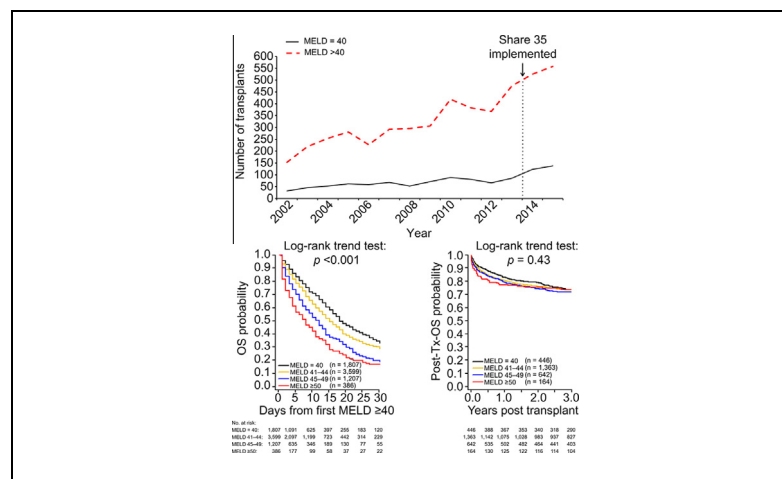


Inequity in organ allocation for patients awaiting liver transplantation: Rationale for uncapping the model for end-stage liver disease

Graphical Abstract



Highlights

- Patients with MELD >40 have significantly greater waitlist mortality than patients with MELD = 40.
- The number of patients transplanted with MELD >40 has increased over the past 15 years.
- There was no difference in survival for patients transplanted with MELD >40 compared to MELD = 40.
- Liver transplant conferred a survival benefit as MELD increased above 40.
- The MELD score should be uncapped to allow equitable distribution of livers to the patients most in need.

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Lay summary

In the United States (US), organs for liver transplantation are allocated by an objective scoring system called the Model for End-stage Liver Disease (MELD), which aims to prioritize the sickest patients for transplant. The greater the MELD score, the greater the mortality without liver transplant. The MELD score, however, is artificially capped at 40 and thus actually disadvantages the sickest patients with end-stage liver disease. Analysis of the data advocates uncapping the MELD score to appropriately prioritize the patients most in need of a liver transplant.

Inequity in organ allocation for patients awaiting liver transplantation: Rationale for uncapping the model for end-stage liver disease

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Background & Aim: The goal of organ allocation is to distribute a scarce resource equitably to the sickest patients. In the United States, the Model for End-stage Liver Disease (MELD) is used to allocate livers for transplantation. Patients with greater MELD scores are at greater risk of death on the waitlist and are prioritized for liver transplant (LT). The MELD is capped at 40 however, and patients with calculated MELD scores >40 are not prioritized despite increased mortality. We aimed to evaluate waitlist and post-transplant survival stratified by MELD to determine outcomes in patients with MELD >40.

Methods: Using United Network for Organ Sharing data, we identified patients listed for LT from February 2002 through to December 2012. Waitlist candidates with MELD $\geq$ 40 were followed for 30 days or until the earliest occurrence of death or transplant.

Results: Of 65,776 waitlisted patients, 3.3% had MELD $\geq$ 40 at registration, and an additional 7.3% had MELD scores increase to $\geq$ 40 after waitlist registration. A total of 30,369 (46.2%) underwent LT, of which 2,615 (8.6%) had MELD $\geq$ 40 at transplant. Compared to MELD 40, the hazard ratio of death within 30 days of registration was 1.4 (95% CI 1.2–1.6) for patients with MELD 41–44, 2.6 (95% CI 2.1–3.1) for MELD 45–49, and 5.0 (95% CI 4.1–6.1) for MELD $\geq$ 50. There was no difference in 1- and 3-year survival for patients transplanted with MELD >40 compared to MELD = 40. A survival benefit associated with LT was seen as MELD increased above 40.

Conclusions: Patients with MELD >40 have significantly greater waitlist mortality but comparable post-transplant outcomes to patients with MELD = 40 and, therefore, should be given priority for LT. Uncapping the MELD will allow more equitable organ distribution aligned with the principle of prioritizing patients most in need.

Lay summary: In the United States (US), organs for liver transplantation are allocated by an objective scoring system called the Model for End-stage Liver Disease (MELD), which aims to prioritize the sickest patients for transplant. The greater the MELD score, the greater the mortality without liver transplant. The MELD score, however, is artificially capped at 40 and thus actually disadvantages the sickest patients with end-stage liver disease. Analysis of the data advocates uncapping the MELD score to appropriately prioritize the patients most in need of a liver transplant.

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Introduction

The disparity between the availability of donor organs and the growing number of patients awaiting transplant is one of the greatest challenges in organ transplantation. A needs-based allocation policy prioritizes those at greatest risk of death on the waitlist while a utility-based policy prioritizes graft and patient survival. In 1998, the United States (US) Department of Health and Human Services adopted the Final Rule, which set guidelines for organ allocation based on medical urgency.¹ The goal was to balance equity and utility in the distribution of organs while avoiding futility. The transplant community continues to debate the relative weights of each.

In response to the increasing demand for liver transplantation (LT) in an era of organ shortage, there have been several liver

Keywords: Model for end-stage liver disease (MELD); Liver transplantation; Waitlist mortality; Liver allocation; Regional disparity; Share 35; Post-transplant outcome.

