

United Network for Organ Sharing regional variations in appeal denial rates with non-standard Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease exceptions: support for a national review board

Gish RG, Wong RJ, Honerkamp-Smith G, Xu R, Osorio RW. United Network for Organ Sharing regional variations in appeal denial rates with non-standard Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease exceptions: support for a national review board.

Abstract: Although it has been generally recognized that there are inconsistencies among Regional Review Boards in the assignment of points for model for end-stage liver disease (MELD)/pediatric end-stage liver disease (PELD) exception patients with resulting considerable variation in appeal denial rates, data to actually prove this have been limited. We reviewed 6533 MELD/PELD exception applications submitted between 2005 and 2008, calculated the variation in approval/denial rates, and followed these cases through mid-2013 to assess the effects on patient outcomes. We found highly significant regional variations in denial rates for appeals by exception patients and in transplantation rates. The odds of transplant for patients whose appeals are approved is 2.45 times that of patients not approved; that this effect does not vary by region suggests that the variation in transplant rates is driven, at least in part, by the variation in appeal denial rates. Health deterioration or death accounts for more than two-thirds of wait list removals among patients removed for reasons other than transplant. Our findings add to the weight of evidence that a national review board that uses current clinical expertise, peer review literature, and data to consistently assign priority could reduce regional inequities and move toward equitable allocation of organs and compliance with the United States Department of Health & Human Services Final Rule.

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Key words: appeal – denial – equitable – liver transplantation – model for end-stage liver disease – non-recognized exceptional diagnoses – non-standard – organ allocation – recognized exceptional diagnoses – regional review board – regional variation

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Conflict of interest: The authors of this manuscript have no conflicts of interest to disclose.

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Accepted for publication 18 March 2015

Regional review boards (RRBs) were created to address the concern that “exception” patients—those with a model for end-stage liver disease (MELD) or pediatric end-stage liver disease (PELD) score that does not accurately represent the severity of their medical illness – might have a progressive disease that ultimately prevents them from obtaining a transplant or results in their dying on the liver transplant waiting list. In such cases, although scores are not elevated by the standard three components of the MELD calculation (creatinine, International Normalized Ratio, and bilirubin), the patient’s advocate interprets their current medical condition as life threatening or believes that there is a risk of wait list removal due to progression of underlying disease. Currently, each of the 11 geographic regions in the United States has a separate RRB that assesses such cases. For certain specific conditions termed *recognized exceptional diagnoses* (REDs; including metabolic diseases, hepatocellular carcinoma, hepatoblastoma, hepatopulmonary syndrome, primary oxaluria, and familial amyloidosis), Organ Procurement and Transplantation Network (OPTN) policies allow exemptions from use of the true MELD/PELD scores to determine transplant priority, and provide guidelines for increases in the scores. With other conditions that are not specifically recognized by OPTN policies (*non-REDs*), it is possible for a physician to request an increased MELD score for any patient whose score is not thought to accurately reflect mortality risk. If the RRB approves, the patient may receive a higher MELD score and thus a higher wait list priority. However, there are no United Network for Organ Sharing (UNOS) guidelines for increases in the scores of patients with many of these non-RED conditions (including benign structural diseases such as cysts and adenomas, cholangitis in primary sclerosing cholangitis, and others). In the end, for all patients whose MELD/PELD scores do not accurately reflect mortality risk, positions on the waiting list, wait list mortality, and wait list removals for medical illnesses that preclude liver transplant will depend on the judgment made by the RRB based on the expert opinions of RRB members.

Unfortunately, because of the lack of well-defined predictive models for estimating the risk of waiting list removal for non-RED conditions, RRBs across the United States have differed very considerably on which conditions should receive additional MELD points and on how exception case requests should be prioritized (1). Although it seems to be generally recognized in the transplant community that this results in considerable

variation across UNOS regions in appeal denial rates for non-RED patients, data to actually prove this and determine the effects of denials on patient outcomes have been limited. A 2005 study found significant variation in the distribution of petitions for non-REDs per region (range 0.7–8.3%), the percentage of petitions approved among regions (range 28–75%), and the scores granted after review (2). However, this study did not assess the effect of denials on patient outcomes. A 2011 study that compared only symptom-based exception likelihoods across regions also found significant variation, with the region-specific percentage of the study population receiving exception awards ranging from 1.5% to 6.2% (3). Transplantation occurred in 69% of patients with granted exception requests compared to 31% of patients with denied requests; only 17% of patients with granted requests suffered waiting list death or removal due to illness compared to 30% of patients with denied requests. Another 2011 study reported that the proportion of patients per region receiving non-HCC exceptions ranged from 3.7% to 9.5% and that patients receiving a MELD exception were transplanted at higher rates and dropped out at lower rates (4). Although it did not assess variation *across* UNOS regions, a 2013 study found that *within* individual UNOS regions, there were substantial between-center differences in the proportions of non-RED exception applications that were approved and that patients with approved non-RED exceptions were significantly more likely to undergo liver transplantation than patients with denied requests (68.3% vs. 53.4%) (5). To assess the specific outcome of RRB decisions on non-RED patient appeals across UNOS regions, we reviewed requests for non-RED MELD/PELD exception applications over three yr’ time, calculated the variation in approval/denial rates and transplantation rates, and followed these cases through mid-2013 to assess the effects on patient outcomes.

