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ORIGINAL ARTICLE

Factors That Affect Deceased Donor Liver Transplantation Rates in the United States in Addition to the Model for End-Stage Liver Disease Score

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Under an ideal implementation of Model for End-Stage Liver Disease (MELD)–based liver allocation, the only factors that would predict deceased donor liver transplantation (DDLT) rates would be the MELD score, blood type, and donation service area (DSA). We aimed to determine whether additional factors are associated with DDLT rates in actual practice. Data from the Scientific Registry of Transplant Recipients for all adult candidates wait-listed between March 1, 2002 and December 31, 2008 (n = 57,503) were analyzed. Status 1 candidates were excluded. Cox regression was used to model covariate-adjusted DDLT rates, which were stratified by the DSA, blood type, liver-intestine policy, and allocation MELD score. Inactive time on the wait list was not modeled, so the computed DDLT hazard ratios (HRs) were interpreted as active wait-list candidates. Many factors, including the candidate's age, sex, diagnosis, hospitalization status, and height, prior DDLT, and combined listing for liver-kidney or liver-intestine transplantation, were significantly associated with DDLT rates. Factors associated with significantly lower covariate-adjusted DDLT rates were a higher serum creatinine level (HR = 0.92, $P < 0.001$), a higher bilirubin level (HR = 0.99, $P = 0.001$), and the receipt of dialysis (HR = 0.83, $P < 0.001$). Mild ascites (HR = 1.15, $P < 0.001$) and hepatic encephalopathy (grade 1 or 2, HR = 1.05, $P = 0.02$; grade 3 or 4, HR = 1.10, $P = 0.01$) were associated with significantly higher adjusted DDLT rates. In conclusion, adjusted DDLT rates for actively listed candidates are affected by many factors aside from those integral to the allocation system; these factors include the components of the MELD score itself as well as candidate factors that were considered but were deliberately omitted from the MELD score in order to keep it objective. These results raise the question whether additional candidate characteristics should be explicitly incorporated into the prioritization of wait-list candidates because such factors are already systematically affecting DDLT rates under the current allocation system. ***Liver Transpl 18:1456-1463, 2012.*** © **2012 AASLD.**

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The Model for End-Stage Liver Disease (MELD) score is the unit of allocation and the donation service area (DSA) is the unit of distribution for deceased donor livers among candidates with chronic liver disease who are listed for deceased donor liver transplantation (DDLT) in the United States.[1]

The MELD score was adopted in February 2002 as the basis for prioritizing candidates with end-stage liver disease awaiting DDLT. The intention was to reduce wait-list mortality through the offering of DDLT according to the severity of liver disease, the minimization of geographic disparities, and the de-

Abbreviations: DDLT, deceased donor liver transplantation; DSA, donation service area; HCC, hepatocellular carcinoma; HR, hazard ratio; ICU, intensive care unit; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; SRTR, Scientific Registry of Transplant Recipients; SSDMF, Social Security Death Master File; TCR, transplant candidate registration; TRR, transplant recipient registration.

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This study was approved by the Scientific Registry of Transplant Recipients project officer of the Health Resources and Services Administration. The Health Resources and Services Administration has determined that this study satisfies the criteria for an institutional review board exemption described in the public benefit or service program provisions of 45 CFR 46.101(b)(5) and in Health Resources and Services Administration circular 03.

emphasis of waiting times.[2,3] The MELD score is a well-validated measure of the wait-list mortality risk (ie, the severity of liver disease).[4,5] In contrast to the Child-Turcotte-Pugh score, which includes 2 subjective components (ascites and hepatic encephalopathy), the MELD score is calculated quantitatively with laboratory values: the total bilirubin level, the international normalized ratio (INR) of the prothrombin time, and the serum creatinine level.[5] Candidates are offered deceased donor livers only if they are listed as active on the wait list.

A DSA is a distinct, nonoverlapping geographic area served by 1 of the 58 federally certified organ procurement organizations. DSAs may include 1 or more transplant programs for a given organ and 1 or more donor hospitals. DSAs are currently the primary units of distribution for deceased donor livers to candidates with chronic liver disease.

