Published in final edited form as:

J Hepatol. 2015 September ; 63(3): 601–608. doi:10.1016/j.jhep.2015.03.034.

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

Therese Bittermann, MD¹, George Makar, MD, MSCE¹, and David S. Goldberg, MD, MSCE^{1,2,3}

¹Division of Gastroenterology, Department of Medicine, University of Pennsylvania

²Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania

³Leonard Davis Institute of Health Economics, University of Pennsylvania

Abstract

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 2002–2013 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 3-, 6-, 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 3-, 6-, and 12-month post-transplant mortality

Corresponding Author: David Goldberg, MD, MSCE, Blockley Hall, 423 Guardian Drive, Room 730, Philadelphia, PA 19104, Phone: 215-746-8598, Fax: 215-349-5915, david.goldberg@uphs.upenn.edu.

Conflicts of Interest: The authors of this manuscript have no conflicts of interest to disclose as it pertains to this manuscript.

Disclosures

None of the authors have any potential conflicts of interest as it pertains to this manuscript. We list the relevant grant information below:

1. This work was supported in part by Health Resources and Services Administration contract 234-2005-37011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, the Center for Medicare and Medicaid Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.
2. David Goldberg: NIH K08 DK098272

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 3-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.

Keywords

MELD score; hospitalization; intensive care unit; interaction; short-term mortality

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, Weismuller et al demonstrated a 10% increase in 3-month mortality at their transplant center in Germany after the adoption of MELD-based allocation as a result of 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 1 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 intensive care unit (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.

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 adult (≥ 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 4 versus 5 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 versus 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 generalized estimating equation (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 centers²⁰ 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 outcomes²¹: 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 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 failure¹⁸ 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 -value was < 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 5 points within a 4 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 4,095 (8.1%) were in an ICU prior to transplantation, and 5,295 (10.4%) had a laboratory MELD score at transplantation ≥ 35 (Table 1). Pre-transplant laboratory MELD

score ranged from 6 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, 3,223 (6.3%) patients received dialysis in the week prior to transplantation, 2,017 (4.0%) were on vasopressors, and 1,507 (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 2002, increasing to 20.5% in 2013) or in an ICU (6.8% in 2002, increasing to 9.7% in 2013; $p<0.001$) prior to transplantation. Of note, during the study period, 18.9% (21,101/111,600) of adult, non-Status 1, liver-alone patients on the waitlist for their first liver transplant during the study period were removed from the waiting list for death or clinical deterioration (defined as dying on the waitlist or being 'too sick' and dying within 90 days of waitlist removal^{26,27}). The median calculated MELD score of these waitlist removals was 22 (IQR: 15–35). Even prior to implementation of Share 35, there was a significant increase in the proportion of transplant recipients with a laboratory MELD score ≥ 35 at transplantation (6.7% in 2002, increasing to 15.0% in transplant recipients in the first half of 2013).

Unadjusted early post-transplant mortality rates

Among the 50,838 transplant recipients from 2/2002–6/2013 included in the analysis, 3,109 (6.1%), 4,348 (8.6%), and 6,227 (12.3%) died within 3, 6, and 12 months of transplantation, respectively. At all three time points, there were significant differences in the proportion of transplant recipients who died based on the hospitalization status prior to transplantation (Figure 1). There was a slight increase in the risk of mortality for transplant recipients who were hospitalized, compared to those who were home prior to transplantation; yet there was a pronounced increase in mortality among transplant recipients in the ICU prior to transplantation compared to those hospitalized but not in an ICU (absolute increase of 7%, 8%, and 9% at 3, 6, and 12 months, respectively; Figure 1).

Multivariable model and adjusted rates of post-transplant mortality

In multivariable GEE models, there was a significant interaction between laboratory MELD score at transplantation and hospitalization status at all three time points ($p=0.007$ for interaction term in 3- month model, and $p=0.002$ in 6- and 12-month models; Table 2). The interaction between MELD score and hospitalization status was most pronounced in patients with laboratory MELD scores at transplantation <25 who were in the ICU prior to transplantation. In fact, this interaction was so strong that, compared to the reference population of recipients with a laboratory MELD score of 30–34 in the ICU prior to transplantation, transplant recipients in the ICU with a MELD score <25 had increased risk

of early post-transplant mortality (albeit only significantly increased for 2/6 pairwise comparisons; Table 3).