Materials and methods

Study population

We reviewed 6533 MELD/PELD exception applications derived and extracted from the UNOS database via a data request submission to the Scientific Registry of Transplant Recipients. These MELD appeals for exception points were submitted to RRBs through UNetSM between 2005 and 2008, representing 3337 patients. This analysis included all sequential initial applications as well

as subsequent appeals of denied applications and three-month extensions for each patient included in the original RRB application. Any application that was in effect at UNOS during this time period but was submitted and approved prior to January 1, 2005, was excluded from this data extraction and analysis. Other exclusions included applications for HCC that did not meet the criteria in Policy 3.6.4.4, including patients with tumors outside the T2 criteria and patients with “downstaged” tumors, because regional variances addressed many of these patients. This analysis also excluded patients automatically not approved due to some administrative reason (e.g., missed extension deadline).

To establish the patients’ clinical profiles for this data analysis, three reviews of the data set were carried out. To maintain consistency in the scoring system, one analyst completed the initial review process and scored each patient blindly, after which two additional analysts did separate reviews to confirm the scoring. The first review established a complete list of all diagnoses that were presented to the RRBs via electronic submission as the reason for the RRB appeal for MELD exception points. The second case review scored each case and each subsequent appeal, if applicable, and identified up to 10 “exception” diagnoses which were placed as the “exception” code(s) for each patient. These codes were either a specific medical diagnosis or a quality of life diagnosis. The third and final review then took place to establish a “primary” exception code because many patients had multiple diagnoses that were included in the appeal for review points and which could be a specific life-threatening disease, such as GI bleeding or infection. These patients would be scored using a “composite” code of multiple diagnoses. An example of the latter would be diagnoses such as GI bleeding and sepsis that could result in being discussed and possibly listed for transplantation with a primary exception score or being listed for retransplantation. These perceived life-threatening medical complications were presented to the RRBs when the patient’s advocate determined that the singular or composite diagnosis could influence wait list mortality or wait list removal as too ill. After completion of this initial process, two additional analysts separately performed secondary validations of the scoring; one analyst reviewed the entire data set; the second analyst reviewed a randomly selected subset representing 10% of the patient cohort; both reviews confirmed the accuracy and consistency of the exception coding.

Statistical analysis

Summary statistics were computed for patient age, sex, and race. The percentage of patients on the liver waiting list with exceptions was calculated using “snapshots” of the waiting list at a point in time. Specifically, 16 end-of-the-month snapshots from 2005 to 2008 were extracted from the OPTN database. The percentage of patients with an exception was calculated as an average across all 16 time points. To include similar candidates in the numerator and denominator, candidates listed as Status 1A/1B or temporarily inactive were excluded. Exceptions for HCC were also excluded. These data were then analyzed for each of the 11 UNOS regions.

The percentage of exception applications that were denied by the RRB was computed for each of the 11 Regions. Differences in that percentage across all regions were tested using the chi-squared test. Region 6 had no denials and was excluded from this part of the analysis. Only initial applications were included in this analysis (appeals and extensions excluded). Due to limitation in the sample sizes when stratified by both region and diagnosis, the analysis was limited to the three most common diagnoses for exception (ascites/hepatic hydrothorax, cholangitis/bacteremia, and bleeding). A generalized linear mixed-effects model with logit link function was fit for the outcome of RRB decision using region as a covariate; a second model was fit to adjust for the number of diagnoses designated as bases for exception as well as region. Both models include a random intercept grouped by patient ID to account for correlation between multiple applications from the same patient. All regions, including the region with no denials, were included in the mixed-effects modeling. Likelihood ratio tests were used to assess the overall significance of the variable Region.

Before further analyzing transplantation rates, the dataset was reduced to one record per unique patient ID by deleting duplicate applications and concatenating or removing multiple applications for the same patient. Patients were followed until July 5, 2013. The rates of removal due to transplant were computed, and homogeneity across regions in the rates was tested using a Pearson’s chi-squared test. The rates were also computed conditional on the exception application status. Independence between RRB decision and removal for transplantation was assessed using a chi-squared test for both the overall sample and within each region, and odds ratios comparing approved and denied patients were computed. P-values for the within-region tests were corrected using the

Holm–Bonferroni method. A likelihood ratio test was used to assess the regional variation in the effect of application status on the odds of receiving transplantation. Mortality rates for exception approved and denied patients were calculated using the Kaplan–Meier estimate; the difference in survival between the groups was assessed using the log-rank test. The hazard ratio for denied vs. approved patients was estimated using the Cox proportional hazards model. Patients with Removal Code 8 in the OPTN database (indicating removal due to death) were recorded as having had the event; survival times for all other removal codes were treated as censored. The analyses were performed using the statistical software R: A Language and Environment for Statistical Computing, version 3.1.1.