In a frictionless system, the DSA, an active status, and the MELD score would be the only factors predicting DDLT rates for blood group types. However, recent studies have shown that female sex is associated with a lower DDLT.[6-9] Hispanics have an 8% lower DDLT rate in comparison with whites, and Asians with MELD scores of 30 to 40 have a 46% lower DDLT rate than whites with comparable disease severity.[8-10] The objective of the current study was to identify other candidate factors that influence DDLT rates for wait-listed candidates in the United States.

PATIENTS AND METHODS

Patient Population and Cohort

This study was based on data obtained from the Scientific Registry of Transplant Recipients (SRTR) and the Social Security Death Master File (SSDMF).[11] The SRTR maintains a database of all candidates for and recipients of solid organ transplants in the United States. Candidates on waiting lists for organ transplantation and candidates who receive organ transplants are tracked on a periodic basis with the use of data collection forms completed by organ transplant programs and submitted to the Organ Procurement and Transplantation Network. The SRTR database has a uniform structure based on mandatory transplant candidate registration (TCR) information provided by the transplant program at the time of placement on the wait list (through a TCR form). Online status updates are required for MELD scores and other clinical measures while a candidate is wait-listed, and information is provided by the transplant program at the time of DDLT [through transplant recipient registration (TRR)]. Transplant follow-up information is required 6 months after transplantation, 1 year after transplantation, and yearly thereafter (through a transplant follow-up form). These data, in addition to data from the Organ Procurement and Transplantation Network regarding candidates on the waiting list and the allocation of organs, are included in the SRTR database.

The SRTR supplements information on vital status with data on deaths from the SSDMF. Data collection by the SRTR is exempt from oversight under the public benefit or service program provisions of the Code of Federal Regulations (45 CFR 46.101[b][5]), as approved by the institutional review board of the Health Resources and Services Administration of the Department of Health and Human Services. The SSDMF includes updated information on all participants in the Social Security system. Information on deaths reported to the Social Security system for the administration of the death, disability, and retirement benefit programs is kept in the SSDMF database.

The study population included all candidates $\geq$ 18 years old who were listed for DDLT between March 1, 2002 and December 31, 2008 (n = 57,503). Status 1 candidates were excluded. Data on each candidate were collected from TCR and TRR forms as well as status update files. Data from the SSDMF were used to ascertain deaths while patients were on the waiting list or after their removal.

Statistical Approach

For descriptive analyses, continuous variables were expressed as medians and interquartile ranges; categorical variables were expressed as percentages. Ascites was reported as none, mild, or moderate to severe; hepatic encephalopathy was reported as none, grade 1 or 2, or grade 3 or 4 on the TCR form and was updated on the TRR form for each candidate. The wait-list data for all variables was complete except for hospitalization status (6% missing data) and serum sodium (38% missing data). The mandatory submission of serum sodium data along with MELD covariates went into effect on November 1, 2004.

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Candidates listed and undergoing transplantation before November 1, 2004 accounted for the missing serum sodium data.

The primary outcome of interest was the receipt of DDLT. Unadjusted DDLT rates were calculated through the division of the number of DDLT procedures by the aggregate patient-years at risk (active on the waiting list), and they were expressed as transplants per 1000 patient-years. For each candidate, the time at risk began on the date of wait listing and ended at the earliest of the following: the receipt of DDLT, the end of the study's observation period (December 31, 2008), the granting of an exception score, or death. Because dead candidates cannot undergo DDLT, pertinent follow-up for such candidates ceased at the time of death. Our primary objective was to model DDLT rates, and candidates can undergo DDLT only while they are listed as active; therefore, only the active wait-list time was modeled, so the covariate-adjusted DDLT hazard ratios (HRs) were interpreted as being for active wait-list candidates, all other factors being equal.

