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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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Donor–recipient match is a matter of debate in liver transplantation. D-MELD (donor age × recipient biochemical model for end-stage liver disease [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% (5yrsPS<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 class B. Other predictors were hepatitis C virus (HCV; OR = 1.42; 95% CI, 1.11–1.81), hepatitis B virus (HBV; OR = 0.69; 95% CI, 0.51–0.93), retransplant (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 was 1.97 (95% CI, 1.59–2.43) for D-MELD class C versus class B and 0.42 (95% CI, 0.29–0.60) for D-MELD class A versus class B. Recipient age, HCV, HBV and retransplant were also significant. The 5yrsPS<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.

Key words: D-MELD, donor–recipient match, liver transplantation, outcome, prognosis, risk factors

Abbreviations: AID, autoimmune disease; ALF, acute liver failure; CI, confidence interval; DCD, donation after cardiac death; D-MELD, arithmetical product of donor age and biochemical MELD; DRI, donor risk index; ELTR, European Liver Transplant Registry; HbcAb, hepatitis B anticore; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; LTA, Lazio Transplant Agency; MELD, Model for End-stage Liver Disease; Mo, month; N, number; OR, odds ratio; UNOS-STAR, United Network for Organ Sharing-Standard Transplant Analysis and Research File; Yr, year; Yrs, years.

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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 mismatch 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 and 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 1 year later in larger series (3,5). Models able to predict 3- and 12-month mortality from donor and recipient parameters have been developed on the European Liver Transplant Registry 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] (8), was developed on the American United Network for Organ Sharing-Standard Transplant Analysis and Research File 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 in Italy than in the United States (3,7,9,10) or elsewhere in Europe (6,11,12). Unlike in major North American studies (1,6,13,14), we used donor age instead of the Donor Risk Index (DRI; Ref. 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, hepato-cellular carcinoma (HCC) patients undergoing liver transplantation commonly show a lower degree of liver function decompensation as compared to hepatitis C virus (HCV) candidates (16).

Primary endpoint of the this 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: (1) patient survival at 90 days and 1 year; (2) graft survival at 90 days, 1 and 3 years and (3) 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% (5yrsPS<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 1, 2002 to December 31, 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 recovered 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 retransplant 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, HCC status, previous abdominal surgery, pretransplant patency of portal vein, renal failure (at least one dialysis during the week before transplantation), biochemical MELD score at transplant, cold ischemia time (CIT), dates of listing, transplant, retransplant, 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 and 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. Because 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. 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).

