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

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 donor-recipient 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 31st 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

(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

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 sub-analyses 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

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 (≥68, upper quartile) and extremely-high (≥75, upper decile) donor age and to high (≥21, upper quartile) and extremely-high (≥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 follow-up, 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 extremely-high 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

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 A and 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

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

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 Center-specific 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.

˜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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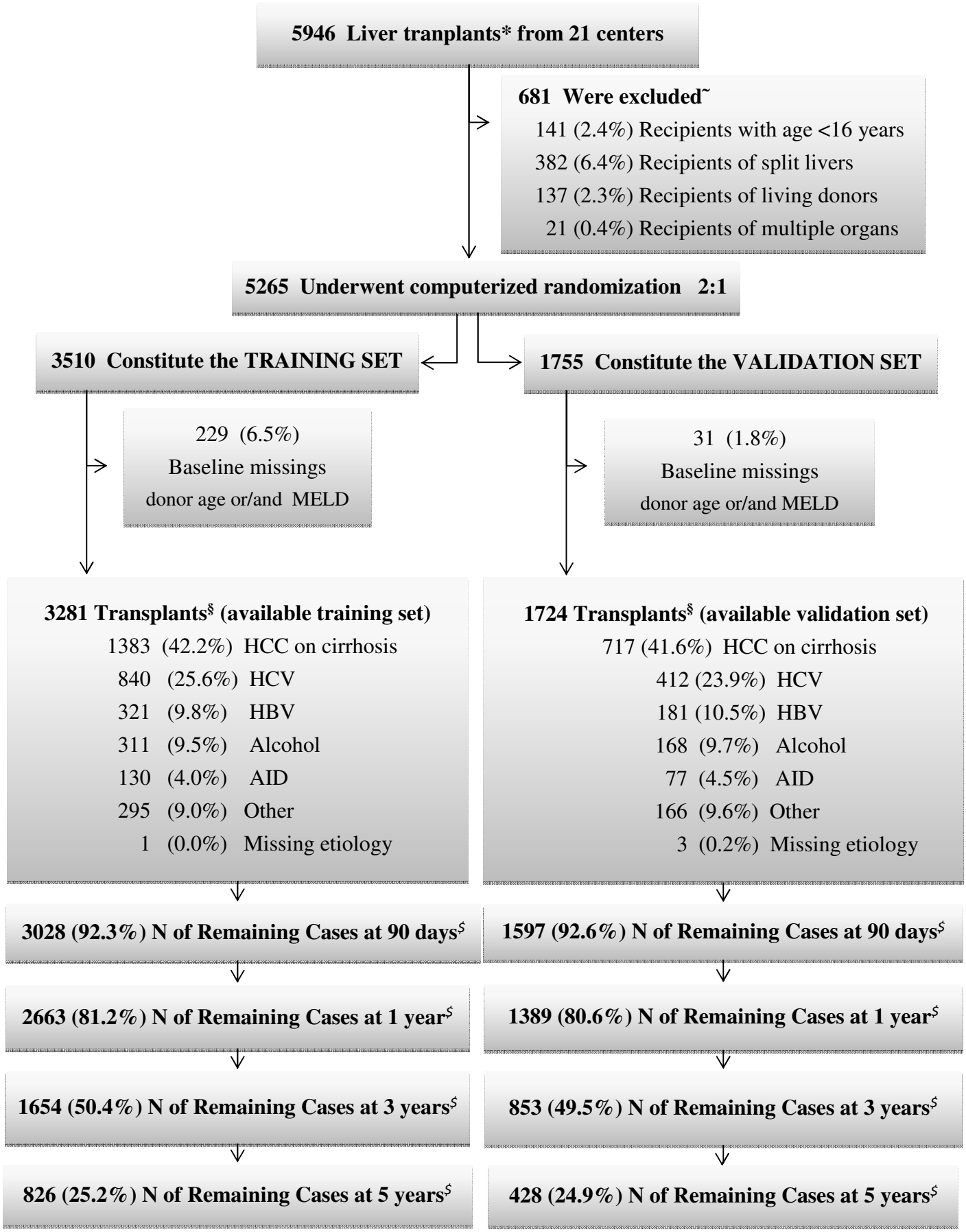
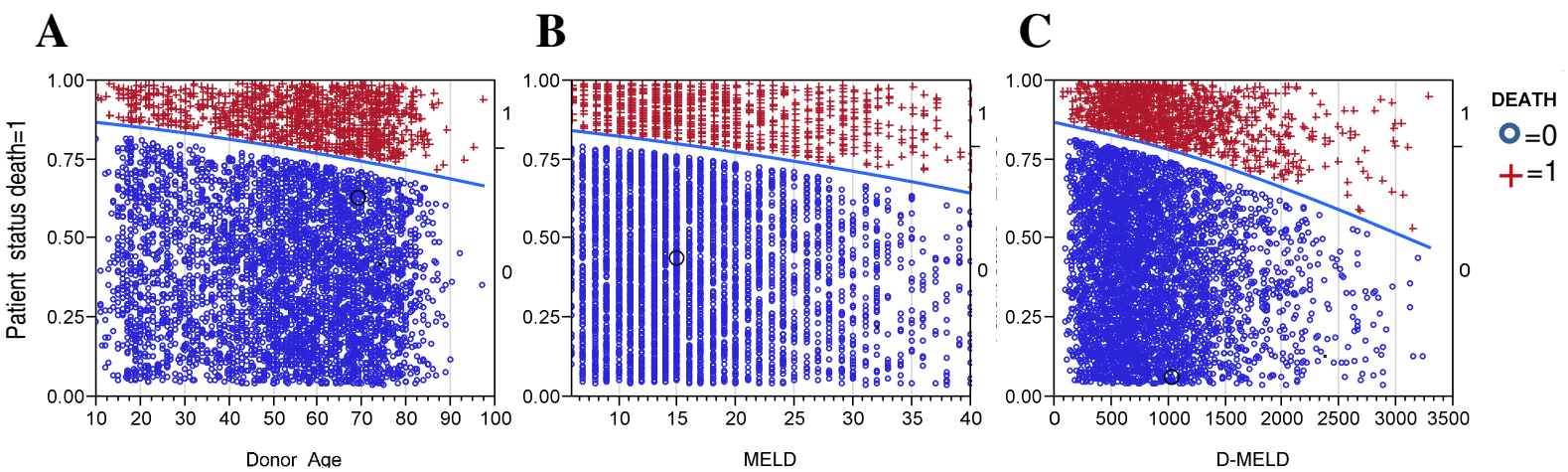
Figure 1


