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H. J. Panchal

J. B. Durinka

J. Patterson

F. Karipineni

S. Ashburn
Northwell Health

See next page for additional authors

Authors
H. J. Panchal, J. B. Durinka, J. Patterson, F. Karipineni, S. Ashburn, E. Siskind, and J. Ortiz

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ORIGINAL ARTICLE

Survival outcomes in liver transplant recipients with Model for End-stage Liver Disease scores of 40 or higher: a decade-long experience

Hina J. Panchal[1], Joel B. Durinka[2], Jeromy Patterson[3], Farah Karipineni[2], Sarah Ashburn[4], Eric Siskind[5] & Jorge Ortiz[6]

[1]Department of Genetics & Genomic Science and Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2]Department of Surgery, Albert Einstein Medical Center, Philadelphia, PA, USA, [3]Department of Surgery, Emory University School of Medicine, Atlanta, GA, USA, [4]Department of Surgery, Hofstra–North Shore LIJ School of Medicine, Hempstead, NY, USA, [5]Department of Transplantation, North Shore LIJ Hospital, Manhasset, NY, USA, and [6]Department of Transplantation, University of Toledo Medical Center, Toledo, OH, USA

Abstract

Background: The Model for End-stage Liver Disease (MELD) has been used as a prognostic tool since 2002 to predict pre-transplant mortality. Increasing proportions of transplant candidates with higher MELD scores, combined with improvements in transplant outcomes, mandate the need to study surgical outcomes in patients with MELD scores of ≥40.

Methods: A retrospective longitudinal analysis of United Network for Organ Sharing (UNOS) data on all liver transplantations performed between February 2002 and June 2011 (n = 33 398) stratified by MELD score (<30, 30–39, ≥40) was conducted. The primary outcomes of interest were short- and long-term graft and patient survival. A Kaplan–Meier product limit method and Cox regression were used. A subanalysis using a futile population was performed to determine futility predictors.

Results: Of the 33 398 transplant recipients analysed, 74% scored <30, 18% scored 30–39, and 8% scored ≥40 at transplantation. Recipients with MELD scores of ≥40 were more likely to be younger ($P < 0.001$), non-White and to have shorter waitlist times ($P < 0.001$). Overall patient survival correlated inversely with increasing MELD score; this trend was consistent for both short-term (30 days and 90 days) and longterm (1, 3 and 5 years) graft and patient survival. In multivariate analysis, increasing age, African-American ethnicity, donor obesity and diabetes were negative predictors of survival. Futility predictors included patient age of >60 years, obesity, peri-transplantation intensive care unit hospitalization with ventilation, and multiple comorbidities.

Conclusions: Liver transplantation in recipients with MELD scores of ≥40 offers acceptable longterm survival outcomes. Futility predictors indicate the need for prospective follow-up studies to define the population to gain the highest benefit from this precious resource.

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Correspondence

Hina J. Panchal, Department of Genetics & Genomic Science and Gastroenterology, Icahn School of Medicine at Mount Sinai, 1470 Madison Avenue, New York, NY 10029, USA. Tel.: +1 917 453 4274. Fax: +1 646 537 2323. E-mail: Hinaben.panchal@mssm.edu

Introduction

The Model for End-stage Liver Disease (MELD) laboratory score was adopted in 2002 to quantify the clinical status of potential liver transplant recipients and to prioritize candidates for the allocation of donor organs.[1] The MELD score is calculated using three objective values: the international normalized ratio (INR); serum creatinine, and serum bilirubin. It reflects a patient's 3-month mortality risk on a scale of 6–40. Priority for liver allocation is given to individuals with the highest scores.[1,2]

The United Network for Organ Sharing (UNOS), a private non-profit organization, governs the allocation of donor organs to transplant candidates within the USA. In 2011, median MELD scores in adults receiving deceased donor livers varied by region from 19.5 to 36.0. The national median MELD score was 27.[4] When the MELD score was implemented, patients with scores of >40 were frequently considered to be too ill to undergo transplantation.[5] Since then, transplants among patients with MELD scores of >40 have increased in frequency

as patient outcomes have improved.[5,6] Between 2006 and 2010, the proportion of transplant recipients with MELD scores of ≥40 increased from 6.8% to 10.7% across the nation.[5] Given their high waitlist mortality rate and short life expectancy, these transplant candidates have also demonstrated in small reports the most significant benefit from liver transplant, regardless of donor allograft quality. Even in patients with very high MELD scores, transplantation has been shown to provide a short-term survival benefit.[7]

Although the MELD score stratifies patients based on their risk for mortality without a transplant, it does not necessarily identify which patients will have the best longterm outcomes from liver transplantation. This has become increasingly important in an era of increased metrics and oversight across health care fields. The present literature addressing liver transplantation in patients with MELD scores of >40 and longer-term post-transplant outcomes among this group of patients is scant. The issue has been evaluated only in a single-centre context[8] and no national multicentre studies exist.

This retrospective cohort study uses the UNOS database to examine post-transplant survival, morbidity and prognostic indicators of survival in liver allograft recipients with MELD scores of ≥40 at the time of transplantation. It also explores futility predictors of early mortality.

Materials and methods

A population-based, longitudinal retrospective review of patients who became transplant recipients during the period from 27 February 2002 to 30 June 2011 was conducted using UNet , a secure UNOS online database that comprehensively shares nationwide information on organ matching.

Inclusion criteria required the patient to have undergone a transplant performed on or after 27 February 2002 and to have had a MELD score of 6–60 (n = 56 470). Exclusion criteria removed patients with approved MELD exception (n = 16 460), a history of one or more liver allograft failures (n = 4380), and simultaneous kidney, pancreas, intestine, lung or heart (n = 4688) transplant. The resulting cohort (n = 33 398) was further divided into three groups based on MELD score at transplant: <30 (n = 24 804); 30–39 (n = 5984), and ≥40 (n = 2610). The primary outcomes of interest were short- and longterm outcomes in patients with scores of ≥40 compared with those in the other groups. Short-term outcomes were defined as length of hospitalization, and 30- and 90-day post-transplantation survival of grafts and patients. Longterm outcomes were defined as 1-, 3- and 5-year survival. To identify potential predictors, multiple univariate Cox regression analyses were completed for clinically suspected risk factors including: donor and recipient characteristics (including age, gender and ethnicity); the medical condition of the patient immediately before transplantation; the cause of the donor's death; allograft type, and organ share type. Covariates including donor and recipient age, gender, body mass index (BMI), waiting time, total warm ischaemia time, share type and cause of donor death were used in the multivariate analysis. Table 1 gives a full list of the variables examined.