Results

The final cohort included 3161 applications for 3060 individual candidates. The median age of patients was 50; 60% were male; 73% were white; 12% Hispanic; and 8.1% black. The top 10 diagnoses and combined diagnoses which were the bases for exceptions for initial applications are shown in Tables 1–4. Diagnoses such as cholangitis, infection, and bacteremia were grouped, as were diagnoses such as quality of life, pain, and pruritus. The number of patients who were appealed for each region ranged from 62 to 443. When adjusted by total number of active, non-Status one patients, the range was 2.7–6.6%, including HCC cases, and 1.1–2.8%, excluding HCC cases. When patients with MELD scores <15 were excluded, the range was 1–3.3%.

The chance of approval by region ranged from 54.7% to 100% ($p < 0.0001$); inversely, denial rates ranged from 0% to 45.3% (Fig. 1). For refractory ascites/hepatic hydrothorax, the denial rate by region ranged from 24.1% to 80% (excluding one region with 0% denials), $p < 0.0001$ (Fig. 1). For cholangitis/bacteremia, the range was 6.1% to 48.5% ($p < 0.0001$) and for bleeding, 8.3% to 75% ($p = 0.0026$; Fig. 1).

Based on the likelihood ratio test, there was significant variation by region in the odds of denial, even when controlling for Number of Diagnoses ($p < 0.0001$). When adjusting for Region, Number of Diagnoses was not found to be significant ($p = 0.074$). Number of Diagnoses did not appear to have a large impact on the effect for Region, as suggested by the relatively small perturbation of estimated effects between the two models displayed in Table 5. Fig. 2 displays a heat map visualizing the proportion of applications denied, cross-tabu-

Table 1. Bases for exception for all applications combined^a: top 10 diagnoses

Diagnosis	Number of patients	Percentage of patients
Refractory ascites/ hepatic hydrothorax	1435	28
Cholangitis/bacteremia	1070	21
Bleeding (gastrointestinal, variceal)	431	8
Quality of life issues (including pain and pruritus)	378	7
Cholangiocarcinoma	283	5
“Pediatric candidate”	212	4
Metabolic disorders	194	4
Hepatic encephalopathy	156	3
Hyponatremia	153	3
Retransplantation candidate	122	2

These top 10 diagnoses represent 85% of all patients.

^aIncluding initial applications, appeals, and extensions.

Table 2. Bases for exceptions for initial applications only: top 10 diagnoses

Diagnosis	Number of patients	Percentage of patients
Refractory ascites/ hepatic hydrothorax	854	31
Cholangitis/bacteremia	500	18
Bleeding (gastrointestinal, variceal)	232	8
Quality of life issues (including pain and pruritus)	134	5
Cholangiocarcinoma	130	5
Hyponatremia	124	4
“Pediatric candidate”	109	4
Hepatic encephalopathy	101	4
Retransplantation candidate	70	3
Metabolic disorders	68	2

These top 10 diagnoses represent 84% of all patients.

lated by Region and Number of Diagnoses. The data for these analyses include region 6, which had no denials.

After reducing the dataset to one record per patient, 2178 subjects had their request for exception points approved and 882 had their request denied. Of these 3060 subjects, 2320 received a transplant, 666 were removed from the list for a reason other than transplant, and 74 had censored removal time. These censored patients were excluded from the following analyses. There was significant evidence that transplantation rate varies by region ($p < 0.001$; Table 6). The chance of removal for transplant was found to be significantly different ($p < 0.001$) between patients approved for exception points (82.4%) and those

Table 3. Bases for exception for all applications combined^a: top 10 pairs of diagnoses

Diagnosis	Number of patients	Percentage of patients
Refractory ascites + hepatic encephalopathy	679	13.0
Cholangitis + biliary stricture(s)	532	10.2
Refractory ascites + wasting	477	9.1
Bleeding + pediatric candidate	339	6.5
Quality of life + pain	333	6.4
Refractory ascites + pediatric candidate	333	6.4
Pediatric candidate + wasting	331	6.3
Hepatic encephalopathy + TIPSS contraindicated	322	6.2
Cholangitis + bacteremia	321	6.1
Cholangitis + retransplant candidate	321	6.1

^aIncluding initial applications, appeals, and extensions.

who were not approved (65.7%; Table 7). The effect of exception application status on the odds of removal for transplant was not found to vary significantly across regions ($p = 0.526$). Corresponding results for removal due to reasons other than transplant are given in Tables 6 and 7; the chance of removal for reasons other than transplant was found to be significantly different ($p < 0.001$) between patients approved for exception points (17.6%) and those who were not approved (34.3%), with the odds for approved patients in the overall sample estimated to be 0.41 times that of patients not approved. Among patients removed from the list for reasons other than transplant, death (40.5%) and deteriorating health condition (26.7%) were the most frequent causes of removal, together accounting for just over two-thirds of all such removals. Improving health conditions were responsible for just 12.6% of all patients removed from the wait list without a transplant (Fig. 3).

