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**A Bayesian methodology to improve prediction of early graft loss after liver transplantation derived from the Liver Match study**

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(Article begins on next page)

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Abstract: To generate a robust predictive model of Early (3 month) Graft Loss (EGL), we used a Bayesian approach to combine evidence from a prospective European cohort (Liver-Match) and the UNOS registry. Liver-Match included 1480 consecutive primary LTs performed from 2007 to 2009 and the UNOS a time-matched series of 9740 LTs. There were 173 and 706 EGL, respectively. Multivariate analysis identified as significant predictors of EGL: donor age, donation after cardiac death, cold ischemia time, donor body mass index and height, recipient creatinine, bilirubin, disease etiology, prior upper abdominal surgery and portal thrombosis. A Bayesian Cox model was fitted to Liver-Match data using the UNOS findings as prior information, allowing to generate an EGL-Donor Risk Index (EGL-DRI) and an EGL-Recipient Risk Index (EGL-RRI). A Donor-Recipient Allocation Model (DReAM), obtained by adding EGL-DRI to EGL-RRI, was then validated in a distinct UNOS (year 2010) cohort including 2964 LTs. Further DReAM updating using the independent Turin Transplant Center dataset, allowed to predict EGL with rather good accuracy (c-statistic: 0.76). In conclusion. DReAM allows a reliable donor and recipient-based EGL prediction. The Bayesian approach permits to adapt the original DReAM by incorporating evidence from other cohorts, resulting in significantly improved predictive capability

Prof. Mario Angelico  
Editor in Chief  
Digestive and Liver Disease

September 10, 2013

**Re: Original article submission to Digestive and Liver Disease**

Dear Prof. Angelico,

please find enclosed the manuscript entitled "A BAYESIAN METHODOLOGY TO IMPROVE PREDICTION OF EARLY GRAFT LOSS AFTER LIVER TRANSPLANTATION. THE LIVER MATCH STUDY, which I am pleased, on behalf of all coauthors, to submit to Digestive and Liver Disease, as an original manuscript. All the listed authors have given relevant intellectual contributions, either in the design and conduction of the study, data analysis, or writing of the final paper. None has conflict of interests in relation to the contents. Data presented herein have not been published anywhere, in whole or in part, except in abstract form.

Briefly, we developed and validated a novel predictive score of early graft loss, an event still representing a significant proportion of liver transplant failures. We used a Bayesian approach to statistical inference to incorporate prior knowledge derived from the UNOS/OPTN series into new evidence emerged from the prospective Liver Match study, which resulted into robust and precise predictions. The newly generated score, DReAM, was validated in a separate series of transplants from the UNOS/OPTN database. DReAM proved to be reasonably accurate in predicting EGL and performed significantly better than other available scores. Notably, we also show how the Bayesian methodology allows the adaptation of the DReAM score to other different geographic realities.

I hope that you this paper could be of interest for your readers.

Yours sincerely

Renato Romagnoli, MD  
Turin University

## CONFLICT OF INTEREST STATEMENT

The Authors of the manuscript entitled "A BAYESIAN METHODOLOGY TO IMPROVE PREDICTION OF EARLY GRAFT LOSS AFTER LIVER TRANSPLANTATION. THE LIVER MATCH STUDY" have no conflicts of interest to disclose.

Best regards

Renato Romagnoli

To the Editor

DLD

**RE: DLD 677 R1**

Dear Editor,

Please find enclosed a corrected version of our paper. Thank you for your consideration for our work and for allowing us to resubmit this paper to DLD.

Renato Romagnoli, MD

Please find also a point-by-point reply related to all changes that has been made:

Reviewer n. 1

- The title has been changed as suggested.
- The abstract has be structured as suggested
- Tables 1-2 have been simplified.
- As for Table 4, we would prefer to keep in the full text as it contains very relevant data for the understanding of the model.

Reviewer n. 2

- We thank the reviewer for his point about the lack of accuracy of the model in predicting graft failure in the first week after LT. We have further expanded the discussion about this important point in the revised version.
- The speculation about adrenal insufficiency in alcohol-related cirrhosis undergoing transplantation as a cause of graft failure, is sound. As this was an unexpected result of Liver Match, we would prefer to analyze these data in greater details in another dedicated paper.
- The analysis was done both including or excluding FHF. Since there were no major changes in the results nor in the strength of the models, we decided to include FHF, so that the new model may occasionally serve also allocation issue for FHF.



A BAYESIAN METHODOLOGY TO IMPROVE PREDICTION OF EARLY GRAFT LOSS  
AFTER LIVER TRANSPLANTATION DERIVED FROM THE LIVER MATCH STUDY

Mario Angelico<sup>1,13</sup>, Alessandra Nardi<sup>2</sup>, Renato Romagnoli<sup>3,13</sup>, Tania Marianelli<sup>1,13</sup>, Stefano Ginanni Corradini<sup>4,13</sup>, Francesco Tandoi<sup>3</sup>, Caius Gavrilă<sup>2</sup>, Mauro Salizzoni<sup>3</sup>, Antonio D. Pinna<sup>5</sup>, Umberto Cillo<sup>6,13</sup>, Bruno Gridelli<sup>7</sup>, Luciano G. De Carlis<sup>8</sup>, Michele Colledan<sup>9</sup>, Giorgio E. Gerunda<sup>10</sup>, Alessandro Nanni Costa<sup>11</sup> and Mario Strazzabosco<sup>12,13</sup>, for the Liver Match study investigators\*

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\*For the composition of the Liver Match study group see appendix

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### **Running Head**

Prediction of early graft loss after liver transplantation

### **Abbreviations**

LT, liver transplantation; ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; EGL, early graft loss; US, United States; DRI, donor risk index; ET-DRI, Eurotransplant DRI; SOFT, survival outcomes following liver transplantation; MELD, model for end-stage liver disease; D-MELD, product of donor age and MELD; BAR, balance of risk model; CIT, cold ischemia time; OPTN, Organ Procurement Transplantation Network; UNOS, United Network for Organ Sharing; AISF, Associazione Italiana per lo Studio del Fegato; CNT, Centro Nazionale Trapianti; FHF, fulminant hepatic failure; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steato-hepatitis; BMI, body mass index; ROC, receiver operating characteristic; DReAM, Donor-



Recipient Allocation Model; INR, international normalized ratio; HR, hazard ratio; EGL-DRI, Early graft loss-related Donor Risk Index; EGL-RRI, Early graft loss-related Recipient Risk Index.

### **Acknowledgments**

This study was funded by the Italian Association for the Study of Liver (AISF) and the Italian National Transplant Center (CNT).

The authors thank UNOS for providing the dataset.

### **Disclosures**

The authors of this manuscript have no conflicts of interest to disclose.

### **\* Appendix: Members of the Liver Match study group**

#### **Liver Match Steering Committee:**

- M. Angelico (study coordinator), U. Cillo, S. Faggioli, M. Strazzabosco
- AISF/CPT Governing Board: P. Caraceni, P.L. Toniutto

- CNT Governing Board: A. Nanni Costa

**Participating Transplant Centres & Investigators:**

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**Abstract (201 words)**

**Background:** To generate a robust predictive model of Early (3 month) Graft Loss (EGL), we used a Bayesian approach to combine evidence from a prospective European cohort (Liver-Match) and the UNOS registry.

**Methods:** Liver-Match included 1480 consecutive primary LTs performed from 2007 to 2009 and the UNOS a time-matched series of 9740 LTs. There were 173 and 706 EGL, respectively. Multivariate analysis identified as significant predictors of EGL: donor age, donation after cardiac death, cold ischemia time, donor body mass index and height, recipient creatinine, bilirubin, disease etiology, prior upper abdominal surgery and portal thrombosis.

**Results:** A Bayesian Cox model was fitted to Liver-Match data using the UNOS findings as prior information, allowing to generate an EGL-Donor Risk Index (EGL-DRI) and an EGL-Recipient Risk Index (EGL-RRI). A Donor-Recipient Allocation Model (DReAM), obtained by adding EGL-DRI to EGL-RRI, was then validated in a distinct UNOS (year 2010) cohort including 2964 LTs. Further DReAM updating using the independent Turin Transplant Center dataset, allowed to predict EGL with rather good accuracy (c-statistic: 0.76).

**Conclusion:** DReAM allows a reliable donor and recipient-based EGL prediction. The Bayesian approach permits to adapt the original DReAM by incorporating evidence from other cohorts, resulting in significantly improved predictive capability.

**Key words**

Donor-recipient match, Risk factors, Transplantation outcome, Hepatitis C, Donor Risk Index, Graft failure

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Liver transplantation (LT) is the only curative treatment for end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC) [1]. The discrepancy between patients in need of LT and the supply of cadaveric organs has led to an increasing use of organs bearing a higher risk of graft failure [2,3], a scenario in which it is crucial to find allocation algorithms able to maximize the utility of all procured livers.

Almost one third of LT failures are concentrated in the first three months after LT [4,5], constituting the event called 'Early Graft Loss' (EGL). EGL may be due to a variety of causes, including intra-operative death, primary or delayed non-function, infections, severe rejection, early vascular complications and renal or multi-organ failure [4,6]. Retrospective analyses identified several risk factors of EGL, including advanced donor age, donor hyponatremia, extended cold ischemia time and significant graft steatosis [4,7-9]. However, in the absence of additional donor or recipient risk factors, even the use of grafts from very old donors can be safe [8,9]. Feng et al. [10] analyzing the United States (US) Transplant Registry data from 1998 to 2002 developed the Donor Risk Index (DRI), a predictive model providing continuous estimates of donor-related risk of graft failure. DRI has been recently validated in the Eurotransplant region [11] and a specific Eurotransplant DRI (ET-DRI) implemented [12].