For the futility analysis, a nested case–control study was designed within the cohort of patients with MELD scores of ≥40 (n = 2610). Transplant recipients with MELD scores of ≥40 who died during the study period were included in this sub-study (n = 660); those with MELD scores of ≥40 who were lost from follow-up or who remained alive at the end of the study (censored) were excluded (n = 1950). Futility was defined as death within 3 months of transplantation. Thus, patients who died within 3 months were designated as futile (n = 282). Patients who died after 3 months were considered as non-futile (n = 378). Multiple logistic regression analyses were performed to identify potential predictors of futility.

Statistical analysis

Descriptive statistics of clinical and demographic characteristics were summarized using the chi-squared test or Fisher's exact test for categorical variables. Normally distributed continuous variables such as BMI were tested using one-way analysis of variance (ANOVA). Non-normally distributed numerical variables such as hospital length of stay (LoS) were tested using the Kruskal–Wallis test. Survival curves for three groups were obtained using the Kaplan–Meier product limit method and compared using the Cox–Mantel log rank statistic. Patient death and graft failure represented the endpoints in the survival analysis. Right censoring was performed for patients who entered the study at a definite time (e.g. transplantation), but ceased to remain in follow-up before the endpoints of the study were observed (e.g. graft failure and death).

For multivariate analysis, predetermined covariates (age, gender, ethnicity, donor and share type) and variates with a P-value of ≤0.1 were included in the final model. All probability values were two-tailed. The type I error rate was set at 0.05. All statistical analyses were performed using IBM SPSS Statistics for Mac OS Version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Of the 33 398 transplant recipients analysed, 74% (n = 24 804) had MELD scores of <30, 18% (n = 5984) had MELD scores of 30–39, and 8% (n = 2610) had MELD scores of ≥40 at transplantation. Overall mortality was directly proportional to MELD score (26%, 28% and 30%, respectively, in recipients with MELD scores of <30, 30–39 and ≥40).

There were 1735 futile transplants in recipients who died within 3 months after transplantation. Analysed according to MELD score subgroup, 4.2% of patients with MELD scores of <30 (n = 1031), 7.1% of patients with MELD scores of 30–39 (n = 422), and 10.8% of patients with MELD scores of ≥40 (n = 282) underwent futile transplants.

Table 1 Pretransplant recipient and liver allograft characteristics by Model for End-stage Liver Disease (MELD) score

Recipient characteristics	MELD score category			*P*-value
	<30 (*n* = 24 804)	30–39 (*n* = 5984)	≥40 (*n* = 2610)	
Age, years, median (IQR)	53 (13)	51 (16)	50 (17)	<0.001
Male, *n* (%)	15 916 (64%)	3567 (60%)	1626 (63%)	<0.001
Obese (BMI ≥30 kg/m^2), *n* (%)	7129 (29%)	1519 (25%)	695 (27%)	<0.001
Ethnicity, *n* (%)				
White	18 811 (76%)	3916 (65%)	1611 (62%)	<0.001
African-American	2214 (9%)	727 (12%)	317 (12%)	
Hispanic/Latino	2885 (12%)	1022 (17%)	496 (19%)	
Asian	636 (3%)	233 (4%)	141 (5%)	
Other[a]/unknown/mixed	258 (1%)	86 (1%)	45 (2%)	
Viral infections, *n* (%)				
HBsAg positive	904 (4%)	329 (6%)	207 (8%)	<0.001
HBcAb positive	3858 (16%)	1015 (17%)	501 (19%)	<0.001
Hepatitis C positive	8171 (33%)	1795 (30%)	769 (30%)	
EBV positive	14 325 (58%)	3096 (52%)	1336 (51%)	<0.001
Other comorbidities at transplant, *n* (%)				
Diabetes	4876 (20%)	983 (16%)	376 (14%)	<0.001
Portal vein thrombosis	1365 (6%)	283 (5%)	132 (5%)	<0.001
PRBC prior to transplant[b]	317 (1%)	137 (2%)	67 (3%)	<0.001
Prior upper abdominal surgery	9299 (38%)	1894 (32%)	733 (28%)	<0.001
TIPS	2332 (9%)	431 (7%)	199 (8%)	<0.001
Encephalopathy at transplant, *n* (%)				
None	6998 (28%)	851 (14%)	252 (10%)	<0.001
Grade I or II	15 000 (61%)	3298 (55%)	1250 (48%)	
Grade III or IV	2101 (9%)	1680 (28%)	1044 (40%)	
Ascites at transplant, *n* (%)				
Absent	3845 (16%)	732 (12%)	354 (14%)	<0.001
Mild	13 673 (55%)	2356 (40%)	904 (35%)	
Moderate	6607 (27%)	2740 (46%)	1297 (50%)	
Waiting time, days, median (IQR)	82 (250)	14 (85)	8 (37)	<0.001
Distance from donor to transplant hospital, miles, median (IQR)	58 (176)	70 (194)	74 (2037)	<0.001
MELD score, mean (SD)	18.4 (5.4)	33.9 (2.8)	44.2 (3.7)	<0.001
Pre-transplant laboratory results				<0.001
Total bilirubin, mg/dl, median (IQR)	3.3 (3.9)	15.9 (21.3)	32.7 (14.3)	
Creatinine, mg/dl, median (IQR)	1.0 (0.6)	2.0 (1.5)	2.5 (2.5)	<0.001
INR, median (IQR)	1.6 (0.6)	2.4 (1.2)	3.1 (1.8)	<0.001
Albumin, g/dl, mean (SD)	2.9 (1.0)	2.6 (1.0)	2.8 (1.0)	<0.001
Dialysis in week prior to transplant, *n* (%)	395 (2%)	1126 (20%)	1221 (47%)	<0.001
Dialysis while on waitlist, *n* (%)	199 (1%)	300 (5%)	273 (11%)	<0.001
Hospitalized pre-transplant,[c] *n* (%)	2968 (12%)	1144 (19%)	459 (18%)	<0.001
Transplant candidate TIPS, *n* (%)	1865 (8%)	311 (5%)	139 (5%)	<0.001
Transplant candidate on life support/ventilator, *n* (%)	428 (2%)	586 (10%)	393 (15%)	<0.001
Medical condition at transplant, *n* (%)				
Hospitalized in ICU	1650 (7%)	2060 (35%)	1424 (55%)	<0.001

