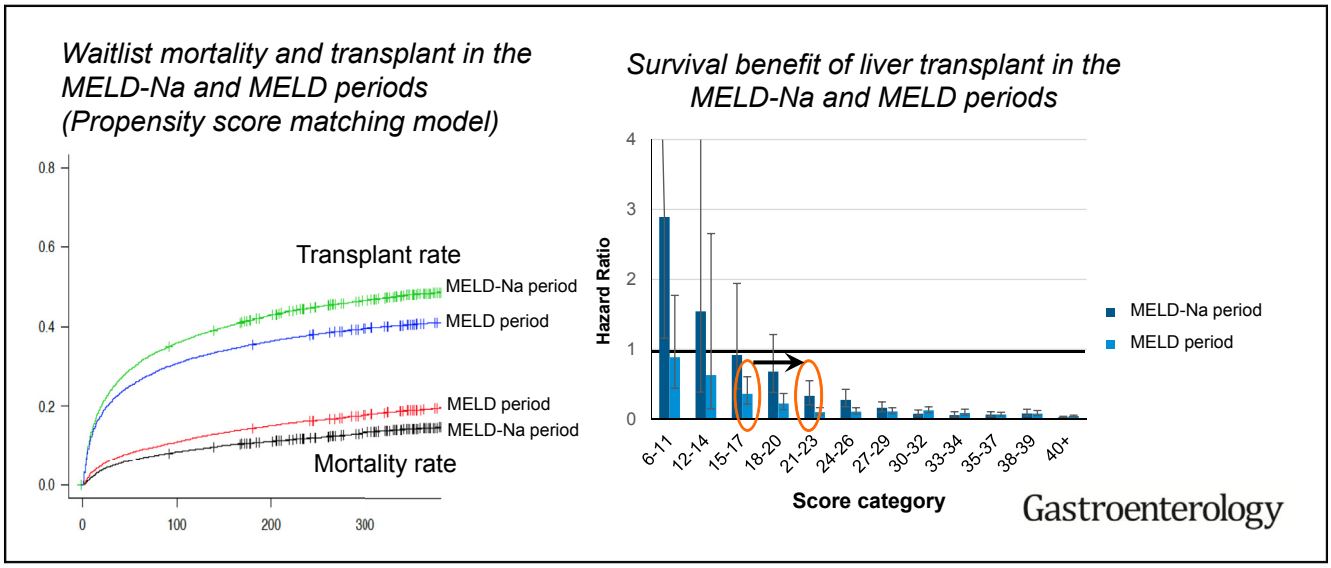
Gastroenterology 2018;155:1451–1462

Effects of Allocating Livers for Transplantation Based on Model for End-Stage Liver Disease–Sodium Scores on Patient Outcomes

Shunji Nagai,[1,*] **Lucy C. Chau**,[1,*] Randolph E. Schilke,[1] Mohamed Safwan,[1] Michael Rizzari,[1] Kelly Collins,[1] Atsushi Yoshida,[1] Marwan S. Abouljoud,[1] and Dilip Moonka[2]

[1]*Transplant and Hepatobiliary Surgery, Henry Ford Hospital, Detroit, Michigan; and* [2]*Gastroenterology, Henry Ford Hospital, Detroit, Michigan*



BACKGROUND & AIMS: The Model for End-stage Liver Disease and Sodium (MELD-Na) score was introduced for liver allocation in January 2016. We evaluated the effects of liver allocation, based on MELD-Na score, on waitlist and post-transplantation outcomes. **METHODS:** We examined 2 patient groups from the United Network for Organ Sharing registry; the MELD-period group was composed of patients who were registered as transplant candidates from June 18, 2013 through January 10, 2016 (n = 18,850) and the MELD-Na period group was composed of patients who were registered from January 11, 2016 through September 30, 2017 (n = 14,512). We compared waitlist and post-transplantation outcomes and association with serum sodium concentrations between groups. **RESULTS:** Mortality within 90 days on the liver waitlist decreased (hazard ratio [HR] 0.738, $P < .001$) and transplantation probability increased significantly (HR 1.217, $P < .001$) in the MELD-Na period. Although mild, moderate, and severe hyponatremia (130–134, 125–129, and <125 mmol/L) were independent risk factors for waitlist mortality in the MELD period (HR 1.354, 1.762, and 2.656; $P < .001$, $P < .001$, and $P < .001$, respectively) compared with the reference standard (135–145 mmol/L), these adverse outcomes were decreased in the MELD-Na period (HR 1.092, 1.271 and 1.374; $P = .27$, $P = .018$, and $P = .037$, respectively). The adjusted survival benefit of transplant recipients vs patients placed on the waitlist in the same score categories was definitive for patients with MELD-Na scores of 21–23 in the MELD-Na era (HR 0.336, $P < .001$) compared with MELD scores of 15–17 in the MELD era (HR 0.365, $P < .001$). **CONCLUSIONS:** Liver allocation based on MELD-Na score successfully improved waitlist outcomes and provided significant benefit to hyponatremic patients. Given the discrepancy in transplantation survival benefit, the current rules for liver allocation might require revision.

Keywords: Hyponatremia; Waitlist Mortality; Survival Benefit; United Network for Organ Sharing.

*Authors share co-first authorship.

Abbreviations used in this paper: **CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; LT, liver transplantation; MELD, Model for End-stage Liver Disease; MELD-Na, Model for End-stage Liver Disease and Sodium; OPTN, Organ Procurement and Transplantation Network; STAR, Standard Transplant Analysis and Research.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2018.07.025

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The OPTN/UNOS introduced the MELD-Na score for the allocation of liver grafts in 2016 in the United States. The impact of the new allocation has not been evaluated.

NEW FINDINGS

The MELD-Na based allocation significantly decreased waitlist mortality. Hyponatremia was no longer a risk factor for waitlist mortality. Survival benefit of liver transplant has shifted towards higher score categories.

LIMITATIONS

The OPTN/UNOS registry is retrospective in nature and lacks detailed clinical information. The effect of the MELD-Na based allocation in patients with exception points remains to be elucidated.

IMPACT

The MELD-Na score-based liver allocation successfully improved waitlist outcomes and hyponatremia was no longer a risk factor for waitlist mortality.

The Model for End-stage Liver Disease (MELD) score had been used for the allocation of deceased donor liver grafts in the United States since 2002.[1,2] The MELD score predicts mortality in patients with liver cirrhosis and prioritizes patients for liver transplantation (LT) on that basis. However, hyponatremia is an independent prognostic factor in patients with cirrhosis but was not included in the original MELD score calculation.[3–5] Kim et al[6] proposed a modified scoring system to further decrease waitlist mortality that incorporates serum sodium concentration into the MELD equation (MELD-Na). This MELD-Na score was officially implemented for liver graft allocation in January 2016.[2]

In the United States, the liver allocation system includes Share 15 and Share 35 rules.[2] The Share 35 rule offers livers to local and regional patients on the waitlist with MELD (and MELD-Na) scores of at least 35. The Share 15 rule offers liver grafts from deceased donors regionally or nationally before returning to local candidates with MELD (and MELD-Na) score lower than 15. Despite implementation of the new allocation using the MELD-Na score, the regional share systems based on specific scores (Share 15 and Share 35) have not been re-evaluated. These rules were determined using data from the MELD period.[7,8] The rationale of Share 15 was derived from the results of a study conducted by Merion et al[9] that evaluated the survival benefit of LT based on MELD score. However, the impact of MELD-Na based allocation on waitlist and post-transplantation outcomes has not previously been investigated.

To better understand the effects of the new liver allocation based on MELD-Na score, we compared waitlist outcomes and post-transplantation outcomes between the MELD and MELD-Na periods after Share 35 was implemented. In addition, we re-evaluated the survival benefit of LT in the MELD-Na period. It should be noted that the 2 major studies by Kim et al[6] (the original study proposing the MELD-Na score) and Merion et al[9] (the original study for the survival benefit of LT) used different end points for waitlist outcome. The study by Kim et al proposed the MELD-Na score by assessing 90-day waitlist outcome. The study by Merion et al investigated the survival benefit of LT by comparing overall waitlist mortality and 1-year post-transplantation patient survival. In this study, we mainly investigated 90-day waitlist outcomes to assess the impact of the MELD-Na based allocation, whereas overall waitlist mortality was evaluated to compare survival benefit of LT in the MELD and MELD-Na periods.

Methods

Patient Selection

This study used data from the Organ Procurement and Transplantation Network (OPTN) and United Network for Organ Sharing (UNOS) contained in the Standard Transplant Analysis and Research (STAR) file, which included data for all patients on the LT waitlist registered up to September 30, 2017. All adult patients (≥18 years old) who were registered after implementation of Share 35 (June 18, 2013) for LT or LT and kidney transplantation were eligible for inclusion in this study. Exclusion criteria included age younger than 18 years, retransplantation, status 1 listing, and LT combined with thoracic organ(s), pancreas, and/or intestine. When patients were removed from the waitlist because transplantation was done at a different center, their waitlist data were excluded from the analysis. Patients who received exception score(s) were censored on the day of exception score approval. The OPTN policy for exception score(s) for hepatocellular carcinoma (HCC) was revised during the study period (October 2015)[10]; therefore, patients with exception score(s) for HCC were excluded. Patients who received living donor liver transplants were censored on the day of transplantation. We examined 2 patient groups; the MELD period group was composed of patients registered on the list from June 18, 2013 to January 10, 2016, and the MELD-Na period group was composed of patients registered from January 11, 2016 to September 30, 2017.

Analysis for Waitlist and Post-transplantation Outcomes

Waitlist patients were classified based on their initial laboratory MELD and MELD-Na scores to analyze waitlist outcomes. Transplant recipients were classified based on their final pretransplantation score to analyze post-transplantation outcomes. These classifications were performed according to MELD score for patients in the MELD period and MELD-Na score for those in the MELD-Na period. Of note, the MELD-Na score is applied when the MELD score is at least 12.[11] Patients were stratified according to MELD and MELD-Na scores (12 groups) and initial serum sodium concentration range groups (5 groups; mild [130–134 mmol/L], moderate [125–129 mmol/L], and severe [<125 mmol/L] hyponatremia, hypernatremia [>145 mmol/L], normal sodium concentration [135–145 mmol/L]). The prognostic impact of hyponatremia

on waitlist outcomes (90-day mortality) was evaluated in the 2 periods.