Few predictive scores based on donor and recipient features have been proposed. A model to predict 3-month survival (Survival Outcomes Following Liver Transplantation, SOFT) has been developed [13] combining 18 donor, recipient and operative variables. SOFT, however, has many practical limitations, as many variables are not at hand and the inclusion of covariates with overlapping information might result in a non-negligible degree of multicollinearity, reducing model robustness. The easiest matching model available is D-MELD, the arithmetical product of donor age and MELD [14], recently validated in a retrospective Italian series [15]. Yet, D-MELD oversimplifies the complexity of donor-recipient matching and the use of D-MELD based futility rules might even

endanger high-risk patients with potentially good outcomes well above the proposed cut-off values. In addition, D-MELD is rather inaccurate to predict short-term outcome [16]. A further Balance of Risk Model (BAR) [17] has been recently developed based on 6 predictors of 3-month survival. The BAR risk score, however, does not translate into survival probabilities and is difficult to interpret. In this study we combined new information deriving from a prospective European study (Liver Match) with prior information deriving from a retrospective, year-matched (2007-2009), series from the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS). A Bayesian Cox model was used to generate and validate a robust composite predictive model of EGL, called Donor-Recipient Allocation Model (DReAM). Notably, the Bayes methodology allows to further refine DReAM predictivity by adapting the new score to the specific features of local series.

## **METHODS**

### **Study population**

We used as derivation sets the database of Liver Match, a cohort study endorsed by the Italian Association for the Study of the Liver (AISF) and the Italian National Transplant Center (CNT), and a year-matched database of the OPTN/UNOS.

Liver Match is an observational study which recruited all LTs performed at 20 out of 21 Italian Transplant Centers. Between June 1, 2007 and May 31, 2009 Liver Match enrolled 1480 consecutive adult patients undergoing first LT from deceased heart-beating donors, including 45 (3%) cases of fulminant hepatic failure (FHF). In Italy, though in the absence of a formal endorsement, a MELD-based [18] allocation policy was adopted at most centers to prioritize patients within their own waiting lists.

The OPTN/UNOS series comprised 9740 first adult LTs from deceased donors performed in the US between June 1, 2007 and May 31, 2009, based on OPTN data as of March 2, 2012, including 391

(4.3%) cases of FHF. US transplants were performed according to UNOS criteria and bylaws, involving a MELD-based allocation policy.

Patients who underwent multiorgan LT or retransplantation were excluded.

### **Data management and quality assessment**

The design of the Liver Match study is described elsewhere [19]. Data were entered into a web-based database of the CNT network by trained data managers and adjusted for errors and incompleteness. At the final multivariable analysis 50 patients (3.4%) had incomplete covariates. The study was overseen by a Steering Committee and through quarterly Investigator Meetings.

OPTN/UNOS data were controlled for inconsistencies and variable definitions were harmonized with those in the Italian study. At the final multivariable analysis 1959 (20.1%) records were incomplete.

EGL, defined as graft failure or patient death within 90 days following LT, was the primary endpoint of the study. Patients who did not experience EGL were censored at 90 days.

The main etiologies leading to LT were categorized as hepatitis B (HBV)-related, hepatitis C (HCV)-related and alcohol-related cirrhosis, FHF, cholestatic or autoimmune liver diseases, cryptogenic cirrhosis or non-alcoholic-steato-hepatitis (NASH), and other less frequent liver disorders.

### **Statistical analysis**

Associations between categorical variables were evaluated by chi-square test, Fisher exact test being preferred in case of sparse tables. Mean values of continuous covariates were compared by t-test or Wilcoxon rank-sum test when a significant departure from normality was detected. Survival curves were estimated using the Kaplan Meier method and compared by the log-rank test.

Post-LT survival was analyzed using the Cox model. Predictors of EGL were identified by a non-automate backward selection, taking correlation structure among covariates and clinical interpretation of their effects into account. The variables originally considered are listed in the supplementary material. The final model consisted of variables selected either in the UNOS or in the Liver Match dataset. Plots and diagnostic statistics based on martingale residuals were used for detecting non linear effects of continuous covariates [20].

To combine information from UNOS and Liver Match data, a Bayesian Cox model was developed [21]. Evidence from the US series was translated into probability, assuming informative normal prior distributions for parameters to be estimated. Prior means were set to the estimated regression coefficients by the Cox model and prior variances derived from corresponding standard errors. A non informative, extremely flat normal prior was assumed for modeling the effect of steroids avoidance that was not recorded in the OPTN/UNOS registry. Prior distributions were updated using information from the Liver Match study, as summarized by the partial likelihood of the Cox model, to obtain posterior distributions of regression parameters [22].

The Adaptive Rejection Metropolis Sampling algorithm was used to draw chain of posterior distribution samples. The convergence of the generated Markov chain was evaluated by several diagnostics (lag1, lag5, lag10, and lag50 autocorrelations, Geweke diagnostic, posterior correlation matrix and effective sample size) and plots (trace, autocorrelation function and posterior density plots). There was no indication that the Markov chain had not reached convergence and identical results were obtained for different choices of starting points.

Posterior survival probabilities at 90 days were estimated for different levels of the proposed score with 95% credible intervals. Poorly predicted post-LT survival times were identified by Normal Deviate residuals [23], which indicate the discrepancy between the observed graft failure time and the median failure time predicted according to the final model. Patients whose Normal Deviate



residuals were lower than -1.96 or greater than 1.96, corresponding to the percentiles of the Normal reference distribution for  $\alpha=0.05$ , were identified as outliers.

To evaluate the ability of the Bayesian-derived score to predict EGL, receiver operating characteristic (ROC) curves were computed in the validation and **updating sets** and the area under the curves (c-statistic) reported. ROC comparisons were based on differences between the areas under the curves [24]. Analyses were performed using SAS version 9.3 statistical package (SAS Institute, Cary, NC).

## RESULTS

### Characteristics of the model derivation cohorts

Donor and recipient characteristics of the Liver Match study were reported elsewhere [19]. A comparison between these patients and those included in the OPTN/UNOS series is shown in **Table 1**. The donor population was older in the Liver Match series: median age was 56 years, 41% of donors were older than 60 years and 3.9% older than 80 years. In the US series the median donor age was 43 years, 15.3% of donors were older than 60 and 0.5% older than 80 years. BMI was higher in the US series (median BMI: 26.1) with 58.8% of donors being overweight and 25.3% obese. In the Liver Match series median BMI was 25, with 50% of the donor population being overweight and 10.2% obese. Split LT was performed more often in the Liver Match (5.3%) than in the US series (1.4%). Donors after cardiac death (DCD) were not used in Liver Match study, but accounted for 5.4% of the US transplants.

The median recipient age was similar in the two series, while BMI was higher in the US series (median: 27.8 vs 25.0). Portal vein thrombosis and previous upper abdominal surgery were more frequent in US than in Liver Match recipients (6.3% vs 2.4% and 39.1% vs 20.3%, respectively).

Serum bilirubin and INR were higher in the US series, contributing to a higher MELD score. In the UNOS series median MELD score was 19, being 12 in patients with HCC and 23 in those without. In the Liver Match cohort median MELD score was 15, being 12 in patients with HCC and 18 in those without. HCC was more frequent in the Italian recipients (45.7% vs 31.1%). In both series HCV-related cirrhosis was the primary indication for LT (about 46% of the whole population). LTs due to HBV-related disease accounted for 19% in the Liver Match and 3.8% in the US cohort, whereas those due to autoimmune, cholestatic and cryptogenic diseases were more common in the US.

In the Liver Match study 173 cases (11.7%) of EGL were recorded: 54 (31.3%) occurred during the first post-operative week, 57 (32.9%) between day 8 and day 30, and 62 (35.8%) between day 31 and day 90. Estimated graft survival probability at 90 days was 0.88 (s.e. 0.118).

In the US population 706 (7.2%) cases of EGL were recorded: 229 (32.5%) occurred during the first week, 212 (30.0%) between day 8 and day 30, and 265 (37.5%) between day 31 and day 90. The estimated graft survival at 90 days was 0.93 (s.e. 0.073).

### **Predictors of EGL at Cox model**

Predictors of EGL at Cox model are shown in **Table 2** with their respective hazard ratios (HR). In the OPTN/UNOS series these included donor age and height, DCD and CIT, while recipient-related predictors of EGL were FHF, MELD, previous upper abdominal surgery and portal vein thrombosis. Analysis of martingale residuals suggested a non-linear effect of both donor age and donor height, with an excess of risk among donors >60 years and height <150 cm, respectively. Among MELD components, only *log* creatinine and *log* bilirubin, but not *log* INR, emerged as significant EGL predictors.