5946 Liver tranplants* from 21 centers
681 Were excluded˜
141 (2.4%) Recipients with age <16 years
382 (6.4%) Recipients of split livers
137 (2.3%) Recipients of living donors
21 (0.4%) Recipients of multiple organs
5265 Underwent computerized randomization 2:1
3510 Constitute the TRAINING SET
1755 Constitute the VALIDATION SET
229 (6.5%)
Baseline missings
donor age or/and MELD
31 (1.8%)
Baseline missings
donor age or/and MELD
3281 Transplants§ (available training set)
1383 (42.2%) HCC on cirrhosis
840 (25.6%) HCV
321 (9.8%) HBV
311 (9.5%) Alcohol
130 (4.0%) AID
295 (9.0%) Other
1 (0.0%) Missing etiology
1724 Transplants§ (available validation set)
717 (41.6%) HCC on cirrhosis
412 (23.9%) HCV
181 (10.5%) HBV
168 (9.7%) Alcohol
77 (4.5%) AID
166 (9.6%) Other
3 (0.2%) Missing etiology
3028 (92.3%) N of Remaining Cases at 90 days$
1597 (92.6%) N of Remaining Cases at 90 days$
2663 (81.2%) N of Remaining Cases at 1 year$
1389 (80.6%) N of Remaining Cases at 1 year$
1654 (50.4%) N of Remaining Cases at 3 years$
853 (49.5%) N of Remaining Cases at 3 years$
826 (25.2%) N of Remaining Cases at 5 years$
428 (24.9%) N of Remaining Cases at 5 years$



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

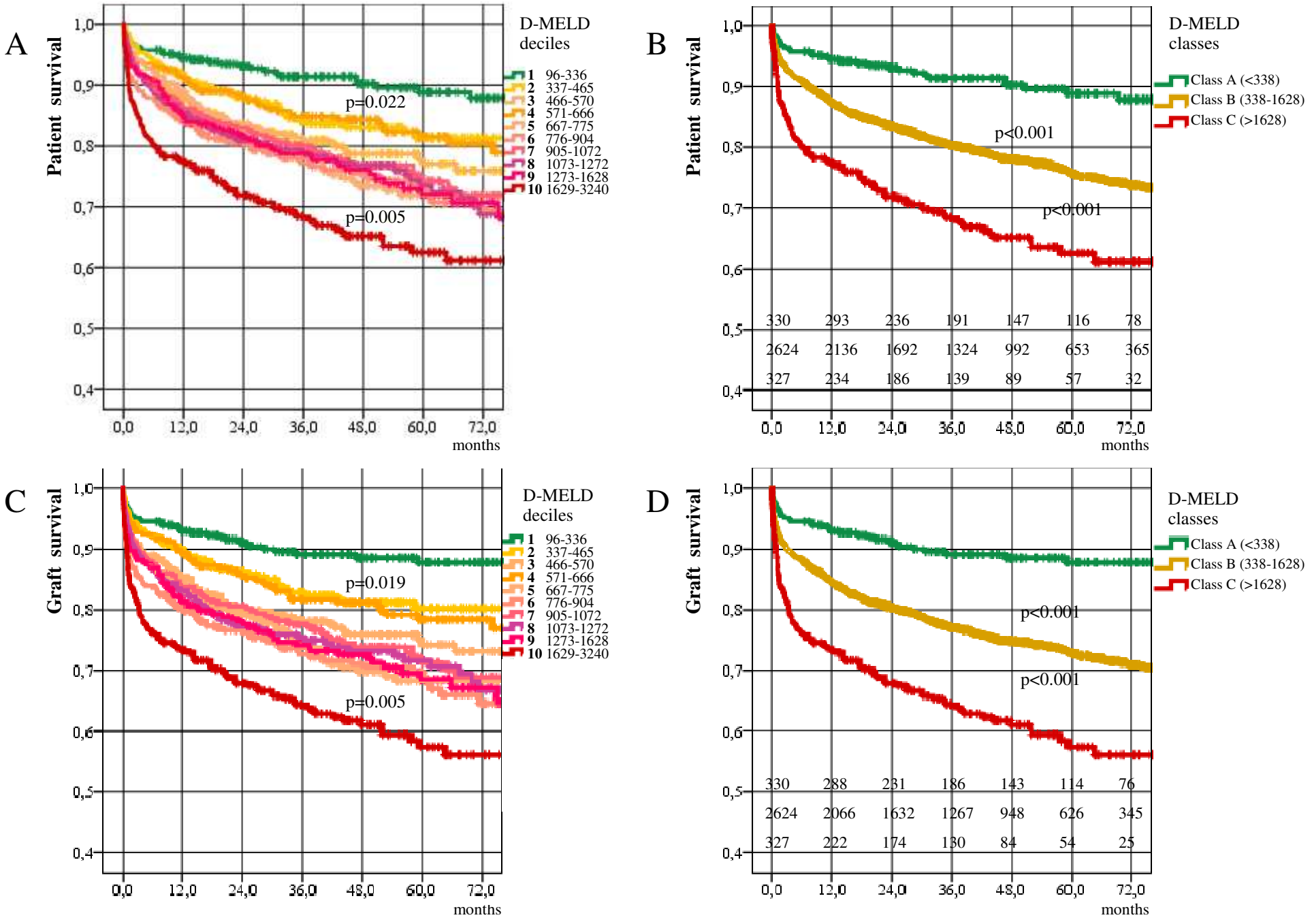

A
Patient survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
p=0.022
p=0.005
0,0
12,0
24,0
36,0
48,0
60,0
72,0
months
D-MELD deciles
1 96-336
2 337-465
3 466-570
4 571-666
5 667-775
6 776-904
7 905-1072
8 1073-1272
9 1273-1628
10 1629-3240
B
Patient survival
p<0.001
p<0.001
330 293 236 191 147 116 78
2624 2136 1692 1324 992 653 365
327 234 186 139 89 57 32
months
D-MELD classes
Class A (<338)
Class B (338-1628)
Class C (>1628)
C
Graft survival
p=0.019
p=0.005
months
D-MELD deciles
1 96-336
2 337-465
3 466-570
4 571-666
5 667-775
6 776-904
7 905-1072
8 1073-1272
9 1273-1628
10 1629-3240
D
Graft survival
p<0.001
p<0.001
330 288 231 186 143 114 76
2624 2066 1632 1267 948 626 345
327 222 174 130 84 54 25
months
D-MELD classes
Class A (<338)
Class B (338-1628)
Class C (>1628)