Table 1 Continued

Recipient characteristics	MELD score category			*P*-value
	<30 (*n* = 24 804)	30–39 (*n* = 5984)	≥40 (*n* = 2610)	
On life support	828 (3%)	1090 (18%)	832 (32%)	
On ventilator	728 (3%)	954 (16%)	711 (27%)	
Hospitalized not ICU	3304 (13%)	2393 (40%)	949 (37%)	<0.001
Not hospitalized	19 759 (80%)	1489 (25%)	216 (8%)	<0.001
Known malignancy since waitlist	410 (2%)	71 (1%)	31 (1%)	<0.001
Share type, *n* (%)				
Local	17 622 (71%)	3940 (66%)	1650 (63%)	<0.001
Regional	5149 (21%)	1792 (30%)	860 (33%)	
National	2030 (8%)	251 (4%)	98 (4%)	
Foreign	3 (0.01%)	1 (0.02%)	2 (0.08%)	
Liver graft type, *n* (%)				
Split	2602 (11%)	186 (3%)	84 (3%)	<0.001
Whole	22 202 (90%)	5798 (97%)	2526 (97%)	

[a]Includes American Indian, Alaskan Native, Native Hawaiian, other Pacific Islander.
[b]Received ≥5 units of packed red blood cells 48 h prior to transplant as a result of spontaneous portal hypertensive bleeding.
[c]Hospitalized within 90 days before transplantation.
BMI, body mass index; EBV, Epstein–Barr virus; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; PRBC, packed red blood cells; SD, standard deviation; TIPS, transjugular intrahepatic portocaval shunt.

Transplant recipient characteristics

The characteristics of transplant recipients are displayed and compared in Table 1. Gender distributions were similar across the groups. At transplantation, recipients with MELD scores of ≥40 were slightly younger (median age: 53 years, 51 years and 50 years, respectively, in recipients with MELD scores of <30, 30–39 and ≥40; $P < 0.001$). Additionally, the group with MELD scores of ≥40 had a higher proportion of non-White recipients, including patients of African-American, Hispanic, Asian, American Indian, Alaskan Native, Native Hawaiian and other Pacific Islander ethnicities ($P < 0.001$). At transplantation, recipients with MELD scores of ≥40 had serum chemistry measurement values higher than those with MELD scores of <30: total bilirubin was 10 times higher; creatinine was 2.5 times higher, and INR was twice as high ($P < 0.001$). Compared with patients with MELD scores of <30 or of 30–39, these high MELD score recipients were also significantly more likely to be dialysed within 1 week prior to transplantation (2%, 20% and 47%, respectively, in recipients with MELD scores of <30, 30–39 and ≥40; $P < 0.001$) and at some other time while on the waiting list (1%, 5% and 11%, respectively, in recipients with MELD scores of <30, 30–39 and ≥40; $P < 0.001$).

A greater proportion of recipients with MELD scores of ≥40 had grade III or IV encephalopathy prior to transplantation. However, fewer patients had a history of diabetes and portal vein thrombosis. They were also less likely to have a history of upper abdominal surgery or a transjugular intrahepatic portocaval shunt (TIPS) ($P < 0.001$). Despite spending significantly less time on the waiting list ($P < 0.001$), they were more likely to have been hospitalized within the 90 days prior to transplantation and to have required mechanical ventilation ($P < 0.001$). The most common indication for transplantation was hepatitis C infection (30%). Recipients with MELD scores of ≥40 were more likely to receive an organ of regional share type ($P < 0.001$). Recipients with MELD scores of <30 were more likely to receive a split liver ($P < 0.001$) or a liver from a local and national share ($P < 0.001$).

Donor characteristics

Donor characteristics are displayed in Table 2. Patients with MELD scores of ≥40 were more likely to receive liver allografts from donors who were younger (median donor age: 41 years, 39 years and 39 years, respectively, in recipients with MELD scores of <30, 30–39 and ≥40; $P < 0.001$), non-White ($P < 0.001$), and obese ($P = 0.001$). These donors were less likely to have a medical history of hypertension and diabetes ($P < 0.001$) or to be extended criteria donors (defined as those aged >60 years or those aged 50–59 years with two of history of hypertension, serum creatinine >1.4 mg/dl and death resulting from stroke). The most common cause of donor death was stroke, followed by head trauma and anoxia, across all three MELD score-stratified recipient groups ($P = 0.404$).

Liver allograft and preservation conditions

The majority of transplanted allografts were whole livers. Average cold ischaemia time was similar across all groups

(8 h; $P = 0.082$). Total warm ischaemia time, including anastomotic time, was significantly longer in the higher MELD score group (38 min, 39 min and 41 min, in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P < 0.001$).

Split- versus whole-liver allografts

Among recipients with MELD scores of <40, short-term patient survival was similar for split- and whole-liver allografts (97%, 95%, and 97%, 94% at 30 days and 90 days, respectively); however, longterm patient survival was better in those who received split grafts (91%, 86%, 82%, and 89%, 81%, 75%, at 1, 3 and 5 years, respectively; $P < 0.001$). Among recipients with MELD scores of ≥40, short-term survival was better in those who received split grafts (93%, 88% and 92%, 87% at 30 days and 90 days, respectively), whereas longterm survival was similar (79%, 79%, 69% and 80%, 73%, 69% at 1, 3 and 5 years, respectively).

