The Impact of Regional Variability in Special Case Exception Awards on Liver Transplantation Waiting List Mortality in the United States

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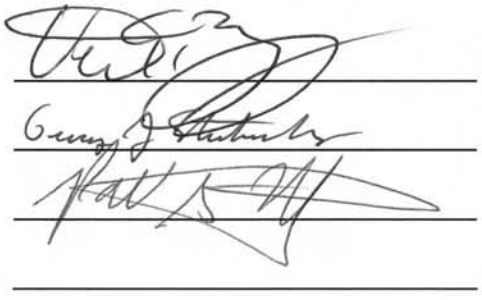
A Thesis presented to the Graduate Faculty
of the University of Virginia in Candidacy for the Degree of
Master of Science

Department of Public Health Sciences

University of Virginia
January, 2007



INTRODUCTION

A major development in deceased donor liver transplantation occurred with the inception of the MELD (Model for End-stage Liver Disease) allocation system on February 27, 2002, in which the United Network for Organ Sharing (UNOS), the national organization entrusted with all organ transplant allocation in the United States, shifted to an allocation system emphasizing medical need of candidates replaced one mainly based on waiting list time.[1,2] The change to using MELD, a formula for awarding points derived from three readily available serum tests (total bilirubin, serum creatinine, INR), was based on the findings by Freeman et al. in 2000 that there was no correlation between waiting list time and waiting list mortality.[3] Multiple studies have shown that the number of new patients listed for liver transplantation and waiting list mortality have decreased since this change.[4,5,6] MELD has since been validated as an excellent predictor of pre-transplantation mortality and is emerging as a predictor of short-term post-transplantation outcome.[7,8,9,10,11,12]

Despite these improvements, the gap between the supply and demand for organs has grown, while pre-transplant care of cirrhosis has improved, the number of donor organs has remained constant. MELD allocation has become increasingly important in justly prioritizing patients for transplantation. Optimal operation of the system and fulfillment of the Institute of Medicine's "Final Rule" regarding geographic equality of allocation depend on regions' equivalent and consistent use of calculated MELD scores to guide organ allocation.

A MELD exception award is an individualized addition of points to a patient's laboratory-based MELD score in conditions where the patient's short-term mortality is not

accurately reflected by MELD.[13] MELD exception awards have been most prominent in issues related to transplantation of patients with hepatocellular carcinoma (HCC),[14,15,16,17,18,19] but MELD exception points may be also awarded for several other specific inherited and metabolic disorders.

In addition to exceptions for HCC and certain unique inherited and metabolic disorders, MELD exceptions may also be requested for more subjective indications such as refractory ascites, refractory encephalopathy, or recurrent cholangitis. In a similar process to that for typical MELD exceptions, special case exceptions (SCE) for these symptom-based indications are typically originated by a physician or other primary provider on behalf of an individual patient to the regional review board (RRB). RRBs review each case in a conference setting and deliver an award of exception points or denial of the request within 30 days. Table 1 provides a list of typical and special case MELD exceptions.

Request and approval rates for typical MELD exceptions for inherited disorders and HCC are similar across regions, but there is significant regional variability in the number of requests for and approvals of special case exceptions.[20,21] The substantial regional variability suggests that standards for requesting and approving SCE by regional review boards differ widely across UNOS regions. These regional differences in SCE awards may impact waiting list mortality.

This study examines the current patterns of regional differences in rates of SCE requests and approvals and the correlation between rates of SCE and waiting list deaths (WLD). Specific correlation patterns indicate that regional variability in SCE awards

likely have a role in the observed differences in waiting list mortality. Multivariable logistic regression was used to assess whether the region of an individual patient's liver transplant listing is an independent predictor for a patient's likelihood of (a) receiving an SCE or (b) dying on the waiting list (WLD) after adjustment for regional differences in confounding patient characteristics.

METHODS

The UNOS Standard Transplant Analysis and Research (STAR) files were queried for patients undergoing transplantation or who were active on the waiting list since the inception of the MELD allocation system through April 24, 2006. Patients undergoing living-donor liver transplantation, repeat transplantation, multiorgan transplantation, or of age less than 18 years at transplantation or at time of waiting list death were excluded. Patient-level data were used to calculate mean laboratory-based MELD scores in patients transplanted with no MELD exception, transplanted patients with a special case exception, transplanted patients with an exception related to a diagnosis of hepatocellular carcinoma, and patients who died on the waiting list for each region.