Because differences in follow-up time can cause a withdrawal bias, patients registered in the MELD and MELD-Na periods were censored on the last day of each period (January 10, 2016 and September 30, 2017, respectively) in the waitlist and post-transplantation outcome analyses. MELD and MELD-Na scores were developed to predict waitlist mortality at 90 days after registration.[6] Therefore, we used 90-day waitlist outcomes as a main end point (mortality and transplantation probability). In addition, we used overall waitlist outcomes as an additional end point. For post-transplantation outcome, 1-year graft survival was set as an end point. A subgroup analysis for waitlist and post-transplantation outcomes was conducted according to hepatitis C virus (HCV) infection status to consider possible cofounding effects of the introduction of new direct-acting antivirals on waitlist and post-transplantation outcomes.

The survival benefit of LT was compared between the 2 periods as a function of MELD and MELD-Na scores. The survival benefit is expressed as a ratio comparing the mortality rate of liver transplant recipients with candidates on the waitlist (death per 1000 patient-years).[9] The waitlisted patients were classified by their final score. In this analysis, waitlist outcome throughout the period and post-transplantation outcome with 1-year follow-up were set as end points.

Definitions of Waitlist Outcomes

In the analysis of waitlist mortality, removal from the waitlist because of deterioration in medical condition (ie, too sick for transplantation) was considered waitlist mortality. Many of these patients were critically ill and died within a short period of waitlist removal. Conversely, the LT survival benefit analysis was performed twice using 2 definitions of waitlist mortality: (1) "too sick for transplantation" was not considered waitlist mortality, which mirrors the methodology in the study by Merion et al,[9] and (2) "too sick for transplantation" was considered waitlist mortality.

Statistical Analysis

Data were summarized using median with interquartile range for continuous variables and number and percentage for discrete variables. Continuous variables were analyzed using the Mann-Whitney *U*-test and discrete variables were analyzed using the χ^2 test. Transplantation probability and waitlist mortality rates were compared by the Gray test to estimate cumulative incidence of competing events, including death, transplantation, and other reasons for removal from the waitlist. Multivariable models were created to elucidate factors that affect waitlist and post-transplantation outcomes. Waitlist mortality and transplantation probability were compared between the MELD and MELD-Na periods using Fine-Gray proportional hazard regression models. The Fine-Gray models allow for the analysis of competing risk events, which in this study included mortality, transplantation, and other reasons for waitlist removal. Post-transplantation outcomes were compared using Cox proportional hazard models. The risk of waitlist mortality was adjusted for recipient age, race, gender, primary diagnosis, listed for LT and kidney transplantation, UNOS region (1–11), history of diabetes, Karnofsky score at registration lower than 30%, presence of ascites, hepatic encephalopathy, and dialysis requirement at registration. The risk of liver graft loss was adjusted for recipient age, race, gender, primary diagnosis, LT and kidney transplantation, UNOS region (1–11), organ share type (local, regional, or national), history of diabetes, Karnofsky score at transplantation lower than 30%, donor age, cold ischemia time, donation after cardiac death, presence of ascites, hepatic encephalopathy, and dialysis requirement at transplantation.[8]

To further validate our analysis of waitlist outcomes between the MELD and MELD-Na periods, we used a propensity score matching model, in addition to the multivariate analysis. We estimated the propensity score by period for each waitlisted patient using a multivariable logistic regression model in which all variables listed earlier were included. Then, we used the propensity score, the single composite variable, to match patients in each period by matching the propensity score using a caliper of 0.20 SD. The 14,244 patients were compared in the MELD and MELD-Na periods. By using the matched groups, 90-day waitlist mortality rate and transplantation probability were estimated and compared by the Gray test and hazard ratios (HRs) were estimated by a Fine-Gray regression model.

In the survival benefit analysis, delta MELD (MELD-Na) score was computed by dividing the change in score by the interval between reported dates of change.[12] Delta MELD (MELD-Na) score was included in the covariates for the multivariable model. The STAR waitlist database was queried for "new final MELD (MELD-Na)" scores within 90 days before recipients' censoring point, that is, transplantation, removal from the waiting list, or end of period. From the identified new final score date, we further identified "prior MELD (MELD-Na)" scores at least 25 days before the newly contrived new final scores. We estimated the 30-day average delta MELD as follows:

$$\textit{Delta MELD} = \left((\textit{New Final MELD} - \textit{Prior MELD}) \times \left(\frac{30\ \textit{Days}}{\textit{Day difference between "New Final MELD" \& "Prior MELD"}} \right) \right)$$

All statistical analyses were completed using SPSS 19 (IBM Corp, Armonk, New York) and R (R Foundation for Statistical Computing, Vienna Austria), and significance was set at .05. Study design, patient cohort and statistical methodologies are summarized in Supplementary Table 1.

Results

Recipient Characteristics

Before applying the inclusion and exclusion criteria, the numbers of waitlisted patients and transplant recipients in the MELD and MELD-Na periods were compared. The total numbers of patients who were added to the waitlist were 30,723 and 22,269 in the MELD period (909 days) and

MELD-Na period (629 days), respectively. The newly listed patients significantly increased in the MELD-Na period (from 1,014 to 1,062 patients per month; $P < .001$). The total numbers of liver transplant recipients were 17,584 and 13,759 in the MELD and MELD-Na periods. The monthly number of transplantations significantly increased in the MELD-Na period (from 580 to 656 transplants per month; $P < .001$).

There were 18,850 patients in the MELD period and 14,512 patients in the MELD-Na period who met inclusion criteria for waitlist outcome analysis. Of these, 6547 and 5862 patients who underwent primary deceased donor LT in the same period were evaluated in the post-transplantation outcome analysis. The actual score at registration and transplantation significantly increased in the MELD-Na period, whereas the proportion of patients with poor performance status at registration (Karnofsky score < 30%) and those requiring dialysis or life support decreased (Table 1). In the MELD-Na period, the score distributions shifted from lower to mid score categories at registration and at transplantation. At registration, 38.3% of patients had a score of 21–34 in the MELD-Na period compared with 29.6% in the MELD period (Figure 1*A*). At transplantation, 52.8% of patients had a score of 21–34 in the MELD-Na period compared with 46.8% in the MELD period (Figure 1*B*). The serum sodium concentration at transplantation in the MELD-Na period was significantly lower in patients with scores of 6–11 and 18–39 (Figure 1*C*).

Comparisons of Waitlist and Post-transplantation Outcomes Between MELD and MELD-Na Periods

Waitlist outcomes at 90 days after registration (mortality and transplantation) and 1-year liver graft loss were compared between the MELD and MELD-Na periods (Figure 2*A–C*). The hazard of 90-day waitlist mortality in the MELD-Na period was 26.2% lower than in the MELD period (HR 0.738, 95% confidence interval [CI] 0.681–0.799, $P < .001$). The 90-day transplantation probability increased by 21.7% in the MELD-Na period (HR 1.217, 95% CI 1.158–1.280, $P < .001$). The risk of 1-year graft loss or patient death was similar between the MELD and MELD-Na periods (graft loss: HR 1.086, 95% CI 0.955–1.235, $P = .21$; patient death: HR 1.068, 95% CI 0.938–1.215, $P = .323$). Overall waitlist outcomes also were compared, which demonstrated similar trends. The overall waitlist mortality in the MELD-Na period was 33.5% lower than in the MELD period (HR 0.665, 95% CI 0.625–0.708, $P < .001$). The overall transplantation probability was 19.7% higher in the MELD-Na period than in the MELD period (HR 1.197, 95% CI 1.146–1.250, $P < .001$; Supplementary Figure 1).

The hazard of 90-day waitlist mortality in the MELD-Na period significantly decreased in patients with normal serum sodium concentration (HR 0.825, 95% CI 0.738–0.922, $P < .001$) and in those with mild (HR 0.656, 95% CI 0.558–0.765, $P < .001$), moderate (HR 0.640, 95% CI 0.513–0.800, $P < .001$), or severe (HR 0.526, 95% CI 0.368–0.752, $P < .001$) hyponatremia.

We performed propensity score matching for waitlisted patients between the MELD and MELD-Na period groups to validate the findings in the waitlist outcome analysis. After propensity score matching, 14,244 waitlisted patients were selected from each group. Compared with the MELD period group, the MELD-Na period group had significantly better 90-day waitlist outcomes with less mortality (8.1% vs 10.5%; $P < .001$) and greater transplantation probability (34.8% vs 30.0%; $P < .001$; Figure 3*A*). When including propensity score in a risk adjustment model, the hazards of 90-day waitlist mortality and transplantation probability were 0.750 (95% CI 0.692–0.813, $P < .001$) and 1.186 (95% CI 0.692–0.813, $P < .001$), respectively. The model achieved a standardized difference less than 0.10 (10%) after matching for all covariates (Figure 3*B*).

Association Between Serum Sodium Concentration and Waitlist Mortality

In the MELD period, the hazards of 90-day waitlist mortality in patients with mild, moderate, and severe hyponatremia were 1.354, 1.762, and 2.656 times those with normal sodium levels (HR 1.354, 95% CI 1.204–1.522, $P < .001$; HR 1.762, 95% CI 1.504–2.064, $P < .001$; HR 2.656, 95% CI 2.217–3.318, $P < .001$, respectively; Figures 4*A–C*). This adverse impact decreased significantly in the MELD-Na period (HR 1.092, 95% CI 0.934–1.276, $P = .27$; HR 1.271, 95% CI 1.042–1.550, $P = .018$; HR 1.374, 95% CI 1.019–1.854, $P = .037$, in those with mild, moderate, and severe hyponatremia, respectively; Figure 4*D–F*). The risk of waitlist mortality associated with hyponatremia was more prominent in patients in the low to middle score categories (score 6–26) in the MELD period; however, this was no longer observed in the MELD-Na period.

Waitlist and Post-transplantation Outcomes According to HCV Infection Status

In the non-HCV group, significant improvement of waitlist outcomes was observed in the MELD-Na period. The hazard of 90-day waitlist mortality was 28.2% lower in the MELD-Na period (HR 0.718, 95% CI 0.658–0.784, $P < .001$), and the likelihood of transplantation increased by 20.8% (HR 1.208, 95% CI 1.144–1.277, $P < .001$). In the HCV group, the risk of 90-day waitlist mortality was comparable between the 2 groups (HR 0.854, 95% CI 0.697–1.048, $P = .13$), but the 90-day transplantation probability increased by 26.3% in the MELD-Na period (HR 1.263, 95% CI 1.118–1.428, $P < .001$). When comparing the MELD and MELD-Na periods, there was no difference in 1-year graft loss for the non-HCV group (HR 1.092, 95% CI 0.947–1.259, $P = .224$) and HCV group (HR 1.018, 95% CI 0.742–1.395, $P = .913$).