Univariate regression analysis showed a split graft to confer no benefit in recipients with MELD scores of ≥40 [hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.50–1.29; $P = 0.357$]. However, it showed a reduced risk for mortality in recipients with MELD scores of <40 (HR 0.70, 95% CI 64–0.78; $P < 0.001$). In multivariate analysis adjusted for donor and recipient age, gender, BMI and waiting time, a split graft showed no significant effect in terms of patient survival in recipients with MELD scores of ≥40 (HR 1.56, 95% CI 0.92–2.66; $P = 0.102$) and some survival benefit in recipients with MELD scores of <40 (HR 0.89, 95% CI 0.80–0.99; $P = 0.032$). After controlling for confounders, graft survival in split-liver transplantations did not differ significantly between the groups [HR 0.72, 95% CI 0.90–1.07 ($P = 0.718$) in recipients with MELD scores of <40; HR 1.59, 95% CI 1.00–2.52 ($P = 0.049$) in recipients with MELD scores of ≥40]. Overall, the survival outcomes of split-liver and whole-liver allografts were similar.

Short-term graft and patient survival

Post-transplant hospital LoS was significantly longer in patients with higher MELD scores (median LoS: 11 days, 14 days and 15 days in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P < 0.001$). Incidences of acute rejection

Table 2 Demographic and clinical characteristics of liver allograft donors by recipient Model for End-stage Liver Disease (MELD) score

Characteristics	MELD score categories of transplant recipients			
	<30 (*n* = 24 804)	30–39 (*n* = 5984)	≥40 (*n* = 2610)	*P*-value
Age, years, median (IQR)	41 (30)	39 (29)	39 (29)	<0.001
Gender, male, *n* (%)	14 537 (59%)	3558 (60%)	1570 (60%)	0.189
Race, *n* (%)				
White	17 473 (70%)	3924 (66%)	1659 (64%)	<0.001
African-American	3809 (15%)	843 (14%)	365 (14%)	
Hispanic/Latino	2771 (11%)	1006 (17%)	478 (18%)	
Asian	452 (2%)	129 (2%)	73 (3%)	
Other[a]/unknown/mixed	298 (1%)	82 (2%)	35 (2%)	
Obesity (BMI ≥30 kg/m^2), *n* (%)	10 292 (42%)	2592 (43%)	1162 (45%)	0.001
ECD,[b] *n* (%)	6028 (27%)	1223 (21%)	540 (21%)	<0.001
Hypertension, *n* (%)	7451 (30%)	1658 (28%)	730 (28%)	<0.001
Diabetes mellitus, *n* (%)	2282 (9%)	487 (8%)	214 (8%)	<0.001
HBV core Ab positive, *n* (%)	1224 (5%)	245 (4%)	101 (4%)	<0.001
Controlled donor, *n* (%)	1075 (4%)	170 (3%)	71 (3%)	<0.001
Liver biopsied, *n* (%)	7793 (31%)	1617 (27%)	657 (25%)	<0.001
Cause of death, *n* (%)				
Anoxia	3787 (17%)	1034 (18%)	434 (17%)	0.404
CVA/stroke	9441 (42%)	2363 (40%)	1055 (41%)	
Head trauma	8850 (39%)	2365 (40%)	1017 (40%)	
CNS tumour	143 (1%)	37 (1%)	16 (1%)	
Other	498 (2%)	114 (2%)	49 (2%)	

[a]Includes American Indian, Alaskan Native, Native Hawaiian, other Pacific Islander.
[b]ECD: extended criteria donors according to the kidney allocation system includes donors aged >60 years or aged >50 years with two of the following: hypertension, serum creatinine >1.5 mg/dl, and death resulting from a stroke.
BMI, body mass index; CNS, central nervous system; CVA, cerebrovascular accident; HBV, hepatitis B virus; IQR, interquartile range.

episodes between transplantation and discharge were similar across groups ($P = 0.350$).

Graft survival at 30 days varied inversely with increasing MELD score (95%, 93% and 92% in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P < 0.001$). The same relationship was observed for graft survival at 90 days (92%, 88% and 87% in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P < 0.001$), patient survival at 30 days (97%, 95% and 92% in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P < 0.001$), and patient survival at 90 days (95%, 91% and 87% in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P < 0.001$). Figure 1 depicts graft and patient survival curves.

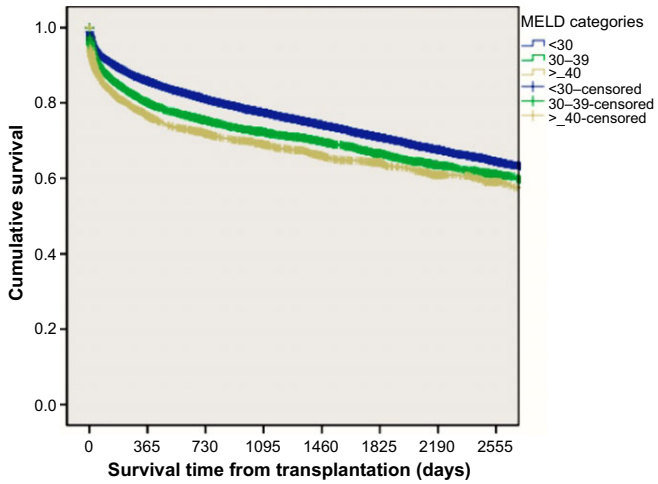
All subgroups had similar rates of graft non-function from all causes, regardless of increasing MELD score (12%, 11% and 12% in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P = 0.009$). Rates of treatment for rejection within 6 months or within 1 year of transplantation did not vary directly with increasing MELD score (10% and 10%, respectively, 7% and 11%, respectively, and 10% and 8%, respectively, in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P < 0.001$). The most common cause of graft failure across the groups was primary graft failure (3%, 3% and 4% in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P < 0.041$). The incidence of recurrent hepatitis leading to graft failure was higher in the subgroup with MELD scores of <30 (3%, 2% and 2% in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P < 0.001$). The frequency of graft failure caused by infection was higher in the group with MELD scores of ≥40 (1%, 1% and 2% in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P < 0.001$). There was no difference across the groups in the frequency of graft failure caused by acute and chronic rejection (1% for all).