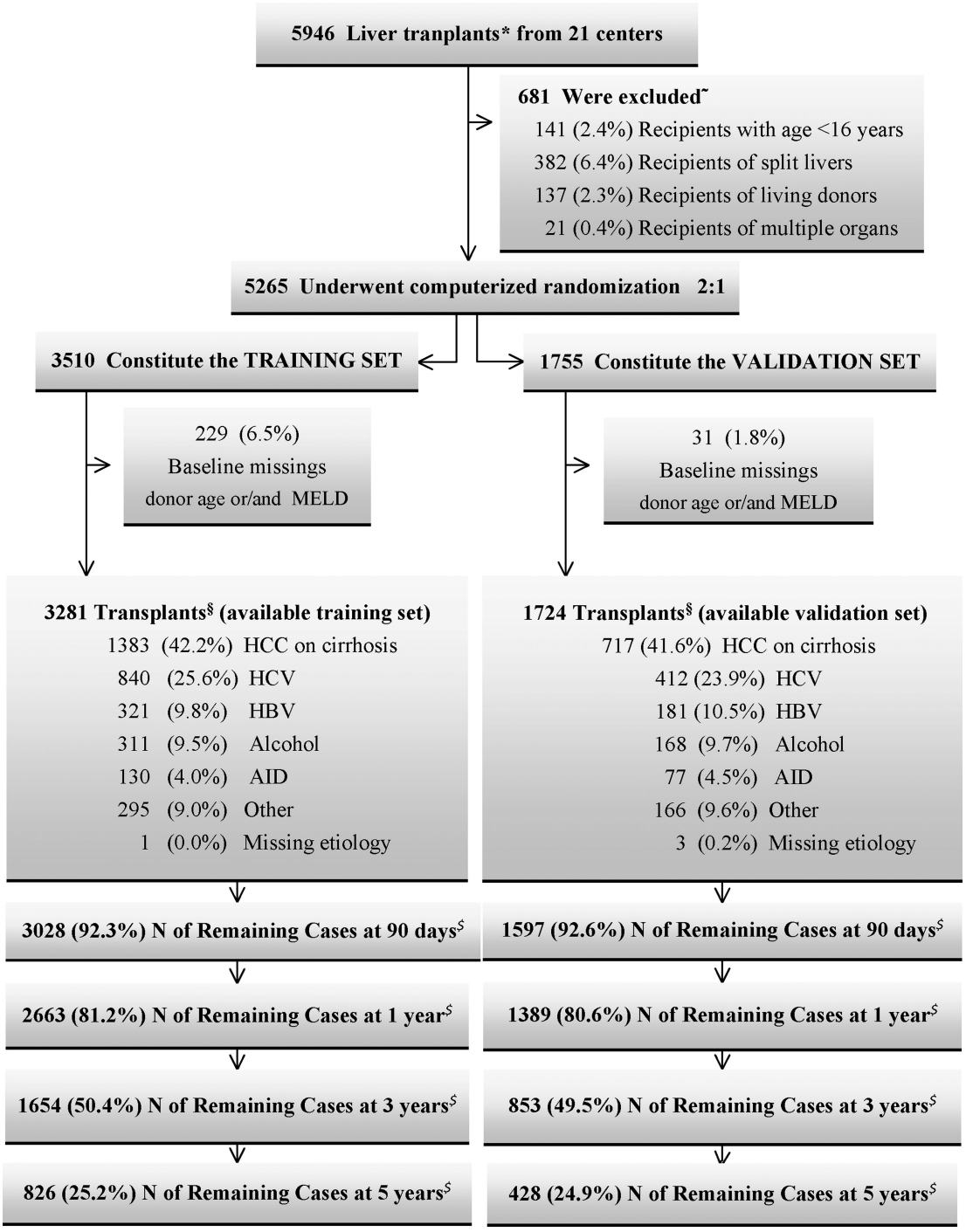


Figure 1: Enrolment and outcomes through month 60. *Patients with acute liver failure (ALF) were included. MELD exception points for patients with hepatocellular carcinoma (HCC) were not considered. Patients with MELD scores >40 (N = 62, 1.2%) were reclassified as MELD 40. ˜Exclusions were performed 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 retransplant. §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. Because 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).

According to Thuluvath et al. (20) and in conformity with statistical guidelines in organ transplantation (21,22), the overall data set was randomly split into a training set (two-third of the records), utilized to generate the main model and a validation set (one-third). 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 performed, 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 $p \leq 0.25$ at univariate analyses entered the models. The results were expressed as odds ratio (OR) and hazard ratio with 95% confidence intervals (95% CI). Statistical evaluation of the model was also performed in order to avoid variable colinearity. 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 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 (SAS Institute Inc., Cary, NC, USA). ver. 9.0 and SPSS (SPSS Inc., Chicago, IL, USA) 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 and 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 (Figures 3A and 3B) and graft survival (Figures 3C and 3D). Significant differences were found solely between decile 1 versus deciles 2–10 and between deciles 1–9 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 toward 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 retransplant 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). Hepatitis B virus (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.