The regression modeling was split into separate stages, each requiring different Cox models. First, to delineate the effects of candidate factors on DDLT rates at a given MELD score, in a given DSA, and among active candidates, we fitted a time-dependent Cox regression model of covariate-adjusted DDLT rates. This model was stratified by the DSA, blood type, liver-intestine policy, and allocation MELD score, with the latter two coded as time-dependent covariates. The allocation MELD score refers to the MELD score at which an actively listed candidate is allocated a deceased donor liver. Starting in March 2005, the liver-intestine policy refers to the additional 10 points given to candidates on both the liver and intestine wait lists.[1] The model included terms for serum creatinine, bilirubin, dialysis, and serum sodium; a candidate's age, sex, race/ethnicity, diagnosis, height, weight, and history of diabetes; ascites; hepatic encephalopathy; hospitalization status; albumin; listing for combined liver-kidney transplantation and listing for combined liver-intestine transplantation; and a history of previous DDLT. The model also included interactions between age and hospitalization status, female sex and height, female sex and creatinine, and creatinine and height.

Second, to quantify the effects of the MELD score on DDLT rates, we fitted a separate covariate-adjusted, time-dependent Cox regression model stratified by the DSA, blood type, and liver-intestine policy. Instead of stratification by the MELD score, the MELD score was included in the model as a set of categorical covariates (1 per MELD score).[12] The goal of this model was to assess the degree to which DDLT rates are monotone with respect to the MELD score.

The third Cox regression model was stratified by the individual MELD score (ie, in addition to the DSA, blood type, and intestine listing policy). Because the model was stratified by the MELD score, we could not directly estimate its effect on DDLT rates. However, the purpose of this component of the analysis was to estimate the impact of the remaining covariates. After fitting this third model, we calculated each candidate's HR with the model covariates (which excluded those for which adjustments were made through stratification). We then divided each candidate-specific HR by its respective MELD score–specific mean so that the scaled candidate-specific HRs would average to 1 within each MELD score. We then examined box-whisker plots for each MELD score. The variability within each MELD score–specific distribution of HRs reflected the systematic heterogeneity in DDLT rates (due to the impact of age, sex, race/ethnicity, diagnosis, height, weight, a history of diabetes, ascites, encephalopathy, diabetes, hospitalization status, serum sodium, albumin, combined liver-kidney listing, combined liver-intestine listing, and a history of previous DDLT). The results were interpreted as being for candidates with the same MELD score and were adjusted for the DSA, blood type, and liver-intestine policy.

TABLE 1. Baseline Characteristics of the Cohort at Listing (n = 57,503)

Variable	Value
Age (years)*	53 (48-59)
Sex (%)	
Males	66
Females	34
Race (%)	
White	72
Hispanic	14
Black	8
Asian	5
Other	1
Hepatitis C (%)	33
HCC (%)	17
Weight (kg)*	82 (70-95)
Height (cm)*	173 (165-180)
Serum creatinine (mg/dL)*	1.0 (0.8-1.3)
Dialysis (%)	4
Serum bilirubin (mg/dL)*	2.2 (1.3-4.4)
INR*	1.4 (1.2-1.6)
Serum sodium $\leq$ 131 mmol/L (%)	9
Ascites (%)	78
Hepatic encephalopathy (%)	
None	38
Grade 1 or 2	57
Grade 3 or 4	5
Previous liver transplantation (%)	6
Hospitalization in ICU (%)	4
Hospitalization not in ICU (%)	10
Blood type (%)	
A	38
AB	4
B	12
O	46
Combined liver-intestine listing (%)	0.5
Combined liver-kidney listing (%)	6

*The data are presented as medians and interquartile ranges.

TABLE 2. Candidate Factors Significantly Associated With DDLT Rates

Factors Associated With Higher Rates	HR	*P* Value	Median or % for Transplant Patients
Age at liver transplantation (per 5-year increase)	1.02	0.001	53 years
Height (per 10-cm increase)	1.03	0.005	173 cm
Hepatitis C (versus all others)	1.07	<0.001	39%
HCC (versus all others)	1.26	<0.001	5%
Grade 1 or 2 hepatic encephalopathy (versus none)	1.05	0.02	64%
Grade 3 or 4 hepatic encephalopathy (versus none)	1.10	0.01	12%
Mild ascites (versus none)*	1.15	<0.001	54%
Hospitalization (versus no hospitalization)			
In ICU	1.19	<0.001	6%
Not in ICU	1.15	<0.001	16%
Combined liver-intestine listing	1.79	<0.001	0.7%
Combined liver-kidney listing	1.90	<0.001	9%
Factors Associated With Lower Rates	**HR**	***P* Value**	**Median or % for Transplant Patients**
Female (versus male)	0.83	<0.001	32%
Serum creatinine (per 1 mg/dL increase)	0.92	<0.001	1.3 mg/dL
Dialysis (versus no dialysis)	0.83	<0.001	11%
Bilirubin (per 1 mg/dL increase)	0.996	0.001	5.1 mg/dL
History of previous liver transplantation (versus none)	0.69	<0.001	8%

*Moderate to severe ascites was not significant.