When stratified by hospitalization status, with transplant recipients with a laboratory MELD score of 30–34 as the reference, transplant recipients with a MELD score ≥ 35 had increased early post-transplant mortality (numerically higher but only significantly higher for two of the comparisons) when transplanted from home or the general medical ward, but no difference among those in an ICU prior to transplantation (Table 2). However, when comparing MELD 30–34 versus MELD ≥ 35 patients with different hospitalization statuses prior to transplantation, controlled for other covariates, the difference in mortality was significantly higher when comparing MELD ≥ 35 transplant recipients in an ICU to MELD 30–34 recipients on a general medical ward prior to transplantation. This increased risk decreased over time from an odds ratio of 1.54 at three months, to 1.25 at 12 months (Table 4).

Post-estimation analyses calculating predicted probabilities of post-transplant survival, holding all covariates constant and accounting for baseline center differences, demonstrated markedly increased mortality rates for transplant recipients in an ICU prior to transplantation at all levels of MELD score. These differences were most pronounced in transplant recipients with a MELD score of 15–24, reflective of the interaction between MELD score and hospitalization status (Figure 2; Supplementary Table 1). Although the sample sizes of transplant recipients in an ICU prior to transplantation were small in the lower MELD score categories, the point estimates for predicted early post-transplant survival was similar for transplant recipients with MELD scores of 15–24 and 30–40. In contrast, transplant recipients with a MELD score of 35–40 transplanted from home had substantially lower predicted survival than recipients with MELD scores <25 (Figure 2; Supplementary Table 1).

Secondary analyses evaluating the impact of an acute rise of 5 points in the MELD score prior to transplantation included 40,590 (79.8%) of transplant recipients with at least two MELD values in the 28-day period pre-transplantation. Of these 40,590 recipients, 7,496 (18.5%) transplant recipients met criteria by virtue of having a MELD increase of at least five points prior to transplantation, with 1,642 (21.9%) being in an ICU prior to transplantation and 2,739 (36.5%) in a general hospital ward. Among transplant recipients with a pre-transplant laboratory MELD score of <15 , 15–19, and 30–34, the proportion with versus without an acute rise in the MELD score was similar among patients transplanted from home, a general medical ward, and an ICU. By contrast, there were statistically significant differences within the other MELD categories of transplant recipients from home, a general medical ward, and an ICU who had an acute rise in the MELD score pre-transplantation: 1) MELD 20–24: 10.0%, 12.5%, 12.3% of transplant recipients from home, a general medical ward, and an ICU had an acute rise in the MELD score, $p=0.02$; 2) MELD 25–29: 25.0%, 28.5%, 31.0%, respectively, $p=0.002$; and 3) MELD 35–40: 63.5%, 51.4%, and 51.9%, respectively, $p<0.001$. However, despite the different distributions of transplant recipients with an acute rise in the MELD score across MELD categories and pre-transplant location, there was no association between this acute rise in the pre-transplant MELD score

and post-transplant mortality in 3-, 6-, and 12-month multivariable models ($p > 0.05$ in each model).

Discussion

In this analysis of liver transplant recipients in the US over an 11-year period, hospitalization status modified the risk of early post-transplant mortality for a given MELD score, with markedly increased risks of early post-transplant mortality in patients transplanted from an ICU. This finding is novel as the interaction between ICU status and MELD score has never been explored as a primary exposure. The influence of hospitalization status, specifically being in an ICU prior to transplantation, was strongest in those transplant recipients with a laboratory MELD score < 25 . On the other hand, among transplant recipients at home prior to transplantation, the increased risk of post-transplant mortality was limited to those with a MELD score ≥ 35 . These data also demonstrate that a shift to transplanting patients with MELD scores ≥ 35 should only impact early post-transplant mortality if policy changes result in increased transplantation of these high MELD patients in an ICU prior to transplantation. Notably, the increased early mortality as a function of ICU status is independent of the increased risks associated with impaired functional status, etiology of liver disease, and use of vasopressors, mechanical ventilation, and/or dialysis prior to transplantation. These data are the first to demonstrate an interaction between MELD score and hospitalization status in a large national cohort, and have implications when considering the utility of transplantation, and predictors of early post-transplant mortality.