Figure 3

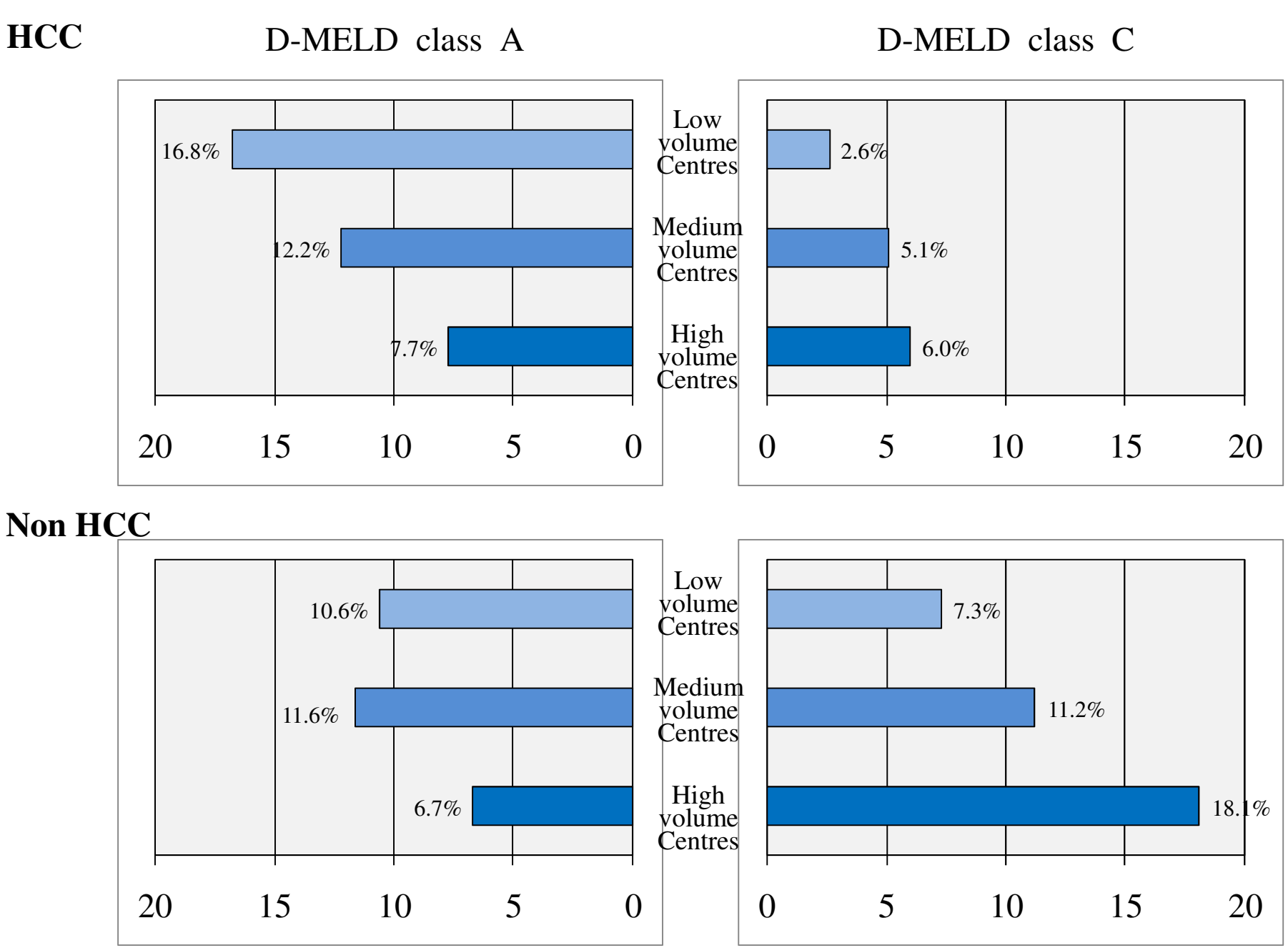

HCC
D-MELD class A
D-MELD class C
16.8%
12.2%
7.7%
Low volume Centres
Medium volume Centres
High volume Centres
2.6%
5.1%
6.0%
20 15 10 5 0
0 5 10 15 20
Non HCC
10.6%
11.6%
6.7%
Low volume Centres
Medium volume Centres
High volume Centres
7.3%
11.2%
18.1%
20 15 10 5 0
0 5 10 15 20