There was a significant difference in survival following RRB decision between approved and denied patients ($p = 0.025$), with denied patients having a higher risk of mortality while on the waiting list than approved patients (hazard ratio 1.322, 95% confidence interval, 1.036, 1.688). Estimated mortality rates for 90-day, 180-day, one-yr, three-yr, and five-yr survival are given in Table 8. Estimates of the survival curves are shown in Fig. 4. Curves for the five most frequent diagnoses specified as the main basis for exception among denied patients are plotted in Fig. 5.

Table 4. Bases for exception for all applications combined^a: top 10 triples of diagnoses

Diagnosis	Number of patients	Percentage of patients
Refractory ascites + hepatic encephalopathy + TIPSS contraindicated	244	4.7
Cholangitis + retransplant + strictures	221	4.2
Refractory ascites + pediatric candidate + wasting	177	3.4
Refractory ascites + hepatic encephalopathy + wasting	169	3.2
Cholangitis + bacteremia + biliary stricture(s)	168	3.2
Refractory ascites + quality of life + hepatic encephalopathy	152	2.9
Pediatric patient + wasting + development delay	150	2.9
Refractory ascites + bleeding + hepatic encephalopathy	147	2.8
Cholangitis + retransplant + bacteremia	136	2.6
Refractory ascites + hepatic encephalopathy + failed TIPPS	134	2.6

^aIncluding initial applications, appeals, and extensions.

Discussion

With the ultimate goal of achieving fair and equitable allocation of organs, a number of modifications of liver allocation policies have been described, including those related to socioeconomic issues, transplant benefit, preventing discrimination, feasibility, and geography. The latter was given particular prominence as an area of concern with the April 1998 publication by United States Department of Health & Human Services (HHS) of the “Organ Procurement and Transplantation Network; Final Rule” which specifically mandated that “Neither place of residence nor place of listing shall be a major determinant of access to a transplant” (6). At the time this rule was announced, HHS summarized its intent as being “to assure that allocation of scarce organs will be based on common medical criteria, not accidents of geography” (7).

More than a decade and a half later, we have found a large and highly statistically significant variation in denial rates in various UNOS regions for appeals by patients with medical illnesses that are not addressed by the MELD components. Although such discrepancies are widely observed and recognized in the transplant community, our study is one of only a handful of studies to both determine the regional variation in RRB approval rates and