Patient characteristics between the HCV and non-HCV groups were compared. In the MELD period, the score distributions at registration in the lower (6–15), middle (16–34), and higher (≥35) score categories were 33.0%, 56.9%, and 10.1% in the HCV group and 28.8%, 59.6%, and 11.6% in the non-HCV group, respectively. In the MELD-Na period, the distributions of these 3 categories were 29.3%, 62.2%, and 8.5% in the HCV group and 23.0%, 65.4%, and 11.6% in

Table 1. Patient Characteristics in MELD and MELD-Na Periods[a]

Waitlist patient characteristics	MELD period (n = 18,850)	MELD-Na period (n = 14,512)	*P* value
Age at listing (*y*)	56.0 [49–62]	56.0 [48–62]	.863
Men	11,390 (60.4)	8651 (59.6)	.134
Race			
White	13,520 (71.1)	10,488 (72.3)	
Black	1661 (8.8)	1054 (7.3)	
Hispanic	2806 (14.9)	2280 (15.7)	<.001
Asian	585 (3.1)	453 (3.1)	
Other	278 (1.5)	237 (1.6)	
Primary liver disease			
HCV	4159 (22.1)	1848 (12.7)	
Nonalcoholic steatohepatitis	3225 (17.1)	3041 (21.0)	<.001
Alcohol	5721 (30.4)	5072 (35.0)	
Other	5745 (30.4)	4551 (31.4)	
Actual score at listing[b]	18 [14–26]	20 [15–28]	<.001
Sodium at listing (*mmol/L*)	136 [133–139]	137 [133–139]	.213
Delta MELD	3.09 (SE 0.17)	3.3 (SE 0.19)	.009
Karnofsky score < 30% at listing	2512 (13.6)	1790 (12.6)	.007
Dialysis at listing	2037 (10.8)	1531 (10.5)	.464
Life support at listing	819 (4.3)	540 (3.7)	.006
Total time on waiting list (*d*)	93 [17–302]	62 [14–199]	<.001
Follow-up time to 90 d (*d*)	90 [17–90]	62 [14–90]	<.001
Waitlist status after 90 d			
Transplant	4871 (25.8)	4666 (32.2)	
Death or removal because too sick	1783 (9.5)	1051 (7.2)	<.001
Censored or other removal reasons	12,196 (64.7)	8795 (60.6)	
Transplant recipient characteristics	**MELD period (n = 6547)**	**MELD-Na period (n = 5862)**	***P* value**
Recipient age at transplantation (*y*)	56 [48.5–62]	56 [48–62]	.703
Male recipient	4191 (64.0)	3733 (63.7)	.708
Actual score at transplantation[b]	30 [23–37]	29 [22–35]	<.001
MELD score at transplantation	30 [23–37]	26 [19–34.6]	<.001
MELD-Na score at transplantation	31.5 [25–37.7]	29 [22–35]	<.001
Sodium at transplantation (*mmol/L*)	136 [132–139]	135 [131–138]	<.001
Waiting time to transplantation (*d*)	25 [7–94]	22 [7–70]	<.001
Cold ischemia time (*h*)	6.0 [4.8–7.5]	5.7 [4.5–7.1]	<.001
Karnofsky score < 30% at transplantation	2121 (35.7)	1596 (27.8)	<.001
Pretransplantation dialysis	1760 (26.9)	1333 (22.7)	<.001
Pretransplantation life support	993 (15.2)	648 (11.2)	<.001
Donor age (*y*)	40 [27–53]	39 [27–53]	.783
Donor body mass index	26.6 [23.4–31.0]	27.0 [23.5–31.5]	.005
Donation after cardiac death	371 (5.7)	391 (6.7)	.02
Donor location			
Local	3812 (58.2)	3544 (60.5)	
Regional	2480 (37.9)	2045 (34.9)	.001
National	255 (3.9)	273 (4.7)	
Distance to donor hospital (*miles*)	88 [13–227]	86 [12–213]	.041
Length of hospital stay (*d*)	12 [8–20]	11 [7–18]	<.001

[a]Data were summarized using median [interquartile range] for continuous variables and number (percentage) for discrete variables.
[b]MELD score in MELD period and MELD-Na score in MELD-Na period.

the non-HCV group, respectively. The odds for patients with HCV being listed in the lower score category compared with those without HCV increased from 1.22 (95% CI 1.134–1.314, $P < .001$) to 1.388 (95% CI 1.245–1.547, $P < .001$), whereas the odds for being listed in the higher score category decreased from 0.852 (95% CI 0.761–0.953, $P = .005$) to 0.709 (95% CI 0.597–0.843, $P < .001$).

Survival Benefit of LT in MELD and MELD-Na Periods

The overall waitlist mortality rates were 169.2 and 170.7 deaths per 1000 patient-years in the MELD-Na and MELD periods, respectively. The mortality rates in transplant recipients with 1-year follow-up were 114.1 and 98.3 deaths per 1000 patient-years in the MELD-Na and MELD periods,

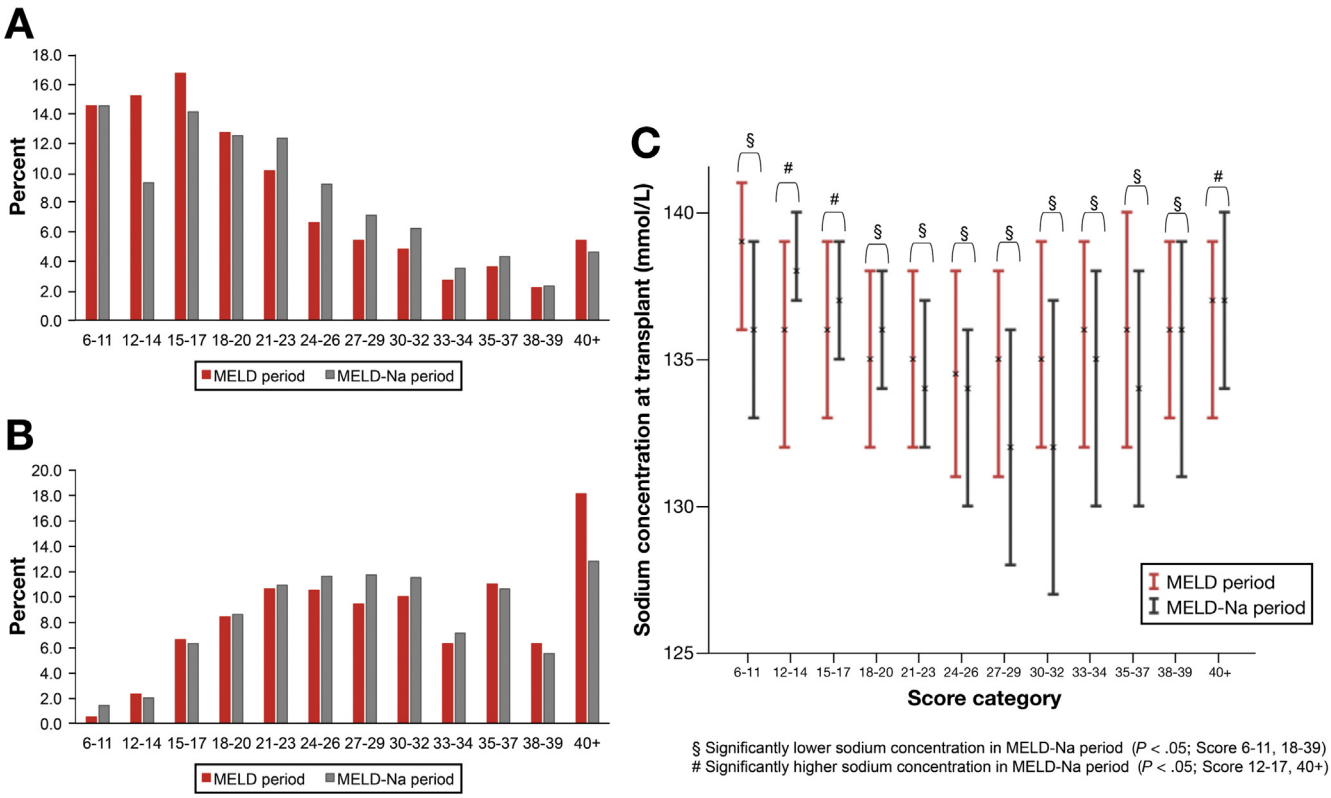
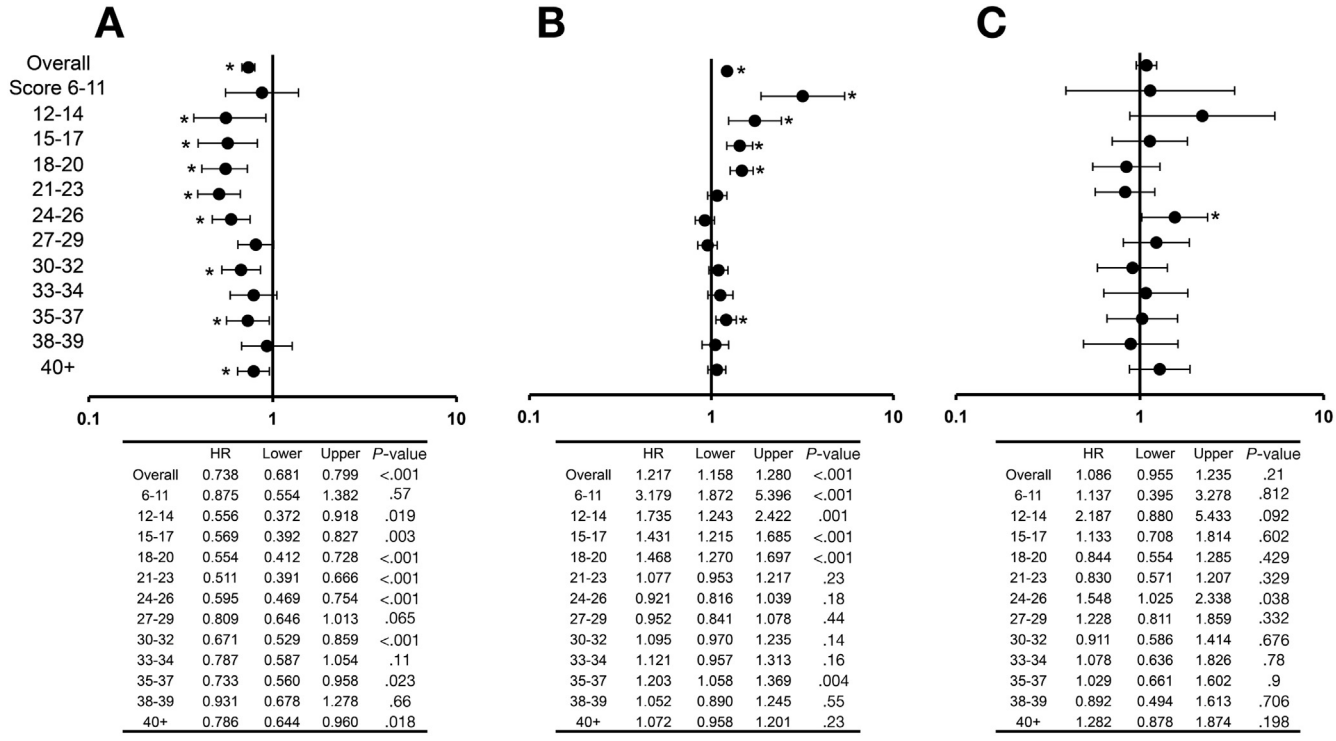


Figure 1. (*A*) Score distribution at registration. (*B*) Score distribution at transplantation. (*C*) Comparisons of serum sodium concentration at transplantation according to score category.