In the Liver Match series Cox model did not identify donor-related predictors of EGL, except BMI. Donor age, despite significantly higher in the Italian population, was not associated with a greater

risk. As in the US series, *log* bilirubin and *log* creatinine, but not *log* INR, were significant predictors of EGL. HBV disease etiology was associated with a markedly reduced risk of EGL as compared to HCV. No other etiology showed a significant effect, yet the HR for FHF was similar to the US cohort. Steroid-free immunosuppression was a risk factor for EGL limited to recipients with alcoholic cirrhosis.

### **Development of a Bayesian predictive model of EGL**

To obtain a robust predictive model of general validity, a final Cox model was obtained combining information from both training cohorts via a Bayesian methodology. Information from the OPTN/UNOS was translated into probability assuming prior Normal distributions for parameters to be estimated, with means set to the corresponding estimated coefficients. Standard errors of covariates from the OPTN/UNOS series were assumed as prior standard deviations, as shown in **Table 3**. The same table also shows the maximum partial likelihood estimates derived from the Liver Match data. A dedicated term was introduced to adjust for the increased risk of EGL due to steroid avoidance in patients with alcoholic cirrhosis.

In order to avoid that, despite the larger amount of missing observations, the greater number of LTs in the US series would overwhelm the evidence provided by Liver Match data, the weight of the US data was reduced multiplying prior variances by a discount factor  $k$ . Values of  $k$  ranging from 2 to 10 were considered and, for each of them, posterior means were computed via the Bayes theorem and a score was derived, whose predictive capability was evaluated by the area under the cross-validated ROC curve in both datasets. As expected, for  $k=2$  posterior means were close to the parameter estimates obtained from the UNOS series, while for larger  $k$  values they approached the estimates derived from the Liver Match data. The final choice of  $k=6$  corresponded to the best average predictive capability. The corresponding final posterior means, shown in **Table 3**, provided updated coefficients which served to build two new scores: the **EGL-related** Donor Risk Index

(EGL-DRI) and the **EGL-related** Recipient Risk Index (EGL-RRI), respectively. The two scores are calculated using the following equations:

$$\text{EGL-DRI} = [(0.027 \text{ if } 60 \leq \text{age} < 70) + (0.254 \text{ if } \text{age} \geq 70) + (0.716 \text{ if DCD}) + (0.582 \text{ if height} \leq 150) + (0.019 \times (\text{BMI} - 25)) + (0.070 \times (\text{CIT in hours} - 8))] \times 10.$$

$$\text{EGL-RRI} = [(0.411 \times \log \text{ creatinine}) + (0.148 \times \log \text{ bilirubin}) - (0.603 \text{ if HBV-related cirrhosis}) - (0.082 \text{ if alcohol-related cirrhosis}) + (0.610 \text{ if FHF}) + (0.389 \text{ if cholestatic or autoimmune disease}) + (0.196 \text{ if cryptogenic cirrhosis or NASH}) + (0.086 \text{ if other etiology different from HCV-related cirrhosis}) + (0.174 \text{ if prior upper abdominal surgery}) + (0.455 \text{ if portal vein thrombosis})] \times 10.$$

The minimum value for both serum creatinine and bilirubin was set to 0.5 mg/dl, while for patients on dialysis at time of LT, serum creatinine was set to 6 mg/dl, if lower. Because both new predictive scores are computed on the *log*-HR scale, a composite Donor-Recipient Allocation Model (DReAM) can be obtained by simply summing EGL-DRI to EGL-RRI. DReAM evaluates the *log* relative risk ( $\times 10$ ) of EGL for any given LT, with specific donor and recipient characteristics, compared to a reference LT. The reference LT is defined by the following features: donor age <60 years, donor height >150 cm, donor BMI=25, no DCD, CIT=8 hours; recipient serum creatinine and bilirubin at LT=1 mg/dl, HCV-related cirrhosis, no previous upper abdominal surgery and no portal thrombosis. Note that the scale we have chosen corresponds to that used to derive the MELD score and that both EGL-DRI and EGL-RRI can assume negative values, indicating a risk lower than the reference cases. The contour plot shown in **Fig. 1A** allows user-friendly estimation of HR and the easy identification of high-risk matching combinations.

In the Liver Match series, the analysis of normal-deviate residuals (**Fig.1B**) identified 33 (2.3%) cases of EGL that were poorly predicted by DReAM, all occurring earlier than their estimated survival probability. Eight outliers were intraoperative deaths and in 21 cases EGL occurred within the first week after LT although DReAM levels were lower than 10. The remaining 4 outliers

developed EGL between day 10 and 13 after LT. The whole set of residuals corresponding to EGLs showed a decreasing trend with increasing DReAM levels, suggesting a better predictive capability of the model at high levels of DReAM.

### **DReAM external validation**

The accuracy and generalizability of DReAM was tested in a distinct UNOS validation set including 2864 LTs performed from January 1, 2010 to August 31, 2010, based on OPTN data as of March 2, 2012 (supplementary Table 5). This series comprised 119 (4.4%) cases of FHF. Compared to the OPTN/UNOS model derivation set, donor features were similar, while recipients were slightly older (median age: 56 vs 55 years) and with higher MELD values (median: 20 vs 19). Portal vein thrombosis was more frequent in the validation set (8.2% vs 6.3%), while HCV and HBV related cirrhosis were fewer (45.2% vs 46.7% and 2.9% vs 3.8%, respectively).

A total of 189 EGLs were observed. ROC curves showed a reasonable EGL predictive capability of DReAM (c-statistic 0.66 in the validation set), which outperformed that of D-MELD (c-statistic 0.58,  $p=0.0003$ ), SOFT (c-statistic 0.59,  $p=0.0715$ ) and BAR (c-statistic 0.57,  $p=0.0067$ ), as shown in the supplementary material.

### **DReAM updating**

To demonstrate the potentiality of the Bayes approach, we further adapted DReAM to the specific features of the largest Italian Transplant Program, by analyzing a cohort of 448 primary LTs performed at the Center of Turin between June 2009 and April 2013. A peculiarity of this cohort, which included 30 EGLs, was the very old donor age (median value: 67 years), mostly died of cerebral hemorrhage (72.5%). All donors underwent liver biopsy: a greater than 25% graft macrosteatosis was observed in 23 donors, while a greater than 50% microsteatosis was found in 62. MELD was similar to the general Liver Match population, but there was a higher number of transplant recipients with HCC (50.2% vs 45.7%)

Actual DReAM coefficients were now regarded as prior means and combined with the evidence from the Turin cohort to obtain new updated coefficients. Note that the Bayesian methodology allows also to introduce new explanatory variables, such as, in this new scenario, the percent micro- and macro-steatosis, two variables unavailable in the other series, and the donor HCV status. In the updated score the predictive weight of donor age >70 years increased substantially, while that of CIT, previous abdominal surgery and donor height <150 cm decreased (see supplementary material). The cross-validated ROC curve showed a significant increase in the predictive capability of the updated DReAM with a c-statistic of 0.76 (**Fig.2**). DReAM levels greater than 15 (**Fig. 3A**) were associated with a significantly worse outcome. Indeed, although in the Turin series the proportion series of EGLs was rather low (6.7%), the estimated survival decreased sharply as DReAM increased above 15 (**Fig. 3B**).

## DISCUSSION

EGL accounts for roughly one third of LT failures and, more importantly, depends on both donor and recipient features, thus a reliable predictive model would be important for decision making in organ allocation. Our intent was to generate a prognostic model of EGL based on donor and recipient data from two different populations: the Liver Match series, a prospectively recruited Italian cohort [19], and a time-matched OPTN-UNOS retrospective series. EGL occurred in 11.7% of the Liver Match cohort and in 7.2% of the US series, a difference consistent with other studies comparing early post-LT survival in the US and Europe [4,17,25].

Risk factors of EGL partly differed in the two model derivation cohorts, reflecting differences in donor and recipient features and different allocation strategies. Donor age, for example, was a significant predictor of EGL in the OPTN/UNOS cohort, as already observed [26], but not in the Liver Match, despite the older donor age of the Italian cohort, suggesting a more **effective**

**management** of old donors in Italy. Donor BMI was a predictor of EGL only in the Italian cohort. As already found by Feng et al. [10], low donor height emerged as a risk factor in the US cohort, possibly reflecting a size imbalance between donors and recipients due to the higher proportion of Hispanics or Orientals and the use of donors <12 years old in adult recipients. Lastly, DCD, currently not performed in Italy, was a risk factor of EGL in the US population.

Among recipient-related factors, only two MELD components (*log* creatinine and *log* bilirubin) were strong predictors of EGL in both series. Prior upper abdominal surgery and portal thrombosis emerged as significant predictors in the US cohort, having limited relevance in the Italian series. In the Liver Match cohort a greater risk of EGL was found in a small subgroup of LT recipients with alcohol-related ESLD receiving steroid-free immunosuppression after LT, suggesting that these patients may have experienced severe adrenal insufficiency [27], eventually improved by steroid administration.

To generate a robust predictive model of EGL, able to capture all the relevant risk factors without over-fitting local data, we combined the evidence resulting from the two cohorts using a Bayesian methodology. The estimated *log* hazard ratios in the two series were merged to generate DReAM, a new model predicting EGL, which was then validated in a distinct OPTN-UNOS cohort. Recipient-related factors gave the greatest weight in generating DReAM, as reflected by the wider range of EGL-RRI compared to EGL-DRI. Inspection of DReAM contour plot allows to easily distinguish EGL-DRI and EGL-RRI combinations associated with excellent (e.g. <2 HR), unsatisfactory (e.g. >6 HR), or wasteful outcomes. Examples of how unsatisfactory matching combinations can be translated into acceptable ones by a better donor-recipient matching are shown in **Table 4**. For an easier use of DReAM in clinical practice, we developed a simple calculator which is available online ([www.webaisf.org](http://www.webaisf.org)).