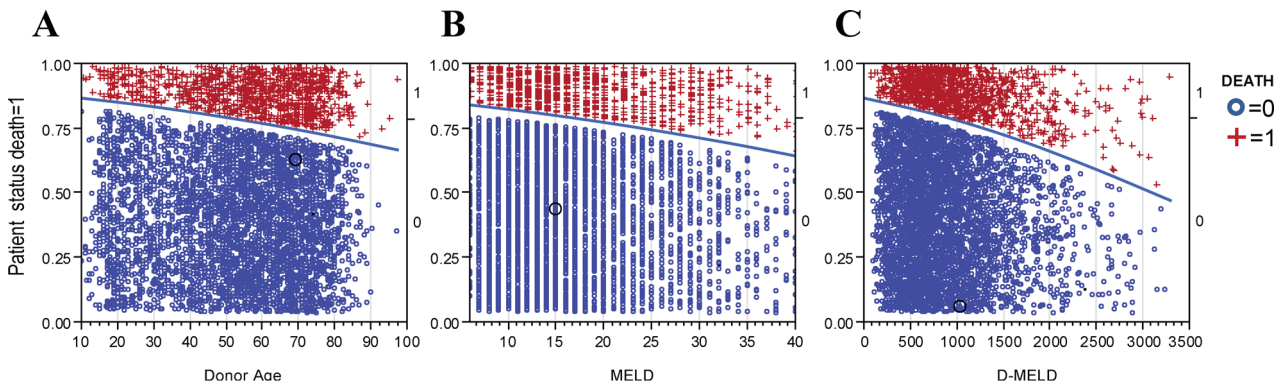
Secondary endpoints and additional analyses

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 retransplant 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 (Table 3).