Mortality, SCE request, and SCE approval ratios were calculated by dividing the observed number of events in each UNOS region by the expected number of events per capita. The expected event rates were calculated by assuming that event rates in each region were equivalent to the rate in the total population. Per capita calculations were made using publicly-available information found on the U.S. Census Bureau website.[22] The adult population (age 18 years or older) in each UNOS region was totaled from year 2000 census data.

Information was also obtained from UNOS concerning exceptions awarded by each region's regional review board (RRB) since inception of MELD allocation, including the number of exceptions requests made to and awarded by each RRB and stratified by presence or absence of HCC. Non-HCC exceptions were stratified into categories of "typical" (i.e. genetic disorders and physiologic sequelae of cirrhosis with estimated mortality of 6 months or less) and "atypical" (i.e. refractory ascites, refractory encephalopathy, refractory variceal bleeding, refractory pruritus, refractory cholangitis). These symptomatic conditions were investigated during the evaluation-phase of MELD and were found to be non-significant predictors for waiting list mortality.[1,2,8] Because of the unique clinical circumstances and prognoses of HCC patients, patients awarded a MELD exception for HCC were not considered in the final calculations of likelihood to receive an SCE or waiting list mortality. This analytical practice is consistent with other studies examining aspects of MELD allocation.[4,5,7,8,23]

Regional differences in organ shortage are likely to account for much of the difference in waiting list mortality across regions.[4,5,8] Regional mean laboratory-based MELD score at transplantation (score calculated from the MELD formula and not including additional points for exceptions) are measures of the average level of "candidate illness" at the time of transplantation. Higher mean laboratory-based MELD scores represent higher levels of candidate illness and thus would reflect regions' levels of organ shortage if MELD worked optimally without exceptions. An "organ shortage ratio" (OSR) variable was created using the available population-based data to more directly compare the degree of organ shortage across UNOS regions. The OSR is a region-specific ratio of a region's number of candidates on the waiting list with laboratory-based MELD score greater than or equal to 15 on April 24, 2006, divided by the number of deceased donor

livers offered by the region in 2005. Pearson correlation coefficients were then calculated to evaluate associations between waiting list mortality, organ shortage, and special case exception request and approval rates across regions.

Multivariable logistic regression was used to estimate the probability of receiving a special case exception or of dying on the waiting list for each patient. Potential predictors were analyzed with univariate t-tests, and those factors with $p \approx 0.05$ were incorporated into the multivariable logistic model. The final logistic regression model included 9 variables: region of listing, lab-based MELD at transplant or death, age at listing, gender, ethnic group, degree of encephalopathy, degree of ascites, year of listing, and ABO blood group.

No internal review board approval was required as only de-identified data was utilized. SAS 9.1.3 (Cary, NC) was used for all data management and calculations. All statistical tests of hypotheses were two-sided and p-values of ≤ 0.05 were used as the standard for determining statistical significance.

RESULTS

MELD-Era Candidates

A total of 141,043 transplant candidates were registered in the UNOS database, and 69,217 patients (19,255 transplanted patients and 49,962 waiting list candidates) met the inclusion criteria. Of the waiting list candidates, 33,851 patients had survived, and 16,111 patients had died on the waiting list or were removed from the list because of illness precluding transplantation. Of the transplanted patients, 5,064 (26% of all transplants) had been awarded a MELD exception. 1,193 (6% of all transplants, 24% of

transplants with exceptions) of those exceptions were “special case” exceptions and 3,871 were HCC-related. 16,111 patients were removed from the waiting list during the analysis period: 12,632 died and 3,479 patients were removed from the waiting list secondary to severe illness precluding transplantation. 15,842 of the patients who died on the waiting list or were removed due to severe illness had no exception, only 269 (2%) of patients removed from the waiting list had an exception, and only 68 (0.4%) of those with a “special case” exception died on the waiting list. Patient inclusion, exclusion, and exception events are represented in Figure 1.