Figure 4

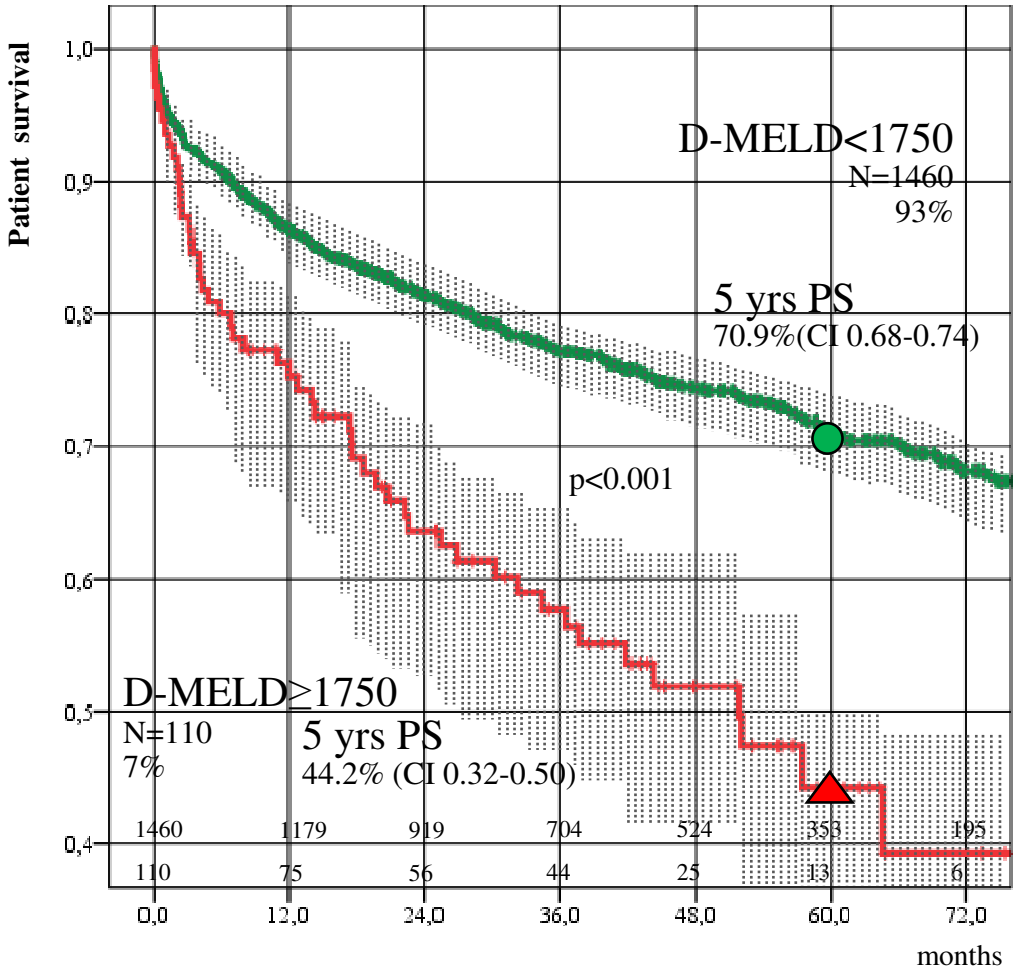

Patient survival
1,0
0,9
0,8
0,7
0,6
0,5
0,4
D-MELD<1750
N=1460
93%
5 yrs PS
70.9%(CI 0.68-0.74)
p<0.001
D-MELD≥1750
N=110
7%
5 yrs PS
44.2% (CI 0.32-0.50)
1460 1179 919 704 524 358 195
110 75 56 44 25 13 6
0,0 12,0 24,0 36,0 48,0 60,0 72,0
months

Figure 5

Table 1. Descriptive statistics according to the D-MELD class in the training set.

	D-MELD Class A (<338) N=332	D-MELD Class B (338-1628) N=2621	D-MELD Class C (>1628) N=328	p-value
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; 100.0%)				
- Positive	3 (0.9)	41 (1.6)	37 (13.3)	**<0.001**
HCC (N=3281; 100.0%)				
- Positive	156 (47.0)	1151 (43.9)	76 (23.2)	**<0.001**
Pre-Tx abdominal surgery (N=2609; 79.5%)				
- Yes	58 (21.6)	365 (18.8)	40 (16.5)	**0.331**
Dialysis (N=2546; 77.6%)				
- Yes	0 (0.0)	8 (0.4)	9 (3.6)	**<0.001**
Pre-Tx portal thrombosis (N= 2814; 85.7%)				
- Yes	14 (5.0)	172 (7.7)	29 (10.1)	**<0.001**
Listing months (N=3038; 92.5%)	8.2±8.6	7.7±8.2	5.9±8.5	**<0.001***
Re-transplant (N=3281; 100.0%)				
- Yes	10 (3.0)	127 (4.8)	21 (6.4)	**0.125**
Donor age (N=3281; 100.0%)	24.3±10.1	54.6±16.3	69.3±10.0	**<0.001***
Donor gender (N=3197; 97.4%)				
- Male	230 (71.2)	1416 (55.5)	163 (50.8)	**<0.001**
Donor HBcAb (N=3070; 93.5%)				
- Yes	34 (11.4)	410 (16.7)	59 (18.7)	**0.003**
Donor-Recipient gender match (N=3190; 97.2%)				
- Female→Female	38 (11.8)	355 (13.9)	57 (17.8)	
- Female→Male	55 (17.0)	783 (30.7)	94 (31.5)	
- Male→Female	46 (14.2)	224 (8.8)	41 (12.8)	
- Male→Male	184 (57.0)	1191 (46.6)	122 (37.9)	**<0.001**
Donor-Recipient gender concordance (N=3197; 97.4%)				
- Yes	222 (68.7)	1547 (60.6)	179 (55.8)	**0.003**
Cold Ischemia Time° (N=2705; 82.4%)	8.2±2.1	9.1±3.3	6.9±2.7	**0.043***
Biennium (N=3281; 100.0%)				
- 2002-2003	66 (19.9)	343 (13.1)	32 (9.8)	
- 2004-2005	79 (23.8)	713 (27.2)	87 (26.5)	
- 2006-2007	96 (28.9)	781 (29.8)	114 (34.7)	
- 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 obtained by Chi^2 test. ° Hour.