In the external validation set, although the c-statistics remained just below 0.7, DReAM proved to be more accurate than other proposed predictive scores, including D-MELD, SOFT and BAR.

However, predictive scores with an even lower c-statistic have been endorsed by UNOS for organ allocation in kidney transplantation, as they are capable to discriminate futile matching combinations [28]. Interestingly, DReAM was less accurate in predicting very early EGL, whose risk factors were not properly captured by the collected information. Cases of poorly predicted EGLs were in fact clustered in the first 7 days after LT, a time frame where complications are mostly related to anatomic or vascular variability and surgical and anesthesiological skills, rather than to graft quality or recipient disease severity.

A major advantage of the Bayesian methodology is that DReAM can be used as a basis to develop further predictive models, tailored to specific environments and therefore more practical and useful for decision making in the real world. DReAM coefficients can be updated using data from other national studies, registries, or even single center series. The example of the Italian Turin Transplant Centre is emblematic. Despite the propensity of using suboptimal donors, this center is characterized by a very low proportion of EGLs as compared to the whole Italian transplant cohort. While the original DReAM was quite inadequate to predict EGL in that reality (c-statistics=0.57), its adaptation based on the last 448 consecutive LT allowed to reach a much better predictive capability as indicated by a c-statistics of 0.76. It is worth to remark that such a limited sample size would not suffice to derive a robust local score.

A further relevant, yet often ignored, issue is that converting hazard ratios to survival probabilities requires the estimation of the baseline survival function, which may substantially differ in different settings. Note that the same level of hazard ratio can be affordable in the presence of a high baseline survival but unacceptable if the baseline survival is suboptimal. Again the Turin example is emblematic: survival estimates based on the whole Italian Liver Match cohort do not fit well to this reality and might even endanger high-risk patients whose survival probability could be underestimated.



All these issues can be overcome using the Bayesian approach that provides a straightforward tool by strengthening prior knowledge with new emerging data. Prior information and new data are considered as part of a continuous data stream, where inferences are being updated whenever new information becomes available. Notably, the Bayesian approach has been endorsed by the Food and Drug Administration as a powerful tool to be used in clinical trials [30].

In conclusion, using a Bayesian Cox model, we combined significant information deriving from a retrospective US and a prospective European series to generate DReAM, a novel predictive model of EGL based on donor-recipient data. DReAM allows easy identification of high risk LTs and can be used as a basis to develop tailored versions with better predictive accuracy of EGL, helpful to avoid wasteful LT outcomes due to inappropriate donor-recipient matching.

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## Figure Legends

Fig. 1 A - Prediction of EGL by DReAM components. Hazard Ratio of Early Graft Loss by EGL-RRI and EGL-DRI

Fig. 1 B - Normal Deviate residuals corresponding to EGLs *vs* DReAM in the Liver Match series. Dots above the reference horizontal line represent outliers (dark grey dots=EGLs within the first week after LT, black dots= EGLs between day 10 and 13). Light grey dots represent EGLs adequately predicted by DReAM

Fig.2 - ROC curve of the DReAM model (with updated coefficients) in the cohort of Turin

Fig. 3 A - Kaplan Meier survival curves stratified by DReAM levels in the cohort of Turin.

Fig. 3B - Posterior estimates of 90 days survival probability by DReAM levels with 95% confidence band (cohort of Turin).

Table 1. Baseline characteristics of donors and recipients in the derivation cohorts

Donor features	Liver Match (n=1480)			OPTN/UNOS(n=9740)		
	Median or n	(Q1-Q3) or %	Missing	Median or n	(Q1-Q3) or %	Missing
Age (years)	56	41-68		43	26-55	
Male gender	817	55.2		5872	60.3	
Cause of death						
<i>Trauma</i>	383	25.9		3535	36.3	
<i>Anoxia</i>	73	4.9		1836	18.8	
<i>Cerebral haemorrhage</i>	841	56.8		4110	42.2	
<i>Other</i>	183	12.4		259	2.7	
Height (cm)	170	162-175	3	173	165-180	66
BMI	25.0	22.9-27.6	3	26.1	23.0-30.1	66
Split liver	78	5.3		135	1.4	
CIT (hours)	7.3	6.0-8.8	8	6.8	5.0-8.5	579
DCD	*			526	5.4	
<b>Recipient features</b>						
Age (years)	54	47-60		55	49-60	
Male gender	1158	78.2		6620	68.0	
Previous upper abdominal surgery	298	20.3	11	3654	39.1	394
Portal vein thrombosis	36	2.4		591	6.3	333
Height (cm)	170	164-176	31	173	165-180	381
BMI	25.0	23.0-27.6	31	27.8	24.3-32.0	381

Serum creatinine at LT	1.00	0.80-1.10	5	1.00	0.80-1.50	55
Serum bilirubin at LT	2.70	1.30-6.20	5	3.60	1.80-8.50	417
INR at LT	1.40	1.20-1.78	5	1.60	1.30-2.10	61
MELD at LT	15	11-21	5	19	13-27	54
HCC	677	45.7		3031	31.1	
Etiology						579
HCV related cirrhosis	687	46.4		4276	46.7	
HBV related cirrhosis	281	19.0		344	3.8	
Alcoholic cirrhosis	237	16.0		1048	11.4	
FHF	45	3.0		391	4.3	
Cholestatic and Autoimmune	98	6.6		929	10.1	
Cryptogenic and NASH	76	5.2		1101	12.0	
Other	56	3.8		1072	11.7	

\* The use of DCD is not allowed in Italy.

Table 2. Donor and Recipient Hazard Ratios for EGL: results from the Cox model in the two derivation cohorts

	<b>OPTN/UNOS n=7781</b>		<b>Liver Match n=1430</b>	
	<b>Events=545 (7.0%)</b>		<b>Events=159 (11.1%)</b>	
	<b>20.1% missing</b>		<b>3.4%missing</b>	
	<b>Hazard Ratio</b>	<b>p-value</b>	<b>Hazard Ratio</b>	<b>p-value</b>
<b>Donor features</b>				
<b>Donor age (ref: &lt; 60 y)</b>		<b>&lt;0.0001</b>		<b>0.3766</b>
≥ 60 y and < 70 y	<b>1.49</b>	0.0013	<b>0.80</b>	0.3089
≥ 70 y	<b>1.89</b>	0.0002	<b>1.13</b>	0.5266
<b>Donor height (≤ 150 cm vs &gt; 150 cm)</b>	<b>2.19</b>	<b>&lt;0.0001</b>	<b>1.66</b>	<b>0.1949</b>
<b>Donor BMI (ref: 25)</b>	<b>1.01</b>	<b>0.4080</b>	<b>1.04</b>	<b>0.0441</b>
<b>DCD (yes vs no)</b>	<b>2.05</b>	<b>&lt;0.0001</b>	*	
<b>CIT (ref: 8 hours)</b>	<b>1.08</b>	<b>&lt;0.0001</b>	<b>1.05</b>	<b>0.1807</b>
<b>Recipient features</b>				
<b>Etiology (ref: HCV related cirrhosis)</b>		<b>0.0134</b>		<b>0.0337</b>
HBV related cirrhosis	<b>0.88</b>	0.6153	<b>0.53</b>	0.0251
Alcoholic cirrhosis	<b>0.97</b>	0.8327	<b>0.91</b>	0.7252
Fulminant hepatitis	<b>1.89</b>	0.0002	<b>1.89</b>	0.0830



Cholestatic and autoimmune disease	<b>1.14</b>	0.4486	<b>1.71</b>	0.0613
Cryptogenic and NASH	<b>1.08</b>	0.5697	<b>1.30</b>	0.4220
Other	<b>1.24</b>	0.1270	<b>0.95</b>	0.9074
<b>Log creatinine (ref: 0)</b>	<b>1.41</b>	<b>&lt;0.0001</b>	<b>1.61</b>	<b>0.0033</b>
<b>Log bilirubin (ref: 0)</b>	<b>1.10</b>	<b>0.0258</b>	<b>1.17</b>	<b>0.0382</b>
<b>Previous surgery (yes vs no)</b>	<b>1.24</b>	<b>0.0146</b>	<b>1.19</b>	<b>0.4030</b>
<b>Portal thrombosis (yes vs no)</b>	<b>1.39</b>	<b>0.0334</b>	<b>1.97</b>	<b>0.1066</b>
<b>Steroid-free immunosuppression in alcoholic cirrhosis (yes vs no)</b>			<b>4.89</b>	<b>0.0003</b>

\* The use of DCD is not allowed in Italy.