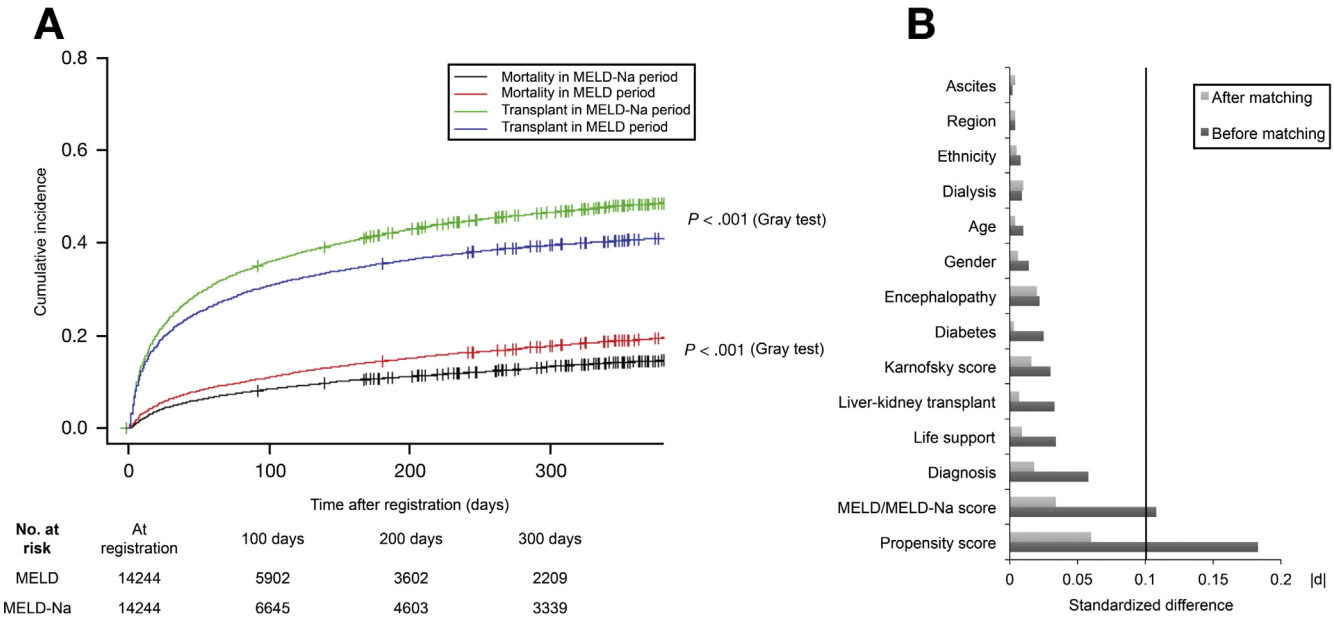


	HR	Lower	Upper	*P*-value
Overall	0.738	0.681	0.799	<.001
6-11	0.875	0.554	1.382	.57
12-14	0.556	0.372	0.918	.019
15-17	0.569	0.392	0.827	.003
18-20	0.554	0.412	0.728	<.001
21-23	0.511	0.391	0.666	<.001
24-26	0.595	0.469	0.754	<.001
27-29	0.809	0.646	1.013	.065
30-32	0.671	0.529	0.859	<.001
33-34	0.787	0.587	1.054	.11
35-37	0.733	0.560	0.958	.023
38-39	0.931	0.678	1.278	.66
40+	0.786	0.644	0.960	.018

	HR	Lower	Upper	*P*-value
Overall	1.217	1.158	1.280	<.001
6-11	3.179	1.872	5.396	<.001
12-14	1.735	1.243	2.422	.001
15-17	1.431	1.215	1.685	<.001
18-20	1.468	1.270	1.697	<.001
21-23	1.077	0.953	1.217	.23
24-26	0.921	0.816	1.039	.18
27-29	0.952	0.841	1.078	.44
30-32	1.095	0.970	1.235	.14
33-34	1.121	0.957	1.313	.16
35-37	1.203	1.058	1.369	.004
38-39	1.052	0.890	1.245	.55
40+	1.072	0.958	1.201	.23

	HR	Lower	Upper	*P*-value
Overall	1.086	0.955	1.235	.21
6-11	1.137	0.395	3.278	.812
12-14	2.187	0.880	5.433	.092
15-17	1.133	0.708	1.814	.602
18-20	0.844	0.554	1.285	.429
21-23	0.830	0.571	1.207	.329
24-26	1.548	1.025	2.338	.038
27-29	1.228	0.811	1.859	.332
30-32	0.911	0.586	1.414	.676
33-34	1.078	0.636	1.826	.78
35-37	1.029	0.661	1.602	.9
38-39	0.892	0.494	1.613	.706
40+	1.282	0.878	1.874	.198

Figure 2. Comparison of waitlist and post-transplantation outcomes between the MELD and MELD-Na periods (reference, MELD period; *$P < .05$). (*A*) HR for 90-day waitlist mortality in the MELD-Na period according to score categories. (*B*) HR for 90-day transplantation probability in the MELD-Na period according to score categories. (*C*) HR for 1-year liver graft loss in the MELD-Na period according to score range categories.



Mortality (%)	90 days	180 days	1 year
MELD period	10.5	14.5	19.2
MELD-Na period	8.1	10.7	14.5

Transplant (%)	90 days	180 days	1 year
MELD period	30.0	35.6	40.8
MELD-Na period	34.8	41.8	48.3

Figure 3. Comparison of cumulative incidence of waitlist mortality and transplantation between propensity score matched groups by period. (*A*) Cumulative incidence of waitlist mortality and transplantation. (*B*) Standardized difference before and after matching. The model achieved a standardized difference less than 0.10 (10%) after matching for all covariates.

respectively (Table 2). Figure 5 shows the potential "benefit of transplantation" described by Merion et al[9] by determining an adjusted mortality risk after transplantation per 1000 patient-years vs waitlist mortality per 1000 patient-years. An HR less than 1.0 favors transplantation. A transition point of LT survival benefit shifted toward a higher score category in the MELD-Na period. The adjusted survival benefit of transplant recipients over waitlisted patients in the same score categories was definitive in those with a MELD-Na score of at least 24 in the MELD-Na period (score 24–26: HR 0.563, 95% CI 0.345–0.918, $P = .021$) compared with a MELD score of at least 18 in the MELD period (score 18–20: HR 0.484, 95% CI 0.285–0.823, $P = .007$; Figure 5*A*).

When considering "removal because too sick for transplantation" as waitlist mortality, transplantation became more favorable but the same trend was observed in a comparison of survival benefit between periods. The rates for waitlist mortality including "removal because too sick for transplantation" were 307.0 and 318.2 per 1000 patients-years in the MELD-Na and MELD periods, respectively (Table 2). Survival benefit of LT was definitive in those with a score category of 15–17 in the MELD period (HR 0.365, 95% CI 0.219–0.609, $P < .001$), whereas this shifted toward the higher score category of 21–23 in the MELD-Na period (HR 0.336, 95% CI 0.205–0.552, $P < .001$; Figure 5*B*).

Share 15 and Share 35 in MELD-Na Period

Hyponatremia drives MELD-Na scores, which might benefit hyponatremic patients whose MELD score do not meet the cutoff for liver regional share (15 or 35). Patients who had an initial and final MELD score lower than 15 but a MELD-Na score of at least 15 had a significantly greater likelihood of transplantation within 90 days in the MELD-Na period at 26.1% vs 12.7% in the MELD period ($P < .001$), and they had significantly lower 90-day waitlist mortality in the MELD-Na period at 1.9% vs 10.6% in the MELD period ($P < .001$; Supplementary Figure 2*a*). The adjusted 90-day transplantation probability was 125.0% higher (HR 2.250, 95% CI 1.512–3.348, $P < .001$), and the adjusted hazard of 90-day waitlist mortality was 70.9% lower (HR 0.291, 95% CI 0.163–0.519, $P < .001$), in the MELD-Na period. Waiting time to transplantation was significantly shorter in the MELD-Na period (39 vs 73 days; $P = .002$; Supplementary Table 2).

In patients whose initial MELD score was lower than 35 but whose MELD-Na score was at least 35, the likelihood of transplantation within 90 days was significantly higher in the MELD-Na period at 80.5% vs 70.2% in the MELD period ($P = .002$; Supplementary Figure 2*b*). There was a decreased 90-day waitlist mortality at 14.3% vs 23.9%, respectively ($P = .023$). The adjusted 90-day transplantation probability was 67.3% higher in the MELD-Na period (HR 1.673, 95% CI 1.293–2.165, $P < .001$), and the adjusted hazard of 90-day waitlist mortality was 37.2% lower in the MELD-Na period, but the difference did not reach statistical significance (HR 0.628, 95% CI 0.382–1.032, $P = .062$). Waiting time to transplantation was significantly shorter in the MELD-Na period (6 vs 9 days; $P = .012$; Supplementary Table 1).