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

	mortality at 90 days			mortality at 1 year			mortality at 3 years			graft failure at 90 days			graft failure at 1 year			graft failure at 3 years		
	OR	**(95% CI)**	***p***	**OR**	**(95% CI)**	***p***	**OR**	**(95% CI)**	***p***	**OR**	**(95% CI)**	***p***	**OR**	**(95% CI)**	***p***	**OR**	**(95% CI)**	***p***
D-MELD[$]																		
Class A vs B	0.46	(0.24-0.86)	*0.015*	0.43	(0.26-0.72)	*0.001*	0.40	(0.24-0.66)	*<0.001*	0.41	(0.24-0.72)	*0.002*	0.41	(0.26-0.66)	*<0.001*	0.42	(0.27-0.67)	*<0.001*
Class C vs B	2.65	(1.81-3.89)	*<0.001*	2.32	(1.68-3.21)	*<0.001*	2.03	(1.44-2.85)	*<0.001*	2.16	(1.54-3.03)	*<0.001*	2.05	(1.52-2.77)	*<0.001*	1.92	(1.39-2.67)	*<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 thrombosis																		
Yes vs no	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	1.26	(0.83-1.91)	*0.287*	0.99	(0.69-1.41)	*0.94*	0.83	(0.61-1.13)	*0.24*	1.21	(0.84-1.74)	*0.304*	0.99	(0.72-1.38)	*0.959*	0.92	(0.69-1.23)	*0.578*
'04-'05 vs '08-'09	0.85	(0.58-1.25)	*0.407*	0.86	(0.63-1.16)	*0.319*	0.75	(0.58-0.97)	*0.027**	0.82	(0.59-1.13)	*0.228*	0.81	(0.61-1.07)	*0.135*	0.72	(0.57-0.92)	*0.009**
'06-'07 vs '08-'09	0.83	(0.57-1.19)	*0.308*	0.85	(0.63-1.14)	*0.282*	-	-	-	0.72	(0.53-0.99)	*0.045**	0.78	(0.59-0.1.02)	*0.068*	-	-	-
Volume of the centre																		
Low vs medium	2.21	(1.56-3.12)	*<0.001*	1.91	(1.43-2.54)	*<0.001**	1.48	(1.11-1.99)	*0.008*	1.56	(1.15-2.12)	*0.004**	1.57	(1.24-2.04)	*0.001**	1.27	(0.96-1.68)	*0.094*
High vs medium	0.64	(0.43-0.94)	*0.022**	0.83	(0.62-1.12)	*0.219°*	0.85	(0.64-1.13)	*0.26*	0.81	(0.59-1.10)	*0.175°*	0.95	(0.73-1.23)	*0.705*	0.91	(0.70-1.19)	*0.503*
Hosmer Lemeshow (training set)			*0.259*			*0.731*			*0.702*			*0.317*			*0.607*			*0.527*
Hosmer Lemeshow (validation set)			*0.444*			*0.31*			*0.643*			*0.9*			*0.132*			*0.862*
°significant in the validation se																		
***NOT significant in the validation set**																		
C-statistic (training set)			*0.690*			*0.664*			*0.667*			*0.640*			*0.624*			*0.633*
C-statistic (validation set)			*0.733*			*0.698*			*0.672*			*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; 1.07 (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.

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

	overall mortality (1 to 90 months)			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*

* 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.

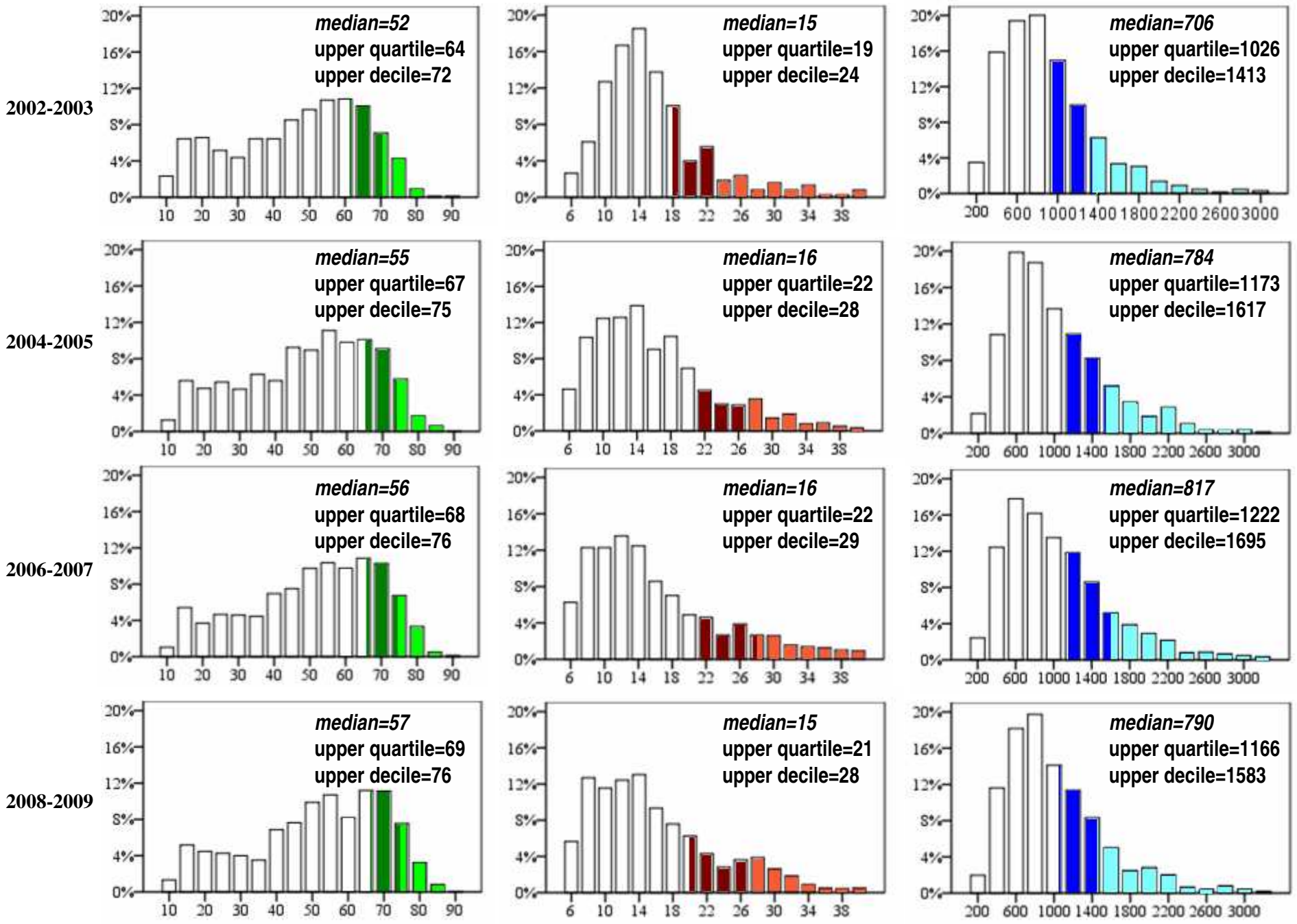

2002-2003
median=52
upper quartile=64
upper decile=72
median=15
upper quartile=19
upper decile=24
median=706
upper quartile=1026
upper decile=1413
2004-2005
median=55
upper quartile=67
upper decile=75
median=16
upper quartile=22
upper decile=28
median=784
upper quartile=1173
upper decile=1617
2006-2007
median=56
upper quartile=68
upper decile=76
median=16
upper quartile=22
upper decile=29
median=817
upper quartile=1222
upper decile=1695
2008-2009
median=57
upper quartile=69
upper decile=76
median=15
upper quartile=21
upper decile=28
median=790
upper quartile=1166
upper decile=1583
DONOR AGE
MELD
D-MELD