Regional Mean MELD Scores

Final lab-based MELD score at date of transplantation was used to compare MELD scores between patient groups with different exception status. Groups were stratified by exception type and region. Lab-based MELD scores at transplantation in patients without a MELD exception, in those with an exception for HCC, and in those with a special case exception varied widely across regions. Region 5 had the highest and region 10 had the lowest mean lab-based MELD scores in all transplanted patients. Regions 9 and 1 respectively had the highest and lowest MELD scores for patients with no exception at transplantation, regions 9 and 10 had the highest and lowest mean scores in transplanted patients with an exception for HCC, and regions 9 and 3 had the highest and lowest scores in transplanted patients awarded special case exceptions. Table 2 presents a summary of regional laboratory-based MELD scores at transplantation.

Regional Waiting List Standardized Mortality Ratios/Regional Exception Award Rates

Table 3 lists the regional rates for typical MELD exceptions. Per capita rates of requests for "typical MELD exceptions" (exceptions for metabolic and inherited disorders) were consistent across regions (Table 3). Typical exception approval rates ranged between 70-100% with a median of 86%. Table 4 displays differences in regional rates of SCE requests, SCE approvals, and waiting list mortality. Rates of MELD exception awards, and particularly special case exceptions, varied widely on a region-by-region basis. Region 5 had the highest standardized request (SRR) and approval (SAR) ratios for special case exceptions by a substantial margin (2.67 and 2.58) compared to the next highest ratios in region 2 (1.47 and 1.73) and compared to the lowest ratios in regions 6 (0.18 and 0.26) and 11 (0.33 and 0.29). Special case exception approval rates ranged between 57-93% with a median of 64%. Regions 9 and 5 had the highest waiting list mortality ratios (WMR) of 1.79 and 1.44 respectively, and regions 6 and 10 had the lowest WMRs of 0.36 and 0.60.

Correlations of Waiting List Mortality, Special Exception Approvals, and Organ Shortage

Table 5 lists Pearson correlation coefficients (PCC) which assess the degree of association between regional parameters of organ shortage (lab-based MELD, organ shortage ratio), waiting list mortality rates, and exception awards. As expected, waiting list mortality and organ shortage ratios (PCC=0.88, p=0.0003) and waiting list mortality and lab-based MELD score at transplantation (PCC=0.716, p=0.0132) were highly positively correlated. Special case exception approvals and organ shortage (PCC=0.6, p=0.05) and special case approval rates and lab-based MELD score at time of transplantation in patients without an exception (PCC=0.33, p=0.3141) were not strongly correlated.

Selection of Predictor Variables for Multivariable Logistic Regression Model

Table 6 shows the univariate analysis of potential predictors for the logistic regression model used to estimate the odds ratios for receiving a special case exception or for dying on the waiting list. Variables with $p \approx 0.05$ in unadjusted univariate analysis of either outcome (special exception award or waiting list death) were included in the model.

Multivariable Logistic Regression Model for Receiving a Special Case Exception

Figure 2 plots the estimated odds ratios for different predictors of receiving an SCE in the model. Region 11 was used as the referent for estimating regional odds ratios for receiving an SCE. Region 9 had the highest odds ratio of 1.647 ($p < 0.0001$), and region 6 had the lowest odds ratio of 0.530 ($p = 0.006$). Younger patients are more likely to receive an SCE (OR = 0.977, $p < 0.0001$). African-Americans were significantly less likely to be awarded an SCE (OR = 0.795, $p = 0.043$). Moderate to severe ascites predicted higher probability of receiving an SCE (OR = 1.637, $p < 0.0001$).

Multivariable Logistic Regression Model for Dying on the Waiting List

Figure 3 plots the estimated odds ratios for predictors of dying on the waiting list. Region 11 served as the reference region for regional comparisons. Region 9 had the highest odds ratio for waiting list mortality (OR = 1.287, $p < 0.0001$), and region 6 had the lowest odds ratio (OR = 0.630, $p < 0.0001$). This estimate means that a patient from region 9 is 28.7% more likely than a patient from region 11 to die on the waiting list, whereas a patient from region 6 is 37% less likely than a patient from region 11 to die waiting for a liver transplant. Regions 1 (OR = 1.211, $p = 0.0078$) and 5 (OR = 1.126, p

= 0.0316) also had higher than standard waiting list mortality. Females were significantly more likely than males to die on the waiting list (OR = 1.113, $p < 0.0001$). Presence of encephalopathy or ascites of any severity predicted significantly higher waiting list mortality, with severe encephalopathy predicting the highest likelihood of waiting list mortality of any predictor (OR = 3.143, $p < 0.0001$). Blood group "O" predicts the highest waiting list mortality of all blood groups.