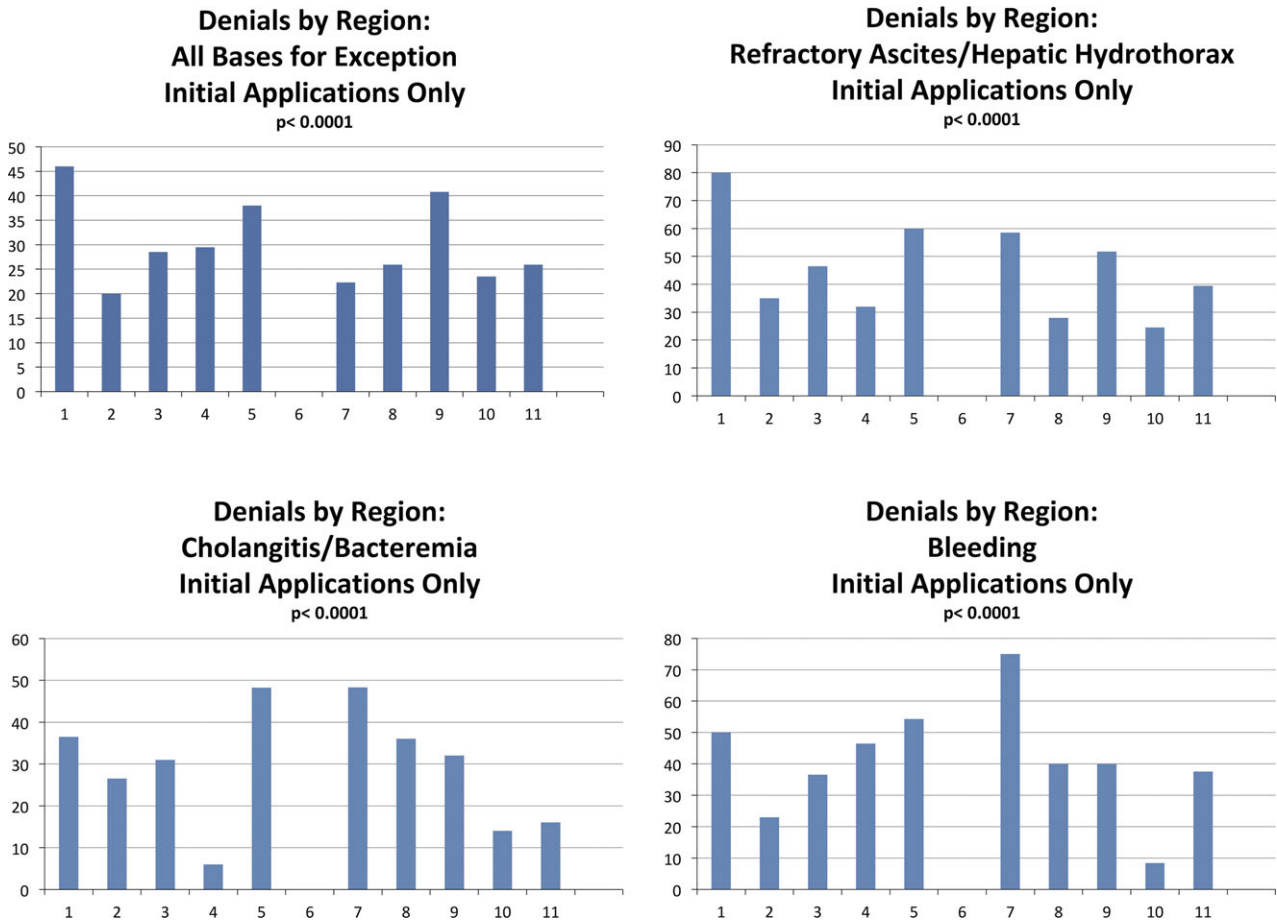


Fig. 1. The percentage of initial exception applications that were denied by regional review boards in each of the 11 regions. The percentage of initial exception applications that were denied is shown on the vertical axis. The 11 regions are shown on the horizontal axis. Top left: all bases for exception; top right: ascites/hepatic hydrothorax only; bottom left: cholangitis/bacteremia only; bottom right: bleeding only. Note that there were no denials in region 6.

show the serious consequences of this variation for the transplantation rates themselves, for which we also found strong evidence of substantial variation by region. It comes as no surprise that approved exception applicants were shown to have a statistically significant increase in the odds of transplantation, with their odds of receiving a transplant approximately two and one-half times that of patients not approved. We found that this effect does not appear to vary by region, suggesting that the variation in transplant rates is driven, at least in part, by the variation in appeal denial rates. We also clearly showed that among those patients who are eventually removed from the wait list for reasons other than transplant, a deterioration in health condition or death account for slightly more than two-thirds of removals. This highlights the accuracy of appeals to RRBs where the providers are predicting a high risk of death or medical deterioration where the patient may

not survive until the liver transplantation using standard MELD criteria for organ allocation. Contrary to the opinion that has sometimes been expressed, only a small percentage of removals (12.6%) are the result of improving health.

A potential limitation of this study is that it does not fully explore the role that may be played by diagnosis type and severity as explanatory factors of the regional variation in RRB decisions. When considering the list of top five diagnoses within each region, refractory ascites and cholangitis appear in the lists for all 11 regions, while hepatocellular carcinoma and bleeding occur in ten and nine of the lists, respectively. Thus, in terms of diagnoses, the regions are fairly similar but not uniform. Estimation of the specific effect of regional differences in diagnosis types is an area for further study. Regional differences in severity may also have some effect on the observed phenomenon. While data on the severity for each case

Table 5. Generalized linear mixed-effects model fits for impact of region on the odds of denial

Covariates	Region		Region + Number of diagnoses	
	Coefficient (SE)	p-Value	Coefficient (SE)	p-Value
Intercept ^a	-0.982 (0.147)	<0.001	-0.850 (0.161)	<0.001
Region 1	0.987 (0.268)	<0.001	0.999 (0.259)	<0.001
Region 2	-0.421 (0.170)	0.014	-0.429 (0.169)	0.011
Region 3	0.148 (0.185)	0.424	0.138 (0.138)	0.448
Region 4	0.092 (0.177)	0.605	0.074 (0.175)	0.673
Region 5	0.750 (0.176)	<0.001	0.783 (0.783)	<0.001
Region 6 ^b	-16.661 (25.600)	0.515	-16.689 (558.346)	0.976
Region 7	-0.287 (0.198)	0.147	-0.330 (0.198)	0.096
Region 9	0.686 (0.187)	<0.001	0.682 (0.183)	<0.001
Region 10	-0.207 (0.189)	0.274	-0.215 (0.187)	0.249
Region 11	-0.096 (0.188)	0.609	-0.127 (0.187)	0.496
# Diagnoses	-	-	-0.034 (0.018)	0.066

The estimated coefficients represent the effects of Region and Number of diagnoses on the log odds of denial; larger values correspond to greater odds that a patient is denied.

^aRegion 8 is used as the reference level and its effect appears as the intercept term.