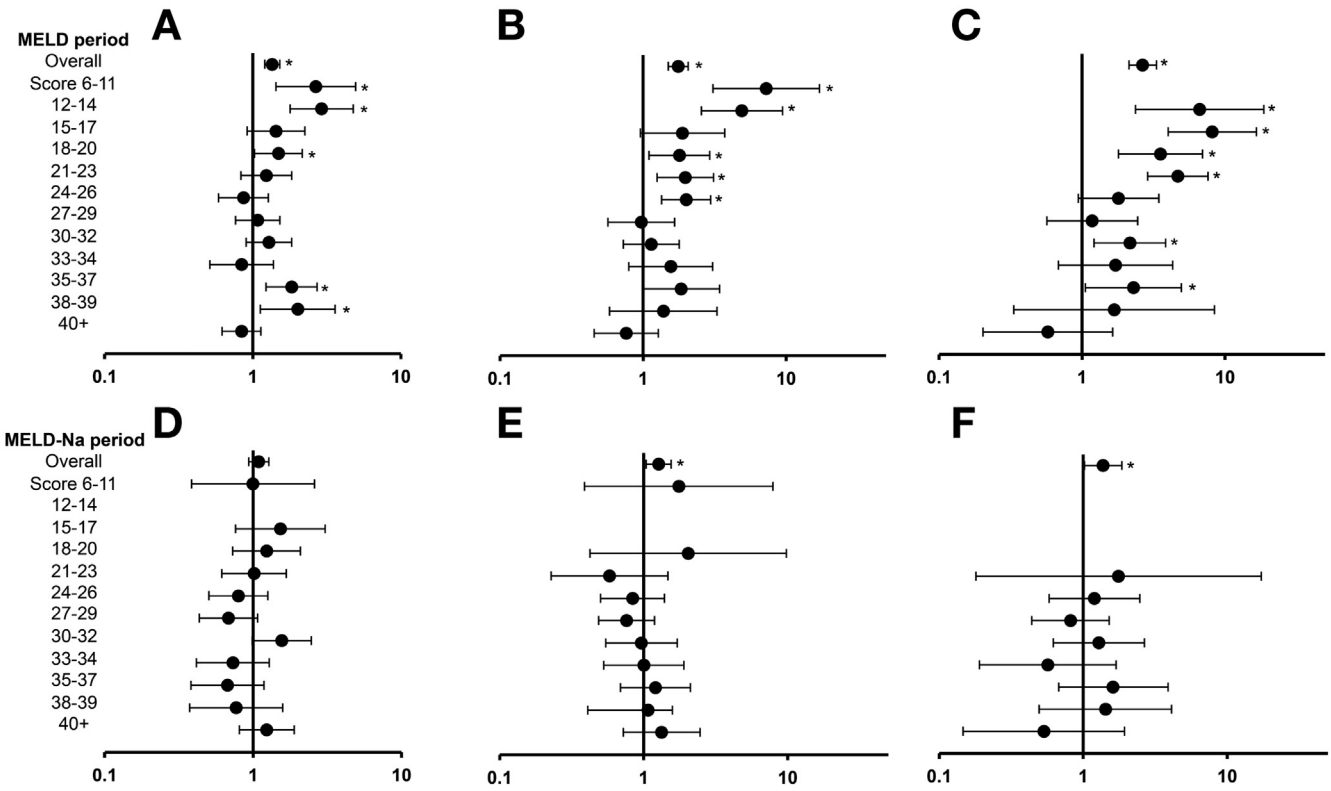


Figure 4. Risk of hyponatremia for 90-day waitlist mortality in the MELD and MELD-Na periods (reference, normal sodium concentration [135–145 mmol/L]; *$P < .05$). (*A*) HR of mild hyponatremia (130–134 mmol/L) in MELD period. (*B*) HR of moderate hyponatremia (125–129 mmol/L) in MELD period. (*C*) HR of severe hyponatremia (<125 mmol/L) in MELD period. (*D*) HR of mild hyponatremia (130–134 mmol/L) in MELD-Na period. (*E*) HR of moderate hyponatremia (125–129 mmol/L) in MELD-Na period. (*F*) HR of severe hyponatremia (<125 mmol/L) in MELD-Na period.

In patients with initial MELD and MELD-Na scores of at least 35, the 90-day transplantation probability increased from 74.7% in the MELD-Na period vs 71.4% in the MELD period ($P = .019$), and 90-day waitlist morality rate decreased significantly to 22.2% vs 25.7% ($P = .006$). The adjusted 90-day transplantation probability was 11.9% higher (HR 1.119, 95% CI 1.033–1.212, $P = .006$), and the adjusted hazard of 90-day waitlist mortality was 18.9% lower (HR 0.811, 95% CI 0.700–0.939, $P = .005$), in the MELD-Na period (Supplementary Figure 2*c*).

Discussion

The MELD-Na score was expected to provide better calibration and discrimination of waitlist mortality.[6,13] This study demonstrated that waitlist outcomes significantly improved in the MELD-Na period compared with the MELD period. We mainly investigated 90-day waitlist outcomes because the MELD-Na score was originally proposed by Kim et al[6] using this end point. Of note, this differs from the methodology by Merion et al[9] in which survival benefit of LT was evaluated using overall waitlist mortality and 1-year post-transplantation survival. When overall waitlist outcomes were assessed in our cohort, similar trends to the results of the analysis for 90-day outcomes were observed (Supplementary Figure 1). Although the number of transplant recipients significantly increased in the MELD-Na period, the number of newly listed patients also significantly increased. The recent increase in the donor pool could be associated with the opioid epidemic and the increased liver graft availability might contribute to the improved waitlist outcome.[14,15] If the increased donor availability in the MELD-Na was the only reason for the findings in this study, then the positive impact should have been equally observed across all score categories. However, there was a discrepancy of impact and the positive impact was more prominent in the lower score categories. In addition, the risk of hyponatremia for waitlist mortality clearly decreased in the MELD-Na period, which cannot be explained by the increased number of liver grafts. These results indicate that liver graft availability was not the main reason for decreased waitlist mortality observed in this study. The MELD-Na score provides 1 to 11 additional points, and maximum additional points are given to patients with low MELD score and severe hyponatremia.[6] Our results suggest that higher scores secondary to hyponatremia probably led to better waitlist outcomes, especially in the population who benefited from Share 15 (ie, patients with MELD score < 15 but MELD-Na score ≥ 15).

As expected, the MELD-Na based allocation helped alleviate the adverse prognostic impact of hyponatremia on waitlist outcomes.[16] Hyponatremia is a well-known factor associated with mortality in patients with liver cirrhosis and this was clearly observed in the MELD period.[3,6] The risk of

Table 2. Unadjusted Waitlist and Transplantation Mortality Rates by Score Category in MELD and MELD-Na Periods

	Waitlist outcome			Waitlist outcome			Post-transplantation outcome (1-y follow-up)		
	Death	PY	Death per 1000 PY	Death + too sick	PY	Death per 1000 PY	Death	PY	Death per 1000 PY
MELD									
6–11	63	2808	22.4	144	2808	51.3	23	280	82.1
12–14	99	1904	52.0	167	1904	87.7	29	321	90.3
15–17	161	1684	95.6	262	1684	155.6	41	595	68.9
18–20	148	1116	132.6	235	1116	210.6	48	673	71.3
21–23	149	846	176.1	275	846	325.0	49	756	64.8
24–26	129	462	279.2	235	462	508.6	54	698	77.4
27–29	116	265	437.9	218	265	823.0	54	567	95.2
30–32	120	222	540.0	219	222	985.5	72	580	124.2
33–34	77	134	575.6	157	134	1173.6	36	359	100.4
35–37	109	188	581.2	247	188	1317.1	61	574	106.2
38–39	87	110	790.9	174	110	1518.8	54	330	163.7
≥40	463	344	1347.5	875	344	2546.7	129	878	146.9
Total	1721	10,082	170.7	3208	10,082	318.2	650	6611	98.3
MELD-Na									
6–11	21	1317	15.9	78	1317	59.2	13	130	100.1
12–14	19	735	25.8	39	735	53.0	6	93	64.4
15–17	44	875	50.3	76	875	86.9	17	216	78.9
18–20	59	667	88.4	93	667	139.4	30	293	102.5
21–23	58	557	104.1	105	557	188.5	46	366	125.7
24–26	73	352	207.6	136	352	386.9	42	369	113.9
27–29	80	210	380.4	142	210	675.2	46	362	127.0
30–32	85	154	553.2	136	154	885.1	28	357	78.4
33–34	59	71	832.4	106	71	1495.5	24	226	106.3
35–37	87	108	808.7	157	108	1459.4	39	354	110.0
38–39	53	46	1153.3	96	46	2089.0	33	174	190.1
≥40	244	120	2038.5	436	120	3642.6	60	428	140.3
Total	882	5211	169.2	1600	5211	307.0	384	3367	114.1

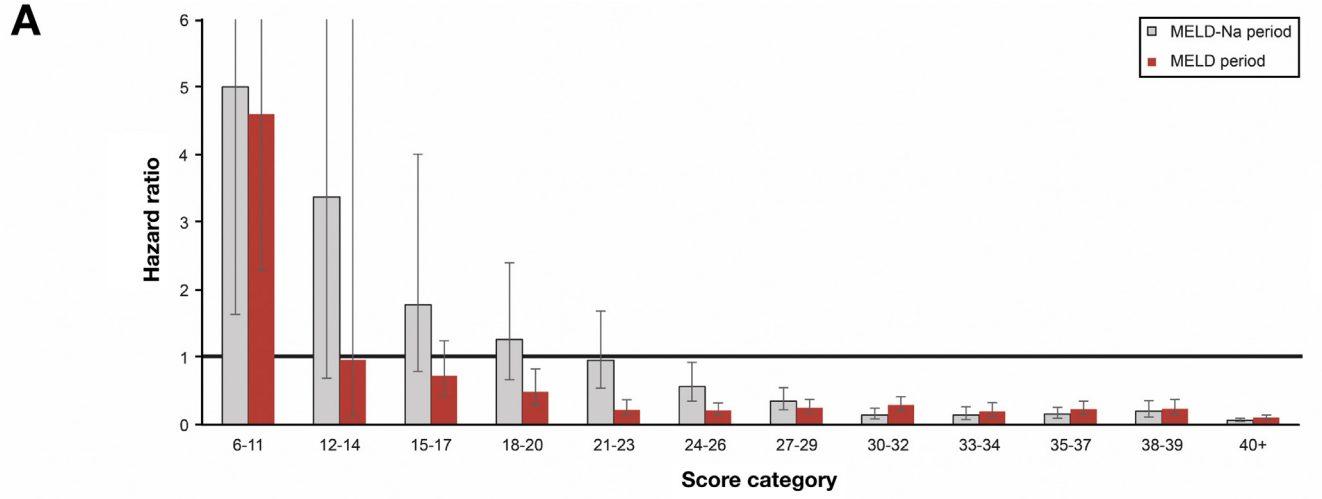
PY, patient-years.

mild hyponatremia disappeared in the MELD-Na period. Moderate and severe hyponatremia remained significant risk factors, but the hazards decreased by 27.9% (1.762 to 1.271) and 48.3% (2.656 to 1.374) in the MELD-Na period. These findings support the rationale for the implementation of MELD-Na score into liver allocation.

