Research Article

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Early post-transplant survival: Interaction of MELD score and hospitalization status

Therese Bittermann[1], George Makar[1], David S. Goldberg[1,2,3,*]

[1]*Division of Gastroenterology, Department of Medicine, University of Pennsylvania, United States;* [2]*Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, United States;* [3]*Leonard Davis Institute of Health Economics, University of Pennsylvania, United States*

Background & Aims: Urgency-based allocation that relies on the MELD score prioritizes patients at the highest risk of waitlist mortality. However, identifying patients at greatest risk for short-term post-transplant mortality is needed in order to optimize the potential gains in overall survival obtained through improved long-term management of transplant recipients. There are limited data on the predictive ability of MELD score for early post-transplant mortality, and no data assessing the interaction between MELD score and hospitalization status.

Methods: We analyzed UNOS data from 2002 to 2013 on 50,838 non-status 1 single-organ liver transplant recipients and fit multivariable logistic models to evaluate the association and interaction between MELD score and pre-transplant hospitalization status on short-term post-transplant mortality.

Results: There was a significant interaction (p <0.01) between laboratory MELD score and hospitalization status on three-, six-, and 12-month post-transplant mortality in multivariable logistic models. This interaction was most pronounced in patients with a laboratory MELD score <25 transplanted from an ICU, whose adjusted predicted three-, six-, and 12-month post-transplant mortality approximated those of patients with a MELD score ⩾30. Compared to hospitalized patients with a MELD score of 30–34, those with a MELD score ⩾35 in an ICU had significantly increased risk of three-month (OR: 1.54, 95% CI: 1.21–1.97), 6-month (OR: 1.35, 95% CI: 1.09–1.67), and 12-month (OR: 1.25, 95% CI: 1.03–1.52) post-transplant mortality.

Discussion: Pre-transplant ICU status modifies the risk of early post-transplant mortality, independent of MELD score. This should be considered when determining candidacy for transplantation in order to optimize efficient use of a scarce resource.

Introduction

Liver transplantation allocation in the United States (US) and in Europe operates under an urgency-based system, such that candidates with the greatest estimated waitlist mortality receive the highest priority. The determination of urgency is based solely on the Model for End-Stage Liver Disease (MELD) score, which is a reliable predictor of waitlist mortality in most patients [1]. Other measures of severity of illness, such as the need for hospitalization, either on a general medical ward or an intensive care unit (ICU) may modify the risk of waitlist mortality differentially based on a patient's MELD score. Despite the emphasis placed on prioritizing the sickest patients for liver transplantation, such considerations may negatively impact the efficiency of a system that focuses on allocating a scarce resource, transplantable livers. With allocation policies in the US focused on giving even greater priority to patients with the highest MELD scores, such as the Share 35 policy initiated on June 18, 2013 that mandates broader regional sharing of organs to patients with a MELD score ⩾35, there is the potential for downstream consequences with regards to maximizing use of a limited supply of organs. Concerns have been raised about the impact of this policy on post-transplant morbidity and mortality because of increased transplantation of "sicker" patients, defined as those with higher MELD scores. Severity of illness, and its impact on post-transplant mortality, may in fact be related to a combination of MELD score and other factors, notably hospitalization status prior to transplantation.

Several studies have evaluated the ability of the MELD score to predict post-transplant mortality with mixed results [2–5]. In Europe, a number of previous studies demonstrated an increase in post-transplant mortality after adoption of the MELD-based allocation system, a change that closely correlated with transplanting candidates with higher MELD scores [6,7]. For example, in 2009, Weismüller *et al* demonstrated a 10% increase in three-month mortality at their transplant center in Germany after the adoption of MELD-based allocation as a result of

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* Corresponding author. Address: Blockley Hall, 423 Guardian Drive, Room 730, Philadelphia, PA 19104, United States. Tel.: +1 215 746 8598; fax: +1 215 349 5915.
E-mail address: david.goldberg@uphs.upenn.edu (D.S. Goldberg).
Abbreviations: MELD, Model for End-Stage Liver Disease; ICU, Intensive care unit; UNOS, United Network for Organ Sharing; OPTN, Organ Procurement and Transplantation Network; SSDMF, Social Security Death Master File; GEE, Generalized estimation equations; SRTR, Scientific Registry of Transplant Recipients; DRI, Donor risk index; HCC, Hepatocellular carcinoma.

pre-transplant factors [7]. However, to date only single-center studies have evaluated the impact on short-term mortality, while larger studies have focused on long-term post-transplant mortality, defined as over one-year, which is less likely to be impacted by severity of illness and the MELD score at the time of transplantation [8,9]. In addition, most of these efforts have not included other variables potentially associated with post-transplant mortality such as hospitalization status and variables linked to ICU management. Furthermore, earlier publications may not fully reflect the current state of organ allocation and transplantation, in which patients are sicker, have more co-morbidities, and have higher MELD scores at transplantation [9].

Changes in allocation policies have also provided additional prioritization through the use of exception points for candidates with other complications of end-stage liver disease that may increase the need for hospitalization or ICU care. Moreover, the decision to transplant patients from the hospital or ICU remains center-based both in the US and in Europe. The potential impact of transplanting high MELD patients in an ICU on post-transplant outcomes has not been fully examined, except in small single-center studies [8]. In addition, the interaction between MELD score and hospitalization status may not only impact those with high MELD scores, but also those with low MELD scores whose severity of illness is not captured by the MELD score. With these issues in mind, our goals were to: 1) evaluate the impact of pre-transplant MELD score and hospitalization status on short-term post-transplant mortality; and 2) the interaction of these two variables.