Table 3. Results from the Bayesian Cox model (prior s.d. was multiplied by square root of 6)

	<b>Prior mean (s.d.)</b>	<b>Maximum partial likelihood estimate from the UNOS cohort</b>	<b>Maximum partial likelihood estimate from the Liver Match cohort</b>	<b>Posterior mean (DReAM)</b>
<b>Donor features</b>				
<b>Donor age (ref &lt; 60 y)</b>				
≥ 60 y and < 70 y	0.396 (0.123)	-0.222 (0.218)		0.027 (0.169)
≥ 70 y	0.631 (0.172)	0.123 (0.194)		0.254 (0.171)
<b>Donor height (≤ 150 cm vs &gt; 150 cm)</b>				
	0.785 (0.199)	0.506 (0.390)		0.582 (0.300)
<b>Donor BMI (ref 25)</b>				
	0.006 (0.007)	0.043 (0.021)		0.019 (0.013)
<b>DCD (yes vs no)</b>				
	0.716 (0.151)	*		0.716 (0.151)
<b>CIT (ref: 8 hours)</b>				
	0.081 (0.015)	0.052 (0.039)		0.070 (0.027)
<b>Recipient features</b>				
<b>Etiology (ref: HCV related cirrhosis)</b>				
HBV related cirrhosis	-0.127 (0.252)	-0.643 (0.287)		-0.603 (0.250)
Alcoholic cirrhosis	-0.030 (0.142)	-0.091 (0.259)		-0.082 (0.206)
Fulminant hepatitis	0.637 (0.173)	0.636 (0.367)		0.610 (0.271)

Cholestatic and autoimmune disease	0.130 (0.172)	0.535 (0.286)	0.389 (0.238)
Cryptogenetic and NASH	0.077 (0.135)	0.263 (0.328)	0.196 (0.245)
Other	0.212 (0.139)	-0.054 (0.467)	0.086 (0.266)
<b>Log creatinine (ref: 0)</b>	0.342 (0.067)	0.477 (0.162)	0.411 (0.119)
<b>Log bilirubin (ref: 0)</b>	0.095 (0.043)	0.159 (0.077)	0.148 (0.061)
<b>Previous surgery (yes vs no)</b>	0.214 (0.088)	0.171 (0.205)	0.174 (0.152)
<b>Portal thrombosis (yes vs no)</b>	0.327 (0.154)	0.679 (0.421)	0.455 (0.294)
<b>Steroid-free immunosuppression in alcoholic cirrhosis (yes vs no)</b>	**	1.587 (0.442)	1.583 (0.431)

\* The use of DCD is not allowed in Italy.

\*\* As no prior knowledge was available regarding the magnitude of risk associated with steroids avoidance in patients with alcoholic cirrhosis, we assumed a Normal prior distribution with a mean of 0 and a variance of  $10^6$ , which is fairly non-informative.

Table 4. Estimated hazard ratios of EGL for different donor-recipient matches (CIT was set to a reference value of 8 hours)

Donor Characteristics				Recipient Characteristics								
Age	Height	BMI	DCD	<b>EGL- DRI</b>	Creat.	Bil.	Etiol.	Prev. Surg.	Port. Thro.	<b>EGL- RRI</b>	<b>DReAM</b>	<b>Est. HR</b>
70	140	30	No	<b>9.3</b>	4	9	HCV	Yes	Yes	<b>15.2</b>	<b>24.5</b>	<b>11.6</b>
40	170	25	Yes	<b>7.1</b>							<b>22.3</b>	<b>9.3</b>
60	170	30	No	<b>1.2</b>							<b>16.4</b>	<b>5.2</b>
40	170	25	No	<b>0</b>							<b>15.2</b>	<b>4.6</b>
70	140	30	No	<b>9.3</b>	1.5	3	HCV	Yes	Yes	<b>9.6</b>	<b>18.9</b>	<b>6.6</b>
40	170	25	Yes	<b>7.1</b>							<b>16.7</b>	<b>5.3</b>
60	170	30	No	<b>1.2</b>							<b>10.8</b>	<b>2.9</b>
40	170	25	No	<b>0</b>							<b>9.6</b>	<b>2.6</b>
70	140	30	No	<b>9.3</b>	2	6	HCV	Yes	No	<b>7.2</b>	<b>16.5</b>	<b>5.2</b>
40	170	25	Yes	<b>7.1</b>							<b>14.3</b>	<b>4.2</b>
60	170	30	No	<b>1.2</b>							<b>8.5</b>	<b>2.3</b>
40	170	25	No	<b>0</b>							<b>7.2</b>	<b>2.1</b>

Figure 1  
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Fig. 1A and B

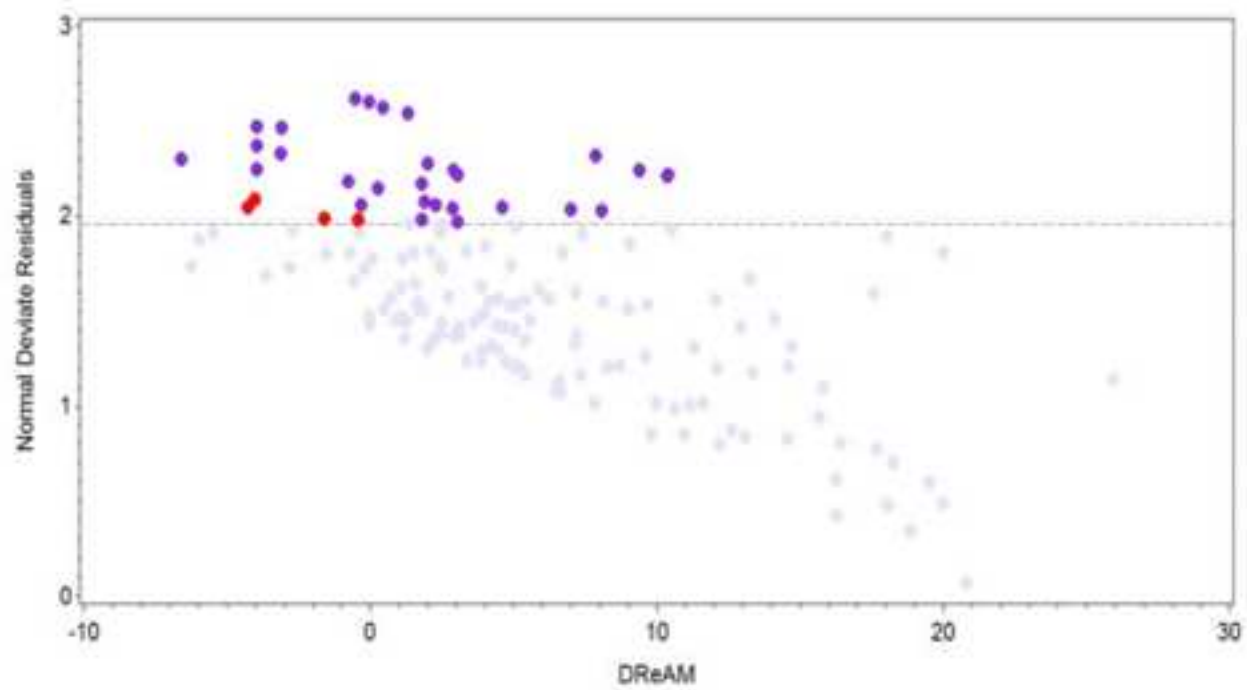
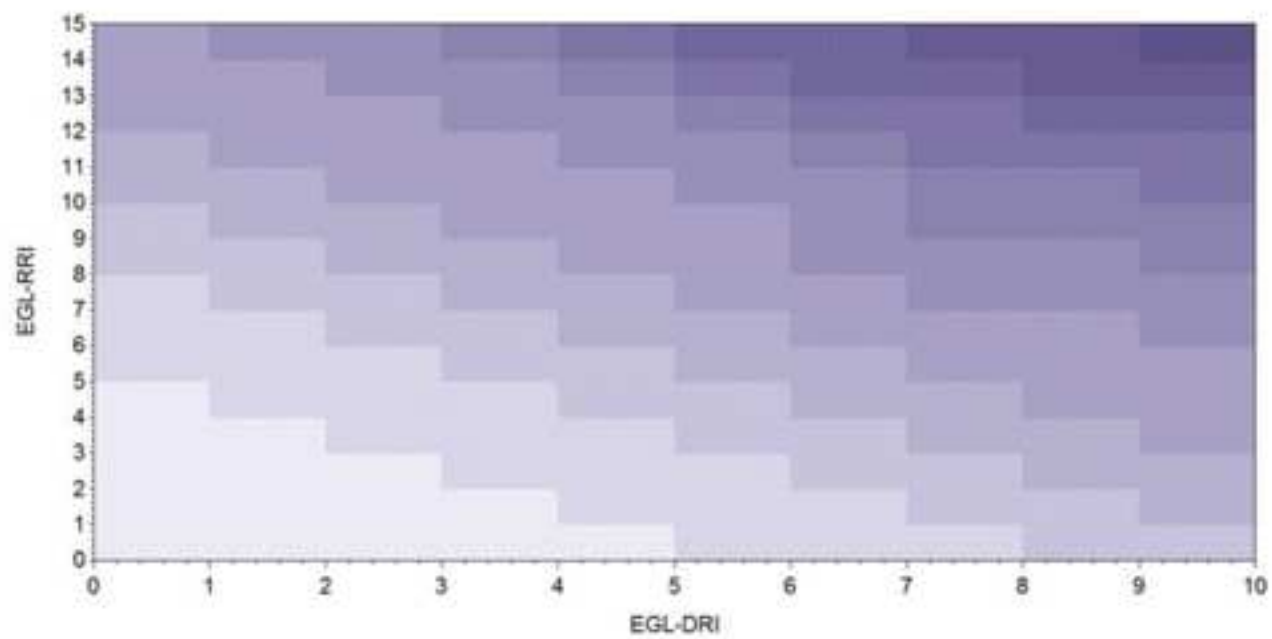