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allocation policy changes over the past two decades in the US aimed at minimizing waitlist mortality without negatively impacting post-transplant survival. Prior to 1998, patients with end-stage liver disease (ESLD) were stratified by time accumulated on the waitlist and hospital status, with patients in the intensive care unit given the highest priority.² In 1998, the United Network for Organ Sharing (UNOS) modified this allocation policy by incorporating the Child-Turcotte-Pugh (CTP) score with the intention of prioritizing patients on the waitlist based on clinical measures of liver dysfunction. However, the system remained flawed because the CTP score required subjective patient assessment, and the emphasis on wait time did not allow the donor organ to be allocated to the patient with the greatest need.³

On February 27, 2002, UNOS implemented the Model for End-stage Liver Disease (MELD) scoring system, which is based on objective laboratory tests (total bilirubin, international normalized ratio and creatinine) and ranges from 6 (less ill) to 40 (gravely ill).^{4–6} The MELD score changed the liver allocation policy in the US from one primarily driven by wait time to a quantitative severity score that prioritized patients with the greatest waitlist mortality.^{7,8} Although most countries have adopted the MELD system for prioritizing patients for transplant,^{9–13} several countries use other criteria to allocate organs, with or without taking into account the MELD score.^{14–18} In India, liver allocation is based on wait time.¹⁵ In the United Kingdom, it is based on the United Kingdom End-stage Liver Disease Score, which directs organs to candidates who have a realistic chance of surviving more than 5 years post transplantation.¹⁴ In Spain, allocation is based on MELD score with several modifications according to factors such as indication, combined transplants, pediatric recipients, possibility of split, and time on the waitlist.¹⁶ In Japan, candidates are assigned a clinical priority based on blood type, degree of sickness (MELD and CTP score, acute liver failure), and wait time.¹⁷

Although patients with greater MELD scores were critically ill, their survival after LT was not inferior compared to the pre-MELD era.^{19,20} The MELD score was arbitrarily capped at 40 based on the presumption that transplanting patients with MELD >40 would be futile.⁵ As a result, patients with MELD >40 receive

the same priority as patients with MELD = 40, differentiated only by their time on the waitlist (Fig. S1). There is no maximum MELD that excludes patients from receiving a LT,²¹ and the decision to delist candidates is institution-specific. Despite the cap at 40, the number of patients transplanted with MELD >40 has increased by nearly 3-fold since 2002 (Fig. 1) with regional differences, the greatest rates seen in Organ Procurement and Transplantation Network (OPTN) Regions 5 and 7 (Fig. 2).

Since the implementation of the MELD for liver allocation, several modifications have been made to further reduce waitlist mortality. One modification in the US grants additional MELD “exception” points to patients with specific diseases (e.g. hepatocellular carcinoma [HCC], hepatopulmonary syndrome) who have low risk of short-term mortality, but require LT prior to developing irreversible complications.^{22,23} These candidates then receive priority based on the exception MELD, which is often a value much higher than the calculated MELD. Patients awaiting combined liver-intestine transplant also receive MELD exception points, with patients less than 18-years of age receiving 23 additional points to their calculated Pediatric End-stage Liver Disease (PELD) scores without being capped at 40 due to their high waitlist mortality.²⁴ Currently, more than half of the pediatric patients on the waitlist are transplanted using exception scores because the calculated PELD often fails to capture mortality risk appropriately. The rising number of adult patients granted MELD exception points in the US has caused an increase in allocation MELD score (the MELD elevator effect) by pushing patients listed with MELD scores based solely on laboratory values to require higher and higher scores to be competitive for transplant in many regions of the country. In Brazil, in addition to HCC and primary liver tumors, patients with complications such as refractory ascites, pruritus, persistent or recurrent hepatic encephalopathy, and recurrent cholangitis are considered special situations and may be granted MELD exception points when severe.¹² In the Euro-transplant system (Germany, Belgium, Croatia, Luxemburg, Netherlands, Austria, Hungary, and Slovenia), MELD exception points are given to patients with pulmonary complications of cirrhosis, recurrent cholangitis in cholestatic liver disease, or HCC within the Milan criteria.¹¹

Another modification in the US was the implementation of “Share 35” on June 17, 2013, which prioritized patients with MELD ≥ 35 within the donor’s OPTN region before any local candidates with MELD <35. The intention was to allow broader distribution of livers to expedite transplantation of the sickest patients in OPTN regions. The goal was more equitable distribution of organs to patients most in need by eliminating local donor service area (DSA) priority that had previously impaired such access. Recent studies have shown that Share 35 has been associated with more transplants, fewer organ discards, and lower waitlist mortality without compromising post-transplant outcomes.^{25–27} Finally, on January 11, 2016, serum sodium was added into the MELD score based on studies demonstrating better prediction of waitlist mortality compared to the MELD score alone.^{28–33}

In the US, these modifications to the liver allocation scheme have focused on prioritizing the sickest patients for LT, calling into question the MELD cap at 40. To determine the effect of capping the MELD, we used OPTN data to analyze the waitlist mortality and post-transplant outcomes of adult patients with MELD >40 compared to patients with MELD = 40. We hypothesized that the MELD cap of 40 disadvantages the sickest patients

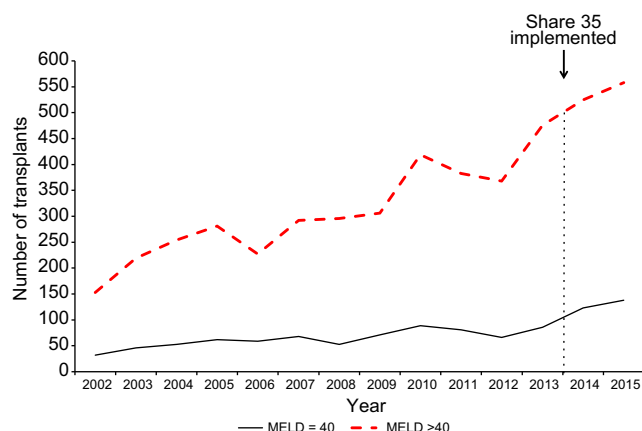


Fig. 1. Number of adult deceased donor liver transplants with Model for End-stage Liver Disease (MELD) ≥ 40 . MELD score was implemented February 27th, 2002. Data from Organ Procurement and Transplantation Network (OPTN) as of May 31, 2015 (<http://optn.transplant.hrsa.gov>). The dashed vertical line marks the implementation of Share 35. (This figure appears in colour on the web.)