Longterm graft and patient survival

Graft survival at 1 year varied inversely with increasing MELD score (86%, 80% and 77% in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P < 0.001$). Graft survival at 3 years and 5 years showed the same trend (77% and 71%, 72% and 67%, and 69% and 64%, respectively; $P < 0.001$). This overall pattern was repeated for patient survival at 1 year (90%, 84% and 80% in recipients with MELD scores of <30, 30–39 and ≥40, respectively), 3 years (83%, 77% and 73%, respectively) and 5 years (77%, 72% and 69%, respectively) (all: $P < 0.001$) (Fig. 1).

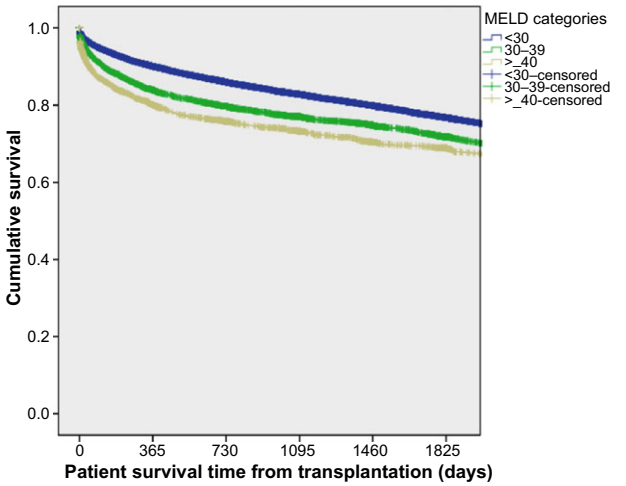
Survival analysis by MELD categories

A separate regression analysis to evaluate the survival hazard of increasing MELD score was carried out using the entire sample stratified by MELD score. In univariate Cox regression analysis, the hazard of graft failure (HRs 1.46, 1.24 and 1.00 in recipients with MELD scores of <30, 30–39 and ≥40, respectively; $P < 0.001$) and patient mortality (HRs 1.66, 1.34 and 1.00, respectively; $P < 0.001$) was significantly higher in the subgroup



Graft	At TX	1 year	2 Year	3 year	4 year	5 year	6 Year	MELD
At Risk	23230	17229	13996	11151	8524	6030	3773	<30
Failed	3373	969	615	471	393	279	182	
At Risk	5398	3406	2591	1976	1454	993	599	30-39
Failed	1109	203	100	71	68	48	22	
At Risk	2336	1374	1034	774	568	397	226	>_40
Failed	573	84	42	33	16	21	7	

(a)



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Failed	573	84	42	33	16	21	7	

(b)

Figure 1 (a) Kaplan–Meier curves depicting liver allograft survival by Model for End-stage Liver Disease (MELD) score category (Mantel–Cox statistic 133.4, $P < 0.001$). (b) Kaplan–Meier curves for patient survival by MELD score category (Mantel–Cox log rank statistic 199.8, $P < 0.001$)

with MELD scores of 40–49. After adjusting for waiting list time, donor and recipient factors including age, gender and BMI, and graft characteristics such as a human leukocyte antigen (HLA) mismatch, share type, and total warm ischaemia time, the subgroup with MELD scores of 40–49 had a higher risk for mortality than the group with MELD scores of 30–39 ($P = 0.006$) and that with MELD scores of <30 ($P = 0.004$). Graft survival did not differ significantly among groups with MELD scores of <30 and 30–39 ($P = 0.086$), or 50–60 ($P = 0.890$).

Potential mortality risk predictors

Multiple univariate Cox regression analyses were performed in groups with MELD scores of ≥40 and <40, respectively, to determine potential predictors of mortality. As expected, the risk for mortality was higher in patients receiving livers from older donors and with MELD scores of ≥40 ($P < 0.001$). Donor obesity ($P = 0.005$) and diabetes ($P < 0.001$) increased the risk significantly. Patients with MELD scores of ≥40 who received livers from African-American donors had a slightly increased risk for mortality (HR 1.27, $P < 0.001$), whereas Hispanic ethnicity in the donor decreased the risk (HR 0.92, $P = 0.011$). Cause of donor death and type of liver (split or whole) were not significant predictors ($P > 0.05$). In both groups, recipient age of 40–59 years doubled ($P < 0.001$ and $P < 0.001$, respectively) and age of ≥70 years ($P < 0.001$) almost quadrupled the patient mortality risk. A requirement for ICU care between admission for transplantation and hospital discharge also increased the risk for mortality by 36% ($P = 0.045$). Diabetes for a duration of longer than 5 years ($P < 0.001$) and 10 years ($P = 0.002$) in the transplant recipient increased the mortality risk (HRs 1.69 and 6.28, respectively) compared with that in recipients without diabetes.

Among patients with MELD scores of ≥40, multivariate analysis adjusting for donor, recipient and graft characteristics confirmed donor and recipient age, a history of upper abdominal surgery, and need for life support at transplantation as significant negative predictors of graft survival. Recipient and donor age, history of upper abdominal surgery, and life support at transplantation were also significant negative predictors of patient survival (Table 3).

Post-transplant futility analysis

Inclusion criteria for the futility analysis were a MELD score of ≥40 and death during the study period ($n = 660$). Patients who were lost from follow-up or who survived for longer than the study period were excluded ($n = 1950$). Those who died within 3 months of transplant were designated as 'futile' ($n = 282$), and the others were designated as 'non-futile' ($n = 378$). Table 4 shows the characteristics of patients in the futile and non-futile groups.

Futile transplant recipients were more likely to be aged <40 years (22% versus 15%; $P = 0.007$) or >60 years (27% versus 23%; $P = 0.007$) than their non-futile counterparts. They were more likely to have received liver allografts of regional (32% versus 28%; $P < 0.001$) or national (6% versus 2%; $P = 0.014$) share type than a local share type (61% versus 70%; $P = 0.014$). Recipient gender ($P = 0.704$), ethnicity ($P = 0.762$) and BMI ($P = 0.597$) were equally distributed across the futile and non-futile groups. Futile donors were more likely to be of non-White ethnicity (African-American: 16% versus 14%; Hispanic: 20% versus 18%; Asian: 6% versus 2%; Other: 2% versus 1%; $P = 0.043$). Futile and non-futile groups were similar in terms of other donor characteristics including age, gender, BMI, presence of diabetes or hypertension, and cause of death.