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



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

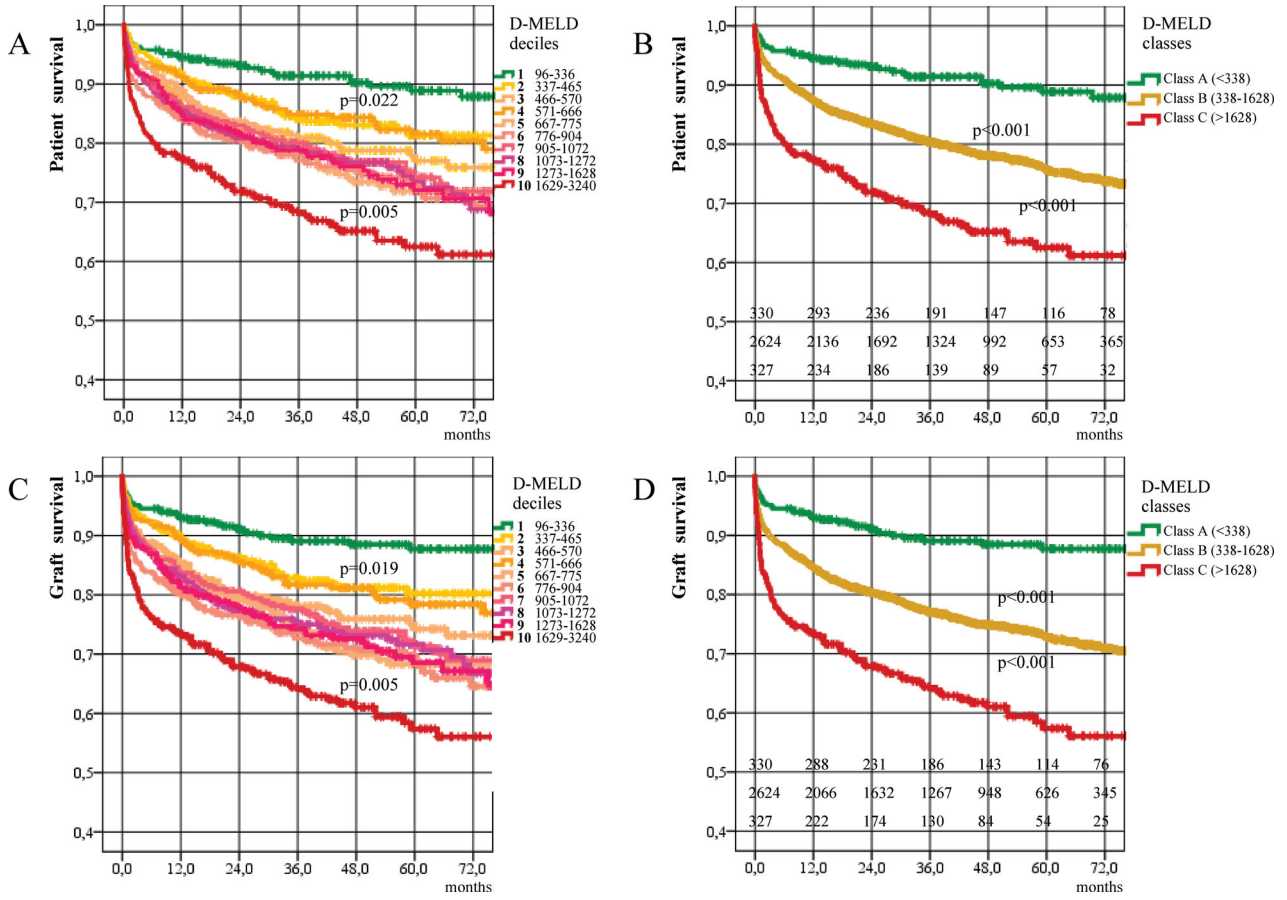


Figure 3: Stratification of D-MELD deciles (A–C) and of D-MELD classes (B–D) in terms of patient and graft survivals.

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[1]
MELD (N = 3281; 100.0%)	11.5 ± 4.3	16.1 ± 6.2	30.5 ± 5.8	<0.001[1]
MELD in HCC+ (N = 1380; 42.1%)	10.1 ± 5.2	13.7 ± 5.5	28.1 ± 5.2	<0.001[1]
MELD in HCV+ (N = 1570; 47.9%)	11.8 ± 4.0	15.6 ± 5.7	29.5 ± 5.4	<0.001[1]
MELD in HCV+ HCC+ (N = 789; 24.1%)	10.5 ± 3.2	13.9 ± 5.3	27.5 ± 4.8	<0.001[1]
MELD in HCV+ HCC− (N = 781; 23.8%)	13.7 ± 4.3	17.5 ± 5.9	30.6 ± 5.4	<0.001[1]
Recipient age (N = 3260; 99.3%)	50.3 ± 11.2	53.5 ± 9.1	49.7 ± 10.5	<0.001[1]
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[1]
Retransplant (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[1]
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[2] (N = 2705; 82.4%)	8.2 ± 2.1	9.1 ± 3.3	6.9 ± 2.7	0.043[1]
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 center (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.
[1]Kruskal–Wallis test; all the other p-values were obtained by Chi-square test.
[2]Hour.

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).

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[1]																		
Class A versus 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 versus 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[2]	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 versus 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[2]
HBV status																		
Positive versus 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[2]	0.86	(0.64–1.16)	0.328[3]	0.72	(0.55–0.94)	0.014	0.72	(0.54–0.95)	0.019
Pre-tx portal thrombosis																		
Yes versus no	1.9	(1.21–2.96)	0.005[2]	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
Retransplant																		
Yes versus 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[2]	–	–	–	–	–	–	–	–	–
Biennium																		
'02–'03 versus '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 versus '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[2]	0.82	(0.59–1.13)	0.228	0.81	(0.61–1.07)	0.135	0.72	(0.57–0.92)	0.009[2]
'06–'07 versus '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[2]	0.78	(0.59–1.02)	0.068	–	–	–
Volume of the center																		
Low versus medium	2.21	(1.56–3.12)	<0.001	1.91	(1.43–2.54)	<0.001[2]	1.48	(1.11–1.99)	0.008	1.56	(1.15–2.12)	0.004[2]	1.57	(1.24–2.04)	0.001[2]	1.27	(0.96–1.68)	0.094
High versus medium	0.64	(0.43–0.94)	0.022[2]	0.83	(0.62–1.12)	0.219[3]	0.85	(0.64–1.13)	0.26	0.81	(0.59–1.10)	0.175[3]	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
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