^bRegion 6 has very large negative coefficients and standard errors because there were zero denials in this region.

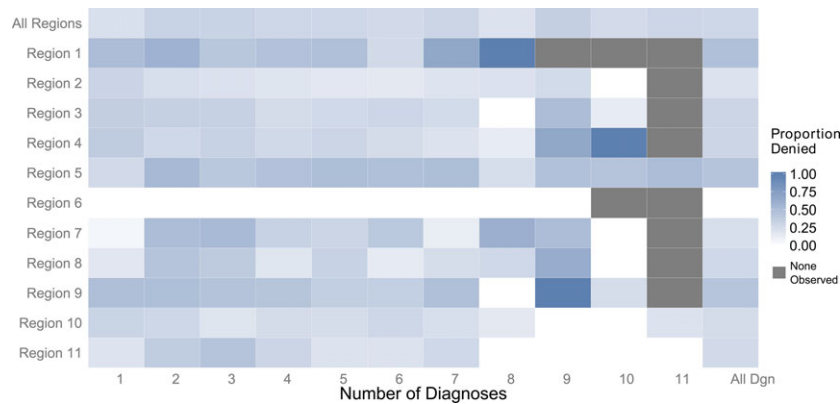


Fig. 2. Heat map displaying proportion of applications denied, cross-tabulated by region and number of diagnoses. Cells for which there were zero applications for a given region and number of diagnoses are colored gray.

were not available, we did attempt to adjust for some measure of patient status by including the number of diagnoses listed as a covariate in the GLM analysis. While not ideal, this measure may capture some of the information on severity and may be considered a partial proxy. Looking at the overall results of our analyses, it seems very clear that, for some patients, accidents of geography are still a factor in determining transplantation outcome and, ultimately, survival.

In June 2010, the OPTN/UNOS Board charged the Liver and Intestinal Organ Transplantation Committee with “making recommendations to reduce geographic disparities in waitlist mortality” (8). With consideration of public feedback, the *Concept Document: Next Steps Toward Improving Liver Distribution* was developed (8). The three key concepts proposed for further consideration were

Share 15 National, expedited graft placement, and tiered regional sharing and sharing threshold. Share 15 National and Share 35 Regional were implemented in June 2013. In Share 15 National, adult deceased donor livers are offered nationally to status 1 patients and patients with MELD 15 or higher before local/regional/national patients with MELD scores <15. In Share 35 Regional, adult deceased donor livers are offered to regional patients with MELD scores above 35 before local patients below a MELD score of 35. All of these concepts assume that MELD scores are assigned in the same manner throughout the nation.

Our data clearly demonstrate wide variations across regions for patients with non-standard MELD exception conditions. As Share 15 National and Share 35 Regional have now been instituted, it will be important to re-assess data

Table 6. Transplantation rates by region

Region	Removed for transplant (%)	Removed for other (%)
Overall	2320 (77.7)	666 (22.3)
1	60 (65.9)	31 (34.1)
2	342 (75.0)	114 (25.0)
3	211 (80.5)	51 (19.5)
4	201 (77.0)	60 (23.0)
5	336 (72.7)	126 (27.3)
6	53 (76.8)	16 (23.2)
7	160 (82.5)	34 (17.5)
8	160 (84.2)	30 (15.8)
9	263 (74.9)	88 (25.1)
10	272 (82.4)	58 (17.6)
11	262 (81.9)	58 (18.1)

on exceptions. However, there have been ongoing and evolving discussions by the Liver and Intestinal Organ Transplantation Committee related to making recommendations to further reduce geographic disparities in wait list mortality by moving to expanded sharing policies. Having agreed in 2012 that the geographic disparities in organ allocation were unacceptably high, the OPTN/UNOS Board of Directors charged the Liver and Intestinal Organ Transplantation Committee to investigate how the current geographic patterns of organ distribution may affect transplant candidates' chances to receive organ offers. In the concept paper presented by the Committee in June 2014, it is clearly acknowledged that despite changes over the years, geographic variation in the level of medical urgency many candidates must reach to receive liver transplants has not been significantly reduced, with candidates in some parts of the country having to wait until they are much more severely ill compared to patients in other areas (9). One possibility suggested to decrease overall variation in MELD/PELD scores at which candidates receive a transplant is organ distribution based on a limited number of allocation districts instead of the exist-

ing local and regional boundaries. Statistical modeling shows that these optimized maps might reduce variation in the MELD/PELD scores at transplant and reduce both waiting list and total deaths. The Committee also proposed consideration of changing to a national review board, noting that, just as we have shown in our study, the current RRB system does not promote consistent reviews of the MELD/PELD scores nationwide.

In an ideal world, research identifying factors associated with wait list removals for patients with each of the non-RED conditions would have been carried out and used to construct a predictive model that accurately estimates risk of waiting list removals. That identified risk could then serve as the measure by which prioritization is determined. Unfortunately, little research has yet been performed and because many such conditions occur infrequently, valid cohort studies that could result in reproducible, clinically relevant results may not be possible in the near term, if ever. Thus, for the foreseeable future, expert opinion will continue to play a key role in prioritization policy.