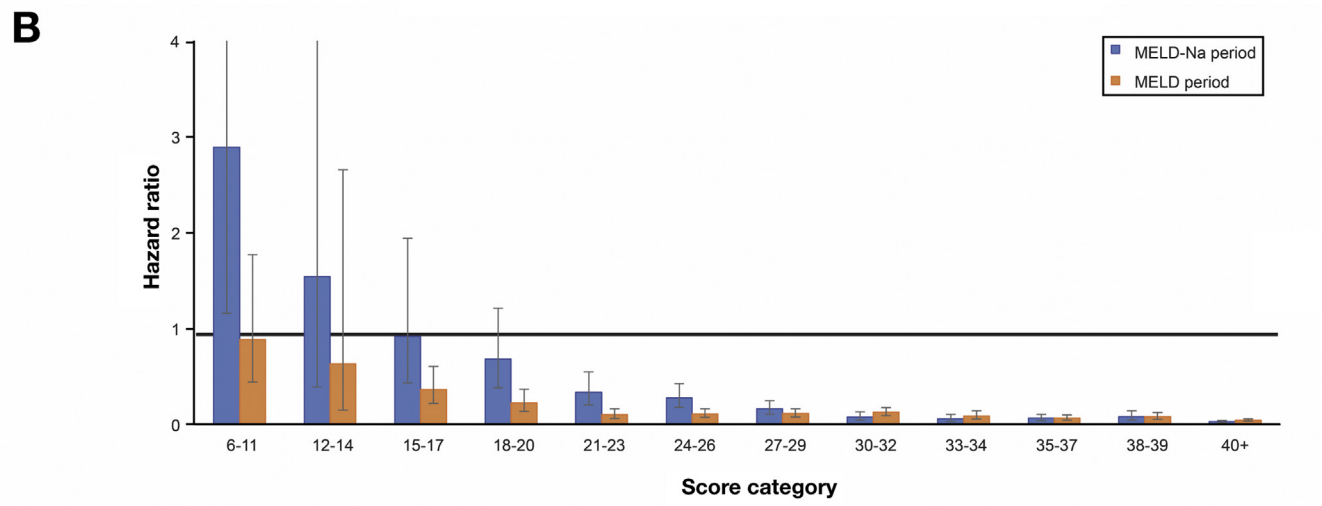
The availability of effective antiviral therapy for HCV in recent years is a potential reason for the improved waitlist outcomes observed in this study.[17,18] However, the subgroup analysis of HCV and non-HCV groups showed that the improvement in waitlist outcomes was more obvious in the non-HCV than in the HCV group. Although the 2 groups had a higher likelihood of transplantation in the MELD-Na period, only the non-HCV group had improved waitlist mortality. Direct-acting antigen antivirals have been clinically available since 2013, and the MELD-Na period began in January 2016. The improved antiviral therapy might have already helped stabilize patients with HCV and decreased their mortality on the waitlist before MELD-Na implementation.[19] Hence, the positive impact of new allocation on the waitlist outcomes in the HCV population was not as obvious as in the non-HCV population.

The impact of the MELD-Na score was less pronounced in patients with higher scores. In part, this is because the additional scores added for hyponatremia are smaller in higher MELD score groups. Although patients whose MELD-Na score was increased by hyponatremia to higher than 35 did benefit with the MELD-Na period, the benefit observed was less obvious than in patients in lower score categories.[20,21] These results suggest that the MELD-Na based allocation potentially provided more benefits to patients in the less medically urgent status categories. Sharma et al[22] suggested that additional scores by serum sodium concentration should be considered for candidates with a MELD score of at least 12, and the MELD-Na score is currently applied to patients whose MELD score is at least 12.[11] The MELD-Na score based allocation might create more competition in the mid to high score categories. As such, the benefit of MELD-Na based allocation might be diminished in the higher score category. Because of the tighter competition within this patient group, new criteria to discriminate medical urgency in the sicker patient population might need to be established.[23–25]

The Share 15 policy mandates that if there is no local candidate with a MELD score of at least 15, organs are offered regionally or nationally before returning to local candidates with a MELD lower than 15.[2] In this study, we found that in the MELD-Na period the survival benefit of LT decreased in the lower score categories, and a transition point justifying survival benefit shifted toward higher score



Score		6-11	12-14	15-17	18-20	21-23	24-26	27-29	30-32	33-34	35-37	38-39	40+
Risk adjusted hazard ratio	MELD-Na	5.001	3.373	1.774	1.260	0.949	0.563	0.344	0.141	0.139	0.154	0.196	0.064
	MELD	4.600	0.957	0.718	0.484	0.218	0.207	0.247	0.286	0.194	0.229	0.234	0.106
P-value	MELD-Na	.005	.136	.168	.481	.859	.021	<.001	<.001	<.001	<.001	<.001	<.001
	MELD	<.001	.967	.235	.007	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001



Score		6-11	12-14	15-17	18-20	21-23	24-26	27-29	30-32	33-34	35-37	38-39	40+
Risk adjusted hazard ratio	MELD-Na	2.893	1.544	0.920	0.683	0.336	0.279	0.165	0.080	0.060	0.068	0.083	0.031
	MELD	0.888	0.633	0.365	0.226	0.104	0.111	0.115	0.129	0.092	0.070	0.083	0.047
P-value	MELD-Na	.023	.537	.827	.193	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
	MELD	.736	.532	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001

Figure 5. Comparison of mortality risk in MELD-Na vs MELD period. Mortality risk by MELD and MELD-Na scores for liver transplant recipients was compared with that of patients on the LT waitlist. The columns showed HRs and *P* values by classifying the patients based on their final scores. Columns highlighted in *light blue*, *gray*, and *orange* represent "not favoring transplantation" (staying on the waitlist), "comparable," and "favoring transplantation." The transition point justifying survival benefit of LT shifted toward a higher score category. (*A*) Waitlist death includes "mortality" only. (*B*) Waitlist death includes "mortality" and "removal because too sick for transplantation."

categories. This transition might result from the combination of the improved waitlist outcomes and worsened post-transplantation outcomes in the MELD-Na period (death per 1000 patient-years in Table 2). The improved waitlist outcomes can be explained by the positive impact of the MELD-Na based allocation, as discussed earlier. Reasons for the slightly worsened post-transplantation outcomes in the MELD-Na period remain unclear. However, we have observed that the LT population has become older. Older recipient age is a known poor prognostic factor in the liver

transplant recipient and might be associated with the findings observed in this study.[26] As such, the current rules for liver allocation might be suboptimal under the MELD-Na based allocation and the criteria for Share 15 might need to be revisited. Based on our findings, the cutoff score for share might be raised to a score of approximately 21, as "Share 21" (the hazard decreased to <1.0 in the score category of 21–23; Figure 5*A*). Of note, our methodology in the survival benefit analysis followed that of Merion et al[9] in which waitlist mortality was defined as death on the waitlist. Aside from the survival benefit analysis, waitlist mortality in this study was defined as death on the waitlist or removal because the patient was "too sick for transplantation." In a subgroup analysis, the survival benefit was recalibrated to consider removal for "too sick for transplantation" as waitlist mortality. Similar trends were still observed when the survival benefit of transplantation shifted to high score ranges in the MELD-Na period (Figure 5*b*). According to this analysis, the survival benefit of LT was definitive in patients with score category of 21–23, which could further validate our proposal to revise Share 15 rule to "Share 21."

The findings of our study might trigger further discussions of liver graft prioritization. According to the Final Rule, the priority rankings shall be ordered from most to least medically urgent.[27] LT in the United States is represented by the OPTN and UNOS liver and intestinal board, which prioritizes transplantation access to the sickest population. The Share 35 rule was designed and implemented in 2013 to fulfill this requirement by sharing liver grafts within a region specifically for patients with very high MELD or MELD-Na scores (≥35). Recently, the OPTN and UNOS liver and intestine board approved of a new enhanced liver distribution system. One criterion in the new liver allocation policy is the following[28]:

> *Additional transplant priority (equivalent to 3 MELD or PELD [Pediatric End-stage Liver Disease] points) will be awarded to liver candidates with a MELD or PELD of* at least 15*, and who are either within the same donor service area as a liver donor or are within 150 nautical miles of the donor hospital but in a different donor service area.*

The Share 15 rule, which was based on the study by Merion et al,[9] has not been reviewed for over a decade but is still maintained in upcoming policy. Our study showed that the MELD-Na based allocation provided significant benefit to hyponatremic patients with a lower MELD score and that survival benefit of LT in patients with MELD-Na score of 15–20 became unclear and questionable in the MELD-Na period. The Final Rule stated, "Allocation policies shall be reviewed periodically and revised as appropriate." We propose a new "Share 21" by raising the cutoff score from 15 to 21 based on our findings. We believe this will eventually promote sicker patient access to transplantation by allocating the liver efficiently.

The effect of the MELD-Na based allocation in patients with exception scores remains to be elucidated. In this study, patients with HCC were excluded because the policy on HCC exception was changed during the study period. Patients with exception scores for other reasons were censored at the time of exception approval, which mirrored the methodology in the study by Merion et al.[9] Of note, some exceptions were approved at the discretion of the regional review board, but not based on the OPTN and UNOS policy.[29] It would be difficult to assess an exact impact of the MELD-Na based allocation in patients with exception scores, because of possible discrepancies of exception practice among UNOS regions. Although the HCC exception policy is nationally based, a decision on approval for exception defers to the regional review board. Although this would be challenging, future studies will be necessary to review exception policies and their possible associations with the MELD and MELD-Na based allocation.

Limitations of this study include the use of the OPTN STAR registry, which is retrospective in nature and lacks detailed clinical information.[30] The follow-up period in the MELD-Na group might be insufficient to draw firm conclusions regarding the impact of the new allocation system on post-transplantation outcomes. To confirm the impact of MELD-Na allocation on post-transplantation outcomes, further investigations need to be conducted over longer follow-up periods. In this study, to minimize a possible bias owing to the discrepancy of follow-up time between these 2 periods, all patients were censored at the end of each period, so that these 2 groups could be compared equally. In addition, we set main end points as 90-day waitlist and 1-year post-transplantation outcomes to decrease bias. We acknowledge that including patients and values from new registrations rather than using prevalent cohorts and longitudinal MELD and MELD-Na score entries might introduce bias in the analysis of entire cohort.