DISCUSSION

Concerns about equality in MELD allocation in liver transplantation have been present since institution of the policy in 2002. Several adjustments have already been made in MELD exception points awards for HCC diagnosis based on changes in waiting list mortality, organ utilization, and advancing technologies in the treatment of HCC prior to transplantation. "Special case" exceptions have been previously investigated and showed variability across regions.[20] Sequelae of these regional differences, such as waiting list mortality, have not previously been investigated. We examined this question using population-based statistical methods to calculate standardized mortality and exception request and approval rates. We then considered the correlation of these rates for patterns in SCE awards and waiting list mortality. To confirm the observed correlations, we used multivariable logistic regression models that controlled for typical confounders and region-specific variables that reflect transplantation tendencies to estimate the impact of region on an individual patient's likelihood to receive a special case exception or die on the waiting list.

We included a factor, lab-based MELD score, which indirectly represents regional organ shortage as a variable in our models. We estimated regional organ shortage in two

ways: by observing the regional mean lab-based MELD score at the time of transplant and an “organ shortage ratio” calculated with a region’s number of waiting list candidates divided by the region’s number of offered deceased donor livers. We assessed organ shortage in these ways for two reasons. First, we wanted to quantify the degree of organ shortage in different regions in order to compare the standardized mortality and SCE rates in regions with comparable levels of shortage. We expected that regions with the most severe organ shortage would have the highest waiting list mortality, a hypothesis that was supported by the high degree of correlation of waiting list mortality and organ shortage by both measures. On the other hand, we were surprised to find the amount of dissimilarity in waiting list mortality and SCE rates within these organ shortage strata. This led us to create multivariable models to characterize the impact of different region-specific factors for these differences. Second, lab-based MELD score could be used to adjust for the regional differences in organ availability at the individual patient level in our models. In this way we were able to estimate the impact of region for listing on likelihood to receive an SCE or suffer waiting list death.

Regional trends in award rates of SCE are evident. Regions with clear issues with organ shortage, as shown by high lab-based MELD score at transplantation and by a high ratio of waiting list size to organs offered, tended to have significantly different SCE approval rates. Regions 1 and 5, for example, have relatively low rates of SCE compared to region 9, which has the highest rate of SCE request and approval. Not surprisingly, waiting list mortality and organ shortage variables were highly correlated, which supports the effectiveness of MELD in allocation. The rates of SCE approval and organ shortage variables, however, were only modestly correlated. The similarity of lab-based MELD score at transplant supports the idea that regions with comparable levels of organ

shortage have similar numbers of patients on the waiting list with severe liver disease. Following from this, the per capita rate of applications for and approvals of SCE in these regions should be similar as well. This discrepancy across regions is independent of typical confounders such as patient gender, age, disease severity, and regional transplantation tendencies. The differences between regions with high degrees of organ shortage are particularly notable.

We postulate that the variability in SCE approval rates and waiting list mortality between severe organ shortage regions are connected. These differences may result from opposing regional strategies in requesting and approving SCE. We show that regions requesting and approving greater numbers of SCE have higher rates of waiting list death when compared to regions with similar degrees of organ shortage that employ a more modest approach to SCE requests and approvals. This hypothesis is strongly supported by our logistic regression results that show region to be an independent predictor for receipt of a SCE and for dying on the waiting list. Region was also a minor predictor for waiting list mortality, again not surprisingly, given regional differences in organ shortage and SCE approval. We conclude that the differences in organ shortage and SCE approval cancel each other out to some degree, thus showing region to be only a modest predictive factor.