Fig. 2

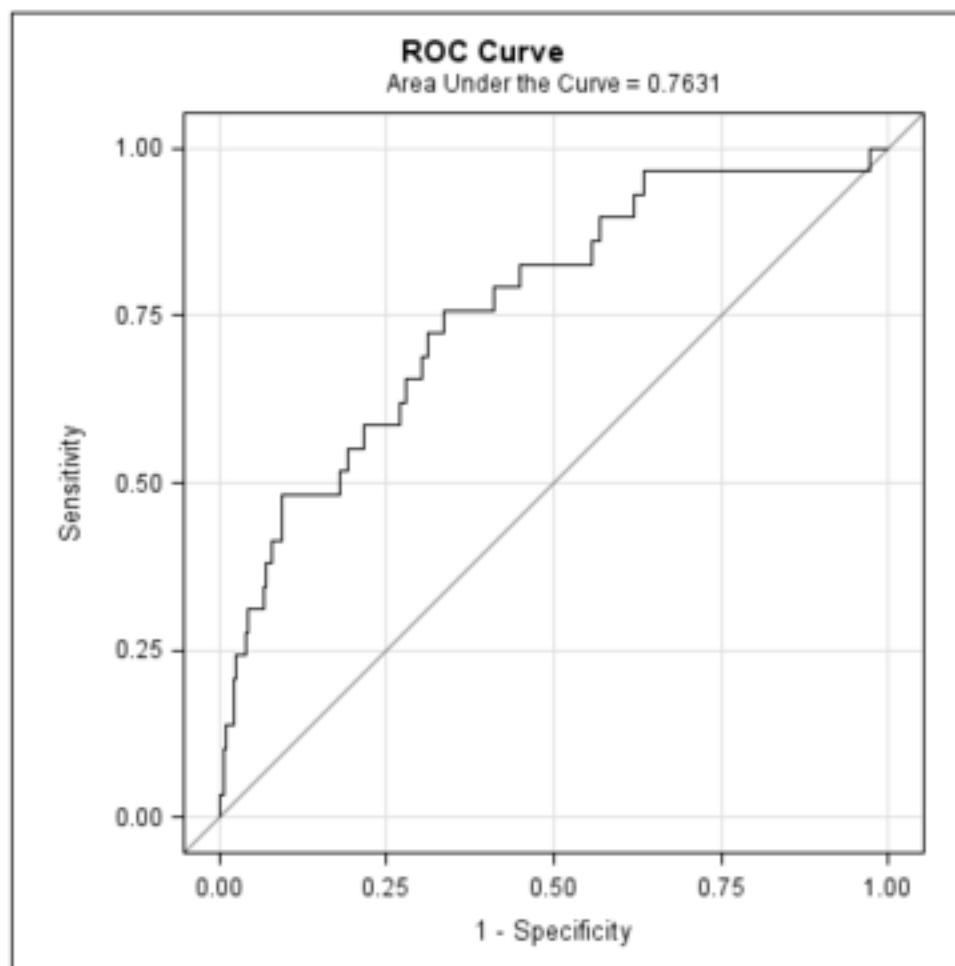
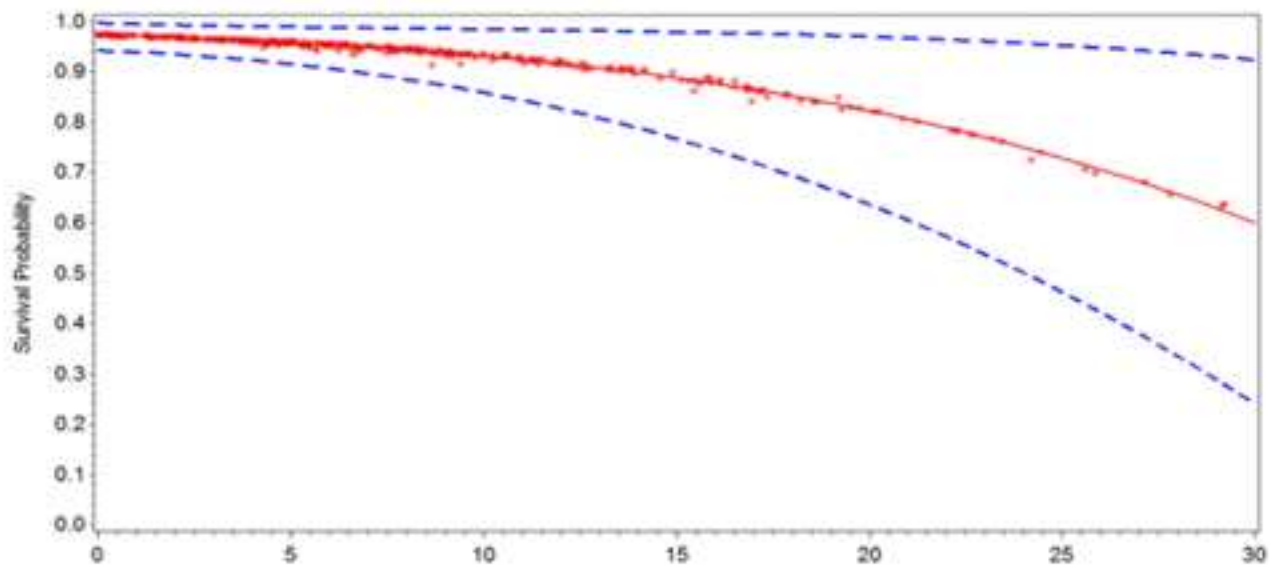
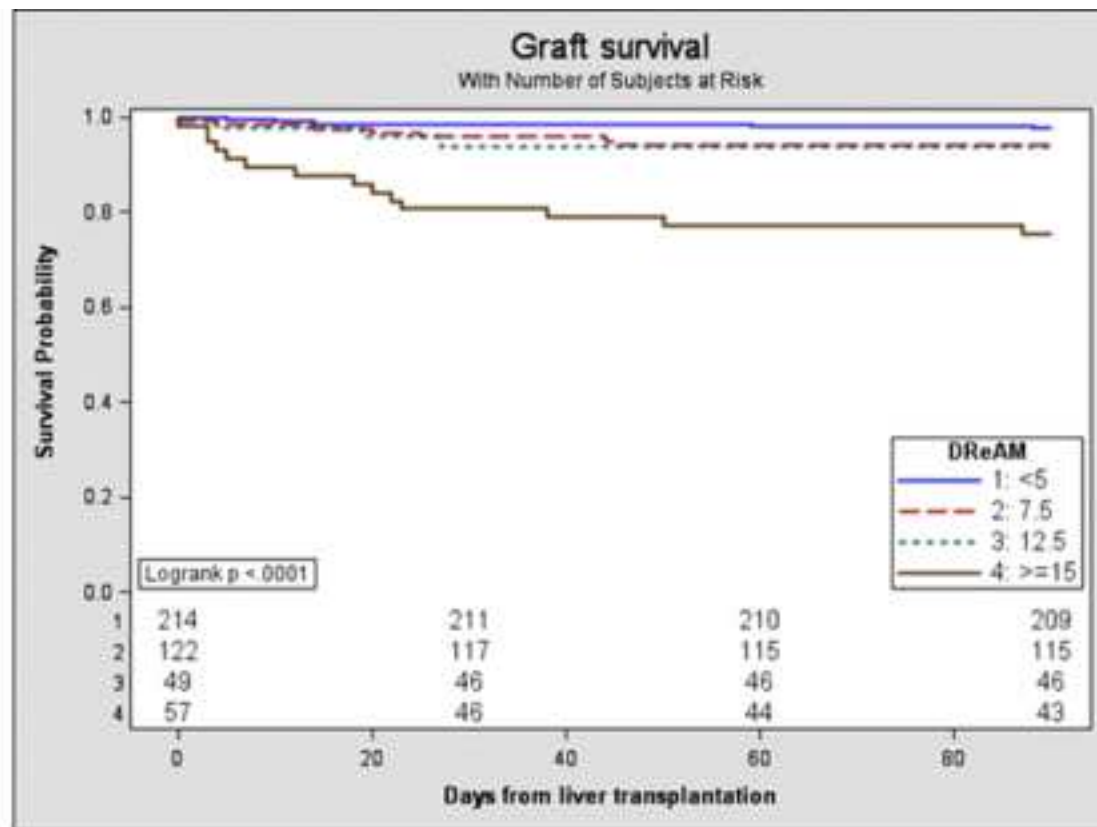