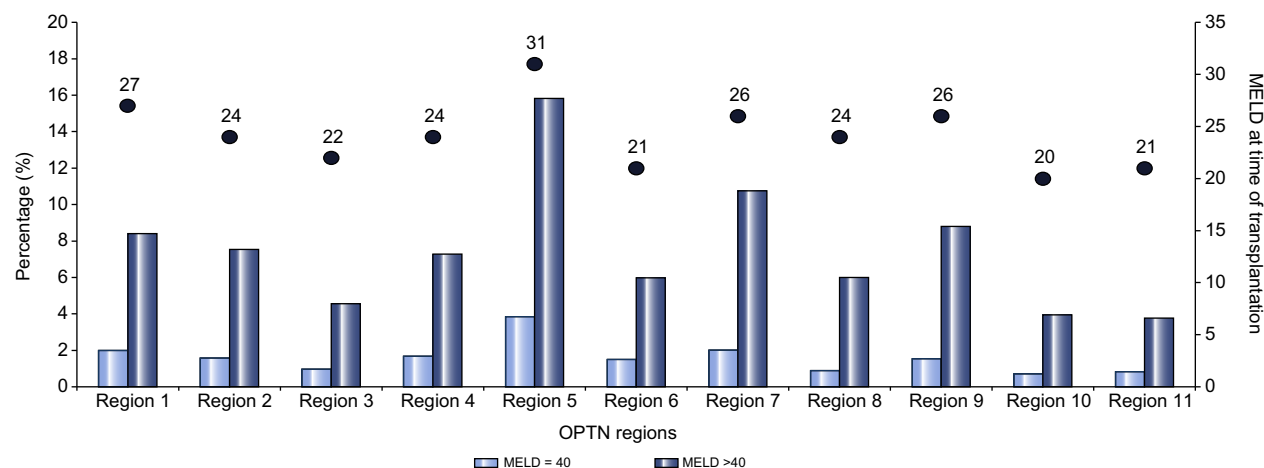


Fig. 2. Percentage of adult deceased donor liver transplants with Model for End-stage Liver Disease (MELD) ≥ 40 and median MELD at time of transplantation in Each Organ Procurement and Transplantation Network (OPTN) region from March 1, 2002 through December 31, 2015. (<http://optn.transplant.hrsa.gov>). States in each OPTN Region (# of adult liver transplant centers): **Region 1:** Connecticut (2), Massachusetts (4), Maine (0), New Hampshire (0), Rhode Island (0), Vermont (0); **Region 2:** District of Columbia (1), Maryland (2), New Jersey (2), Pennsylvania (10), Delaware (0), West Virginia (0); **Region 3:** Alabama (1), Arkansas (1), Florida (7), Georgia (2), Louisiana (3), Mississippi (1), Puerto Rico (1); **Region 4:** Oklahoma (2), Texas (10); **Region 5:** Arizona (4), California (9), Utah (2), Nevada (0), New Mexico (0); **Region 6:** Hawaii (1), Oregon (3), Washington (2), Alaska (0), Idaho (0), Montana (0); **Region 7:** Illinois (5), Minnesota (3), Wisconsin (3), North Dakota (0), South Dakota (0); **Region 8:** Colorado (3), Iowa (1), Kansas (1), Missouri (3), Nebraska (1), Wyoming (0); **Region 9:** New York (7), Vermont (0); **Region 10:** Indiana (1), Michigan (3), Ohio (4); **Region 11:** Kentucky (2), North Carolina (3), South Carolina (1), Tennessee (2), Virginia (2).

with ESLD and that rank ordering by calculated MELD score may decrease waitlist mortality and provide survival benefit to patients with the greatest MELD scores.

Methods and materials

Patients

With permission, data were obtained from the UNOS Standard Transplant Analysis and Research File, which included pre-transplant, transplant and follow-up data from the OPTN database, supplemented by the mortality information from the Social Security Death Master File. We analyzed all adult candidates (age ≥ 18 years) who were listed for LT from February 27, 2002 (date of implementation of MELD) until December 31, 2012 to allow for 3-year follow-up for all transplanted patients. Excluded from the analyses were patients listed as status 1A (candidates with sudden and severe onset of liver failure with a very short life expectancy without LT), recipients of dual organ transplantation (other than kidney), patients with MELD exception points, recipients of living donor LT, and patients with incomplete data (Fig. 3). Thirty-day waitlist survival was selected due to the continued high mortality rate of patients with MELD ≥ 40 after 14 days.

Statistical analyses

Analyses were performed to estimate overall survival (OS) of patients on the LT waitlist, post-transplant OS (Post-TX-OS), and to assess whether waitlist OS or Post-TX-OS varied among patients with MELD ≥ 40 . In addition, analyses were conducted to evaluate the benefit of having a LT for patients with different MELD scores.