All statistical analyses were conducted with SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics of the Cohort at Listing

The characteristics of the 57,503 candidates at listing are shown in Table 1. The median age of the cohort was 53 years; 66% were male; and 72% were Caucasian, 8% were African American, 14% were Hispanic, 5% were Asian American, and less than 1% were of another race or ethnicity. Twenty-two percent of the candidates did not have ascites, 53% had mild ascites, and 25% had moderate to severe ascites at listing. Sixty-two percent had hepatic encephalopathy; 5% had grade 3 or 4 hepatic encephalopathy. The median serum bilirubin, serum creatinine, INR, and serum sodium levels were 2.2 mg/dL, 1.0 mg/dL, 1.4, and 137 mmol/L, respectively. At listing, 4% of the candidates were on dialysis, and 9% had serum sodium levels $\leq$ 131 mmol/L.

Unadjusted DDLT Rates Among Active Candidates

During the study period, there were 57,503 active wait-list candidates, and DDLT was performed 21,730 times. The characteristics of the DDLT recipients are listed in Table 2. The median time to DDLT for recipients was 67 days. The overall unadjusted DDLT incidence rate was 415 transplants per 1000 patient-years.

Factors Other Than the MELD Score, DSA, and Blood Type Associated With Significantly Higher or Lower DDLT Rates

The top half of Table 2 shows the main effects associated with higher DDLT rates. Every 5-year increase in the candidate's age was associated with a 2% higher DDLT rate. Candidate characteristics such as hepatitis C, hepatocellular carcinoma (HCC), hepatic encephalopathy, and mild ascites were independently associated with significantly higher DDLT rates. Candidates who were hospitalized [whether in the intensive care unit (ICU) or not] had a higher DDLT rate than nonhospitalized candidates. Each 10-cm increase in height was associated with a 3% higher DDLT rate (HR = 1.03, P = 0.005). Listing for combined liver-kidney transplantation and combined liver-intestine transplantation was associated with 79% and 90% higher DDLT rates, respectively.

Candidate factors associated with lower DDLT rates are shown in the bottom half of Table 2. DDLT rates were 17% lower for females versus males. Prior DDLT