At the time of listing, futile transplant recipients ($n = 282$) were less likely to be hospitalized, but more likely to be mechanically ventilated if hospitalized (21% versus 12%; $P = 0.002$). There was no difference in grade III and IV encephalopathy, risk for portal vein thrombosis, spontaneous bacterial peritonitis, marked muscle wasting, history of TIPS, or previous upper abdominal surgery. Furthermore, futile patients were more likely to have required ICU admission (64% versus 52%; $P = 0.002$) and mechanical ventilation (43% versus 26%; $P < 0.001$). However, they were less likely to have mild to moderate ascites (83% versus 89%; $P = 0.002$), or suffer from spontaneous bacterial peritonitis (8% versus 10%; $P = 0.023$) (Table 4).

In the futile group, 21 patients experienced primary graft failure. Other causes of graft failure were infection ($n = 12$), vascular thrombosis ($n = 8$), biliary complications ($n = 4$), and hepatitis recurrence ($n = 4$). In the non-futile group, the most common cause of graft failure was hepatitis recurrence ($n = 42$), followed by infection ($n = 24$), primary graft failure ($n = 30$), vascular thrombosis ($n = 12$), non-hepatitis disease recurrence ($n = 17$), acute rejection ($n = 9$) and biliary complications ($n = 7$). The average length of post-transplant hospitalization was slightly longer in the futile group (26 days versus 24 days; $P < 0.001$). Of the futile transplants, 23.8% of recipients ($n = 67$) underwent retransplantation after experiencing graft failure. As expected, discharge laboratory values revealed significantly increased levels of aspartate aminotransferase (AST) ($P < 0.001$) and alanine aminotransferase (ALT) ($P < 0.001$) in the futile group.

In univariate Cox regression analysis, patients with futile transplants had a significantly higher risk for graft loss (HR 133.06, 95% CI 92.00–192.45; $P < 0.001$) and mortality (HR 133.87, 95% CI 77.82–166.62; $P < 0.001$) In a univariate binomial logistic regression analysis, recipients aged <40 years had a significantly higher risk for futility than those aged 40–60 years ($P = 0.004$). Compared with liver allografts from White donors, receipt of a graft from an Asian donor conferred a 3.12-fold increased futility risk (95% CI 1.30–7.43; $P = 0.011$). Liver allografts from the national share were associated with significantly increased futility [odds ratio (OR) 3.07, 95% CI 1.35–6.99; $P = 0.008$]. Recipients requiring ICU

Table 3 Multivariate Cox regression analyses of graft and patient survival in transplant recipients with Model for End-stage Liver Disease (MELD) scores of ≥40

			Graft survival		Patient survival	
Factors	**Levels**	***n***	**AHR (95% CI)[a]**	***P*-value**	**AHR (95% CI)[a]**	***P*-value**
Recipient age, years	<18	109	Ref			
	18–39	276	1.78 (0.98–3.24)	0.059	1.95 (0.95–4.03)	0.070
	40–59	908	1.93 (1.08–3.45)	0.027	2.41 (1.20–4.86)	0.014
	60–69	277	2.63 (1.44–4.82)	0.002	3.72 (1.81–7.63)	<0.001
	≥70	22	3.31 (1.34–8.20)	0.010	4.65 (1.68–12.93)	0.003
Donor age, years	<18	140	Ref		Ref	
	18–39	704	1.61 (1.00–2.58)	0.048	1.53 (0.91–2.60)	0.108
	40–59	564	2.08 (1.30–3.35)	0.002	1.86 (1.10–3.13)	0.020
	60–69	139	2.57 (1.51–4.40)	0.001	2.28 (1.26–4.12)	0.006
	≥70	45	2.59 (1.32–5.08)	0.005	1.64 (0.72–3.74)	0.241
Recipient ethnicity	White	963				
	African-American	201	1.12 (0.84–1.50)	0.426	1.31 (0.95–1.89)	0.099
	Hispanic	314	1.21 (0.94–1.57)	0.148	0.79 (0.58–1.07)	0.126
	Asian	85	1.47 (0.88–2.48)	0.144	0.39 (0.20–0.76)	0.006
	Other[b]	29	1.37 (0.60–3.10)	0.453	2.29 (1.23–4.25)	0.009
Previous abdominal surgery	No	1056	Ref			
	Yes	469	1.24 (1.00–1.54)	0.052	1.27 (0.99–1.61)	0.056
Gancyclovir	Yes	542	Ref		Ref	
	No	1050	0.79 (0.64–0.98)	0.008	0.72 (0.56–0.92)	0.009
Valgancyclovir	Yes	907	Ref		Ref	
	No	685	1.25 (1.00–1.54)	0.044	1.18 (0.93–1.50)	0.176
Life support at transplant	No	1042	Ref		Ref	
	Yes	550	1.49 (1.21–1.83)	<0.001	1.61 (1.28–2.02)	<0.001
Share type	Local	988	Ref			
	Regional	547	0.95 (0.77–1.18)	0.668	0.94 (0.74–1.19)	0.612
	National	56	1.42 (0.83–2.44)	0.204	1.28 (0.67–2.44)	0.456

[a]AHR: adjusted hazard ratio for donor and recipient age, gender, ethnicity, body mass index, diabetes status, graft type, share type, cold ischaemia time, waiting time, valgancyclovir, gancyclovir, previous abdominal surgery, life support at transplantation.
[b]Other: American Indian, Alaskan Native, Native Hawaiian, Pacific Islander, unknown and mixed race.

care prior to transplantation had a more than two-fold greater risk for futility than those not hospitalized at the time of transplant (OR 2.62, 95% CI 1.35–5.08; $P = 0.005$). In the same vein, requirements for mechanical ventilation or inotropic drugs at transplantation were significantly associated with futility (OR 2.09, 95% CI 1.46–2.76; $P < 0.001$). Patients on gancylovir were more likely to have futile transplants (OR 1.76, 95% CI 1.16–2.68; $P = 0.008$), whereas those on valgancyclovir were associated with the opposite outcome (OR 0.59, 95% CI 0.39–0.90; $P = 0.002$). At discharge, increased INR (OR 4.48, 95% CI 2.83–7.09; $P < 0.001$) significantly increased futility. Cold ischaemia time, total warm ischaemia time, and waitlist time did not affect futility. Donor age, gender, diabetes status, cause of death, and distance from the transplant hospital also did not predict futility.