For the OS of waitlist patients who reached a MELD ≥ 40 , we focused on 15- and 30-day survivals because, once candidates reached a MELD ≥ 40 , their mortality was quite high after 30 days without transplant. OS of waitlist patients with a MELD ≥ 40 were analyzed in the following ways: 1) Patients whose MELD reached ≥ 40 at any time during waitlist registration. OS was defined as the time between the date of first reported MELD ≥ 40 during waitlist registration and the date of death or removal from waitlist due to "too sick for transplant". Patients who received a transplant were censored at the time of transplant.^{28,34} The analysis focused on the first 30 days after patients had a first reported MELD ≥ 40 . OS probabilities within 30 days after the first reported MELD ≥ 40 were calculated using the product-limit method with Greenwood standard errors and were plotted for patients with MELD = 40, 41–44, 45–49, and ≥ 50 . Waitlist patients who

died on the same day of a reported MELD ≥ 40 were excluded from this analysis. 2) Patients who were registered on the waitlist with an initial MELD ≥ 40 . OS was defined as the time from the date of initial waitlist registration to the date of death or removal from waitlist due to "too sick for transplant". 3) Cox regression analysis, with MELD as a time-dependent covariate, to estimate the hazard ratio (HR) of death for patients according to the MELD score at each time point, all compared to the corresponding group of patients with MELD = 40. Smoothing splines³⁵ were used to illustrate the relative risk of death of patients with different MELD scores. 4) Cumulative incidence analyses to estimate the proportion of patients who received a LT and the proportion of patients who died on the waitlist in each MELD category, with LT or death on the waitlist considered as two competing events. This analysis used the same group of patients as in analysis 1.

For the analyses of Post-TX-OS, we focused on the first 3 years after transplant. Post-TX-OS was defined as time from transplant to date of death or date of the last follow-up. Post-TX-OS probabilities were calculated using the Kaplan-Meier method with Greenwood standard errors, and were plotted for patients transplanted at MELD = 40, 41–44, 45–49, or ≥ 50 . Cox regression models were used to estimate the HR of death for patients transplanted at MELD > 40 compared to the group of patients transplanted at MELD = 40. Transplant benefit was determined using a Cox regression model for survival from date of waitlist registration, with MELD and LT as time-dependent covariates, and HRs were calculated for patients receiving a LT compared to those who did not for the first 30 days or the first 90 days from date of waitlist registration.

All statistical analyses were performed in STATA (Version 11.2, StataCorp, College Station, Texas). A *p* value of < 0.05 was considered statistically significant.

For further details regarding the materials used, please refer to the [CTAT table](#).

Results

Patient characteristics

A total of 65,776 candidates on the waitlist and 30,369 LT recipients were included in the analysis. Patient characteristics are shown in [Table 1](#). The median age was 53 with the majority being Caucasian men with blood types O and A. Among the 2,615 (8.6%) who had capped MELD scores of 40 at the time of transplant, 2,169 (83%) had calculated MELD scores > 40 . Characteristics of patients on the waitlist with MELD ≥ 40 at time of waitlist registration and those transplanted with MELD ≥ 40 are shown in [Table 2](#).

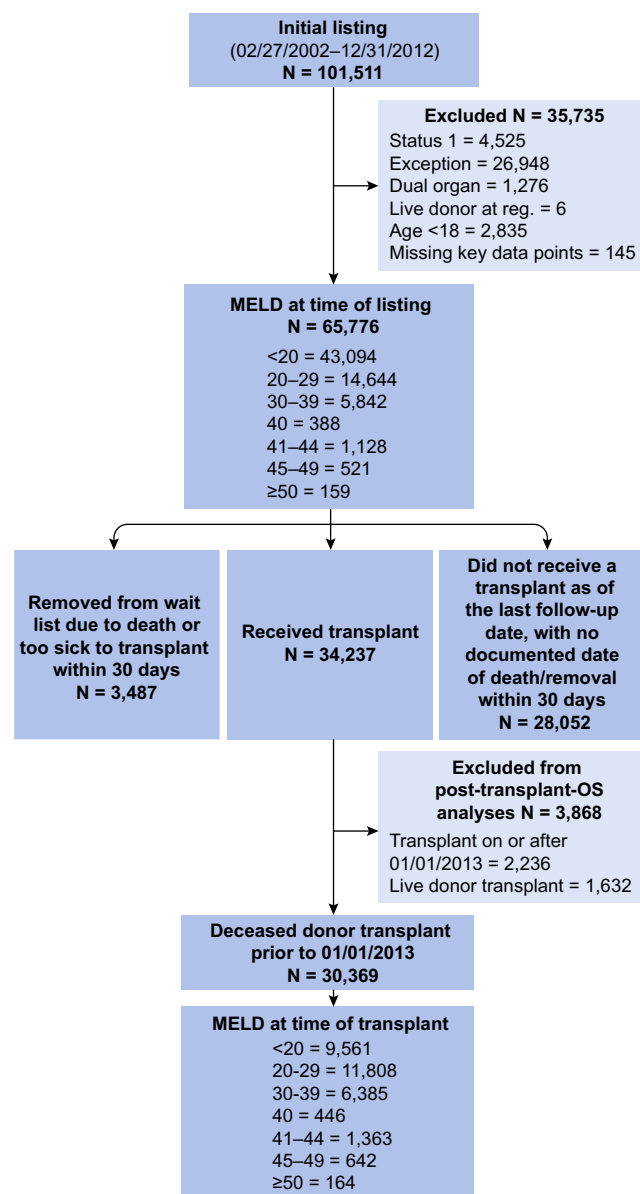


Fig. 3. Flow diagram of the cohort of patients included in the study.

Waitlist and post-transplant survival

Using data on changes in MELD for patients registered on the waitlist, with MELD treated as a time-dependent covariate, analyses showed that compared to MELD = 40, the relative risk of death within 30 days after waitlist registration (as measured by the HR) increased monotonically as MELD increased from 20 to 40 and continued to increase as MELD went above 40 (Fig. 4). Compared to MELD = 40, the HR of death within the first 30 days of waitlist registration was 1.4 (95% CI 1.2–1.6) for patients with MELD 41–44, 2.6 (95% CI 2.1–3.1) for MELD 45–49, and 5.0 (95% CI 4.1–6.1) for MELD ≥50.