Patients and methods

Study population

All analyses were based on Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) data from February 27, 2002 through June 4, 2014. All adults ($\geqslant$18 years of age) initial single-organ transplant recipients prior to June 1, 2013 were included in order to evaluate outcomes prior to the implementation of the Share 35 policy on June 18, 2013, and to allow for ascertainment of outcomes among all transplant recipients. We excluded re-transplant and multi-organ transplant recipients because the selection process and post-transplant outcomes for such recipients are inherently different [10–12]. Patients listed as status 1 for fulminant hepatic failure were also excluded as these waitlist candidates were not impacted by the Share 35 policy, and continue to maintain the highest waitlist priority [13].

Outcome

The primary outcomes were post-transplant patient mortality at 3, 6, and 12 months. Post-transplant mortality at 12 months equated to overall mortality. Death was modeled as a binary, rather than a time-to-event outcome. Given the short time horizons assessed for the primary outcomes, deaths during each time period would be considered equivalent (i.e. in practice a death at four *vs.* five months are the same) [14–16]. Additionally, the binary outcomes allowed for appropriate analytic models that accounted for correlation of patient outcomes due to clustering within transplant centers [17–19]. Post-transplant deaths included transplant recipients with the post-transplant status code of "died," or those without this code, but a confirmed Social Security Death Master File (SSDMF) death date in the OPTN/UNOS dataset, within the specified time period.

Statistical analysis

Demographic and clinical characteristics of transplant recipients who died *vs.* survived were compared using standard descriptive statistics. Chi square tests were used to determine the differences in the proportion of transplant recipients who died at 3, 6, and 12 months according to pre-transplant hospitalization status. Multivariable logistic models were fit to evaluate the association and interaction between MELD score and pre-transplant hospitalization status on short-term post-transplant mortality. The primary analyses of death at 3, 6, and 12 months utilized GEE models with a logit link, an exchangeable correlation structure, and a robust variance estimator to account for patient clustering within transplant centers. Such models were chosen because of baseline differences in post-transplant outcomes across centers [20] and variable center-specific decisions on transplant eligibility of ICU patients, which could be accounted for in GEE models that accounted for patient clustering within centers [18,19].

Covariates evaluated for inclusion in the final model were those either independently associated with post-transplant mortality in previous studies [14–16] or variables included in the Scientific Registry of Transplant Recipients (SRTR) risk-adjusted models for center-specific outcomes [21]: recipient age, race/ethnicity, sex, albumin at transplant, laboratory MELD score at transplant, pre-transplant hospitalization status, functional status, mechanical ventilation, life-support, dialysis, and primary diagnosis. Functional status was defined according to the following Karnofsky score classification: moderate to severe impairment (Karnofsky score of 10–40%), mild impairment (50–70%) and no impairment (80–100%). Laboratory MELD score at transplant was modeled as a categorical variable, with an upper cut-point of $\geqslant$35 to identify patients who receive greater priority under the Share 35 policy [13]. For patients with exception points, the calculated MELD score was based on laboratory data at transplantation available in the UNOS dataset. In addition, given UNOS caps prioritization at MELD score of 40, patients with calculated MELD of >40 were classified as having a MELD of 40. Functional status was modeled as a categorical variable as per SRTR categorization [17]. Donor risk index (DRI), a marker of graft quality and predictive of graft failure [18] was evaluated in secondary models, due to missing data (notably cold ischemic time) needed to calculate the DRI. We used a backwards elimination process, and included covariates that were independently associated with mortality (p <0.10) or were confounders and changed the odds ratio of the two primary exposure variables (MELD score and pre-transplant hospitalization status) by 10%. We tested for the interaction of MELD score * pre-transplant hospitalization status, and included it in final models if the p <0.10.

We performed a secondary analysis to evaluate the association between an acute rise in the MELD score prior to transplantation, and early post-transplant mortality, and how it may mediate the results. We were able to use the robust laboratory data available in UNOS we used alternative definitions based on pre-transplant changes in MELD score. Specifically, we defined an acute rise in the MELD score as absolute increase of at least five points within a four week period between the minimal pre-transplant MELD in the 28 day pre-transplant period and the MELD at transplantation [22–25]. For these analyses, only transplant recipients with at least two MELD values, including the value at transplantation, were included.

Results

There were 50,838 transplants initial liver transplant recipients during the study period. Of these 4095 (8.1%) were in an ICU prior to transplantation, and 5295 (10.4%) had a laboratory MELD score at transplantation $\geqslant$35 (Table 1). Pre-transplant laboratory MELD score ranged from six to 40. In the study population, 12,992 (25.6%) were transplanted with HCC exception points. With regards to other factors hypothesized to be associated with early post-transplant mortality, 3223 (6.3%) patients received dialysis in the week prior to transplantation, 2017 (4.0%) were on vasopressors, and 1507 (3.0%) were on a ventilator prior to transplantation. These factors were significantly less prevalent among 'low MELD' patients with a laboratory MELD score of <20 prior to transplantation. Among the 27,617 transplant recipients with a laboratory MELD score <20.31 (0.1%) were on dialysis prior to transplantation, 130 (0.5%) were receiving mechanical ventilation, and 173 (0.6%) were receiving vasopressors. Nearly two-thirds of patients were reported as having some degree of functional impairment, as measured by the Karnofsky score, with 12,828 (25.2%) patients having moderate to severe impairment (Karnofsky score of 10–40%). Secondary models were unchanged with inclusion of DRI as a covariate.

Over time, there was a significant increase in the proportion of transplant recipients that were either hospitalized (14.1% in