Figure 3  
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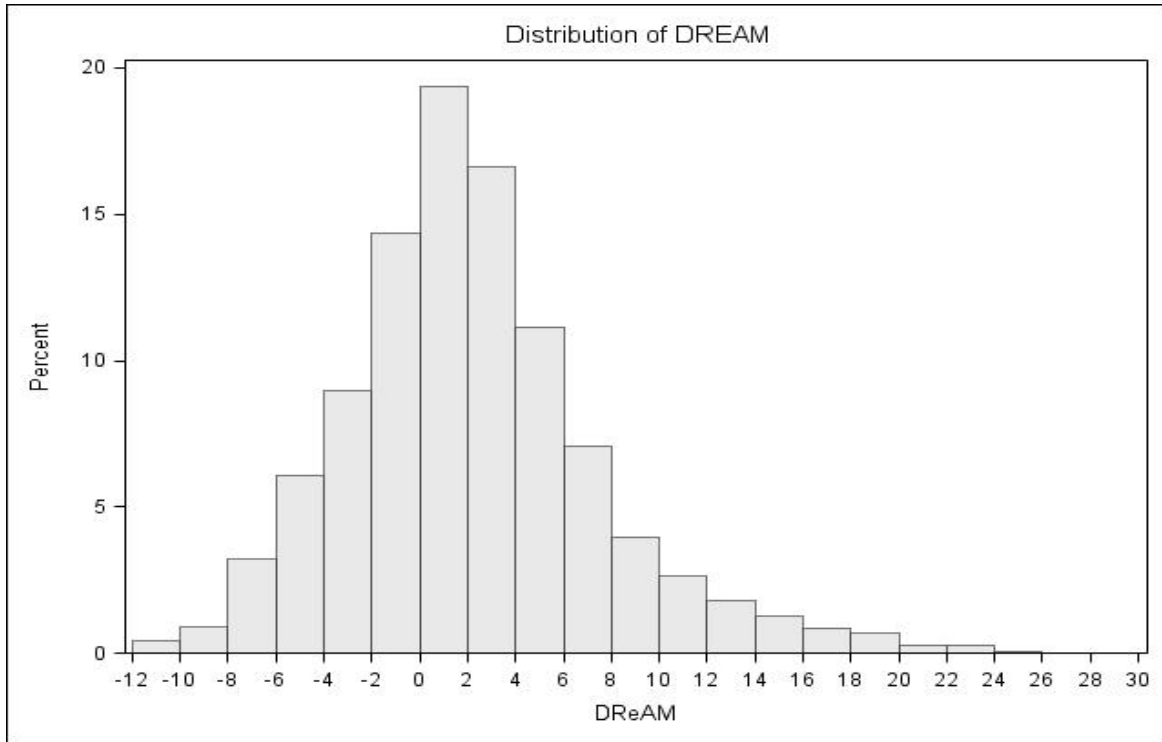
Fig 3 A  
and B