[1]D-MELD was analyzed also as a continuous variable. To comply with the four digit integers, D-MELD values were divided by 100 to achieve two digit decimals of Odd Ratio (OR). OR, 95% CI and significances at 90 days, 1 year, 3 years for the continuos model, 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.

[2]Not significant in the validation set.

[3]Significant in the validation set.

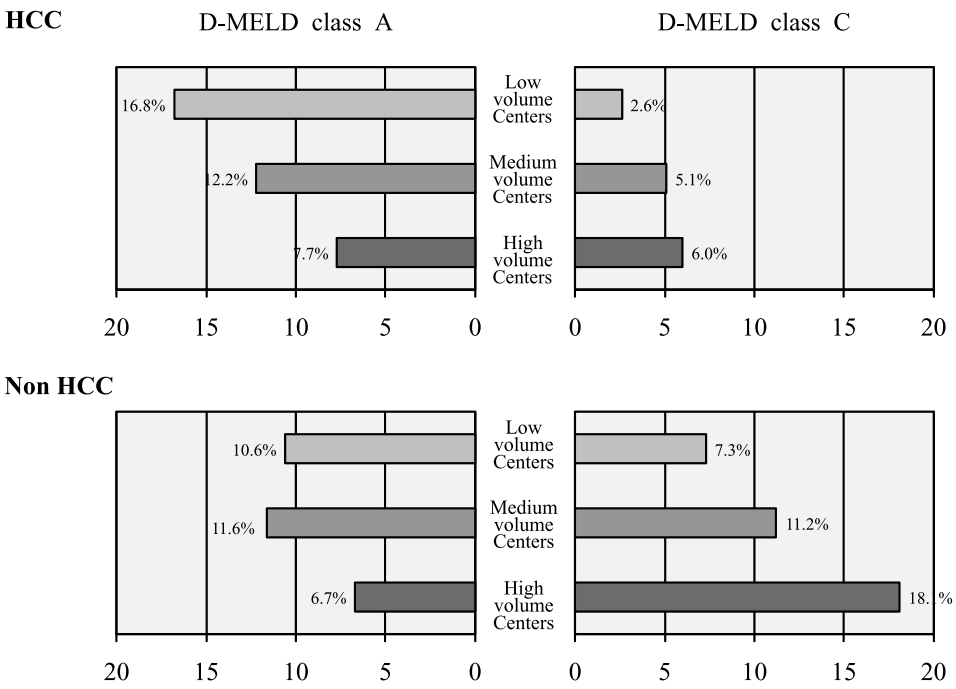


Figure 4: Prevalences of D-MELD class A and D-MELD class C in HCC and non-HCC patients according to the transplant volume of the center ($p < 0.001$). Variability of D-MELD reflects different policies concerning donor age limit and severity of recipient liver disease, in relation to different match modalities.

To explore potential clinical applications of D-MELD, we searched for specific patients subgroups with a 5yrsPS<50% predictable by D-MELD. The cutoff value predicting the 5yrsPS<50% was identified in HCV patients only (D-MELD $\geq$ 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 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 (26,27). 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, pretransplant portal thrombosis, retransplant, biennium of transplantation and center volume. As recently reported (28), 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, whereas HBV has a protective effect and the effect of the primary disease is generally more evident in the long run (11,13,29,30). However, the prognostic power of HCV, portal thrombosis

