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An Examination of Liver Offers to Candidates on the Liver Transplant Wait-List

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See editorial on page 1141.

BACKGROUND & AIMS: We aimed to characterize offers of organs to candidates awaiting liver transplantation (LT). **METHODS:** We analyzed data from the United Network for Organ Sharing registry on all US LT candidates with nonfulminant disease who were offered livers from February 1, 2005, to January 31, 2010, and ultimately received transplants. We excluded candidates with a final Model for End-stage Liver Disease score of less than 15. Livers were classified as high quality if they were from donors 18–50 years of age who were ≥170 cm tall, of non-black race, suffered brain death secondary to trauma, hepatitis C antibody-negative, not categorized as high risk by the Centers for Disease Control, and locally or regionally located. **RESULTS:** Of 33,389 candidates for LT, 20% died or were removed from the list and 64% received LT; the median (interquartile range) number of liver offers for all candidates was 5 (range, 2–12). Of those who died or were removed from the list, 84% received 1 or more liver offers. Overall, 55% of those who died or were removed from the list, and 57% of those who received LT, received 1 or more offers of a high-quality liver when they had Model for End-stage Liver Disease scores of 15 or greater ($P = .005$). However, the proportion of last liver offers of high quality to patients who underwent LT was twice that of patients who died or were removed from the list (28% vs 14%; $P < .001$). Most liver offers (68%) were refused for reasons related to donor quality. **CONCLUSIONS: Most candidates for LT who died or were removed from the list received 1 or more offers of a liver beforehand, and 55% received 1 or more offers of a high-quality liver. These findings indicate that a substantial proportion of wait-list mortality results in part from declined livers, rather than lack of opportunity, for transplantation. Understanding the real-time factors involved in the complex decision to accept a liver offer is vital to reducing wait-list mortality for LT candidates.**

Keywords: Graft; Availability; Database Analysis; Surgery.

Under the current liver allocation system, patients are prioritized by their risk of wait-list mortality, as determined by their Model for End-stage Liver Disease (MELD) score. Once a liver graft becomes available, it is offered to the candidate who is first on the wait-list. Depending on the quality of the donor liver relative to the perceived need of the candidate, this liver offer may be accepted for transplantation. Alternatively, at the discretion of the center to which the graft was offered, this liver offer may be declined, in which case it will be offered to the candidate who is next on the wait-list, and similarly down the wait-list, until it finally is accepted for transplantation. This donor offer process has been incompletely described. Therefore, we aimed to characterize liver offers from the perspective of the liver transplant wait-list candidate.

Materials and Methods

Study Population

We evaluated liver offers to all liver transplant candidates ≥18 years of age who were wait-listed for indications other than fulminant hepatic failure in the United States from February 1, 2005, through January 31, 2010 (n = 53,659). We included only offers of livers that ultimately were transplanted. The study period was selected to correspond to the implementation of the "Share 15" policy, in which livers first are allocated locally, and then regionally to wait-list candidates with MELD scores of 15 or greater before they are offered locally to candidates with MELD scores of less than 15.[1] Because a prior study has shown that patients with a MELD score of less than 15 may not derive survival benefit from liver transplantation vs continued waiting on the wait-list,[2] only candidates with a MELD score of 15 or higher at the time of their final wait-list event (eg, death, removal, transplant) were included in this study. We excluded candidates listed with MELD exception points for reasons other than hepatocellular carcinoma because these patients fit into a heterogeneous group whose MELD score may not directly reflect their need for transplantation.

Data on match-runs were obtained from the United Network for Organ Sharing/Organ Procurement Transplantation Network (UNOS/OPTN) as of June 30, 2010. Data on wait-list candidates and their donors were obtained from the Standard Transplant Analysis and Research files as of the same date.

Abbreviations used in this paper: CDC, Centers for Disease Control; DCD, donation after cardiac death; HCV, hepatitis C virus; MELD, model for end-stage liver disease; UNOS/OPTN, United Network for Organ Sharing/Organ Procurement and Transplantation Network.

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Characteristics Evaluated

Wait-list candidates. Demographic data on wait-list candidates included sex, race, age, and height at the time of listing. Etiologies of liver disease were grouped into the following categories: hepatitis C (HCV), hepatitis B, alcoholic liver disease, nonalcoholic fatty liver disease (including cryptogenic and nonalcoholic steatohepatitis), autoimmune (including autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis), and other (including α1-antitrypsin deficiency, Budd–Chiari, hemochromatosis, and others). Candidates listed with HCV in addition to other diagnoses were categorized as HCV. Only candidates listed as having moderate or severe ascites or encephalopathy in the UNOS/OPTN registry were classified as having ascites or encephalopathy in our study.