In conclusion, the new liver allocation based on the MELD-Na score successfully decreased waitlist mortality. Hyponatremic patients with low MELD scores received significant benefit from MELD-Na based allocation and the Share 15 rule, whereas the positive impact was less pronounced in patients with higher scores. The survival benefit of LT has shifted toward a higher score category in the MELD-Na period; therefore, liver allocation rules such as Share 15 and Share 35 need to be revised to fulfill the Final Rule under the MELD-Na based allocation.[27]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.07.025.

References

1. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–470.
2. Organ Procurement and Transplantation Network Liver and Intestine Committee. Allocation of livers and liver-intestines. Available at: https://optn.transplant.hrsa.gov/governance/policies/. Effective September 1, 2018. Accessed October 7, 2018.

3. Biggins SW, Kim WR, Terrault NA, et al. Evidence-based incorporation of serum sodium concentration into MELD. Gastroenterology 2006;130:1652–1660.
4. Bernardi M, Gitto S, Biselli M. The MELD score in patients awaiting liver transplant: strengths and weaknesses. J Hepatol 2011;54:1297–1306.
5. Ruf AE, Kremers WK, Chavez LL, et al. Addition of serum sodium into the MELD score predicts waiting list mortality better than MELD alone. Liver Transpl 2005;11:336–343.
6. Kim WR, Biggins SW, Kremers WK, et al. Hyponatremia and mortality among patients on the liver-transplant waiting list. N Engl J Med 2008;359:1018–1026.
7. Feng S, O'Grady J. Share 35: a liver in time saves lives? Am J Transplant 2015;15:581–582.
8. Halazun KJ, Mathur AK, Rana AA, et al. One size does not fit all—regional variation in the impact of the Share 35 Liver Allocation Policy. Am J Transplant 2016;16:137–142.
9. Merion RM, Schaubel DE, Dykstra DM, et al. The survival benefit of liver transplantation. Am J Transplant 2005; 5:307–313.
10. Organ Procurement and Transplantation Network, Revised liver policy regarding HCC exception scores. Available at:, https://optn.transplant.hrsa.gov/news/revised-liver-policy-regarding-hcc-exception-scores/. 2015. Accessed October 7, 2018.
11. Organ Procurement and Transplantation Network. Upcoming MELD serum sodium policy implementation. Available at: https://transplantpro.org/news/li/upcoming-meld-serum-sodium-policy-implementation/. 2015. Accessed October 7, 2018.
12. Merion RM, Wolfe RA, Dykstra DM, et al. Longitudinal assessment of mortality risk among candidates for liver transplantation. Liver Transpl 2003;9:12–18.
13. Fisher RA, Heuman DM, Harper AM, et al. Region 11 MELD Na exception prospective study. Ann Hepatol 2012;11:62–67.
14. Durand CM, Bowring MG, Thomas AG, et al. The drug overdose epidemic and deceased-donor transplantation in the United States: a national registry study. Ann Intern Med 2018;168:702–711.
15. Gonzalez SA, Trotter JF. The rise of the opioid epidemic and hepatitis C-positive organs: a new era in liver transplantation. Hepatology 2018;67:1600–1608.
16. Kalra A, Wedd JP, Biggins SW. Changing prioritization for transplantation: MELD-Na, hepatocellular carcinoma exceptions, and more. Curr Opin Organ Transplant 2016; 21:120–126.
17. Terrault N, Berenguer M, Strasser S, et al. International Liver Transplant Society consensus statement on hepatitis C management in liver transplant recipients. Transplantation 2017;101:956–967.
18. Herzer K, Gerken G. When and how to treat HCV infection with the new antivirals before or after liver transplantation. Visc Med 2016;32:258–262.
19. Flemming JA, Kim WR, Brosgart CL, et al. Reduction in liver transplant wait-listing in the era of direct-acting antiviral therapy. Hepatology 2017;65:804–812.
20. Massie AB, Chow EK, Wickliffe CE, et al. Early changes in liver distribution following implementation of Share 35. Am J Transplant 2015;15:659–667.
21. Murken DR, Peng AW, Aufhauser DD Jr, et al. Same policy, different impact: center-level effects of share 35 liver allocation. Liver Transpl 2017;23:741–750.
22. Sharma P, Schaubel DE, Goodrich NP, et al. Serum sodium and survival benefit of liver transplantation. Liver Transpl 2015;21:308–313.
23. Nadim MK, DiNorcia J, Ji L, et al. Inequity in organ allocation for patients awaiting liver transplantation: Rationale for uncapping the model for end-stage liver disease. J Hepatol 2017;67:517–525.
24. Orman ES, Ghabril M, Chalasani N. Poor performance status is associated with increased mortality in patients with cirrhosis. Clin Gastroenterol Hepatol 2016; 14:1189–1195 e1.
25. Ruebner R, Goldberg D, Abt PL, et al. Risk of end-stage renal disease among liver transplant recipients with pretransplant renal dysfunction. Am J Transplant 2012; 12:2958–2965.
26. Halazun KJ, Rana AA, Fortune B, et al. No country for old livers? Examining and optimizing the utilization of elderly liver grafts. Am J Transplant 2018;18:669–678.
27. Organ Procurement and Transplantation Network. Final rule. Available at: https://optn.transplant.hrsa.gov/governance/about-the-optn/final-rule/. 2000. Accessed October 7, 2018.
28. Organ Procurement and Transplantation Network. Board approves enhanced liver distribution system. Available at: https://optn.transplant.hrsa.gov/news/board-approves-enhanced-liver-distribution-system/. 2018. Accessed October 7, 2018.
29. Organ Procurement and Transplantation Network. Liver and Intestine Committee, guidance on MELD PELD exception review. Available at: https://optn.transplant.hrsa.gov/resources/by-organ/liver-intestine/guidance-on-meld-peld-exception-review/. 2015. Accessed October 7, 2018.
30. Massie AB, Kucirka LM, Segev DL. Big data in organ transplantation: registries and administrative claims. Am J Transplant 2014;14:1723–1730.

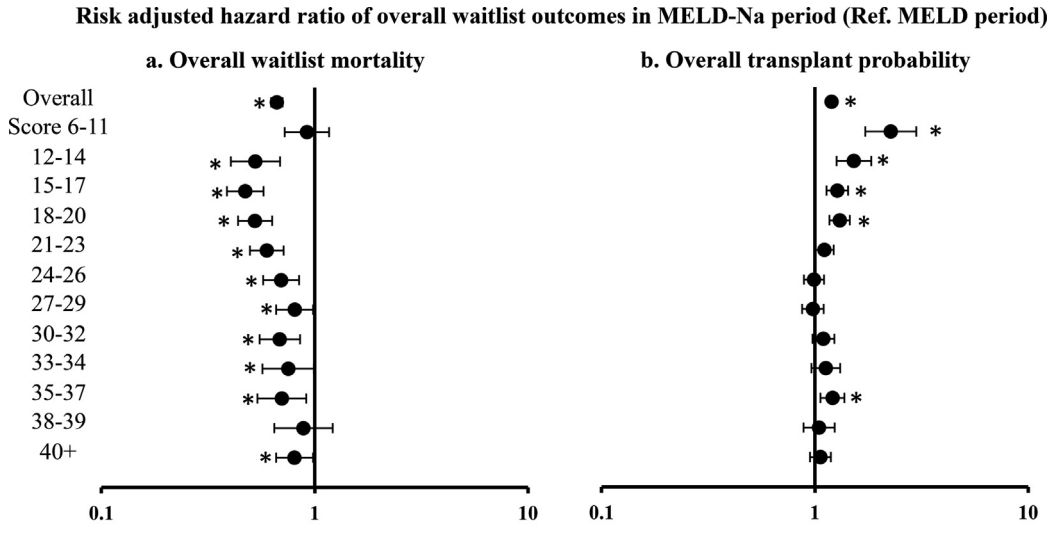
Received February 2, 2018. Accepted July 20, 2018.

Reprint requests
Address requests for reprints to: Shunji Nagai, MD, PhD, Transplant and Hepatobiliary Surgery, Henry Ford Hospital, 2799 W Grand Boulevard, CFP-2, Detroit, MI 48202. e-mail: snagai1@hfhs.org.

Acknowledgements
The data reported here have been supplied by the UNOS as the contractor for the OPTN. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the OPTN or the U.S. Government.

Author contributions
Shunji Nagai, Lucy C. Chau, Dilip Moonka, Mohamed Safwan, Atsushi Yoshida, and Marwan S. Abouljoud conceived and designed the study. Shunji Nagai, Lucy C. Chau, Mohamed Safwan, Randolph E. Schilke, Kelly Collins, and Michael Rizzari acquired and interpreted the data. Shunji Nagai, Lucy C. Chau, Mohamed Safwan, Randolph E. Schilke, and Dilip Moonka drafted the manuscript. Kelly Collins, Michael Rizzari, Atsushi Yoshida, and Marwan S. Abouljoud critically reviewed the manuscript. Shunji Nagai, Lucy C. Chau, and Randloph E. Schilke performed statistical analysis. Dilip Moonka, Atsushi Yoshida, and Marwan S. Abouljoud supervised the study.

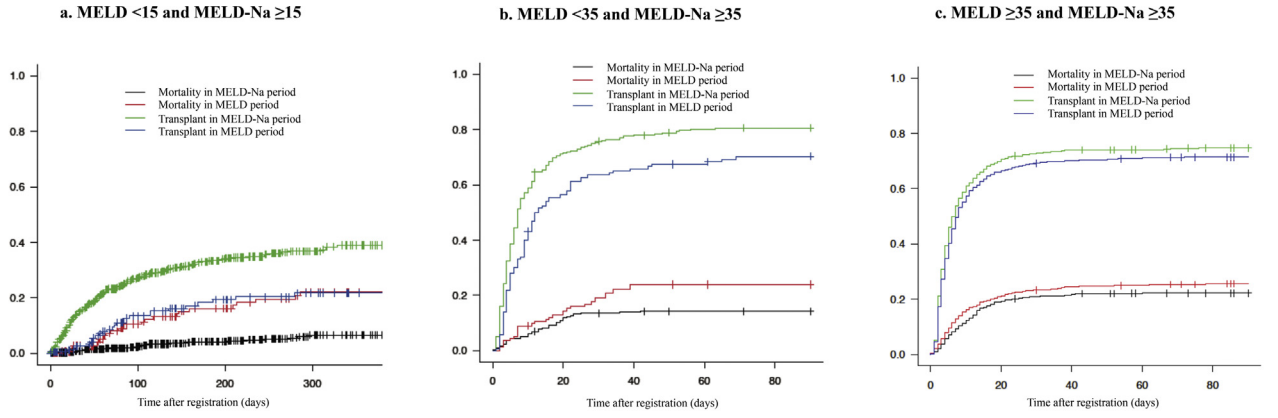
Conflicts of interest
The authors disclose no conflicts.