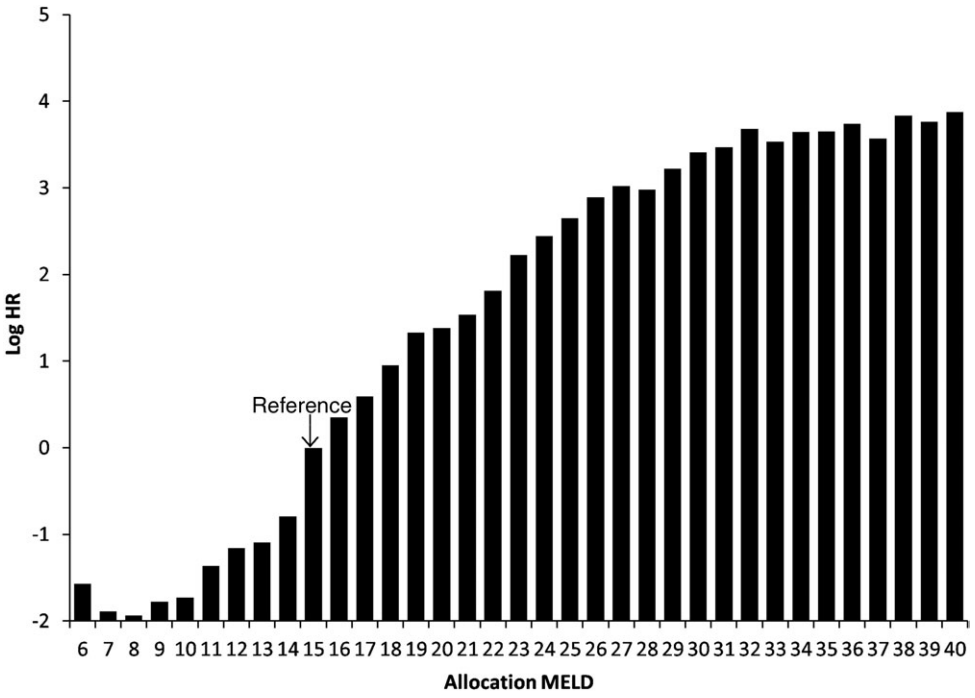

Figure 1. Effect of the allocation MELD score (per single level change) on the DDLT rate. MELD score–specific HRs were estimated with a model stratified by the DSA, blood type, and intestine listing policy. Each score was compared to the reference MELD score of 15 (HR = 1).

and higher bilirubin levels were also associated with significantly lower DDLT rates. Each unit increase in serum creatinine and the receipt of dialysis were associated with 8% and 17% lower DDLT rates, respectively.

In a supplementary analysis, the interaction between height and creatinine was also found to be significant (HR = 1.001, $P = 0.03$). This suggested that the DDLT rate was lower for shorter candidates than taller candidates at a given creatinine level and at a given MELD score. Interactions between age and hospitalization in the ICU ($P = 0.23$), between age and hospitalization not in the ICU ($P = 0.78$), between female sex and creatinine ($P = 0.90$), and between female sex and height ($P = 0.23$) were not significant. Race/ethnicity did not affect the DDLT rates.

Association of the MELD Score and Other Factors With DDLT Rates

Figure 1 depicts the effect of the MELD score (ie, the current allocation MELD score) on DDLT rates. The MELD score was used as a time-dependent covariate such that the fitted model incorporated changes in each candidate's MELD score during the follow-up period. A MELD score of 15 served as the reference score and hence had an HR set equal to 1 (log HR = 0). As expected, higher MELD scores tended to be associated with higher covariate-adjusted DDLT rates. Figure 1 confirms that the DDLT rates increased strongly with increasing MELD scores, as would be expected. However, certain traits of this plot are noteworthy. First, candidates with a MELD score of 6 had a higher transplant rate than candidates with a MELD score of 7, 8, 9, or 10. In fact, DDLT rates actually decreased across the MELD score range of 6 to 8. Between a MELD score of 9 and a MELD score of 27, the DDLT rates increased nearly monotonically, as expected, and this continued up to a MELD score of 32. Although the DDLT rate was highest for candidates with a MELD score of 40, the DDLT rates were fairly similar for patients with MELD scores of 32 to 40. Figure 2 shows the variability in DDLT rates within each given allocation MELD score, with adjustments for the DSA, blood type, and liver-intestine policy. For each MELD score, the box represents the 75th and 25th percentiles, and the whiskers denote the 95th and 5th percentiles. The horizontal line within each box denotes the median, which was very close to 1 in each case; this was a result of scaling the HRs within each MELD score to have a mean of 1.0. Approximately 50% of the distribution of HRs was within the 0.9 to 1.1 interval, and this meant that at a given MELD score, half of the candidates were within 10% of the average predicted DDLT rate. However, an examination of the whiskers revealed that at most MELD scores, approximately 10% of the candidates were $\geq$30% away from the MELD score–specific average (ie, the HR was either < 0.7 or > 1.3).