Our results show higher waiting list mortality to be strongly correlated with higher rates of SCE approval. Our logistic regression results show region to be an independent factor for both SCE approval and waiting list mortality. The higher waiting list mortality rates associated with higher request and approval rates for SCE are troublesome and suggest that a conservative approach to granting SCE is preferable to minimize waiting list

mortality given that regions with similar degrees of organ shortage had significantly different waiting list mortality and SCE approval rates. While SCE are certainly not the only factor associated to increased waiting list mortality, our results indicate that regions' philosophies regarding SCE requests and approvals very likely affect regional waiting list mortality.

Our study has several limitations. We used a large database with patient-level information collected for research and funding purposes. Information bias is likely present given the different levels of data reporting observed. Certain variables have subjective components (i.e. degree of encephalopathy, severity of ascites) that may affect their interpretability across regions and may thus have affected the regression results. Some patients had missing data and thus were not included in the regression analysis. While we did not detect a systematic basis for data omissions from the database, such errors could exist and lead to selection bias. Our logistic regression results estimate odds ratios and do not imply causality but suggest that high rates of SCE approval have been negatively associated with waiting list mortality since the inception of organ allocation using MELD score. The C-indexes for both logistic regression models were only moderately robust which signifies that other predictors, both measured and unmeasured, impact the probability of receiving an SCE or dying on the waiting list besides those included in the models.

These results suggest that an examination of SCE approval criteria is needed, and that standardization of the criteria may positively impact waiting list mortality. Such efforts should use criteria standards of regions with the highest degrees of organ shortage and lowest waiting list mortality. Other avenues of investigation may include standardization

of regional organ-sharing procedures and agreements between neighboring regions as well. More investigation into additional factors accounting for the differences in regional waiting list mortality may recommend other areas to maximize equality in MELD allocation of deceased donor liver grafts.

Table 1: Typical and Special Case MELD Exceptions

Typical Exceptions	Special Case Exceptions
Familial Amyloidosis	Refractory Ascites
Hepatocellular Carcinoma	Refractory Cholangitis
Hepatic Artery Thrombosis	Refractory Encephalopathy
Hepatopulmonary Syndrome	Refractory Pruritis
Ornithine Transcarbamylase Deficiency	Refractory Variceal Hemorrhage
Crigler-Najjar Disease	Bile Duct Injury
Portopulmonary Hypertension	
Primary Oxaluria	

