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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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ABSTRACT

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

1. Introduction

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

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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 hypernatremia, extended cold ischaemia 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 U.S. 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.

2. Methods

2.1. 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 Centre (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 Centres. 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 centres to prioritize patients within their own waiting lists.

The OPTN/UNOS series comprised 9740 first adult LTs from deceased donors performed in the U.S. between June 1, 2007 and May 31, 2009, based on OPTN data as of March 2, 2012, including 391 (4.3%) cases of FHF. U.S. transplants were performed according to UNOS criteria and bylaws, involving a MELD-based allocation policy.

Patients who underwent multiorgan LT or retransplantation were excluded.

2.2. 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 end-point of the study. Patients who did not experience EGL were censored at 90 days.

The main aetiologies 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 steatohepatitis (NASH), and other less frequent liver disorders.

2.3. 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 modelling 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