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[1]						
Class A versus class B	0.42	(0.29–0.60)	<0.001	0.41	(0.29–0.58)	<0.001
Class C versus 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[2]
HCV status						
Positive versus negative	1.43	(1.21–1.70)	<0.001	1.40	(1.20–1.64)	<0.001[3]
HBV status						
Positive versus negative	0.72	(0.58–0.89)	0.002	0.75	(0.62–0.91)	0.004
Retransplant						
Yes versus no	2.21	(1.70–2.87)	<0.001	–	–	–
Biennium						
2002–2003 versus 2008–2009	1.28	(0.99–1.65)	0.096	1.14	(1.07–1.71)	0.010[2]
2004–2005 versus 2008–2009	1.06	(0.84–1.33)	0.627	1.03	(0.84–1.27)	0.784
2006–2007 versus 2008–2009	1.28	(0.99–1.65)	0.056	1.09	(0.89–1.33)	0.416
Volume of the Center						
Low versus medium	1.35	(1.11–1.65)	0.003[1]	1.19	(0.99–1.45)	0.059
High versus 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

[1]D-MELD was analyzed also as a continuous variable. To comply with the four digit integers, D-MELD values were divided by 100 to achieve two 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.

[2]Not significant in the validation set.

[3]0.051 in the validation set.

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 pretransplant abdominal surgery, gender match, gender concordance, CIT and HBcAb-positivity, although these factors were found significant by other authors (6,9,13,19,31–33). Because of the peculiar donor characteristics, extreme attention was paid to keep 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 because of the fact that the majority of patients complied with Milan criteria, a condition that keeps down the risk of recurrence (16,34). Because of 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, whereas 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 subanalyses to be performed to identify the 5yrPS<50% cutoff. The concept of the 5yrsPS<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 (37). However, in both approaches, the 50% value and its 5-year time limit were arbitrarily set. As yet, stratification in relation to the 5yrsPS<50% cutoff has not been performed using a single quantitative parameter (38,39) nor have different percentages and time-limits been identified according to etiology. In this study HCV and HBV had a predictive role in several prognostic models. Since HBV patients had a more favorable outcome, the 5yrsPS<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 because of 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 data set, an even poorer prognosis was predicted by the 5yrsPS<50% cutoff (D-MELD $\geq$ 1750) in HCV patients.