Figure 1: Patient Inclusions and Exclusions

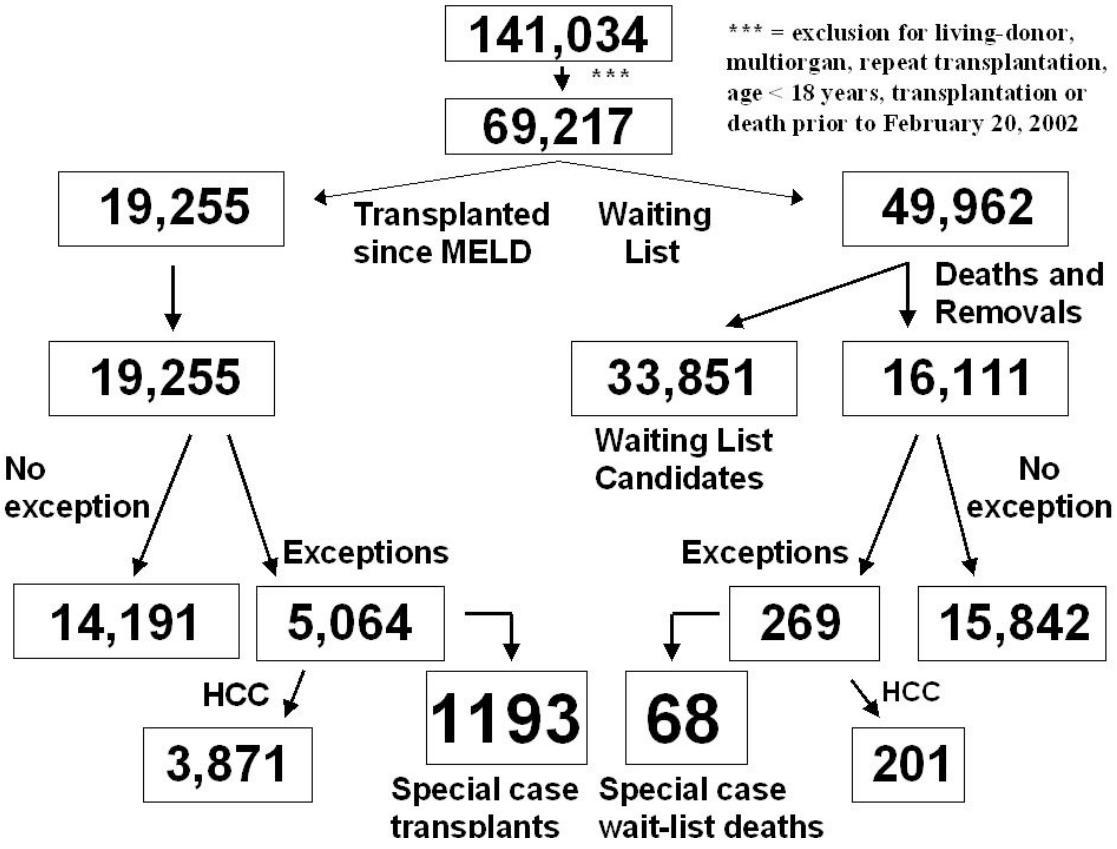


Table 2: Regional Lab-Based MELD Scores at Transplantation

Region	Mean Lab-Based MELD at Transplant	Mean Lab-Based MELD at Transplant in Patients without an Exception	Mean Lab-Based MELD at Transplant in Patients with an Exception	Mean Lab-Based MELD at Transplant in Patients with an HCC-Exception
1	20.9	26.3	20.9	12.5
2	19.8	21.9	19.8	12.3
3	19.2	20.9	19.2	12.8
4	19.5	22.3	19.5	12.7
5	22.8	27.6	22.8	12.4
6	19.2	21.7	19.2	12.6
7	20.6	24.2	20.6	12.3
8	21.0	23.8	21.0	12.9
9	21.3	25.7	21.3	13.1
10	17.0	18.6	17.0	11.2
11	20.3	22.3	20.3	13.0

Table 3: Typical MELD Exception Rates

Region	Per Capita Typical Exception Requests	Per Capita Typical Exceptions Approvals	Typical Exceptions Percent Approved
1	0.0080	0.0071	89
2	0.0046	0.0033	72
3	0.0036	0.0030	83
4	0.0054	0.0048	88
5	0.0051	0.0035	70
6	0.0007	0.0007	100
7	0.0064	0.0055	85
8	0.0040	0.0035	87
9	0.0072	0.0051	71
10	0.0032	0.0029	89
11	0.0023	0.0020	86

Regional rates are number of requests or approvals per 1000 adults.

Table 4: Rates of SCE Requests and Approvals by Region

Region	SCE Requests Per Capita	SCE Request Ratio (SRR)	SCE Approvals Per Capita	SCE Approval Ratio (SAR)	Waiting List Mortality Ratio (WMR)	Mean Lab-MELD at Transplant in Patients without an Exception	Organ Shortage Ratio (OSR)
1	0.0253	0.73	0.0184	0.72	1.25	26.3	4.00
2	0.0404	1.47	0.0315	1.73	1.39	21.9	2.63
3	0.0194	0.66	0.0122	0.58	0.67	20.9	0.95
4	0.0398	1.39	0.0251	1.20	0.93	22.3	2.50
5	0.0292	1.01	0.0190	0.96	1.44	27.6	4.00
6	0.0065	0.18	0.0061	0.26	0.36	21.7	1.79
7	0.0338	1.17	0.0221	1.08	1.04	24.2	2.44
8	0.0328	1.23	0.0243	1.34	0.89	23.8	1.82
9	0.0690	2.67	0.0448	2.58	1.79	25.7	4.76
10	0.0215	0.61	0.0161	0.77	0.60	18.6	1.16
11	0.0134	0.33	0.0087	0.29	0.61	22.3	1.69

Ratios (observed events/expected events per capita) and request and approval rates per capita are using regional population data available from U.S. Census Bureau, http://www.census.gov/prod/2001pubs/c2kbr01-2.pdf and http://www.census.gov/prod/2004pubs/censr-14.pdf, accessed July 24, 2006.

