75	77				79	74	71	67	66	63	
47	- < 60 years	89	85	82	80	79	77	<().001		87	83	80	78	77	75	<0.001
48	Donor gender	07	07	00		74	70				0.4	70	76	74	70	60	
49	- Male - Female	87 87	82 83	80 80	77	76	75	0.	.501		84 83	79 79	70 75	73	$\frac{72}{72}$	69 71	0.799
50	Donor HBcAb	0.2	70	75	70	71	71				70	75	71	(0	<u> </u>		
51	- Positive - Negative	83 88	83	80	77	75	73	0.	.106		79 84	75 79	76	69 74	08 72	00 71	0.119
52	Donor-recipient gender match	0.0	0.0	0.0	=	= (0.4	70		70	70	71	
53	- Female->Male - Female->Female	86 86	83	80 80	76 77	76 75	75 74				84 83	78 78	75 75	73	72	/1 71	
54	- Male->Female	81	77	75	73	72	69	•	501		77	73	71	69	69	67	0.425
55	- Male->Male Donor-recipient gender concordance	88	84	80	//	/5	72	0.	.531		86	81	/8	15	72	/0	0.435
56	- Yes	88	84	80	77	75	73	•	-00		85	78	77	74	72	70	0.000
57	- No Cold ischemia time	85	81	79	76	74	73	0.	.589		81	11	74	72	71	70	0.339
58	$- \ge 8$ hours	85	83	80	78	75	73				83	80	77	76	74	72	
59	- < 8 hours	87	85	82	79	76	75	0.	.538		85	82	79	75	74	73	0.597
60	Biennium - 2002-2003	80	85	83	80	77	75				85	81	70	75	73	71	
	- 2004-2005	86	82	<u>79</u>	77	25	74				83	79	76	74	73	71^{+1}	
	- 2006-2007 - 2008-2009	84 80	80 83	77	74	74		A	296		81 86	77 80	77	71	71		0 353
	Centre volume	07			_	_		U	<u>1</u> 70		00		_	_	_	-	0.353
	- Low - Medium	85 86	80 83	77 80	74 78	72 76	71 74				83 82	78 79	74 76	71 74	70 73	69 70	
	- High	87	84	81	78	76	74	0	.139	1) 004 440	85	80	77	74	73	70	0.558
		3	CUO	orar	UN	ะ รเ	ihb,	ort	. (434	+) 904 410	U						

p values were obtained by Mantel Cox tests.

Table S4. Expected and observed number of deaths and failures at 1 and 3 years stratified in deciles of estimated risk in the training set and in the validation set (Hosmer-Lemeshow test).

		Exit	us	Exit	us	Fail	ure	Failure			
At 1 years		Trainin	ng set	Validati	on set	Trainii	ng set	Validat	ion set		
	Decile	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected		
	1	12	12.9	8	5.1	21	19.4	9	8.0		
	2	20	19.3	11	7.9	24	28.4	15	11.4		
	3	25	23.1	9	10.7	32	34.5	13	14.7		
	4	24	26.4	10	12.6	35	38.0	17	19.0		
	5	34	29.7	12	14.8	53	41.4	17	22.1		
	6	33	33.5	16	17.1	40	45.2	32	24.3		
	7	37	39.5	18	20.4	52	50.0	19	27.3		
	8	50	48.0	18	24.4	59	56.4	35	30.3		
	9	47	57.7	37	30.2	62	64.7	28	33.7		
	10	85	76.9	54	49.7	78	78.0	63	57.2		
Hosmer-Lemeshow test			0.731	7/6	0.310		0.607		0.132		

		Exit	us	Exit	tus	Failı	ıre	Fail	ure
At 3 years		Trainir	ng set	Validat	ion set	Trainir	ng set	Validat	ion set
	Decile	Observed	Expected	Observed	Expected	Observed	Expected	Observed	Expected
	1	9	15.3	9	8.1	14	21.3	11	10.9
	2	24	23.1	15	11.4	35	30.8	15	14.4
	3	31	27.9	14	13.8	37	35.6	15	17.8
	4	31	32.4	14	16.5	38	40.7	26	21.7
	5	38	36.8	17	19.3	51	44.8	22	24.9
	6	39	40.5	23	21.8	47	48.0	27	27.2
	7	49	45.4	23	24.8	53	53.7	32	29.4
	8	57	51.4	23	28.0	64	58.1	27	32.1
	9	60	59.5	39	32.1	66	65.0	38	35.8
	10	69	74.8	41	42.2	71	78.2	48	46.8
Hosmer-Lemeshow test			0.259		0.643		0.527		0.862

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