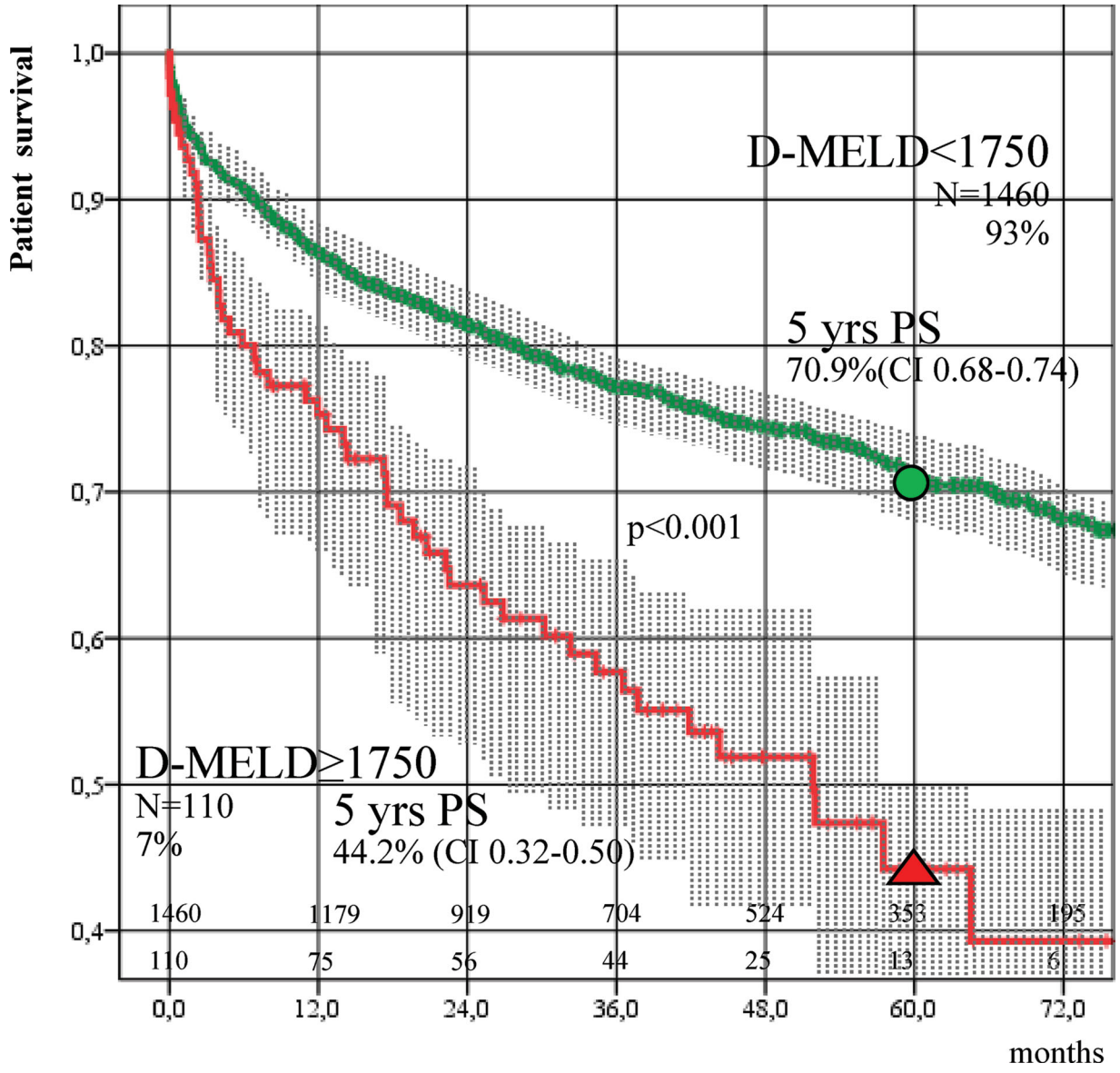


Figure 5: D-MELD cutoff identifying a population characterized by 5-year patient survival <50% (5yrsPS<50%) among HCV positive patients (including those with HCC). The cutoff (unsustainable match cutoff) was identified at D-MELD value 1750 in the training set (5-year patient survival = 44.2%, 95% CI 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, the model was built keeping the upper limit of the confidence interval below 50% at 5 years in both sets.*

Using the 5yrsPS<50% cutoff could be misleading because it is not evidence based. However, it identifies a subgroup of HCV patients with a performance status below the currently defined minimal survival requirements. The 5yrsPS 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 5yrsPS<50% *transplant cutoff* toward 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 second 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.

Although 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 retransplantation 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. First, to provide a direct example of how donor and recipient factors interact in determining prognosis. Second, to help hepatologists, transplant surgeons and transplant coordinators in the everyday practice of matching donor and recipient factors when choosing the recipient. Finally, 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. First, 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). Second, 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 5yrsPS<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. Second, the high number of patients harboring HCC may represent a selection bias. It means that coefficients, analyses and conclusions obtained in this Italian study may not be directly applicable to countries with different donor and recipient populations. Third, 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 5yrsPS<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*.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1: Histograms of donor age, MELD, and D-MELD according to the 4 study biennia.

Figure S2: Overall patient survival for recipients (A) by donor age $\geq$68 (upper quartile), (B) by donor age $\geq$75 (upper decile), (C) by MELD $\geq$21 (upper quartile), and (D) by MELD $\geq$28 (upper decile).

Table S1: *p*-Values obtained by KaplanMeier comparison among D-MELD deciles in the training set

Table S2: Kaplan–Meier curves in the training set

Table S3: Kaplan–Meier curves in the validation set

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)

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