Donors. Donors were characterized by factors included in the donor risk index[3] including sex, race, age, height, HCV antibody status, Centers for Disease Control high risk for disease transmission status (CDC high risk), cause of death (eg, trauma, anoxia, stroke, other), and donation after cardiac death (DCD). Split liver status was not considered because these data were available only in the UNOS/OPTN registry for the transplanted liver (eg, last offer) but not necessarily for the donor liver offers before the final acceptance.

Characteristics of each donor liver were available only at transplant. Therefore, we obtained characteristics of the donor offer by matching the donor identification number of the offer with the transplant donor identification number. Cut-off values for selected variables that were considered implausible for an adult recipient were as follows: recipient height shorter than 120 cm or taller than 240 cm, recipient weight less than 30 kg or more than 180 kg, donor height shorter than 100 cm or taller than 240 cm, donor weight less than 20 kg or more than 180 kg, cold ischemia time less than 1 hour or more than 24 hours, and warm ischemia time less than 10 minutes or more than 120 minutes. Observations including these implausible values were set to missing.

Liver offers were classified as high quality if they were from donors between the ages of 18 and 50 years old, $\geq$170 cm in height, of non-black race, suffered brain death secondary to trauma, HCV-antibody negative, not CDC high risk, and locally or regionally located. A sensitivity analysis was performed to evaluate whether livers that were classified as high quality behaved as expected with respect to graft failure rates.

Reasons for refusal of liver offers. Refusal codes of liver offers were obtained from the UNOS/OPTN database. We categorized these refusal codes into 6 broad categories, as follows: (1) donor age or quality, this was a single refusal code in the UNOS database; (2) donor size/weight; (3) other donor factors (eg, ABO blood group, social history, positive serologic tests, organ preservation, organ anatomic damage or defect, organ-specific donor issue; (4) recipient readiness (eg, patient's condition improved, patient ill, unavailable, refused, or temporarily unsuitable, multiple organ transplant or different laterality is required); (5) programmatic (eg, heavy workload, operational at transplant center, exceeded 1-hour response time, surgeon unavailable, distance to travel or ship); and (6) other (eg, multi-organ placement, directed donation, and so forth).

Statistical Analysis

Among candidates who received 1 or more liver offer(s), we compared dead/delisted with transplanted candidates using the chi-square, Wilcoxon, and Kruskal–Wallis tests for categoric and continuous variables as appropriate. Parameter estimates were made using list-wise deletion under the assumption that missing data were missing completely at random. A sensitivity analysis to confirm that our classification of high-quality livers behaved as expected was conducted using a Cox proportional hazards model for graft failure adjusted for MELD score, recipient age at transplant, and UNOS region. Analyses were performed using Stata 11.0 statistical software (College Station, TX).

The institutional review board at the University of California San Francisco approved the use of UNOS/OPTN registry data for this study.

Results

Of the 33,389 candidates included in our study, 6737 (20%) died or became too sick for transplant (dead/delisted), 21,258 (64%) underwent deceased donor liver transplantation (transplanted), 2030 (6%) were removed for other reasons, and 3364 (10%) were still awaiting liver transplantation at the end of the study period. Of the dead/delisted, 5680 (84%) received 1 or more liver offer(s) before death/delisting from the wait-list.

Characteristics of Wait-List Candidates

The characteristics of the dead/delisted candidates with 1 or more offer(s) vs transplanted candidates, categorized by HCC exception point status, are shown in Table 1.

Without HCC. MELD score at listing, first offer, last offer, and final wait-list event was 17, 17, 21, and 27 for candidates who died/were delisted compared with 20, 20, 24, and 24, respectively, for candidates who were transplanted ($P < .001$ between groups). Wait-list time was significantly longer (230 vs 60 days) for the dead/delisted vs transplanted candidates, respectively ($P < .001$ for both). While on the wait-list, the dead/delisted candidate group received a median of 6 liver offers compared with 4 offers for the transplanted group ($P < .001$); the median time from first to last offer was 92 vs 29 days for the dead/delisted vs transplanted candidates, respectively ($P < .001$) (Table 1).