Of the LT candidates, 2,196 patients had a MELD ≥40 at time of waitlist registration, and an additional 4,803 patients had a MELD ≥40 reported after waitlist registration. OS estimates from

the time of waitlist registration for patients with initial MELD = 40, 41–44, 45–49, or ≥50 are shown in Fig. 5A, and OS estimates from the first MELD ≥40 for patients on the waitlist with MELD = 40, 41–44, 45–49, or ≥50 are shown in Fig. 5B. The two figures show very similar patterns, demonstrating that waitlist survival rates decreased dramatically as MELD score increased above 40 ($p < 0.001$). At day 15, after patients had a first reported MELD ≥40, the estimated OS rates were 58% (95% CI: 55–61%) for patients with MELD = 40 and decreased to 49% (95% CI: 47–52%) for MELD 41–44, 37% (95% CI: 34–41%) for MELD 45–49, and 28% (95% CI: 23–34%) for MELD ≥50 (Fig. 5B). Similar differences were observed at day 30 with the estimated OS rates being 33% (95% CI: 29–37%) for patients with MELD = 40, 29% (95% CI: 26–31%) for MELD 41–44, 19% (95% CI: 15–23%) for MELD 45–49, and 17% (95% CI: 12–23%) for MELD ≥50.

Post-TX-OS rates at 1 and 3 years for patients transplanted with MELD >40 were not significantly different compared to MELD = 40 ($p = 0.43$) (Fig. 5C). One-year Post-TX-OS rates were 83% (95% CI: 79–86%) for MELD = 40, 80% (95% CI: 78–82%) for MELD 41–44, 79% (95% CI: 76–82%) for MELD 45–49, and 78% (95% CI: 70–83%) for MELD ≥50. Three-year Post-TX-OS rates were also similar among the four groups. Compared to MELD = 40, the HR of death within the first 3 years post-transplant was 1.0 (95% CI: 0.8–1.3) for patients transplanted at MELD 41–44, 1.1 (95% CI: 0.9–1.4) for MELD 45–49, and 1.1 (95% CI: 0.8–1.5) for MELD ≥50.

Impact of transplant on survival for waitlisted patients

Among patients with MELD ≥40, the cumulative incidence rates of LT decreased as the MELD increased, while the cumulative incidence rates of deaths on the waitlist increased. By day 30, the cumulative incidence rates of transplant were 60% (95% CI: 58–63%), 54% (53–56%), 46% (44–49%), and 34% (95% CI: 30–39%) for patients with MELD = 40, 41–44, 45–49, and ≥50, respectively, and the cumulative incidence rates of death on the waitlist were 33% (95% CI: 31–36%), 40% (95% CI: 38–41%), 49% (95% CI: 47–52%), and 60% (95% CI: 55–65%), respectively.

Significant transplant survival benefit was seen at MELD >20, and the magnitude of transplant benefit increased with increasing MELD score (Table 3). Compared to patients with MELD = 40, there was a greater transplant survival benefit at 30 days in patients with MELD 45–49 (HR 0.72, 95% CI: 0.35–1.48) and MELD ≥50 (HR 0.50, 95% CI: 0.25–1.36); the survival benefit was statistically significant by 90 days for patients with MELD 45–49 (p value = 0.041) and MELD ≥50 (p value = 0.009).

Discussion

In 2015, 11,951 adult patients in the US were added to the LT waitlist, 6,230 underwent cadaveric LT, and 2,917 were removed due to death or being too sick for transplant (<https://optn.transplant.hrsa.gov>), illustrating how the allocation of livers is complicated by an organ supply that cannot meet the present need. In the current system in the US, all patients with MELD scores of 40 and greater are listed at 40 (not their actual calculated MELD scores) and ranked by time on the waitlist at that score. Patients thus stop accruing MELD points once they reach a score of 40 despite the escalating risk of death on the waitlist. Our study is the first to evaluate waitlist outcomes of patients with MELD

Table 1. Patient characteristics at the time of waitlist registration and transplantation.

Variables	Patients on waitlist (N = 65,776)	Patients transplanted (N = 30,369)
Age, median years (range)	53 (18–83)	52 (18–83)
Gender, n (%)		
Female	24,039 (37)	9,997 (33)
Male	41,737 (63)	20,372 (67)
Ethnicity, n (%)		
White	47,729 (73)	22,297 (73)
Black	5,421 (8)	2,928 (10)
Hispanic	9,848 (15)	3,992 (13)
Asian	2,006 (3)	818 (3)
Other	772 (1)	334 (1)
Blood type, n (%)		
A	24,806 (38)	11,243 (37)
B	8,003 (12)	4,114 (14)
O	30,337 (46)	13,233 (44)
AB	2,630 (4)	1,779 (6)
MELD, n (%)		
<15	26,213 (40)	2,943 (10)
15–19	16,881 (26)	6,618 (22)
20–29	14,644 (22)	11,808 (39)
30–39	5,842 (9)	6,385 (21)
=40	388 (<1)	446 (1)
41–44	1,128 (2)	1,363 (4)
45–49	521 (<1)	642 (2)
≥50	159 (<1)	164 (1)
Organ transplanted, n (%)		
Liver alone	60,858 (93)	27,895 (92)
Simultaneous liver-kidney	4,918 (7)	2,474 (8)
Diabetes, n (%)	15,732 (24)	6,976 (23)
Dialysis, n (%)	1,658 (3)	4,380 (14)
sCr, mg/dl (median)	1	1.3
ICU, n (%)	1,330 (2)	3,745 (12)
On ventilator, n (%)	n.a.	1,432 (5)
Primary diagnosis, n (%)		
Hepatitis B	1,538 (2)	700 (2)
Hepatitis C	19,438 (30)	8,576 (28)
NASH	4,699 (7)	2,297 (8)
Cryptogenic cirrhosis	5,555 (8)	2,411 (8)
Alcoholic liver disease	17,677 (27)	7,544 (25)
Autoimmune hepatitis	2,094 (3)	948 (3)
Cholestatic	5,601 (9)	2,842 (9)
Other	9,170 (14)	5,051 (17)

ICU, intensive care unit; MELD, Model for End-Stage Liver Disease; n.a., not available; NASH, non-alcoholic steatohepatitis; sCr, serum creatinine.