A re-examination of Fig. 2 shows that if the MELD score were actually the only factor (other than the DSA, blood type, and liver-intestine policy) to affect DDLT rates, there would be no distribution of HRs; at a given MELD score, each candidate would have the same predicted DDLT rate, which after scaling would equal 1. The whiskers for each MELD score–specific distribution of HRs reflects the systematic heterogeneity in DDLT rates (due to the impact of age, sex, diagnosis, height, weight, a history of diabetes, ascites, encephalopathy, diabetes, hospitalization status, serum sodium, albumin, interaction between height and creatinine, listing for combined liver-kidney

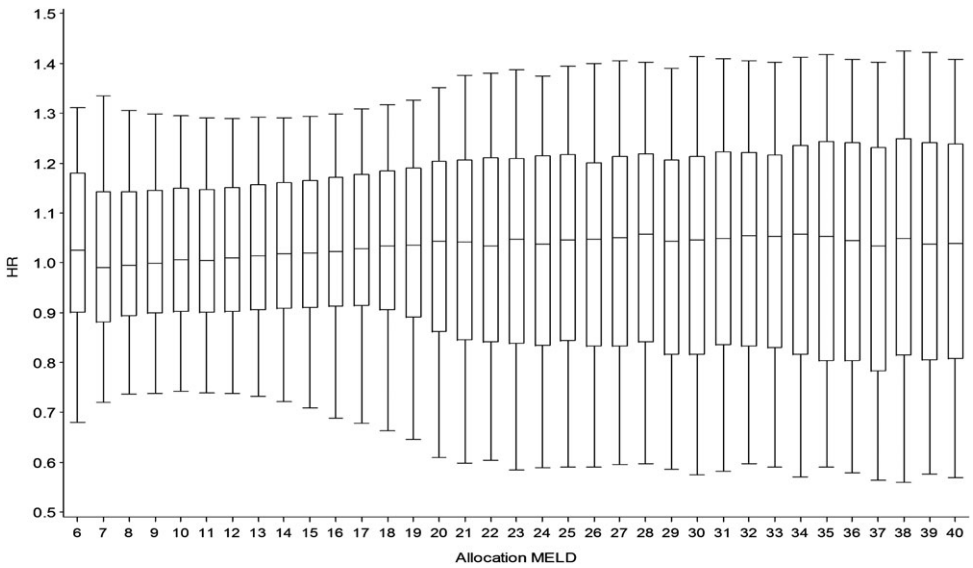

Figure 2. MELD score–specific box-whisker plots of DDLT HRs. The HRs were estimated with a model stratified by the MELD score, DSA, blood type, and intestine listing policy. Candidate-specific HRs were estimated with all remaining covariates and were scaled by their MELD score–specific means so that they averaged to 1. For each MELD score, the box represents the 75th and 25th percentiles, whereas the whiskers denote the 95th and 5th percentiles. The line in the middle of each box denotes the median, which tends to be very close to 1 because the HRs within each MELD score were scaled so that they averaged to 1. If the MELD score were the only factor (other than the DSA, blood type, and liver-intestine policy) to affect DDLT rates, there would be no distribution of HRs; with a given MELD score, each candidate would have the same predicted DDLT rate, which would equal 1 after scaling. The whiskers for each MELD score–specific distribution of HRs reflect the systematic heterogeneity in DDLT rates due to various candidate factors.

transplantation, listing for combined liver-intestine transplantation, and a history of previous DDLT). The variation in Fig. 2 reveals, for example, that candidates may have a predicted DDLT rate that is 30% greater or 30% less than their respective MELD score–specific average because of the combination of their adjustment covariate profile, as described previously (ie, age, sex, diagnosis, height, weight, a history of diabetes, ascites, encephalopathy, hospitalization status, serum sodium, albumin, listing for combined liver-kidney transplantation, listing for combined liver-intestine transplantation, and a history of previous DDLT).

DISCUSSION

Our study has identified the important candidate factors—poor renal function, dialysis, poor liver function, and a history of previous liver transplantation—that negatively affect DDLT rates in actual clinical practice for wait-listed candidates. We have also validated a previously identified factor, female sex, as an important determinant of DDLT rates. In addition, our study has found that some new candidate factors such as age, height, hospitalization status, hepatitis C, HCC, complications of portal hypertension such as hepatic encephalopathy and mild ascites, listing for combined liver-kidney transplantation, and listing for combined liver-intestine transplantation are associated with high DDLT rates.