Figure S1

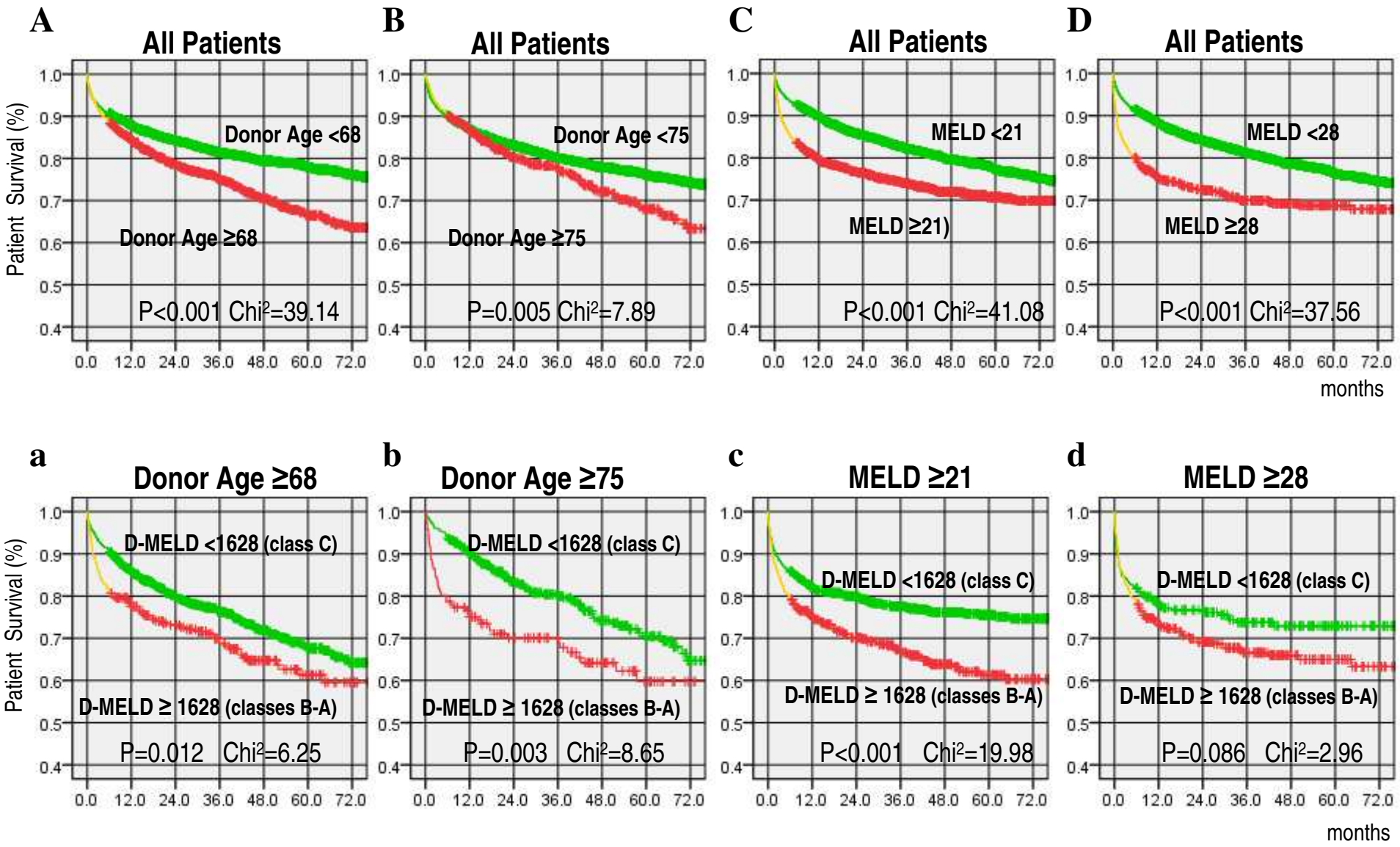

A
All Patients
Donor Age <68
Donor Age ≥68
P<0.001 Chi²=39.14
B
All Patients
Donor Age <75
Donor Age ≥75
P=0.005 Chi²=7.89
C
All Patients
MELD <21
MELD ≥21)
P<0.001 Chi²=41.08
D
All Patients
MELD <28
MELD ≥28
P<0.001 Chi²=37.56
Patient Survival (%)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.0 12.0 24.0 36.0 48.0 60.0 72.0
months
a
Donor Age ≥68
D-MELD <1628 (class C)
D-MELD ≥ 1628 (classes B-A)
P=0.012 Chi²=6.25
b
Donor Age ≥75
D-MELD <1628 (class C)
D-MELD ≥ 1628 (classes B-A)
P=0.003 Chi²=8.65
c
MELD ≥21
D-MELD <1628 (class C)
D-MELD ≥ 1628 (classes B-A)
P<0.001 Chi²=19.98
d
MELD ≥28
D-MELD <1628 (class C)
D-MELD ≥ 1628 (classes B-A)
P=0.086 Chi²=2.96
Patient Survival (%)
months

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
		p	*p*	*p*	*p*	*p*	*p*	*p*	*p*	*p*
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

	D-MELD decile	1	2	3	4	5	6	7	8	9
		p	*p*	*p*	*p*	*p*	*p*	*p*	*p*	*p*
Mantel Cox	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 training set.