>40 compared to patients with MELD = 40. We demonstrate that the relative risk of death on the LT waitlist does not stabilize at MELD = 40, but rather increases as the calculated MELD score increases above 40. Patients with MELD 45–49 are 2.6 times more likely to die, and patients with MELD ≥50 are 5.0 times more likely to die on the waitlist compared to patients with MELD = 40. Uncapping the MELD score is the first step toward better determination of the sickest patients for urgent organ allocation.

Once patients reach a MELD >20, there is a significant benefit to LT that increases with the MELD score, and there is no MELD score above which LT seems futile. Despite concerns about futility at MELD >40, at least 200 such patients per year were transplanted over the study period, and mortality HR continued to favor transplant in patients with MELD >40. Importantly, there were no significant differences in 1- and 3-year survival rates after LT for patients with MELD >40 when compared to patients

with MELD = 40. A recent study analysing LT candidates following the implementation of Share 35 also demonstrated similar post-transplant outcomes in patients transplanted with MELD ≥40; however, waitlist outcomes were not analysed in this study.³⁶ Despite the similarity in survival rates after LT among the four MELD groups (40, 41–44, 45–49, ≥50) and the greater survival benefit of LT for patients with MELD 45–49 or ≥50 compared to MELD = 40, we were able to demonstrate that a smaller proportion of patients in the higher MELD categories received LT compared to patients in the lower MELD groups under the current LT allocation policy. Therefore, a capped MELD score misrepresents the medical urgency of LT and disadvantages a substantial and growing group of patients with ESLD.

The number of patients transplanted with MELD >40 increased over the study period and likely will continue to increase, attributable to improvements in the pre-transplant care

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Table 2. Characteristics of patients with MELD ≥ 40 while on waitlist and at transplant.

	MELD at time of waitlist registration				MELD at time of transplant			
	40 (n = 388)	41–44 (n = 1,128)	45–49 (n = 521)	≥ 50 (n = 159)	40 (n = 446)	41–44 (n = 1,363)	45–49 (n = 642)	≥ 50 (n = 164)
Male, %	66	66	71	74	69	67	72	66
Age, years (range)	52 (18–74)	53 (18–78)	52 (18–73)	53 (22–74)	53 (20–75)	53 (18–80)	53 (18–74)	51 (23–73)
Ethnicity, %								
White	61	61	56	60	65	63	59	59
Black	15	14	14	16	10	10	11	12
Hispanic	18	18	22	15	21	21	22	20
Asian	5	6	6	7	3	5	6	7
Other	1	1	2	2	1	1	2	2
Blood type, %								
A	36	36	33	39	37	37	34	40
B	15	12	12	15	11	11	11	13
O	46	49	49	42	48	49	51	42
AB	3	3	6	4	4	3	4	5
Primary diagnosis, %								
Hepatitis B	5	4	8	9	3	3	8	9
Hepatitis C	27	21	26	28	28	29	29	27
NASH	6	6	4	1	6	7	4	2
Cryptogenic	7	7	7	9	8	6	5	5
Alcoholic liver disease	28	33	29	21	25	25	25	20
Autoimmune hepatitis	3	3	4	3	3	4	4	4
Cholestatic	5	5	3	2	11	8	4	6
Other	20	20	19	26	16	18	20	26
sCr, mg/dl (median)	3.1	3.4	3.5	3.9	2.8	2.9	3.3	3.1
Dialysis, %	15	16	14	14	50	58	64	64
ICU, %	15	19	16	22	39	46	52	54
On ventilator, %	n.a.	n.a.	n.a.	n.a.	16	20	19	25
SLK, %	12	17	17	18	13	12	15	8
OPTN region, %								
1	4	4	4	7	5	4	4	6
2	13	12	10	12	13	10	10	10
3	12	10	12	7	10	10	9	8
4	11	8	8	10	7	9	8	6
5	24	24	23	22	32	29	28	26
6	2	3	2	6	2	2	2	3
7	14	12	12	9	10	14	14	14
8	3	6	5	9	5	5	7	7
9	5	9	12	9	6	8	9	10
10	6	6	6	3	5	5	4	3
11	6	6	6	6	5	4	5	7
Survival, % (95% CI)								
15-day	62 (55–69)	54 (50–58)	42 (36–48)	29 (20–39)	-	-	-	-
30-day	39 (30–48)	30 (25–35)	19 (14–26)	16 (8–25)	-	-	-	-
1-year	-	-	-	-	83 (79–86)	80 (78–82)	79 (76–82)	78 (70–83)
3-year	-	-	-	-	73 (69–77)	73 (71–75)	72 (68–75)	73 (66–80)

The overall survival and post-transplant survival probabilities were calculated using the Kaplan-Meier method, and confidence intervals were based on Greenwood standard errors. Data for age is median (range).