Table 5: Pearson Correlations of Mortality, Measures of Organ Shortage, and Special Exception Approvals

Variables	Correlation Coefficients	P-value
WMR and SAR	0.815 (0.387, 0.946)	0.0022
WMR and OSR	0.884 (0.576, 0.967)	0.0003
WMR and Lab-based MELD	0.716 (0.169, 0.915)	0.0132
OSR and SAR	0.598 (-0.033, 0.875)	0.0020
OSR and Lab-based MELD	0.857 (0.497, 0.959)	0.0008
SAR and Lab-based MELD	0.335 (-0.346, 0.772)	0.3141

WMR = Waiting List Mortality Ratio = regional waiting list mortality rate referent to region with lowest rate

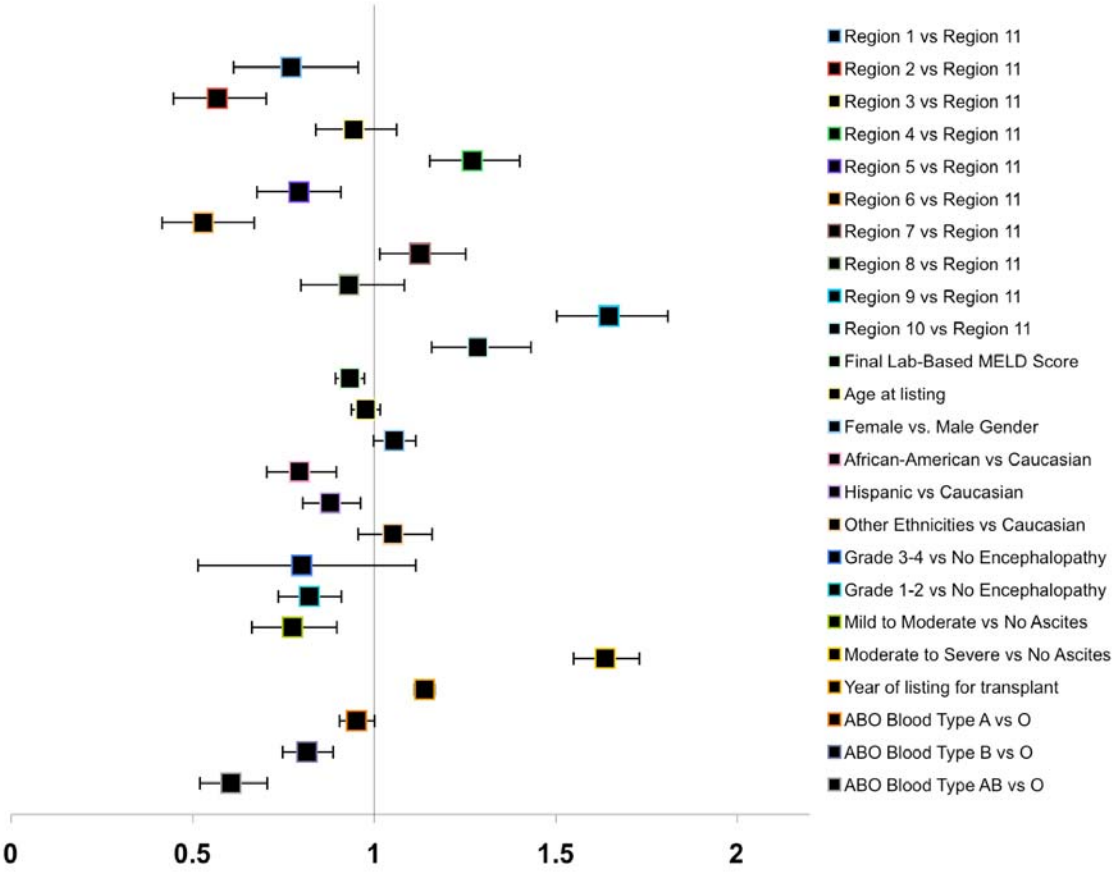
SAR = SCE Approval Ratio = regional approval rate for SCE referent to region with lowest rate

OSR = Organ Shortage Ratio = $\frac{\text{region's number of waiting list candidates with lab- MELD} \geq 15}{\text{region's number of deceased donor livers offered in 2005}}$