The acceptance of an organ and the actual receipt of each DDLT offer constitute a complex process. It involves collective decision making that depends on many measured and unmeasured candidate- and donor-related factors, which include but are not limited to the candidate's clinical condition at the time of the offer, donor availability, donor type, donor-recipient size matching, and so forth. It is plausible that physician judgment, donor factors, and unmeasured candidate factors resulted in higher DDLT rates for those listed for combined liver-kidney transplantation or combined liver-intestine transplantation, and hospitalized candidates had higher DDLT rates despite stratification by the allocation MELD score.

Although the allocation MELD score (urgency) was still the major determinant of DDLT rates in the United States, there was a great deal of variation in the distribution of DDLT rates at a given MELD score. This variation reflects the significant contribution of additional candidate factors that result in the actual acceptance of an offer and receipt of DDLT and is consistent with physician judgment. We found that DDLT rates did not increase monotonically with the allocation MELD score after adjustments for the DSA, blood type, and intestine policy. There was a steady increase in the DDLT rates from a MELD score of 15 to a MELD score of 32. However, there appeared to be little increase in DDLT rates from a MELD score of 32 to a MELD score of 40, even though the risk of wait-list death has previously been shown to increase dramatically across this range.

Our study showed that high serum creatinine levels and the receipt of dialysis (components of the MELD score) were associated with lower DDLT rates in the MELD era. We have previously demonstrated that at a given MELD score, every unit increase in serum

creatinine is associated with lower wait-list mortality. The association of lower DDLT rates with high creatinine levels at a given MELD score in the current study demonstrates the evidence-based clinical practice of allocating scarce resources to the sickest first. However, the negative effect of creatinine on DDLT rates was ameliorated by the increase in height. Candidates on dialysis at the time of transplantation overall have a significant but lower survival benefit from DDLT in comparison with their counterparts not on dialysis at a given MELD score.[9,13] This perception of a lower but significant survival benefit associated with dialysis at a given MELD score may affect clinical practice and result in lower DDLT rates for such candidates.

The current study confirms the association of lower DDLT rates with female sex.[6,7,9,10,17] It has been speculated that lower DDLT rates among females versus males could be due to lower creatinine levels (a MELD covariate) and/or recipient size mismatching. To tease out why females had lower DDLT rates, we looked at the interactions between female sex and creatinine and between female sex and height; however, neither of these interactions was significant, and this suggests that the lower DDLT rates among females at a given MELD score are not affected by creatinine or height.

Even though the time at risk ended with the granting of an exception MELD score, candidates with HCC had higher DDLT rates than others. Because MELD exceptions were applied to candidates with stage T1 or T2 HCC before July 1, 2005 and to candidates with stage T2 HCC after July 1, 2005, the HCC candidates examined in our study had either stage T1 HCC (after July 2005) or stage T3 HCC (beyond the Milan criteria), did not receive an exception, and underwent transplantation with their laboratory MELD scores. We speculate that such candidates may undergo DDLT using marginal and high-risk donor organs, and this might be driving the higher DDLT rates among HCC candidates.

One of the goals of the MELD-based allocation and distribution policy was to provide transplantation to the sickest candidates first. The higher DDLT rates among hospitalized candidates in ICU and non-ICU settings versus nonhospitalized candidates suggest that MELD-based allocation has done fairly well in this regard. Our current study and previous studies[12,19,20] evaluating the effectiveness of the MELD-based allocation policy have provided evidence that the current allocation policy is meeting its goal of balancing the needs of the most medically urgent candidates against the practical limitations of extensive sharing across large geographic areas.

The main limitations of this study are its retrospective, observational design and associated problems that may have affected the results, such as a selection bias, an inability to assess the effects of unmeasured candidate characteristics, and missing data for some candidate-level variables. The grading of ascites and hepatic encephalopathy was based on program reporting using subjective definitions and may have been subject to misclassification. Despite these limitations, our results show that DDLT rates among active candidates are affected by many candidate factors other than the DSA and the allocation MELD score. Furthermore, had our covariates been measured more precisely and been subject to less error, we would have had greater statistical power, and perhaps additional significant findings would have emerged.

In conclusion, under the current allocation rules, the MELD score and the DSA are the most important determinants of DDLT rates, but other measured candidate characteristics are systematically affecting which candidates do or do not undergo DDLT within the same DSA, with the blood type, and with the same MELD score.

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