	HR	Lower	Upper	P value
Overall	0.665	0.625	0.708	<0.001
6-11	0.919	0.724	1.168	0.490
12-14	0.527	0.404	0.689	<0.001
15-17	0.473	0.388	0.576	<0.001
18-20	0.525	0.437	0.632	<0.001
21-23	0.595	0.496	0.715	<0.001
24-26	0.696	0.574	0.845	<0.001
27-29	0.806	0.659	0.984	0.035
30-32	0.686	0.551	0.854	<0.001
33-34	0.751	0.570	0.990	0.043
35-37	0.702	0.539	0.914	0.009
38-39	0.886	0.646	1.214	0.45
40+	0.803	0.658	0.982	0.032

	HR	Lower	Upper	P value
Overall	1.197	1.146	1.250	<0.001
6-11	2.268	1.721	2.988	<0.001
12-14	1.524	1.265	1.837	<0.001
15-17	1.274	1.133	1.432	<0.001
18-20	1.307	1.171	1.458	<0.001
21-23	1.106	0.998	1.227	0.055
24-26	0.990	0.888	1.104	0.860
27-29	0.978	0.870	1.100	0.710
30-32	1.096	0.974	1.234	0.130
33-34	1.125	0.962	1.315	0.140
35-37	1.209	1.063	1.375	0.004
38-39	1.047	0.886	1.238	0.590
40+	1.062	0.948	1.189	0.300

Supplementary Figure 1. Comparison of waitlist and post-transplantation outcomes between MELD and MELD-Na periods (reference, MELD period; *$P < .05$). (*a*) HR for overall waitlist mortality in MELD-Na period according to score categories. (*b*) HR for overall transplantation probability in MELD-Na period according to score categories.



No. at risk	At registration	100 days	200 days	300 days
MELD	181	89	60	42
MELD-Na	714	344	204	118

No. at risk	At registration	20 days	40 days	60 days	80 days
MELD	137	39	13	10	6
MELD-Na	281	48	22	13	11

No. at risk	At registration	20 days	40 days	60 days	80 days
MELD	2122	258	100	67	50
MELD-Na	1342	131	100	32	23

Mortality (%)	90 days	180 days	1 year	
MELD period	10.6	16.2	22.1	P <0.001 (Gray test)
MELD-Na period	1.9	4.2	6.5	
Transplant (%)	90 days	180 days	1 year	
MELD period	12.7	18.3	21.7	P <0.001 (Gray test)
MELD-Na period	26.1	33.1	39.0	

Mortality (%)	30 days	60 days	90 days	
MELD period	19.2	23.9	23.9	P =0.023 (Gray test)
MELD-Na period	13.5	14.3	14.3	
Transplant (%)	30 days	60 days	90 days	
MELD period	63.5	67.4	70.2	P =0.002 (Gray test)
MELD-Na period	75.6	80.1	80.5	

Mortality (%)	30 days	60 days	90 days	
MELD period	23.3	25.0	25.7	P =0.019 (Gray test)
MELD-Na period	21.0	22.2	22.2	
Transplant (%)	30 days	60 days	90 days	
MELD period	69.2	71.2	71.4	P =0.006 (Gray test)
MELD-Na period	72.8	74.1	74.7	

Supplementary Figure 2. Comparison of cumulative incidence of transplantation and waitlist mortality. (*a*) Patients whose initial and final MELD score was lower than 15 but whose MELD-Na score was at least 15. (*b*) Patients whose initial MELD score was lower than 35 but whose MELD-Na score was at least 35. (*c*) Patients with initial MELD and MELD-Na scores of at least 35.

Supplementary Table 1. Summary of Study Design and Methodologies

	End points	Events	Statistical methods	Patient cohort
Waitlist outcome analysis	90-d mortality and transplantation probability	Transplantation	Fine-Gray regression multivariable model	All patients on waitlist who met inclusion criteria (waitlisted patients)
	Overall mortality and transplantation probability	Waitlist mortality	Figures 2 and 4: 90-d outcomes	
		Death + removal because too sick for transplantation	Supplementary Figure 1: overall outcomes	
		Waitlist removal for other reason(s)		
			Validation analysis by propensity score matching model: Gray test and Fine-Gray regression model (Figure 3)	Propensity score matched waitlisted patient groups
Post-transplantation outcome analysis	1-y liver graft survival	Post-transplant liver graft loss	Cox regression multivariable model (Figure 2)	All transplanted patients
	1-y patient survival	Post-transplantation patient death		
Survival benefit analysis	Overall waitlist mortality	Waitlist mortality	Comparison of "death per 1000 patient-years" between waitlist and transplantation groups	Waitlisted patients and transplant recipients
	1-y post-transplantation mortality	Death only	Figure 5*a*: waitlist mortality defined as death only[a]	
		Death + removal because too sick for transplantation	Figure 5*b*: waitlist mortality defined as death + removal because too sick for transplantation	
		Post-transplantation death		

[a]Mirrors methodology in the study by Merion et al.[9]

Supplementary Table 2. Comparison of Waitlist Patient Characteristics Between Periods, Within Subcategories Defined by Each Patient's Calculated MELD and MELD-Na Scores[a]

	MELD < 15 + MELD-Na ≥ 15			MELD < 35 + MELD-Na ≥ 35			MELD + MELD-Na ≥ 35		
	MELD period (n = 181)	MELD-Na period (n = 714)	*P* value	MELD period (n = 137)	MELD-Na period (n = 281)	*P* value	MELD period (n = 2,122)	MELD-Na period (n = 1,342)	*P* value
Age at listing (*y*)	58 [52–63]	58 [50–63]	.552	55 [48–61]	53 [44–60]	.033	54 [45–60]	53 [45–60]	.268
Men	128 (70.7)	488 (62.7)	.046	89 (65.0)	179 (63.7)	.829	1298 (61.2)	816 (60.8)	.83
Race									
White	142 (78.5)	556 (77.9)		108 (78.8)	200 (71.2)		1342 (63.2)	863 (64.3)	
Black	4 (2.2)	27 (3.8)		10 (7.3)	20 (7.1)		2828 (13.3)	130 (9.7)	
Hispanic	29 (16.0)	107 (15.0)	.889	13 (9.5)	50 (17.8)	.286	380 (17.9)	268 (20.0)	.012
Asian	4 (2.2)	17 (2.4)		4 (2.9)	7 (2.5)		87 (4.1)	53 (3.9)	
Others	2 (1.1)	7 (1.0)		2 (1.5)	4 (1.4)		31 (1.5)	28 (2.1)	
Primary diagnosis									
HCV	39 (21.5)	92 (12.9)	<.001	32 (23.4)	35 (12.5)	.031	418 (19.7)	122 (9.1)	<.001
Nonalcoholic steatohepatitis	40 (22.1)	176 (24.6)		14 (10.2)	40 (14.2)		244 (11.5)	190 (14.2)	
Alcohol	62 (34.3)	266 (37.3)		59 (43.1)	142 (50.5)		818 (38.5)	636 (47.4)	
Other	40 (22.1)	180 (25.2)		32 (23.4)	64 (22.8)		642 (30.3)	394 (29.4)	
Body mass index	27.9 [24.8–31.4]	27.4 [24.4–31.0]	.667	28.6 [24.3–32.8]	28.2 [24.1–32.5]	.783	29.0 [24.7–33.9]	29.0 [25.0–34.3]	.522
Actual score at listing[b]	13 [13–14]	17 [16–18]	<.001	34 [33–34]	35 [35–36]	<.001	39 [37–42]	39 [37–42]	.014
MELD score at listing	13 [13–14]	13 [12–14]	.009	34 [33–34]	34.1 [33.3–34.5]	<.001	39 [37–42]	39 [37–42.7]	.28
MELD-Na score at listing	17 [16–19]	17 [16–18]	.07	35.4 [35.1–35.6]	35 [35–36]	<.001	39.2 [37.2–42]	39 [37–42]	.338
Sodium at listing (*mmol/L*)	135 [131–136]	134 [132–136]	.912	128 [124–131]	130 [127–135]	<.001	136 [133–139]	137 [133–140]	.021
Karnofsky score < 30% at listing	3 (1.7)	5 (0.7)	.214	46 (34.1)	111 (40.2)	.237	1283 (61.6)	826 (62.6)	.562
Dialysis at listing	0 (0)	0 (0)	—	24 (17.5)	56 (19.9)	.598	984 (46.4)	654 (48.7)	.184
Life support at listing	0 (0)	1 (0.1)	>.9	9 (6.6)	18 (6.5)	>.9	483 (22.8)	300 (22.5)	.9
Waitlist status after 90 d									
Transplantation	14 (7.7)	162 (22.7)		92 (67.2)	221 (78.6)		1482 (69.8)	963 (71.8)	
Death or removal because too sick	17 (9.4)	12 (1.7)	<.001	31 (22.6)	39 (13.9)	.034	524 (24.7)	279 (20.8)	.003
Censored or other	150 (82.9)	540 (75.6)		14 (10.2)	21 (7.5)		116 (5.5)	101 (7.5)	
Total time on waiting list (*d*)	91 [30–283]	94 [29–229]	.372	9 [4–21]	7 [3–15]	.003	5 [3–11]	5 [3–11]	.075
Follow-up time to 90 d (*d*)	90 [30–90]	90 [29–90]	.799	9 [4–21]	7 [3–15]	.003	5 [3–11]	5 [3–11]	.075
Waiting time to transplantation (*d*)[c]	73 [49–125]	39 [17–84]	.002	9 [4–15]	6 [3–11]	.012	5 [3–8]	4 [2–8]	.007

[a]Data were summarized using median [interquartile range] for continuous variables and number (percentage) for discrete variables.
[b]MELD score in MELD period and MELD-Na score in MELD-Na period.
[c]In patients who received deceased donor liver transplant (excluding patients with an exception score).