A formal consideration of ICU status in the determination of transplant eligibility could help minimize the transplantation of candidates at higher risk for short-term mortality and allow for a more efficient utilization of a scarce resource—transplantable organs. Faced with increasing organ shortages worldwide, the goal of organ allocation should be to maximize use of a limited resource, which should therefore include post-transplantation mortality. While patients with the highest MELD scores have the highest waitlist mortality, they only derive greater benefit from transplantation than patients with lower MELD scores if post-transplantation mortality remains comparable. The results of this study demonstrate that regardless of center practice variability, there are significant downsides to transplanting patients from the ICU. The incorporation of ICU status into the allocation process could therefore help guide transplant centers and aid in the counseling of patients and families.

While MELD-based allocation prioritizes candidates with higher pre-transplant mortality with a limited assessment of their post-operative risk, several investigators have evaluated factors predictive of post-transplant mortality. Previous work focused on survival benefit-based allocation by Schaubel et al. evaluated the role of MELD score in evaluating survival benefit accounting for both waitlist mortality and post-transplant survival.^{2,3} However, unlike the current study, that manuscript only evaluated transplant recipients from 2001–2007, included re-transplant candidates in the survival model, and did not include MELD score in their post-transplant survival model. In addition, it used a time horizon of five years post-transplantation, whereas a shorter time horizon would be more reflective of severity of illness at the time of transplantation and less subject to additional variables acquired after

transplantation.^{2,3} Additionally, a recent systematic review identified 37 studies (all case series) that evaluated the association between pre-transplant MELD score and post-transplant mortality. In 15 of the studies, there was no statistically significant association between pre-transplant MELD score and post-transplant mortality, while there was a small, but statistically significantly increased risk of post-transplant mortality with increasing pre-transplant MELD score.⁵ However, these studies had several limitations and differences from the current study: 1) the sample sizes were substantially smaller than our study cohort; 2) the specific interaction of MELD score and hospitalization status was not explored; and 3) overall post-transplant mortality was the outcome in nearly all of the studies, and not short-term post-transplant mortality.

Several investigators in Europe have demonstrated an increase in 3-month and 1-year mortality with the transition to a MELD-based allocation system in 2006.^{6,7,28} While increasing MELD scores at transplantation have been proposed as a primary reason, the use of pre-transplant life-support has also been shown to impact post-transplant mortality.^{6,7,28} Interestingly, in Dutkowski et al's publication from 2011, which compared UNOS data to single-center data from Zurich, there was not only an association between pre-transplant life-support and post-transplant mortality, but the use of life-support prior to transplantation in their patient population was considerably higher than in the US (9.8% vs 4.1%).²⁸ While the allocation system in Europe continues to be primarily dependent on the MELD score, there is no doubt that transplant candidate populations and medical practices differ between the United States and Europe. Therefore, policies created by UNOS may not be "one size fits all" and could produce different results in different parts of the world. This study demonstrates a clear interaction between MELD score and hospitalization status in the US, a finding which can help guide transplant centers elsewhere. However, these results should also be evaluated in large multi-center or multi-national European cohorts. On the whole, there still remains the common need for better evidence-based guidance in the selection of candidates transplanted from the ICU.

The UNOS database has a robust amount of laboratory data, allowing for identification of patients with a rapid pre-transplant rise in their MELD score. We used this to define an acute decompensation prior to transplantation, as UNOS lacks the necessary clinical data (i.e., hypoxemia) to categorize a patient as having acute-on-chronic liver failure (ACLF). We found that a relatively greater proportion of patients with an acute rise in the MELD score were in a hospital or an ICU prior to hospitalization compared to those without an acute rise in the MELD score. Despite this, there was no association between the presence of an acute rise in the MELD score and early post-transplant mortality when adjusting for other factors. This finding is not surprising given that the cohort included in these analyses was restricted to transplant recipients. As a result, although an acute rise in the MELD score is associated with a high 28-day mortality among patients with cirrhosis, the lack of association between pre-transplant an acute rise in the MELD score and post-transplant mortality is likely related to selection bias in analyses of transplant recipients, who by definition, exclude those with an acute rise in the MELD score who died without a transplant. These findings however are consistent with prior published reports.²⁴