Discussion

Over the past decade, the gradual rise in the number of liver transplant registrants with very high MELD scores has led to increasing interest in outcomes among this patient population. Currently, 8% of liver transplants are performed in patients with MELD scores of ≥40. The few single-centre studies to have addressed this topic have demonstrated mixed outcomes. Some report outcomes comparable with those of transplants in patients with lower MELD scores,[3] whereas others note inferior survival.[7–10] This is the first nationwide longitudinal study to explore survival outcomes and futility predictors in a cohort of patients with MELD scores of ≥40 who were transplanted during the period from 2002 to 2011. The study confirms the current literature on graft and patient survival among patients

Table 4 Demographic and clinical characteristics of transplantations in recipients with Model for End-stage Liver Disease (MELD) scores of ≥40 by futility status

Characteristics	Futile (*n* = 282)	Non-futile (*n* = 378	*P*-value
Recipient age, years, median (IQR)	53 (16)	53 (12)	0.953
Recipient age categories, *n* (%)			
≤17 years	14 (5%)	8 (2%)	0.007
18–39 years	48 (17%)	47 (12%)	
40–59 years	145 (51%)	237 (63%)	
60–69 years	67 (24%)	83 (22%)	
≥70 years	11 (4%)	3 (1%)	
Recipient gender male, *n* (%)	181 (64%)	248 (66%)	0.704
Donor age, years, median (IQR)	43 (29)	42 (29)	0.831
Donor gender male, *n* (%)	168 (60%)	219 (58%)	0.673
Recipient race, *n* (%)			
White	187 (66%)	246 (65%)	0.762
Hispanic	39 (14%)	64 (17%)	
African-American	39 (14%)	45 (12%)	
Asian	8 (3%)	13 (3%)	
Mixed/unknown/other	9 (3%)	10 (3%)	
Recipient BMI, kg/m^2, median (IQR)	27.3 (8.8)	28.2 (7.4)	0.186
Recipient obesity (BMI ≥30 kg/m^2), *n* (%)	89 (32%)	97 (26%)	0.096
Donor BMI, 30 kg/m^2, median (IQR)	26.2 (8.3)	25.8 (6.7)	0.200
Donor obesity (BMI ≥30 kg/m^2), *n* (%)	131 (47%)	186 (49%)	0.484
Dialysis in week prior to transplant, *n* (%)	147 (52%)	204 (54%)	0.639
Previous upper abdominal surgery, *n* (%)	91 (32%)	131 (35%)	0.555
Diabetes mellitus, *n* (%)	52 (18%)	96 (25%)	0.336
Recipient on life support, *n* (%)	138 (49%)	122 (32%)	<0.001
Medical condition at transplant, *n* (%)			
ICU	181 (64%)	197 (52%)	0.002
Hospitalized but not ICU	87 (31%)	144 (38%)	
Not hospitalized	13 (5%)	37 (10%)	
Recipient on gancyclovir	75 (51%)	88 (37%)	0.007
Recipient on valgancyclovir	59 (40%)	126 (53%)	0.013
Extended criteria donors, *n* (%)	74 (27%)	94 (25%)	0.673
Living donors, *n* (%)	7 (2%)	10 (3%)	0.896
Donor race, *n* (%)			
White	159 (56%)	247 (65%)	0.043
Hispanic	57 (20%)	67 (18%)	
African-American	16 (6%)	8 (2%)	
Asian	16 (6%)	8 (2%)	
Mixed/unknown/other	6 (2%)	4 (1%)	
Donor diabetes mellitus, *n* (%)	34 (12%)	39 (10%)	0.405
Deceased donor cause of death, *n* (%)			
Head trauma	38 (4%)	68 (18%)	0.538
Stroke	138 (49%)	165 (44%)	
Anoxia	95 (34%)	132 (35%)	
Other/unknown	7 (2%)	10 (3%)	
Share type, *n* (%)			
Local	172 (61%)	264 (70%)	0.014
Regional	91 (32%)	105 (28%)	
National	18 (6%)	9 (2%)	
Regional	1 (0.4%)	0	

BMI, body mass index; ICU, intensive care unit; IQR, interquartile range.

with high MELD scores. Although findings showed that overall mortality was statistically higher among patients with MELD scores of ≥40, the difference was clinically less significant: the cohort with MELD scores of ≥40 recorded a 30% mortality rate, whereas the cohort with MELD scores of <30 recorded a 26% mortality rate.

In the present sample, the better than expected survival in the cohort with MELD scores of ≥40 may be attributed to the younger age of recipients, and lower prevalences of diabetes, portal vein thrombosis, hepatitis C virus and Epstein–Barr virus (EBV) infection. These patients were also less likely to have required a TIPS procedure for portal hypertensive bleeds, a marker that is not reflected in the MELD score. They were less likely to have had previous upper abdominal surgery. The cohort also had a higher proportion of allografts of regional share type, indicating the prioritization of these patients over other candidates on the basis of acuity. Despite having fewer preoperative comorbid conditions, these recipients required more health care resources, represented by pre-transplant hospitalization, ICU admission, mechanical ventilation and a longer LoS.

The benefits of transplantation in a patient with a MELD score of >40 must be weighed against both the greater risks and increased resource utilization required. Patients with high MELD scores have been found to have increased incidences of post-transplant infection, longer ICU and general hospital stays, and imply increased overall costs.[3,8] Several single-institution reports have demonstrated poorer post-transplant

survival among recipients stratified by increasing MELD scores.[10–13] However, Alexopoulos *et al.* reported a 1-year survival rate of 89% among patients with MELD scores of >40, which was similar to the 1-year survival rate among patients with MELD scores of <40.[5] The 1-year patient survival rate identified in the present study is, at 80%, inferior to that reported by Alexopoulos *et al.*,[5] which implies that nationally patients with MELD scores of >40 do slightly worse overall than those with lower MELD scores.