With HCC. The MELD score at listing was 13 for the dead/delisted candidates and was 11 for transplanted candidates ($P < .001$). The MELD score at the final wait-list event was higher for those who died/were delisted than for those who were transplanted (24 vs 22; $P < .001$). Both groups received a median of 6 liver offers ($P = .002$), with a median of 96 vs 71 days for dead/delisted and transplanted candidates, respectively ($P < .001$) (Table 1).

Donor Characteristics of the Liver Offers

Donors of livers that were offered to dead/delisted vs transplanted candidates were clinically comparable but statistically different ($P < .001$ for all) (Table 2). Donors of the last liver offer to those who died/were delisted with 1 or more offer(s) compared with those who were transplanted were older (49 vs 43 y), more likely to be African American (16% vs 13%), die from stroke (45% vs 43%),

Table 1. Characteristics of Candidates Awaiting Liver Transplantation, by Wait-List Outcome (Dead/Delisted Versus Transplanted) and by HCC Exception Point Status

Characteristics	All wait-list candidates (n = 33,389)	Dead/delisted with ≥1 offer(s) (n = 5680)		Transplanted (n = 21,258)	
		Without HCC (n = 4916)	With HCC (n = 764)	Without HCC (n = 14,982)	With HCC (n = 6276)
Demographics					
Female sex	32%	40%	23%	33%	22%
Age at listing, *y*	54 (49–60)	55 (49–60)	56 (52–61)	53 (48–59)	56 (52–61)
African American race	9%	8%	10%	10%	9%
Etiology of liver disease					
Hepatitis C	44%	41%	53%	41%	58%
Alcoholic	16%	16%	11%	19%	8%
Nonalcoholic fatty liver	7%	7%	3%	9%	4%
Cholestatic	10%	10%	3%	13%	3%
Other	23%	26%	30%	18%	27%
Disease severity					
Ascites	37%	51%	28%	47%	16%
Encephalopathy	17%	36%	16%	18%	6%
MELD score at listing	16 (12–22)	17 (13–23)	13 (10–16)	20 (15–26)	11 (8–14)
MELD score at first liver offer	18 (15–25)	17 (14–24)	22 (14–22)	20 (16–27)	22 (18–22)
MELD score at last liver offer	22 (18–28)	21 (16–32)	22 (22–25)	24 (19–32)	22 (22–25)
MELD score at wait-list event	23 (19–29)	27(19–38)	24 (22–28)	24 (19–31)	22 (22–25)
Wait-list time, days	130 (28–449)	230 (56–733)	233 (102–634)	60 (13–244)	110 (38–260)
Offers					
Offers per candidate	5 (2–12)	6 (2–14)	6 (3–15)	4 (2–9)	6 (2–13)
Time from first offer to last offer, days	65 (6–260)	92 (9–383)	96 (25–258)	29 (1–159)	71 (14–190)
Time from last offer to wait-list event, days	—	17 (4–57)	24 (7–75)	—	—

NOTE. n (%) or median (interquartile range) is shown.

DCD (12% vs 6%), be nationally offered (25% vs 12%), be HCV-antibody positive (6% vs 3%), or be categorized as CDC high risk (12% vs 9%) ($P < .001$; Table 2).

It is of interest to examine the acceptance of organs that may be considered high-quality. As a point of reference, only 28% of transplanted livers were considered high quality by these criteria. Among livers classified as high quality, 56% were accepted on the first offer compared with 39% of lower-quality livers ($P < .001$). As expected, adjusted risk of graft failure was significantly lower for high-quality livers compared with the other livers (hazard ratio, 0.76; 95% confidence interval, 0.71–0.81; $P < .001$).

Table 2. Characteristics of All Liver Offers Versus Last Liver Offer to Candidates Who Died/Were Delisted Compared With Those Who Underwent Transplantation

Characteristics[a]	Among dead/delisted candidates with ≥1 offer(s) (n = 64,742)		Among candidates who underwent transplantation (n = 184,576)	
	All offers	Last offer	All offers	Last offer
Donor age	51 (36–65)	49 (32–62)	50 (35–64)	43 (26–55)
Donor African American race	14%	16%	16%	13%
Donor height	170 (163–179)	172 (163–179)	173 (163–180)	173 (165–180)
Cause of death				
Anoxia	23%	24%	22%	18%
Trauma	24%	27%	26%	37%
Stroke	49%	45%	48%	43%
Other	4%	4%	4%	3%
Donation after cardiac death	13%	12%	12%	6%
Nationally offered	22%	25%	21%	12%
Donor HCV-antibody positive	8%	6%	7%	3%
CDC high risk	12%	12%	11%	9%
High quality[a]	11%	14%	13%	28%

NOTE. Comparisons between the 2 groups (dead/delisted vs DDLT) were significant at a *P* value of less than .001. Data are shown as follows: n (%) or median (interquartile range).