The large variation across UNOS regions in denial rates for patient appeals which we report here gives strong support for the creation of an alternate system. We suggest simultaneously moving toward super regional/national sharing concepts and, as has been proposed by the Liver and Intestinal Organ Transplantation Committee and other authors (2, 5), a national review board to replace the current RRB system for non-standard conditions which require MELD exceptions. Ideally, a national review board process that uses current clinical knowledge combined with standardized data collection methods and analysis protocols could assign priority on a consistent basis. A new program that includes a national policy with consistency in the medical criteria and scores

Table 7. Transplantation rates by region, according to regional review board decision

Region	Approved (%)	Not approved (%)	p-Value	Odds Ratio (confidence intervals)
Overall	1764 (82.4)	556 (65.7)	<0.001	2.45 (2.04, 2.93)
1	35 (76.1)	25 (55.6)	0.195	2.55 (1.04, 6.24)
2	278 (79)	64 (61.5)	0.004	2.35 (1.47, 3.76)
3	165 (87.8)	46 (62.2)	0.001	4.37 (2.30, 8.29)
4	153 (82.7)	48 (63.2)	0.008	2.79 (1.53, 5.09)
5	219 (76.8)	117 (66.1)	0.063	1.7 (1.12, 2.58)
6	53 (76.8)	0 (0)		
7	121 (85.8)	39 (73.6)	0.195	2.17 (1, 4.7)
8	116 (85.9)	44 (80)	0.426	1.53 (0.67, 3.46)
9	194 (81.5)	69 (61.1)	<0.001	2.81 (1.71, 4.64)
10	224 (85.8)	48 (69.6)	0.015	2.65 (1.43, 4.92)
11	206 (85.8)	56 (70)	0.015	2.6 (1.42, 4.73)

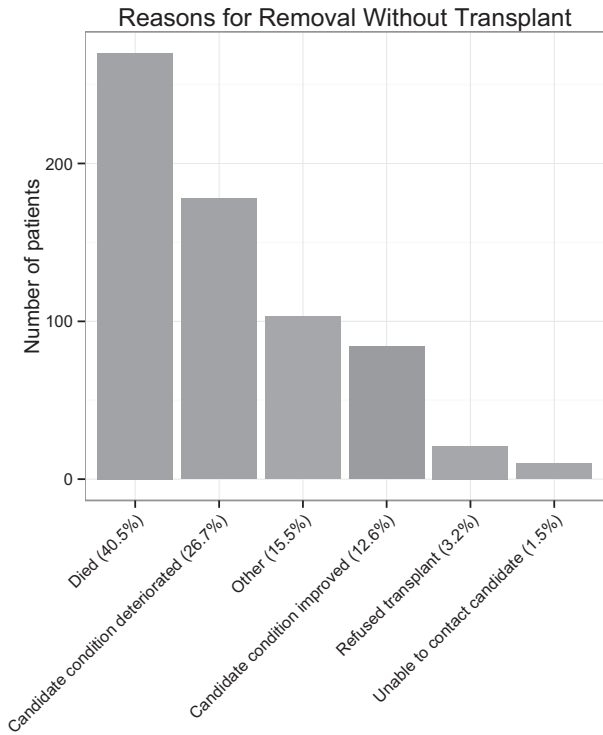


Fig. 3. Reasons for removal from the wait list other than receiving transplant.

Table 8. Kaplan–Meier estimates of mortality (95% confidence intervals)

	Approved	Not approved
90 days	0.04 (0.03, 0.05)	0.07 (0.05, 0.09)
180 days	0.09 (0.07, 0.10)	0.11 (0.08, 0.13)
1 yr	0.15 (0.12, 0.18)	0.16 (0.12, 0.19)
3 yr	0.24 (0.19, 0.29)	0.28 (0.22, 0.32)
5 yr	0.29 (0.20, 0.36)	0.38 (0.30, 0.45)

assigned for non-RED conditions could help to prevent “MELD creep” or MELD inflation, greatly reduce regionally driven MELD inequities, and disincentivize today’s situation in which some patients with resources (especially financial) pursue centers with high rates of approval for exceptions and shorter wait times.