Table 6: Univariate Analyses of Predictors for Receiving a Special Case Exception and Dying on the Waiting List

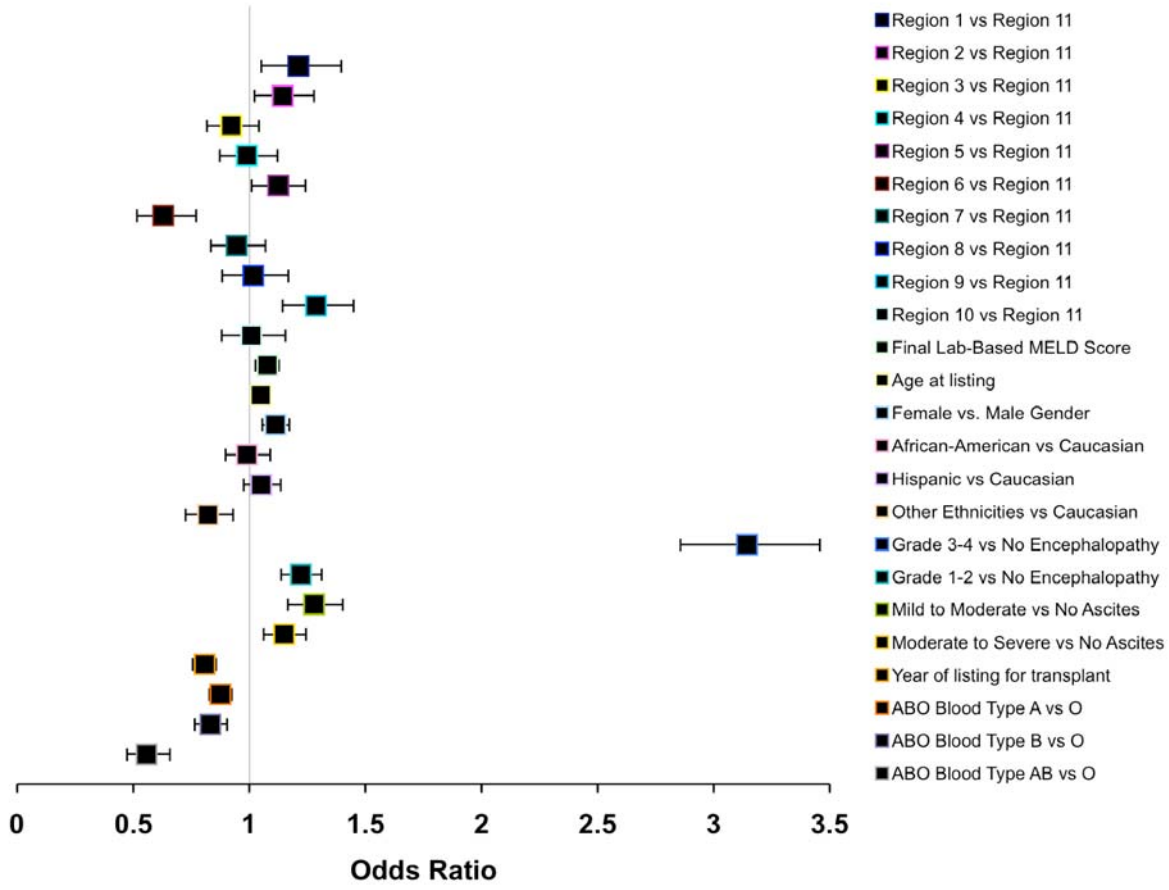
Predictor	Special Case Exception	Waiting List Death
Gender	0.291	< 0.001
Lab-Based MELD Score	< 0.001	< 0.001
Severity of Ascites	< 0.001	< 0.001
Severity of Encephalopathy	< 0.001	< 0.001
Ethnicity	< 0.001	< 0.001
Age at listing for transplant	0.081	0.074
Year of listing for transplant	< 0.001	< 0.001
ABO Blood Group	0.785	< 0.001

Figure 2: Odds Ratios for Receiving a Special Case Exception



C-statistic = 0.699
P-value for entire model <0.0001

Figure 3: Odds Ratios for Dying on the Waiting List



C-statistic = 0.786
P-value for entire model < 0.0001

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