CI, confidence interval; ICU, intensive care unit; MELD, Model for End-stage Liver Disease; n.a., not available; NASH, non-alcoholic steatohepatitis; OPTN, Organ procurement and transplant network; sCr, serum creatinine; SLK, simultaneous liver-kidney.

of critically ill patients.^{37,38} Patients with MELD ≥ 40 represented 8.6% of all patients transplanted during the study period, of which 83% had MELD scores >40 . The large regional variation in the distribution of patients with MELD >40 in the US may partly explain institutional differences in thresholds to care for and transplant high MELD patients. In addition, where a patient lives in the US affects their likelihood of receiving a LT because of regional variation in population demographics, prevalence of liver disease, organ donation rates, transplant center acceptance rates, and median MELD at transplant. In certain regions of the country

(OPTN region 10), the median transplant MELD is as low as 20, whereas in region 5 (California and surrounding states) the median transplant MELD is 31, accounting for the highest percentage of patients being transplanted with MELD ≥ 40 (Fig. 2). These and other regional differences such as use of MELD exception points contribute to the problem of unequal access to LT in the US. Liver redistricting is currently being evaluated and may help level geographic disparity in the US.³⁹

Over the past two decades, efforts have focused on lowering waitlist mortality without compromising post-transplant out-

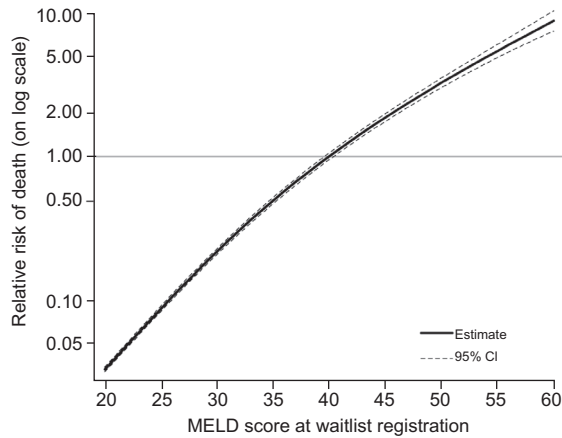


Fig. 4. Model for End-Stage Liver Disease (MELD) score for patients waiting for LT and relative risk of death. Cox regression analysis, with MELD as a time-dependent covariate, was used to estimate the hazard ratio (HR) of death for patients according to their MELD score at each time point, all compared to the corresponding group of patients with MELD = 40. Smoothing splines were used to illustrate the relative risk of death of patients with different MELD scores.

comes. Nonetheless, it can be difficult to identify candidates who are too sick for LT to prevent futile transplants.⁴⁰ Implementation of the MELD was the first and most important change in liver allocation, redirecting donor organs to the sickest patients and decreasing waitlist mortality.^{19,41–44} To allow broader distribution of livers to patients with the greatest medical urgency and further decrease waitlist mortality, Share 35 and MELD sodium were recently introduced in the US.^{25–31} Since Share 35, waitlist mortality for patients with MELD >30 decreased by 30% (HR 0.7, $p < 0.001$)²⁷ with no change in waitlist mortality for patients with lower MELD scores and no significant negative impact on post-transplant outcomes.^{25–27,45} Despite the positive impact,

the number of patients with MELD >40 has increased since the implementation of Share 35 in 2013. However, with more regional sharing of patients with high MELD scores since Share 35, uncapping the MELD would likely further decrease disparities within regions as the sickest patients would get transplanted sooner. Thus, share 35 and MELD sodium are important modifications, but more change is needed to remedy inequity in the current liver allocation system. The arbitrary capping of the MELD at 40 has resulted in an unforeseen lack of objectivity for patients with MELD >40 who are unjustifiably disadvantaged in a system designed to prioritize patients most in need. Uncapping the MELD score is another necessary step in the evolution of liver allocation and patient prioritization.

A significant number of patients with MELD >40 likely suffer from acute-on-chronic liver failure (ACLF), a recently recognized syndrome characterized by acute liver decompensation, other organ system failures, and high short-term mortality in patients with ESLD.^{46–54} A capped MELD score fails to capture acute liver decompensation adequately, and data suggest that a model incorporating sudden increases in MELD predicts waitlist mortality better.^{27,55} New scoring systems for ACLF have been shown to predict waitlist mortality better than the MELD score itself, perhaps because the MELD cap limits the discrimination of high acuity patients.^{49,53} However, the UNOS database does not capture all the variables necessary to determine whether or not a patient has ACLF, therefore, only waitlist outcomes can be determined based on MELD score. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) has recently been shown to be increased in patients with ACLF and improved the accuracy of MELD score in predicting 28-day mortality in patients on the waitlist.⁵⁶ In the future, the use of an ACLF score in conjunction with biomarkers such as uNGAL may improve organ allocation and add to the prognostic value of the MELD. At present, however, while scoring systems for ACLF may help centers decide who to transplant, the scores do not affect organ allocation; it is still the MELD score