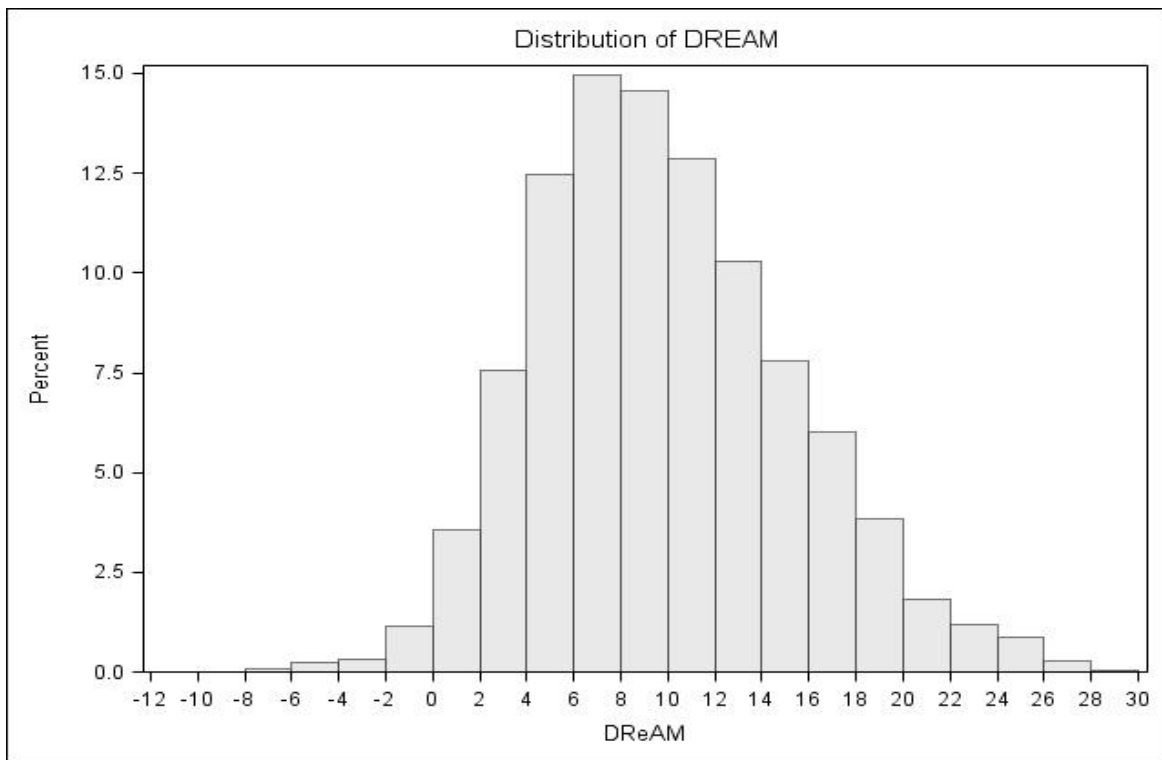
## Supplementary material

### Supplementary Fig. 5 Distribution of DReAM

#### a) Liver Match model derivation cohort



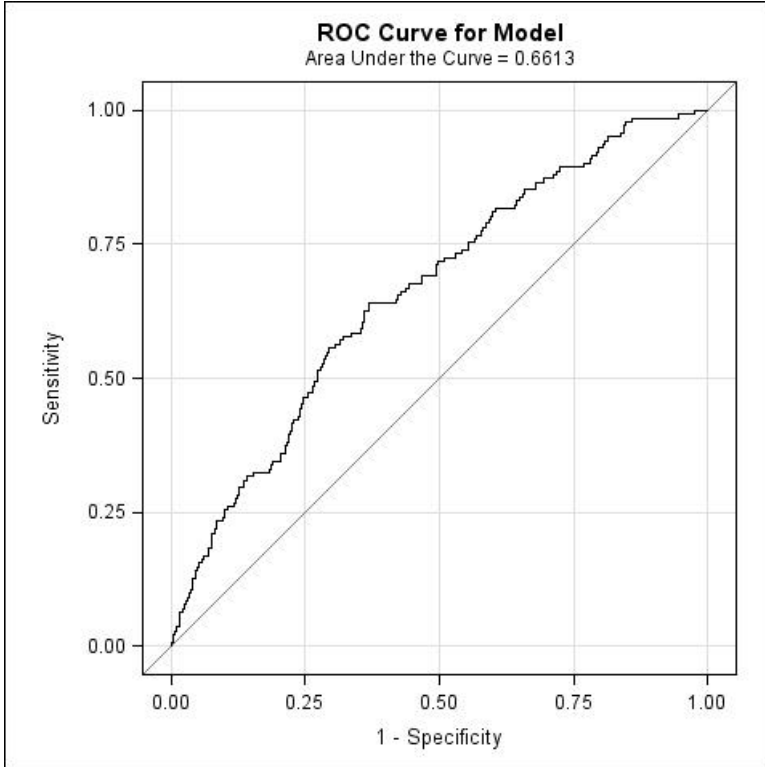
#### b) UNOS validation set



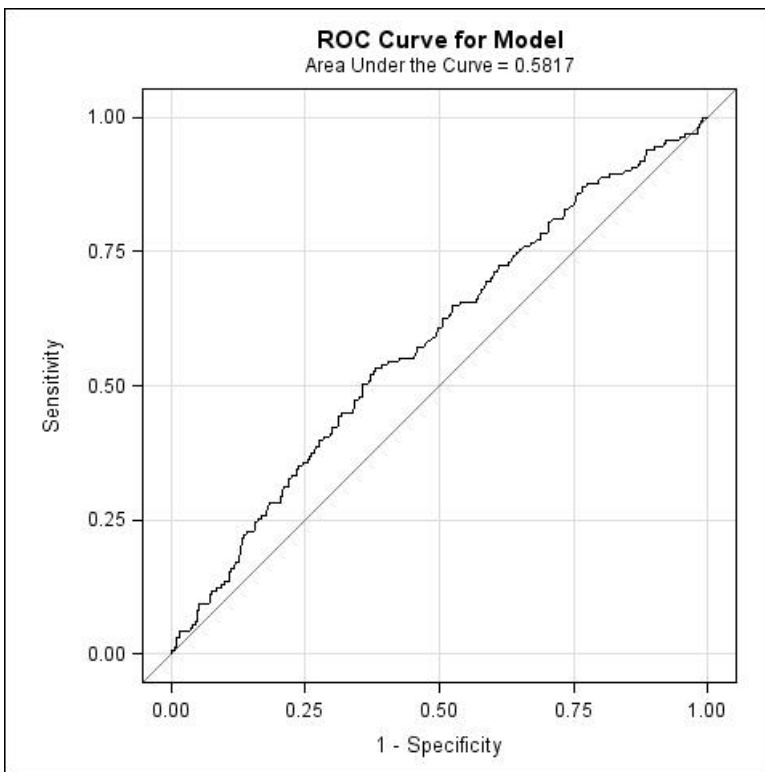


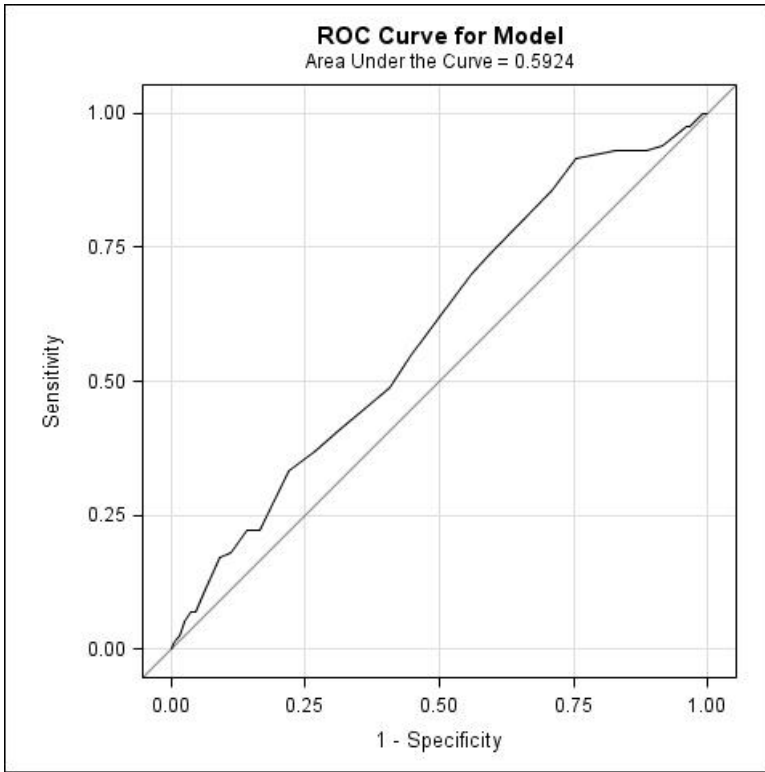
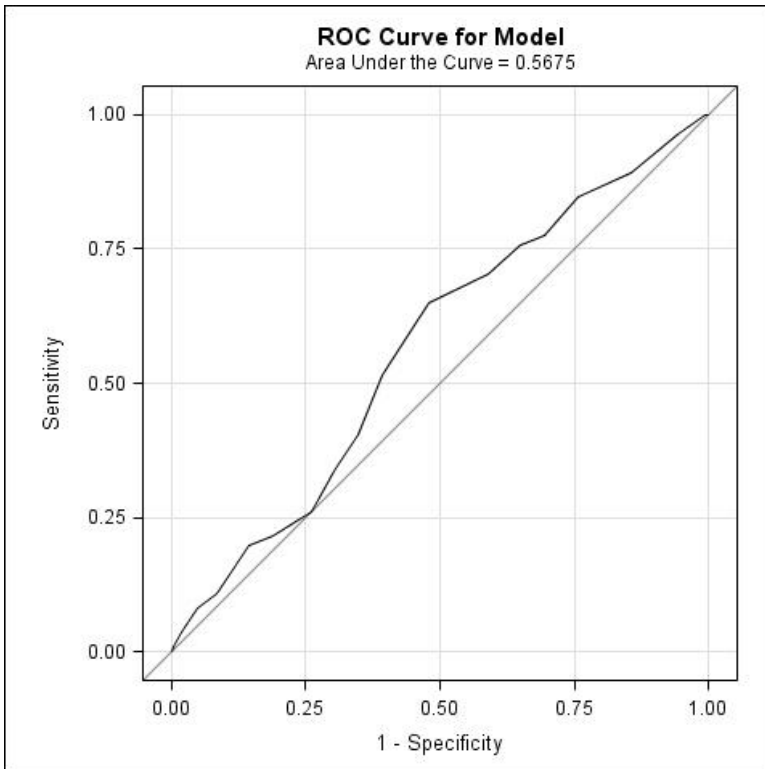
Supplementary Fig. 6 ROC curves: UNOS validation set

**a) DReAM**



**b) D-MELD**



**c) SOFT****d) BAR**

**Supplementary Table 5**

Baseline characteristics of donors and recipients in the OPTN/UNOS validation cohort and in the cohort of Turin

Donor features	Validation cohort (n=2864)			Updating cohort (n=448)		
	Median or n	(Q1-Q3) or %	Missing	Median or n	(Q1-Q3) or %	Missing
Age (years)	42	27-55		67	53-75	
Male gender	1673	58.41		263	58.71	
Cause of death						
<i>Trauma</i>	969	33.83		89	19.87	
<i>Anoxia</i>	667	23.29		27	6.03	
<i>Cerebral haemorrhage</i>	1145	39.98		325	72.54	
<i>Other</i>	83	2.90		7	1.56	
Height (cm)	173	165-178	2	170	165-175	
BMI	26.5	23.1-30.7	2	25.4	23.1-27.8	
Split liver	31	1.08	3	3	0.67	
CIT (h)	6.11	5.00-7.93	521	7.76	6.61-8.60	
DCD	144	5.03	1	-	-	
<b>Recipient features</b>						
	Median or n	(Q1-Q3) or %	Missing	Median or n	(Q1-Q3) or %	Missing
Age (years)	56	50-61		56	49-61	
Male gender	1902	66.41		348	77.68	
Previous upper abdominal surgery	946	39.63	477	73	16.29	
Portal vein thrombosis	198	8.18	443	6	1.34	
Height (cm)	173	165-180	454	170	165-175	
Body Mass Index (BMI)	27.7	24.3-32.0	454	25.3	23.4-27.6	
Serum creatinine at LT	1.09	0.80-1.60		0.90	0.75-1.08	
Serum bilirubin at LT	4.00	1.90-10.10	98	2.70	1.40-6.15	
INR at LT	1.66	1.30-2.20	18	1.48	1.24-1.82	
MELD at LT	20	14-29		16	11-20	
HCC	926	33.51	16	225	50.22	
Etiology			179			
HCV related cirrhosis	1213	45.18		184	36.83	
HBV related cirrhosis	79	2.94		127	28.35	
Alcoholic cirrhosis	327	12.18		69	15.40	
Fulminant hepatitis	119	4.44		6	1.34	
Cholestatic and Autoimmune	274	10.20		32	7.14	
Cryptogenic and Nash	359	13.37		30	6.70	
Other	314	11.69		19	4.24	

### Supplementary Table 6

DReAM updated coefficients for the cohort of Turin

	Original coefficients	Updated coefficients
<b>Donor features</b>		
<b>Donor age (ref &lt; 60 y)</b>		
≥ 60 y and < 70 y	0.027 (0.169)	0.041 (0.379)
≥ 70 y	0.254 (0.171)	0.629 (0.714)
<b>Donor height (≤ 150 cm vs &gt; 150 cm)</b>	0.582 (0.300)	0.310 (0.801)
<b>Donor BMI (ref 25)</b>	0.019 (0.013)	0.022 (0.028)
<b>DCD (yes vs no)</b>	0.716 (0.151)	
<b>CIT (ref: 8 hours)</b>	0.070 (0.027)	0.039 (0.068)
<b>Macro steatosis (&lt;30% vs ≥30%)</b>	*	1.732 (0.573)
<b>Micro steatosis (&lt;20% vs ≥ 20%)</b>	*	0.962 (0.417)
<b>HCV positive</b>	*	1.621 (0.707)
<b>Recipient features</b>		
<b>Etiology (ref: HCV related cirrhosis)</b>		
HBV related cirrhosis	-0.603 (0.250)	-0.686 (0.577)
Alcoholic cirrhosis	-0.082 (0.206)	0.100 (0.401)
Fulminant hepatitis	0.610 (0.271)	0.352 (0.740)
Cholestatic and autoimmune disease	0.389 (0.238)	-0.052 (0.542)
Cryptogenetic and NASH	0.196 (0.245)	0.204 (0.547)
Other	0.086 (0.266)	0.799 (0.577)
<b>Log creatinine (ref: 0)</b>	0.411 (0.119)	0.447 (0.311)
<b>Log bilirubin (ref: 0)</b>	0.148 (0.061)	0.124 (0.129)
<b>Previous surgery (yes vs no)</b>	0.174 (0.152)	-0.011 (0.343)
<b>Portal thrombosis (yes vs no)</b>	0.455 (0.294)	0.629 (0.714)

\* As no prior knowledge was available regarding the magnitude of risk associated with donor macrosteatosis, microsteatosis and HCV status, we assumed a Normal prior distribution with a mean of 0 and a variance of  $10^6$ , which is fairly non-informative.

Note that DCD is not allowed in Italy.

**List of variables collected in the Liver Match study and included in multivariate analysis:**

Donor-related data include: age, gender, cause of death (trauma, cerebrovascular accident, anoxia and other), height, body mass index, history of insulin-dependent diabetes mellitus, markers of exposure to hepatitis B (HBV), use of a split or partial liver graft and serum sodium.

Recipient-related data included: age, gender, body mass index, history of insulin-dependent diabetes mellitus, etiology of liver disease, severity of liver disease at listing and at time of transplantation as assessed by Model for End-Stage Liver Disease (MELD) scores, including their individual components (bilirubin in mg/dl, creatinine in mg/dl, INR), conventional serum biochemistries, presence and staging of hepatocellular carcinoma (HCC) when present.

Pre-operative and post-operative parameters were also investigated, including the distance from the site of organ procurement and the site of transplantation, cold ischemia time (CIT), and the early use of steroids.