	% Patient survival								% Graft survival							
	12	24	36	48	60	72	mo	P	12	24	36	48	60	72	mo	P
D-MELD																
- Class A (66-336)	95	93	92	90	89	88			93	91	89	88	88	87		
- Class B (338-1628)	88	84	80	78	76	74			85	80	77	75	73	71		
- Class C (1632-3240)	77	72	69	65	63	61	**<0.001**		73	68	65	62	58	56	**<0.001**	
Donor age																
- 1 decile (12-24)	89	88	87	86	85	84			89	87	86	85	84	84		
- 2 decile (24-35)	93	91	89	86	86	86			91	89	86	84	84	84		
- 3 decile (35-44)	87	83	82	80	79	79			84	80	78	76	76	76		
- 4 decile (44-51)	87	83	79	77	75	71			84	80	76	75	73	69		
- 5 decile (51-56)	87	86	82	81	78	77			84	82	77	76	74	74		
- 6 decile (56-60)	87	82	79	75	73	69			83	79	75	72	69	66		
- 7 decile (60-66)	87	81	78	77	74	70			83	79	74	71	69	66		
- 8 decile (66-70)	85	81	78	75	73	72			83	79	77	73	71	70		
- 9 decile (70-76)	85	79	73	69	63	62			82	75	70	66	61	60		
- 10 decile (76-97)	87	79	77	73	70	63	**<0.001**		80	73	71	68	65	58	**<0.001**	
MELD																
- 1 decile (6-8)	94	90	86	85	83	83			91	86	82	82	80	80		
- 2 decile (9-10)	90	88	85	81	77	75			88	85	81	78	74	72		
- 3 decile (11-12)	93	86	82	81	80	79			90	83	79	78	77	76		
- 4 decile (13-13)	87	82	78	76	75	73			81	77	74	72	70	69		
- 5 decile (14-15)	87	83	80	78	78	76			85	80	78	76	76	73		
- 6 decile (16-17)	90	86	82	78	73	72			87	81	78	73	69	68		
- 7 decile (18-19)	88	84	81	78	76	70			86	81	78	77	74	67		
- 8 decile (20-22)	82	80	80	78	74	72			81	79	79	77	73	71		
- 9 decile (23-28)	84	82	78	74	72	72			80	77	73	70	68	68		
- 10 decile (29-41)	77	72	70	70	70	69	**<0.001**		74	70	67	67	67	65	**<0.001**	
Recipient age																
- ≥ 60 years	85	80	77	74	72	69			83	78	75	72	70	68		
- < 60 years	88	84	81	80	77	75	**0.002**		85	81	77	76	74	72	**0.048**	
Recipient gender																
- Male	88	84	80	78	75	73			85	81	78	74	72	70		
- Female	85	81	79	77	76	74	**0.596**		82	77	75	74	73	72	**0.624**	
HCV status																
- Positive	86	80	76	73	69	66			82	77	73	70	66	64		
- Negative	87	86	84	83	82	81	**<0.001**		86	83	81	80	79	78	**<0.001**	
HBV status																
- Positive	91	88	86	85	83	83			88	85	83	82	81	80		
- Negative	87	82	78	75	73	70	**<0.001**		83	78	75	72	70	68	**<0.001**	
Alcohol status																
- Positive	87	85	81	79	77	75			84	81	77	75	74	72		
- Negative	87	83	80	78	76	74	**0.672**		84	80	77	75	73	71	**0.895**	
Acute liver failure status																
- Positive	75	73	73	71	71	71			75	73	71	69	69	69		
- Negative	87	84	80	78	76	74	**0.044***		85	80	77	75	73	71	**0.161**	
HCC status																
- Positive	89	84	80	78	75	73			87	82	77	75	72	71		
- Negative	86	83	80	78	75	73	**0.703**		82	80	77	75	73	71	**0.271**	
Pre-Tx abdominal surgery																
- Yes	86	82	80	78	76	76			82	78	76	73	72	72		
- No	87	83	80	77	75	72	**0.796**		84	80	77	74	73	70	**0.621**	
Pre-Tx portal thrombosis																
- Yes	82	80	77	74	74	72			78	75	72	69	69	67		
- No	87	83	80	78	75	73	**0.306**		84	80	76	74	72	70	**0.103**	
Dialysis																
- Yes	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***	
Listing days																
- ≥90	86	83	80	77	76	73			82	77	74	73	70	70		
- <90	88	84	81	79	77	74	**0.286**		85	80	77	75	73	71	**0.352**	
Re-transplant																
- Yes	74	69	65	59	55	50										
- No	88	84	81	79	77	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**	
Donor gender																
- Male	87	83	80	76	75	74			84	80	76	74	72	71		
- Female	87	83	80	78	75	74	**0.981**		84	80	77	75	73	70	**0.894**	
Donor HBcAb																
- Positive	87	83	80	78	76	73			84	80	76	76	70	69		
- Negative	88	83	80	77	75	74	**0.971**		84	80	77	75	73	71	**0.524**	
Donor-recipient gender match																
- Female->Male	88	84	80	78	76	73			85	81	77	75	73	70		
- Female->Female	85	81	80	78	76	74			82	77	76	74	73	71		
- Male->Female	85	81	79	76	76	75			82	78	76	74	73	72		
- Male->Male	87	84	80	77	75	73	**0.972**		84	81	77	74	72	70	**0.928**	
Donor-recipient gender concordance																
- Yes	87	83	80	77	75	73			84	80	76	74	72	70		
- No	87	83	80	78	76	74	**0.835**		85	80	77	75	73	71	**0.608**	
Cold ischemia time																
- ≥ 8 hours	86	82	79	76	75	73			83	80	76	75	74	73		
- < 8 hours	87	84	81	78	76	74	**0.641**		84	81	78	76	75	74	**0.721**	
Biennium																
- 2002-2003	86	83	80	78	74	71			82	78	75	73	70	68		
- 2004-2005	87	82	80	78	77	75			84	80	78	75	74	73		
- 2006-2007	87	83	80	77	76				85	81	76	74	73			
- 2008-2009	88	85					**0.274**		85	82					**0.107**	
Centre volume																
- Low	84	81	78	76	74	70			82	79	76	74	73	69		
- Medium	88	84	80	79	76	76			85	80	77	75	73	72		
- High	89	85	82	79	77	75	**0.016***		85	81	78	75	73	72	**0.394**	

*Not significant in the validation set.

Table S3. Kaplan Meier curves in the validation set.