[a]Livers were defined as high quality if they were from donors between the ages of 18 and 50 years old, ≥170 cm in height, of non-black race, suffered brain death secondary to trauma, HCV-antibody negative, not CDC high risk, and were locally or regionally located.

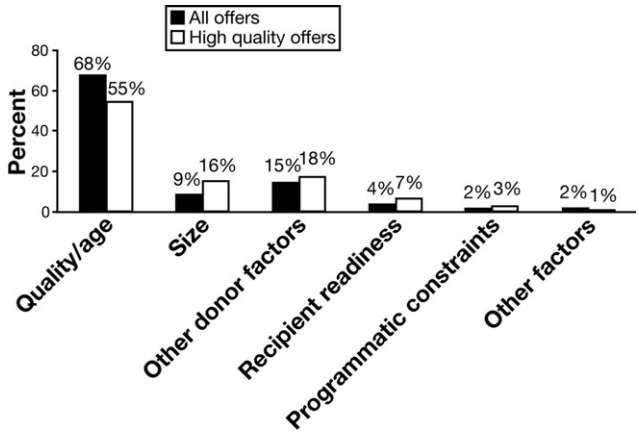

Figure 1. Reasons for refusal of all vs high-quality liver offers. Livers were defined as high quality if they were from donors between the ages of 18 and 50 years old, ≥170 cm in height, of non-black race, suffered brain death secondary to trauma, HCV-antibody negative, not CDC high risk, and were locally or regionally located.

In a subgroup analysis restricted to only the high-quality livers, adjusted graft failure for recipients who received a high-quality liver that was refused at least once was similar to graft failure for recipients who received a high-quality liver that was accepted on the first offer (HR, 0.95; 95% confidence interval, 0.83–1.07; $P = .38$).

Overall, 55% of dead/delisted and 57% of transplanted candidates received 1 or more high-quality liver offers at a MELD score of 15 or greater ($P = .005$). Among all liver offers, high-quality livers accounted for 11% of livers offered to died/delisted and 13% offered to transplanted candidates ($P < .001$) (Table 2). The proportion of last liver offers that were of high quality to those who were transplanted (ie, the accepted liver) was twice as high as the proportion offered to those who died/were delisted (28% vs 14%) ($P < .001$; Table 2).

Reasons for Liver Offer Refusal

The majority (68%) of liver offer refusals for organs that subsequently were transplanted were reported under a single UNOS refusal code for donor quality/age. An additional 9% were refused for size, 15% were refused for other donor factors, 4% were refused for recipient readiness, and 4% were refused for programmatic or other reasons. Compared with all liver offers, a greater proportion of the high-quality offers (as previously defined) were refused for reasons related to size (16%) and recipient readiness (7%). Nevertheless, the majority of high-quality liver offers were refused for reasons related to donor quality/age or other donor-related factors (73%) (Figure 1).

Among all livers refused at least once, 92% were transplanted into patients with the same or a lower MELD score than the first candidate to whom it was offered (eg, 8% of livers were transplanted into patients with a higher MELD score than the first candidate).

Discussion

By integrating data regarding liver offers with donor and candidate characteristics, we found that the vast majority (84%) of wait-listed candidates who died or were delisted at a MELD score of 15 or higher had received liver offers that ultimately were transplanted into lower-priority candidates. More surprisingly, these candidates received not just 1 or 2, but a median of 6, liver offers during their time on the wait-list. These findings suggest that wait-list mortality is not simply a result of not having the opportunity for transplantation, as many of us assume. Rather, wait-list mortality appears to result from opportunities for transplantation that were declined.