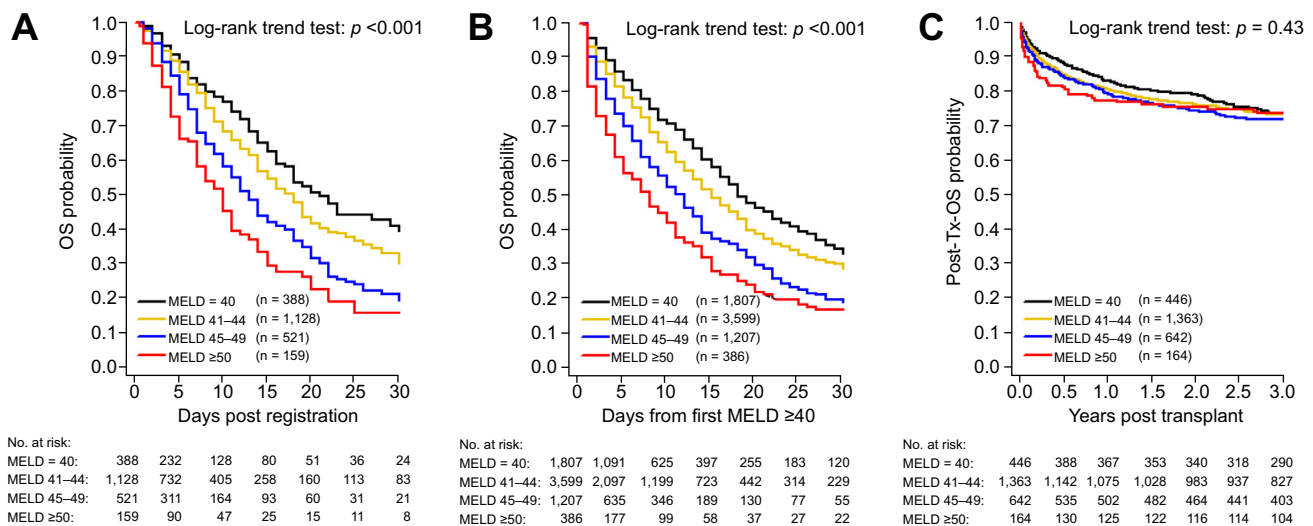


Fig. 5. Kaplan-Meier overall patient survival estimates at (A) 30 days from waitlist registration among patients with Model for End-Stage Liver Disease (MELD) ≥ 40 at time of waitlist registration, (B) 30 days from first MELD ≥ 40 among patients whose MELD reached ≥ 40 on waitlist at anytime and (C) 3 years post liver transplantation. The overall survival and post-transplant survival probabilities were calculated using the Kaplan-Meier method with Greenwood standard errors. p values were based on log-rank trend tests.

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Table 3. Mortality hazard ratios (transplant relative to waitlist) within 30 and 90 days post waitlist registration by Model for End-stage Liver Disease (MELD) score category.

MELD	Impact of transplant on survival at 30 days		Impact of transplant on survival at 90 days	
	HR (95% CI)	p value	HR (95% CI)	p value
<15	13.40 (8.4–21.4)	<0.001	6.10 (4.7–7.9)	<0.001
15–19	2.20 (1.5–3.4)	<0.001	1.60 (1.3–2.0)	<0.001
20–29	0.66 (0.53–0.82)	<0.001	0.44 (0.39–0.50)	<0.001
30–39	0.14 (0.12–0.17)	<0.001	0.082 (0.073–0.093)	<0.001
40	0.066 (0.036–0.12)	<0.001	0.040 (0.026–0.060)	<0.001
41–44	0.061 (0.053–0.095)	<0.001	0.039 (0.032–0.048)	<0.001
45–49	0.047 (0.033–0.069)	<0.001	0.024 (0.018–0.031)	<0.001
≥50	0.039 (0.022–0.068)	<0.001	0.018 (0.011–0.028)	<0.001
41–44 vs. 40	1.08 (0.55–2.13)	0.83	0.98 (0.62–1.54)	0.93
45–49 vs. 40	0.72 (0.35–1.48)	0.38	0.60 (0.37–0.98)	0.041
≥50 vs. 40	0.50 (0.25–1.36)	0.21	0.45 (0.24–0.82)	0.009

Hazard ratios (HR) and *p* values for post-transplant mortality risk based on MELD score at transplant compared to mortality risk of patients on the waitlist with the same MELD score. MELD subgroup for patients on waitlist was a time-dependent covariate in the Cox regression analyses. For patients who received transplant, MELD at transplant was used for the follow-up time post-transplant. HR <1 indicates that there is decreased mortality (and therefore, increased survival benefit) associated with transplant over the first 30 and 90 days post-transplant. Transplant benefit was determined using a Cox regression model for survival from date of waitlist registration, with MELD and LT as time-dependent covariates, and HRs were calculated for patients receiving a LT compared to those who did not for the first 30 days or the first 90 days from date of waitlist registration.

CI, confidence interval; HR, hazard ratio; LT, liver transplant; MELD, Model for End-Stage Liver Disease.

that ultimately determines organ allocation in most countries, including the US.

The strength of our study is the use of a large national transplant registry of patients (*n* = 65,776 patients registered and *n* = 30,369 patients transplanted) over a ten-year period with three years of follow-up, which allowed us to conduct whole population-based analyses to examine the liver allocation strategy while minimizing potential sample bias. The limitations are the retrospective design and that factors relating to a patient's suitability for transplantation or to a center's decision to accept or reject a liver allograft, both of which affect graft and patient survival, were not accounted for in the analysis. Despite these limitations, the study results have important implications for improving the current liver allocation policy.

As long as there is a shortage of donor organs, any organ allocation system will disadvantage a subgroup of patients on the waitlist for transplantation. Despite improvements in the current liver allocation system, patients with the greatest waitlist mortality do not receive appropriate priority for LT, and policy makers must critically evaluate the MELD cap at 40. Analysis of OPTN data suggests that uncapping the MELD may further decrease waitlist mortality, preserve post-transplant outcomes, and provide transplant benefit to patients with the greatest MELD scores. We advocate uncapping the MELD score to allow more equitable distribution of livers and to better align the current liver allocation policy with the fundamental principle of prioritizing the patients most in need.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Please refer to the accompanying [ICMJE disclosure](#) forms for further details.

Authors' contribution

All authors participated in the design and analysis of the data and editing the manuscript. Statistical analysis was performed by LJ and SG.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jhep.2017.04.022>.

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