Based on recently available OPTN/UNOS data that includes follow-up until June 4, 2014, the Share 35 policy has fulfilled its intended goal of increasing access for patients with the highest laboratory MELD scores, at the greatest risk of waitlist mortality. Because of this policy's recent implementation, post-transplant follow-up data are limited. However, our findings suggest that changes in organ allocation resulting in increased transplantation rates of patients with the highest laboratory MELD scores has the potential to impact post-transplant outcomes if such patients not only have the highest MELD scores, but also are transplanted from the ICU. In turn, this may lead to a prioritization system that is inefficient from the standpoint of maximizing potential graft-years from the limited organ supply. However, the impact of hospitalization status is not limited to high MELD patients only, as these data also demonstrate a novel finding of the strong interaction between low MELD score and hospitalization status on post-transplant outcomes. Akin to MELD-Na, whereby hyponatremia has the greatest impact on waitlist mortality in patients with the lowest MELD scores,²⁹ these data identify that being transplanted from an ICU has the greatest impact on post-transplant mortality in recipients with MELD scores <25. This effect modification of their risk of early post-transplant mortality is independent of other factors associated with being in an ICU, including need for vasopressors, dialysis, or mechanical ventilation. Mechanistically, these patients with lower MELD scores likely have other markers of illness not captured by the MELD which contribute to their need for ICU care as well as a greater degree of frailty. While the concept of frailty in liver transplantation candidates has recently been explored with regards to waitlist mortality,³⁰ how this marker of illness impacts post-transplantation outcomes is still poorly understood. Recently, several authors have developed prediction scores that include non-laboratory markers of frailty in order to predict post-transplantation mortality. For example, the MELD-psoas and MELD-sarcopenia scores have been demonstrated to be superior to the MELD alone in several small cohorts.^{31–33} However, larger studies are still needed to further validate these scoring systems and their continued utility remains dependent on their practicality and ease of use in everyday practice.

The focus of this analysis was short-term post-transplant mortality, unlike other studies evaluating long-term post-transplant mortality. This is important for several reasons. First, pre-transplant risk factors of MELD score and hospitalization status, which are markers of severity of illness, would be expected to more directly impact short-term post-transplant mortality than long-term outcomes which are affected by other variables such as recurrent disease, cardiovascular disease, or complications of immunosuppressive therapy. Second, 1-year post-transplant mortality is a metric used by American insurers to determine transplant center eligibility for high distinction and inclusion as "Centers of Excellence."²⁰ Third, candidate selection is in part based on their potential for long-term survival, which is not only influenced by short-term post-transplant mortality risks (i.e., infection or surgical complications), but also delayed complications such as recurrent disease, chronic kidney disease, cardiovascular disease, and de-novo malignancies. As a result of more formalized recommendations and increased awareness of complications specific to liver transplantation, the care of transplanted patients has improved significantly over the last decade and is expected to continue to progress. Thus a renewed focus on minimizing short-term mortality is critical in order to improve overall survival. Yet these data highlight that transplanting

patients at the highest-risk of early post-transplant mortality may limit the potential benefits of such improved care by compromising early post-transplant survival. This study had several limitations. First, ICU admission criteria, the number of ICU beds available, and the decision to transplant a patient from the ICU vary across transplant centers. We accounted for baseline center-level variability though using GEE models. Furthermore, the association between ICU status and post-transplant mortality was quite strong, and not likely to be solely explained by such among-center differences. In addition, there is practice variability not only between transplant centers but also within individual ICUs at the patient level. However, the use of clustering still accounts for this variability and the magnitude of the association was significant enough such that it would not be accounted for by chance alone. Second, while we were able to adjust for several factors that may implicate increased post-transplant mortality related to hospitalization status (i.e. ventilator and vasopressor requirements), other variables were not available (i.e. presence of multi-drug resistant organisms). However, regardless of these secondary risk factors, ICU status overall was associated with an increased risk of early post-transplant mortality. Lastly, coding of UNOS variables such as ICU status, use of vasopressors, dialysis, and/or mechanical ventilation have not been validated. Additionally, the UNOS data do not provide full clinical information to calculate the chronic liver failure-sequential organ failure assessment (CLIF-SOFA) scores or other clinical score most commonly used to diagnose ACLF (i.e., hypoxemia).^{22,34} As a result, we used a rapid rise in the MELD score to define pre-transplant decompensation which could be calculated for nearly 80% of the cohort. In these analyses, there was no association between an acute rise in the MELD score and early post-transplant mortality after adjustment for other factors, and do not think that using the CLIF-SOFA definitions would have let to different findings. UNOS does not include data on pre-wait-listing laboratory values, or other clinical parameters needed to determine if patients had chronic kidney disease (e.g., proteinuria, renal ultrasound), thus we could not differentiate those with acute kidney injury versus chronic kidney disease prior to transplantation.