Although each declination is associated with a specific refusal code, the dominant use of the single code donor quality or age, even when the liver appears to be of high quality, strongly suggests that the UNOS/OPTN data do not accurately or fully capture the true refusal reason. However, we found no difference in the risk of graft failure among high-quality livers that were accepted on the first offer compared with high-quality livers that were turned down at least once, suggesting that there were no systematic differences inherent to the fact that they were refused, despite the fact that the most common refusal code registered in UNOS was donor age/quality. There are undoubtedly reasons in addition to a single unfavorable donor factor, such as recipient-donor interactions or the transplant centers' philosophy about the utility of transplantation given certain donor and recipient characteristics, that drive the real-time decisions to decline a liver offer. The nuances of these refusals cannot be determined in the absence of more granular, center-level data.

Nevertheless, in considering the rhythm and patterns of daily clinical practice, we suggest that there are 3 major categories of factors that influence this complex and dynamic decision.

Candidate factors. For most patients with cirrhosis, the progression of liver disease is a nonlinear process characterized by sudden deteriorations related to events such as variceal hemorrhage, spontaneous bacterial peritonitis, or hepatorenal syndrome. During the course of these events, candidates may be perceived to have excess perioperative and short-term post-transplant risk (eg, sepsis) rendering the candidate temporarily or permanently unsuitable for transplantation, necessitating refusal of liver offers. Second, a candidate may be actively listed but still completing the pretransplant evaluation and, therefore, essentially is not ready for transplantation. It is also a possibility that transplant clinicians perceive candidates to be well enough to wait for a better graft, especially when faced with an offer of lower quality. Finally, candidates, themselves, can refuse a transplant opportunity presented to them by their transplant physician secondary to logistical constraints, concerns regarding donor quality, or nonmedical limitations.

Donor factors. The quality of donor livers has been decreasing over time,[4] with only 29% of livers trans-

planted during our 5-year study period meeting the definition of high quality. We have increasingly sophisticated knowledge of interactions between donor characteristics and recipient outcome, as seen with HCV-infected recipients receiving older donor livers[5] and possibly with DCD livers.[6,7] Finally, there is a strong mandate that any and all aspects of a donor that pose increased risk must be fully disclosed to and discussed with a potential recipient. This heightened awareness of all dimensions of donor risk likely discourages acceptance of nonideal transplant opportunities.

Center factors. The current regulatory environment focused on transplant center performance and outcomes may, consciously or subconsciously, influence offer acceptance vs declination decisions. This may be especially relevant for low-volume transplant centers for whom even a small number of poor outcomes associated with grafts that have been declined by other centers (most often for low quality) may make a relatively large difference in the center's perceived performance.[8] Moreover, the financial implications of transplant decisions are substantial, particularly if the candidate has high disease severity and/or the donor liver is of suboptimal quality.[9] Finally, factors such as competition with other centers and availability of surgeons and operating room space also may play a role in the decision to accept offers at certain times.

Understanding the real-time factors involved in these decisions is vital to improving the wait-list process for liver transplant candidates. Although some of the factors are beyond control, others can be managed. For example, centers should encourage wait-list candidates to complete their liver transplant work-up (eg, cardiac testing, age-appropriate cancer screening, tuberculosis testing) as expeditiously as possible to avoid having liver offers turned down simply because they are not ready. Patients with a MELD score of 15 or higher should be thoroughly educated about the unpredictability of death on the wait-list and their survival benefit of transplantation with any graft relative to continued waiting on the list[10] to reduce patient refusal of otherwise suitable organs. This education effort might include a prospective assessment of the individual candidate's willingness to accept increased donor risk in exchange for more expeditious transplantation (thereby reducing wait-list mortality), as has been proposed by Volk et al.[11] Given the increasing risk profile of deceased liver donors, efforts should be made in the transplant community to reduce the stigma associated with nonideal livers and set realistic expectations for wait-listed candidates. Perhaps, liver offer acceptance practices should be taken into consideration in assessing center performance, as a means of encouraging centers to accept more livers for their candidates.

In conclusion, our data show that the current liver allocation system has provided one or more transplant opportunities to nearly all candidates before death/delisting. Therefore, simply increasing the availability of deceased donor livers or the number of offers may not substantially reduce wait-list mortality. It is worth noting that all centers/physicians are provided with the same information about the donors, so differential decisions regarding declining or accepting a liver offer cannot be based solely on donor factors. Efforts must be directed at reducing offer declination rates through identification of modifiable barriers that may exist at multiple levels—candidate, physician, center, as well as donor—to proceeding with timely transplantation to avoid death or delisting as the terminal wait-list event.

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Reprint requests

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Conflicts of interest

The authors disclose no conflicts.

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