At the same time, data on transplant benefit and wait list removals for disease progression should be collected for each non-RED condition to improve the knowledge base with which guidelines can be developed. Ultimately, a rational approach to a national system created through changes in UNOS policy may be our best hope for equalizing the assignment of MELD exception points and providing equity for transplant candidates in all regions with the singular or composite medical

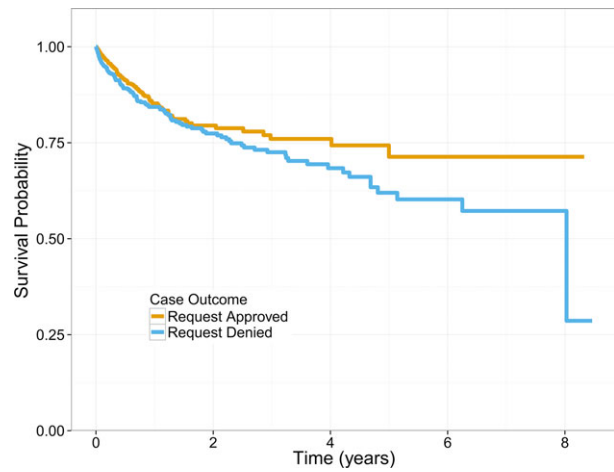


Fig. 4. Kaplan–Meier curves for approved and denied patients. Times are measured from date of regional review board decision.

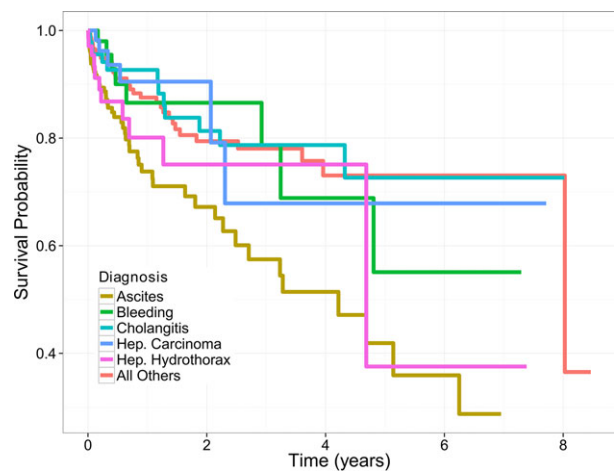


Fig. 5. Kaplan–Meier curves within denied patients, stratified by top five most frequent diagnoses. Times are measured from date of regional review board decision.

illnesses that currently fall in the category of non-RED conditions.

Acknowledgements

This manuscript was not funded or prepared in any part by a commercial organization. This project was partially supported by the National Institutes of Health, Grant UL1TR000100. The authors would like to express their gratitude to Dr. Lark Lands for her invaluable assistance in preparing the manuscript for publication.

Authors’ contributions

Robert G. Gish: Concept/design, data collection, drafting article, critical revision of article, and approval of article; Robert J. Wong: Data analysis/interpretation, critical revision of article, and approval of article; Gordon Honerkamp-Smith:

Statistics, data analysis/interpretation, critical revision of article, and approval of article; Ronghui Xu: Statistics, data analysis/interpretation, approval of article; Robert W. Osorio: Data analysis/interpretation, drafting article, critical revision of article, and approval of article.

References

1. FREEMAN RB Jr, GISH RG, HARPER A et al. Model for end-stage liver disease (MELD) exception guidelines: results and recommendations from the MELD exception study group and conference (MESSAGE) for the approval of patients who need liver transplantation with diseases not considered by the standard MELD formula. *Liver Transpl* 2006; 12(Suppl 3): S128.
2. RODRIGUEZ-LUNA H, VARGAS HE, MOSS A, REDDY KS, FREEMAN RB, MULLIGAN D. Regional variations in peer reviewed liver allocation under the MELD system. *Am J Transplant* 2005; 5: 2244.
3. ARGO CK, STUKENBORG GJ, SCHMITT TM, KUMER SC, BERG CL, NORTHUP PG. Regional variability in symptom-based MELD exceptions: a response to organ shortage? *Am J Transplant* 2011; 11: 2353.
4. MASSIE AB, CAFFO B, GENTRY SE et al. MELD exceptions and rates of waiting list outcomes. *Am J Transplant* 2011; 11: 2362.
5. GOLDBERG DS, MAKAR G, BITTERMANN T, FRENCH B. Center variation in the use of nonstandardized model for end-stage liver disease exception points. *Liver Transpl* 2013; 19: 1330.
6. The "Final Rule." Part 121—Organ Procurement and Transplantation Network. U.S. Department of Health and Human Services, Washington, DC, 1998.
7. HHS Rule Calls for Organ Allocation Based on Medical Criteria, not Geography. U.S. Department of Health and Human Services, Washington, DC, 1998.
8. ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK (OPTN)/UNITED NETWORK FOR ORGAN SHARING (UNOS) LIVER AND INTESTINAL ORGAN TRANSPLANTATION COMMITTEE. Concept Document: Next Steps Toward Improving Liver Distribution. United Network for Organ Sharing (UNOS), Richmond, VA, 2011.
9. ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK (OPTN)/UNITED NETWORK FOR ORGAN SHARING (UNOS) LIVER AND INTESTINAL ORGAN TRANSPLANTATION COMMITTEE. Redesigning Liver Distribution to Reduce Variation in Access to Liver Transplantation. Washington, DC: OPTN/UNOS, 2014.