Many studies demonstrate increased perioperative complications and resource utilization in transplant recipients with higher MELD scores. Axelrod *et al.*[9] found that patients with MELD scores of 30 utilized 10 times more Medicare spending than those with MELD scores of 20.[10] Given that average annual spending on an end-stage liver disease patient is reported to be US$22 424,[10] prioritizing of the most critically ill patients for transplantation is increasingly important. In the present cohort of recipients with MELD scores of ≥40, nearly half of all patients received pre-transplant dialysis. More than half were in the ICU prior to transplantation, and one-third needed some modality of life support, including mechanical ventilation and inotropic drugs, during their hospital stay. This finding is consistent with those of other studies[5] and confirms that patients with MELD scores of >40 utilize a disproportionately higher amount of health care resources. Nonetheless, the rate of retransplantation attributable to graft failure, the rate of post-transplant infection leading to graft failure, and postoperative LoS were all lower in the present study than in that reported by Alexopoulos *et al.*[5] These findings suggest that transplantation in patients with very high MELD scores may be sound and necessitate further investigation.

It is important to identify donor and recipient outcome predictors to determine which of the patients with MELD scores of ≥40 will survive transplantation. The present regression analysis revealed that a recipient age of 60–69 years, diabetes duration of >10 years, African-American ethnicity, donor diabetes and obesity were significant negative predictors. Although Alexopoulos *et al.* attributed poor outcomes among patients with MELD scores of ≥40 to the deleterious effects of prolonged pre-transplant waiting,[5] the present study did not find waiting time to be a predictor of futility.

Although the difference in overall and 1-, 3- and 5-year mortality among MELD subgroups was not large, 30-day mortality was found to increase significantly as MELD scores increased. Patients with MELD scores of ≥40 were more than twice as likely to die within 30 days of transplant as those with MELD scores of <30. Thus, the present futility analysis reveals that there is a subgroup of patients with MELD scores of ≥40 who will not benefit from transplantation, and whose allocated organs may be better used in patients with more favourable prognoses. The present study found that recipient age of >60 years, a BMI of >30 kg/m^2, requirements for ICU care or life support on the waiting list, and liver allograft of national share, were predictors of futility. Furthermore, high INR, ALT and AST values at the time of discharge were also positive predictors of futility. As these were postoperative laboratory values, they will not help in patient selection, but will be useful in helping the clinician to monitor such patients more closely. In Cox regression analysis, after controlling for age, gender, BMI, HLA mismatch, cold ischaemia time, total warm ischaemia time, waiting time, share type, and cause of donor death, patients with MELD scores of 40–49 were found to have a risk for mortality that was increased by 95% and 29% over those with MELD scores of <30 and of 30–39, respectively. After adjusting for confounders, patients with MELD scores of 40–49 had a graft failure rate that was 60% and 28% higher than those with MELD scores of <30 and 30–39, respectively. Furthermore, patients in this futile transplant subgroup were more likely to experience preoperative acute comorbidities such as portal vein thrombosis, renal failure requiring dialysis prior to transplantation, transfusions for a portal hypertensive bleed, history of TIPS and prior upper abdominal surgery, as is representative of a sicker population with increased utilization of health care resources.

Overall, the present findings suggest that candidates with MELD scores of ≥40 on the liver transplant waiting list can derive benefit from the receipt of an allograft. Despite significantly higher futility (43%, 32% and 21% in patients with MELD scores of ≥40, 30–39 and <30, respectively; $P < 0.001$), increased overall mortality (25%, 22% and 20% in patients with MELD scores of ≥40, 30–39 and <30, respectively) and a probable increase in health care expenses as a result of the provision of longer post-transplant inpatient care, these patients meet the expected survival of >50% at 5 years (64% graft survival and 69% patient survival) and therefore warrant attention.[14] In characterizing the subset of patients with MELD scores of ≥40 among whom transplantation may be futile, the present authors conclude that patients aged >60 years, patients with obesity, those who are hospitalized in the ICU requiring ventilation, and those with multiple comorbidities are at risk for futile transplantation. Additionally, postoperative laboratory studies should be used to identify patients at high risk for adverse outcomes, and should demand greater clinician attention. Despite having fewer preoperative comorbid conditions, the futile group required more health care resources such as peri-transplant hospitalization, ICU care and life support measures.

Strengths and limitations

The present study has several strengths. The most significant is that it is a population-based effectiveness study that used a robust national database and a follow-up period extending to almost a decade to elucidate an inadequately studied issue. The study addressed the timely topic of surgical outcomes in patients with MELD scores of ≥40 and the causes of futility in

this particular group, in comparison with groups with lower MELD scores. The study also adds substantial information on prognosis after liver transplantation in the most critically ill patients as defined by UNOS, which may assist clinicians in making decisions on the allocation of liver allografts. This information has the potential to influence future guidelines on managing this particular type of patient. Additionally, because it is a longitudinal study, the present study is devoid of selection bias. Two control groups, consisting of patients with MELD scores of, respectively, <30 and 30–39, were used to compare survival.

The study has a few limitations. Because of its retrospective nature, confounding attributable to unobserved variables is more likely. This limits the present authors' ability to comment accurately on the more detailed variables such as primary non-function, post-transplant ICU stay and utilization of rehabilitation services, or on direct causes of futility. Additionally, the study design was not that of a randomized prospective clinical trial. Hence, potential bias may have been introduced in addition to the instability of the univariate and multivariate models.

Conclusions

Although the benefits of liver transplantation in patients with MELD scores of ≥40 must be weighed against the increases in risk and resource utilization, liver transplantation in recipients with MELD scores of ≥40 demonstrates a significant increase in post-transplant survival that is greater than expected. The subset of patients with higher MELD scores in whom transplant may have inferior survival outcomes includes those aged >60 years, those with obesity, multiple comorbidities or pre-transplant ICU hospitalization, and those receiving allografts from obese or expanded criteria donors. Future prospective studies are required to further characterize the subset of patients with MELD scores of ≥40 who are most likely to benefit from transplantation in order to continue to improve the allocation of this vital resource and to avoid futile transplantation in the most critically ill patients.

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Conflicts of interest

None declared.

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