In conclusion, these data demonstrate that there is a strong interaction between hospitalization status and MELD score on post-transplant mortality in the US, which modifies the risk of early post-transplant mortality in both high and low MELD patients. With improvements in post-transplant care, including emerging therapies for hepatitis C, risk stratifying patients with early post-transplant mortality is important in order to ensure maximal efficiency of a scarce resource. Although liver transplant allocation continues to be urgency-based, consideration of the risks associated with short-term post-transplant mortality is needed, otherwise efforts to improve overall transplant-related survival will fall short.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grants and Financial Support:

1. David Goldberg: NIH K08 DK098272
2. This work was supported in part by Health Resources and Services Administration contract 234–2005–37011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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

References

1. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology*. 2003; 124(1):91–96. [PubMed: 12512033]
2. Schaubel DE, Sima CS, Goodrich NP, Feng S, Merion RM. The survival benefit of deceased donor liver transplantation as a function of candidate disease severity and donor quality. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2008; 8(2):419–425.
3. Schaubel DE, Guidinger MK, Biggins SW, et al. Survival benefit-based deceased-donor liver allocation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2009; 9(4 Pt 2):970–981.
4. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2005; 5(2):307–313.
5. Klein KB, Stafinski TD, Menon D. Predicting survival after liver transplantation based on pre-transplant MELD score: a systematic review of the literature. *PLoS One*. 2013; 8(12):e80661. [PubMed: 24349010]
6. Weismuller TJ, Fikatas P, Schmidt J, et al. Multicentric evaluation of model for end-stage liver disease-based allocation and survival after liver transplantation in Germany--limitations of the 'sickest first'-concept. *Transpl Int*. 2011; 24(1):91–99. [PubMed: 20819196]
7. Weismuller TJ, Negm A, Becker T, et al. The introduction of MELD-based organ allocation impacts 3- month survival after liver transplantation by influencing pretransplant patient characteristics. *Transpl Int*. 2009; 22(10):970–978. [PubMed: 19619170]
8. Saab S, Wang V, Ibrahim AB, et al. MELD score predicts 1-year patient survival post-orthotopic liver transplantation. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*. 2003; 9(5):473–476.
9. Xia VW, Taniguchi M, Steadman RH. The changing face of patients presenting for liver transplantation. *Current opinion in organ transplantation*. 2008; 13(3):280–284. [PubMed: 18685318]