	% Patient survival								% Graft survival							
	12	24	36	48	60	72	mo	P	12	24	36	48	60	72	mo	P
D-MELD																
- Class A (66-336)	96	92	90	88	88	87			94	90	88	87	87	86		
- Class B (338-1628)	88	83	80	77	75	73			84	79	76	73	72	70		
- Class C (1632-3240)	71	68	67	63	61	61	**<0.001**		64	62	61	58	58	58	**<0.001**	
Donor age																
- 1 decile (12-24)	90	87	84	82	82	82			88	84	81	80	80	80		
- 2 decile (24-35)	88	84	83	81	79	74			85	82	81	79	77	74		
- 3 decile (35-44)	90	87	85	82	81	81			89	85	82	80	79	79		
- 4 decile (44-51)	89	85	82	80	79	79			86	83	80	78	75	75		
- 5 decile (51-56)	89	84	80	79	78	75			86	80	77	76	75	71		
- 6 decile (56-60)	88	84	77	72	71	71			88	83	75	73	70	70		
- 7 decile (60-66)	88	83	80	80	78	75			85	79	77	76	75	72		
- 8 decile (66-70)	83	76	74	72	72	70			80	72	72	68	68	66		
- 9 decile (70-76)	77	72	69	64	57	54			72	66	62	58	55	52		
- 10 decile (76-97)	87	85	80	69	68	68	**<0.001**		79	78	73	64	61	61	**<0.001**	
MELD																
- 1 decile (6-8)	92	88	83	78	77	73			90	84	80	75	73	70		
- 2 decile (9-10)	93	88	85	81	81	79			89	85	81	78	76	74		
- 3 decile (11-12)	93	91	88	84	84	84			90	87	84	80	80	80		
- 4 decile (13-13)	87	81	79	77	73	70			83	78	75	75	75	69		
- 5 decile (14-15)	91	88	82	79	77	77			89	86	80	77	76	76		
- 6 decile (16-17)	89	82	79	79	77	72			85	78	75	74	73	68		
- 7 decile (18-19)	85	80	77	74	71	67			81	76	73	70	67	64		
- 8 decile (20-22)	87	82	81	76	73	73			83	76	75	71	67	65		
- 9 decile (23-28)	81	77	75	75	75	73			78	74	72	72	72	70		
- 10 decile (29-41)	69	67	63	62	60	60	**<0.001**		65	63	60	60	60	60	**<0.001**	
Recipient age																
- ≥ 60 years	83	77	74	72	69	65			80	75	72	70	68	64		
- < 60 years	89	84	81	78	77	75	**<0•001**		85	80	77	75	73	72	**0.017**	
Recipient gender																
- Male	87	83	80	77	75	73			84	80	77	74	72	70		
- Female	85	80	77	75	74	72	**0.102**		81	76	73	71	71	69	**0.289**	
HCV status																
- Positive	85	79	75	71	70	67			82	76	72	68	66	64		
- Negative	89	86	84	82	80	78	**<0.001**		85	82	80	78	77	76	**<0.001**	
HBV status																
- Positive	92	88	86	84	83	82			90	87	85	83	82	81		
- Negative	85	80	77	74	72	70	**<0.001**		82	76	73	70	69	66	**<0.001**	
Alcohol status																
- Positive	88	84	82	80	77	77			83	79	77	75	74	73		
- Negative	87	82	79	76	74	72	**0.198**		84	79	76	73	72	70	**0.626**	
Acute liver failure status																
- Positive	75	75	75	71	71	71			69	69	69	65	65	65		
- Negative	87	83	79	77	75	73	**0.264**		84	79	76	74	72	70	**0.124**	
HCC status																
- Positive	89	84	80	76	73	71			88	82	78	74	71	68		
- Negative	85	81	79	77	76	74	**0.859**		81	77	75	73	72	71	**0.202**	
Pre-Tx abdominal surgery																
- Yes	86	83	81	76	74	72			84	80	78	75	75	70		
- No	86	82	78	75	74	73	**0.727**		83	78	75	72	71	70	**0.424**	
Pre-Tx portal thrombosis																
- Yes	82	74	70	70	70	70			78	70	66	66	66	66		
- No	87	83	79	76	74	73	**0.133**		83	79	76	73	71	70	**0.129**	
Dialysis																
- Yes	58	58	58	58	58	58			58	58	58	58	58	58		
- No	88	84	80	77	75	74	**0.018**		85	80	76	73	72	71	**0.061**	
Listing days																
- ≥90	88	84	81	78	76	74			85	80	78	75	73	72		
- <90	86	81	78	75	74	72	**0.163**		82	77	73	72	70	68	**0.091**	
Re-transplant																
- Yes	67	61	61	55	53	50										
- No	88	84	80	80	76	75	**<0.001**									
Donor age																
- ≥ 60 years	84	79	76	72	75	77			79	74	71	67	66	63		
- < 60 years	89	85	82	80	79	77	**<0.001**		87	83	80	78	77	75	**<0.001**	
Donor gender																
- Male	87	82	80	77	74	72			84	79	76	74	72	69		
- Female	87	83	80	77	76	75	**0.501**		83	79	75	73	72	71	**0.799**	
Donor HBcAb																
- Positive	83	79	75	72	71	71			79	75	71	69	68	66		
- Negative	88	83	80	77	75	73	**0.106**		84	79	76	74	72	71	**0.119**	
Donor-recipient gender match																
- Female->Male	86	83	80	76	76	75			84	78	75	73	72	71		
- Female->Female	86	83	80	77	75	74			83	78	75	73	72	71		
- Male->Female	81	77	75	73	72	69			77	73	71	69	69	67		
- Male->Male	88	84	80	77	75	72	**0.531**		86	81	78	75	72	70	**0.435**	
Donor-recipient gender concordance																
- Yes	88	84	80	77	75	73			85	78	77	74	72	70		
- No	85	81	79	76	74	73	**0.589**		81	77	74	72	71	70	**0.339**	
Cold ischemia time																
- ≥ 8 hours	85	83	80	78	75	73			83	80	77	76	74	72		
- < 8 hours	87	85	82	79	76	75	**0.538**		85	82	79	75	74	73	**0.597**	
Biennium																
- 2002-2003	89	85	83	80	77	75			85	81	79	75	73	71		
- 2004-2005	86	82	79	77	75	74			83	79	76	74	73	71		
- 2006-2007	84	80	77	74	74				81	77	77	71	71			
- 2008-2009	89	83					**0.296**		86	80					**0.353**	
Centre volume																
- Low	85	80	77	74	72	71			83	78	74	71	70	69		
- Medium	86	83	80	78	76	74			82	79	76	74	73	70		
- High	87	84	81	78	76	74	**0.139**		85	80	77	74	73	70	**0.558**	

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).

	Exitus		Exitus		Failure		Failure	
At 1 years	Training set		Validation set		Training set		Validation 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**		**0.310**		**0.607**		**0.132**

	Exitus		Exitus		Failure		Failure	
At 3 years	Training set		Validation set		Training set		Validation 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**