10. Abt PL, Mange KC, Olthoff KM, Markmann JF, Reddy KR, Shaked A. Allograft survival following adult-to-adult living donor liver transplantation. *Am J Transplant*. 2004; 4(8):1302–1307. [PubMed: 15268732]
11. Nadim MK, Sung RS, Davis CL, et al. Simultaneous liver-kidney transplantation summit: current state and future directions. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2012; 12(11):2901–2908.
12. Locke JE, Warren DS, Singer AL, et al. Declining outcomes in simultaneous liver-kidney transplantation in the MELD era: ineffective usage of renal allografts. *Transplantation*. 2008; 85(7):935–942. [PubMed: 18408571]
13. [Accessed June 18, 2014] OPTN UNOS Allocation Policy 3.6. 2013. http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_8.pdf
14. Cholongitas E, Senzolo M, Patch D, et al. Risk factors, sequential organ failure assessment and model for end-stage liver disease scores for predicting short term mortality in cirrhotic patients admitted to intensive care unit. *Aliment Pharmacol Ther*. 2006; 23(7):883–893. [PubMed: 16573791]
15. Das V, Boelle PY, Galbois A, et al. Cirrhotic patients in the medical intensive care unit: early prognosis and long-term survival. *Critical care medicine*. 2010; 38(11):2108–2116. [PubMed: 20802324]
16. Bahirwani R, Ghabril M, Forde KA, et al. Factors that Predict Short-Term Intensive Care Unit Mortality in Patients with Cirrhosis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2013
17. [Accessed 3/14/12] <http://www.stata.com/capabilities/generalized-estimating-equations/>
18. Localio AR, Berlin JA, Ten Have TR, Kimmel SE. Adjustments for center in multicenter studies: an overview. *Ann Intern Med*. 2001; 135(2):112–123. [PubMed: 11453711]
19. Berlin JA, Kimmel SE, Ten Have TR, Sammel MD. An empirical comparison of several clustered data approaches under confounding due to cluster effects in the analysis of complications of coronary angioplasty. *Biometrics*. 1999; 55(2):470–476. [PubMed: 11318202]
20. Asrani SK, Kim WR, Edwards EB, et al. Impact of the center on graft failure after liver transplantation. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*. 2013; 19(9):957–964.
21. [Accessed 1/18/12] OPTN/SRTR Annual Report. Technical Notes and Analytic Methods. 2009. http://optn.transplant.hrsa.gov/ar2009/Tech_Notes_AR_CD.htm#6
22. Jalan R, Pavesi M, Saliba F, et al. The CLIF Consortium Acute Decompensation score (CLIF-C ADs) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure. *Journal of hepatology*. 2014
23. Bahirwani R, Ghabril M, Forde KA, et al. Factors that predict short-term intensive care unit mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2013; 11(9):1194–1200. e1192. [PubMed: 23602820]
24. Bahirwani R, Shaked O, Bewtra M, Forde K, Reddy KR. Acute-on-chronic liver failure before liver transplantation: impact on posttransplant outcomes. *Transplantation*. 2011; 92(8):952–957. [PubMed: 21869735]
25. Novelli G, Rossi M, Ferretti G, et al. Predictive parameters after molecular absorbent recirculating system treatment integrated with model for end stage liver disease model in patients with acute-on-chronic liver failure. *Transplantation proceedings*. 2010; 42(4):1182–1187. [PubMed: 20534256]
26. Goldberg D, French B, Abt P, Feng S, Cameron AM. Increasing disparity in waitlist mortality rates with increased model for end-stage liver disease scores for candidates with hepatocellular carcinoma versus candidates without hepatocellular carcinoma. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society*. 2012; 18(4):434–443.
27. Goldberg DS, French B, Forde KA, et al. Association of distance from a transplant center with access to waitlist placement, receipt of liver transplantation, and survival among US veterans. *Jama*. 2014; 311(12):1234–1243. [PubMed: 24668105]

28. Dutkowski P, Oberkofler CE, Slankamenac K, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. *Ann Surg.* 2011; 254(5):745–753. discussion 753. [PubMed: 22042468]
29. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. *The New England journal of medicine.* 2008; 359(10):1018–1026. [PubMed: 18768945]
30. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. *Am J Transplant.* 2014; 14(8):1870–1879. [PubMed: 24935609]
31. Durand F, Buyse S, Francoz C, et al. Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography. *Journal of hepatology.* 2014; 60(6):1151–1157. [PubMed: 24607622]
32. Montano-Loza AJ. Muscle wasting: a nutritional criterion to prioritize patients for liver transplantation. *Current opinion in clinical nutrition and metabolic care.* 2014; 17(3):219–225. [PubMed: 24613858]
33. Montano-Loza AJ, Meza-Junco J, Prado CM, et al. Muscle wasting is associated with mortality in patients with cirrhosis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2012; 10(2):166–173. 173 e161. [PubMed: 21893129]
34. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology.* 2013; 144(7): 1426–1437. 1437 e1421–1429. [PubMed: 23474284]

Figure 1.

Early post-transplant mortality based on location prior to transplantation, 2002–2013

Figure 2.
(three panels)

- a. Figure 2a: Predicted 3-month post-transplant survival according to pre-transplant hospitalization status and pre-transplant calculated MELD score based on multivariable GEE models*.

- b. Figure 2b: Predicted 6-month post-transplant survival according to pre-transplant hospitalization status and pre-transplant calculated MELD score based on multivariable GEE models*.

- c. Figure 2c: Predicted 12-month post-transplant survival according to pre-transplant hospitalization status and pre-transplant calculated MELD score based on multivariable GEE models*.

- d. *Footnote: Confidence intervals for survival listed in Supplemental Table 1. $P < 0.05$ for comparisons within each MELD category. MELD score 35–40 includes patients with a laboratory MELD score > 40 .

Table 1

Demographic and clinical characteristics of transplant recipients from 2002–2013 included in analysis, n=50,838

Characteristic	N, (%) [*]
Age in years, median (IQR)	55 (49–60)
Male sex	35,205 (69.3)
Race/ethnicity	
White	37,021 (72.8)
Black	4,401 (8.7)
Hispanic	6,541 (12.9)
Asian	2,309 (4.5)
Other	566 (1.1)
Primary diagnosis	
Hepatitis C	21,769 (42.8)
Alcohol	8,067 (15.9)
NASH/cryptogenic	7,128 (14.0)
Cholestatic	4,303 (8.5)
Hepatitis B	1,868 (3.7)
Autoimmune hepatitis	1,608 (3.2)
Other	6,094 (12.0)
Laboratory MELD score at transplantation, median (IQR)	18 (12–26)
Transplanted with exception points	17,181 (33.0)
Hospitalization status at transplant [†]	
Home	38,252 (75.4)
Hospitalized	8,407 (16.6)
ICU	4,095 (8.1)
On ventilator at transplantation	1,507 (3.0)
On vasopressors at transplantation	2,017 (4.0)
Received dialysis during one week prior to transplantation	3,223 (6.3)
Functional status at transplantation [‡]	
No impairment	11,802 (23.2)
Mild impairment	21,293 (41.9)
Moderate to severe impairment	12,828 (25.2)
Missing	4,915 (9.7)
Deaths	
3 months	3,109 (6.1)
6 months	4,348 (8.6)
12 months	6,227 (12.3)

^{*} Unless otherwise specified

[†] Data missing on 83 transplant recipients

[‡] Moderate to severe: Karnofsky score of 10–40%; Mild: Karnofsky score of 50–70%; No impairment: Karnofsky score of 80–100%

Table 2Within-hospital status results of multivariable logistic model evaluating early post-transplant mortality[†]

	Multivariable odds ratio for mortality		
	3-months	6-months	12-months
Home			
Lab MELD 30–34	1	1	1
Lab MELD <15	0.81 (0.64–1.03)	0.76 (0.62–0.92)*	0.74 (0.63–0.88)*
Lab MELD 15–19	0.77 (0.61–0.98)*	0.71 (0.58–0.87)*	0.68 (0.58–0.81)*
Lab MELD 20–24	0.83 (0.65–1.06)	0.80 (0.65–0.98)*	0.78 (0.66–0.93)*
Lab MELD 25–29	0.86 (0.66–1.13)	0.85 (0.68–1.06)	0.81 (0.67–0.98)*
Lab MELD 35+	1.26 (1.04–2.04)*	1.24 (0.93–1.66)	1.18 (0.92–1.51)
Hospitalized			
Lab MELD 30–34	1	1	1
Lab MELD <15	0.99 (0.68–1.46)	1.11 (0.81–1.52)	1.21 (0.93–1.59)
Lab MELD 15–19	0.92 (0.65–1.30)	1.04 (0.78–1.38)	1.06 (0.83–1.35)
Lab MELD 20–24	1.01 (0.76–1.35)	0.95 (0.74–1.22)	1.02 (0.82–1.26)
Lab MELD 25–29	1.04 (0.80–1.35)	1.03 (0.83–1.30)	1.02 (0.84–1.24)
Lab MELD 35+	1.30 (1.03–1.64)*	1.18 (0.97–1.44)	1.16 (0.97–1.38)
ICU			
Lab MELD 30–34	1	1	1
Lab MELD <15	1.28 (0.80–2.05)	1.05 (0.67–1.64)	1.03 (0.68–1.55)
Lab MELD 15–19	1.61 (1.06–2.46)*	1.59 (1.01–2.20)*	1.32 (0.91–1.91)
Lab MELD 20–24	1.31 (0.92–1.86)	1.15 (0.83–1.59)	1.15 (0.85–1.55)
Lab MELD 25–29	0.86 (0.62–1.20)	0.83 (0.62–1.12)	0.83 (0.63–1.09)
Lab MELD 35+	0.96 (0.75–1.21)	0.85 (0.69–1.06)	0.86 (0.70–1.05)

[†] 50,754 transplant recipients used in each model. Interaction term of hospitalization status and MELD score significant in all three GEE models (p=0.007 for 3-month and 6-month models, and p=0.002 for 12-month model).

* p<0.05

Table 3

Other covariates included in multivariable GEE models evaluating early post-transplant mortality*

	Multivariable odds ratio for mortality		
	3-months	6-months	12-months
Male sex	0.96 (0.89–1.04)	0.98 (0.92–1.05)	0.98 (0.92–1.04)
Age [†]	1.12 (1.10–1.15)	1.14 (1.12–1.16)	1.13 (1.11–1.15)
Race/ethnicity [‡]			
White	1	1	1
Black	1.08 (0.95–1.24)	1.10 (0.98–1.23)	1.20 (1.08–1.31)
Hispanic	0.93 (0.83–1.04)	0.91 (0.83–1.01)	0.91 (0.84–0.996)
Asian	0.93 (0.76–1.14)	0.88 (0.74–1.05)	0.90 (0.77–1.04)
Other	0.97 (0.69–1.37)	0.94 (0.70–1.28)	0.98 (0.76–1.27)
Serum albumin at transplant	0.93 (0.89–0.99)	0.92 (0.88–0.96)	0.92 (0.88–0.95)
Functional status			
No impairment	1	1	1
Minimal impairment	1.32 (1.17–1.48)	1.33 (1.20–1.46)	1.29 (1.19–1.40)
Moderate to severe impairment	2.04 (1.79–2.34)	1.86 (1.66–2.09)	1.76 (1.60–1.94)
Missing	2.38 (2.05–2.78)	2.15 (1.88–2.45)	2.00 (1.79–2.24)
Primary diagnosis [‡]			
Hepatitis C	1	1	1
Alcoholic liver disease	1.04 (0.94–1.16)	0.87 (0.79–0.95)	0.74 (0.68–0.80)
Hepatitis B	1.16 (0.94–1.44)	0.94 (0.78–1.14)	0.76 (0.64–0.90)
NASH/cryptogenic	1.22 (1.09–1.36)	1.02 (0.93–1.12)	0.84 (0.77–0.91)
Cholestatic	0.91 (0.78–1.05)	0.78 (0.69–0.89)	0.62 (0.55–0.70)
Autoimmune hepatitis	1.12 (0.90–1.38)	0.99 (0.82–1.19)	0.86 (0.74–1.02)
Other	1.23 (1.09–1.39)	1.07 (0.97–1.19)	0.96 (0.88–1.05)
Use of vasopressors prior to transplantation	1.38 (1.05–1.18)	1.35 (1.06–1.73)	1.38 (1.10–1.73)
Mechanical ventilation prior to transplantation	1.41 (1.06–1.87)	1.40 (1.09–1.82)	1.36 (1.07–1.73)
Dialysis in week prior to transplantation	1.22 (1.06–1.41)	1.31 (1.16–1.49)	1.35 (1.20–1.51)

* 50,754 transplant recipients used in each model. Primary exposure covariates presented in Table 2

[†] Every increase in 5 years at transplantation[‡] p<0.05 for each category in each of the GEE mortality models

Table 4

Adjusted odds ratios for early post-transplant mortality based on hospitalization status and laboratory MELD score at transplantation: Comparing to MELD 30–34 to MELD 35+ transplant* recipients*

MELD 35+ group	Control MELD 30–34 group	Multivariable odds ratio for mortality		
		3-months	6-months	12-months
In hospital	At home	1.09 (0.83–1.42)	0.99 (0.79–1.26)	0.91 (0.75–1.11)
In ICU	At home	1.29 (0.97–1.71)	1.14 (0.89–1.45)	0.99 (0.80–1.23)
In ICU	In hospital, non -ICU	1.54 (1.21–1.97)**	1.35 (1.09–1.67)**	1.25 (1.03–1.52)**

* Comparisons based on results of multivariable model presented in Tables 2 and Supplementary Table 1, which accounts for final laboratory MELD score, hospitalization status, and interaction term of hospitalization status and MELD score, in addition to serum albumin at transplant, use of vasopressors or mechanical ventilation prior to transplantation, dialysis in the week prior to transplantation, race/ethnicity, primary diagnosis, and age at transplantation.

**
p<0.05