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Reframing the impact of combined heart-liver allocation on liver transplant waitlist candidates

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Abstract

Simultaneous heart-liver transplantation, although rare, has become more common in the U.S. When the primary organ is a heart or liver, patients receiving an offer for the primary organ automatically receive the second, non-primary organ from that donor. This policy raises issues of equity—i.e. whether liver transplant-alone candidates bypassed by heart-liver recipients are disadvantaged. No prior published analyses have addressed this issue, and few methods have been developed as a means to measure the impact of such allocation policies. We analyzed OPTN match run data from 2007-2013 to determine whether this combined organ allocation policy disadvantages bypassed liver transplant waitlist candidates in a clinically meaningful way. Among 65 heart-liver recipients since May 2007, 42 had substantially higher priority for the heart relative to the liver, and bypassed 268 liver-alone candidates ranked 1-10 on these match runs. Bypassed patients had lower risk of waitlist removal for death or clinical deterioration compared to controls selected by match MELD score (HR: 0.56, 95% CI: 0.40-0.79), and similar risk as controls selected by laboratory MELD score (HR: 0.91, 95% CI: 0.63-1.33) or on match runs of similar graft quality (HR: 0.97, 95% CI: 0.73-1.37). The waiting time from bypass to subsequent transplantation was significantly longer among bypassed candidates versus controls on match runs of similar graft quality (median: 87 (IQR: 27-192) days versus 24 (5-79) days; $p < 0.001$). Although transplant is delayed, liver transplant waitlist candidates bypassed by heart-liver recipients do not have excess mortality compared to three sets of matched controls. These analytic methods serve as

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a starting point to consider other potential approaches to evaluate the impact of multi-organ transplant allocation policies

Keywords

multi-organ transplantation; MELD score; bioethics

Introduction

Within the United States there has been an increasing practice of certain types of simultaneous multi-organ transplants (MOT), including combined liver-kidney and heart-liver (H-L) transplants.¹⁻⁷ This demand is attributable to several factors, including an aging population with congenital heart disease and congestive hepatopathy,⁶ as well as increased prevalence of chronic kidney disease in liver and heart transplant candidates.³⁻⁶ The need for the second organ may be for end-stage disease in the non-primary organ necessitating a transplant independent of the primary organ (e.g. a patient with decompensated cirrhosis on hemodialysis), or end-stage disease in the non-primary organ without overt clinical symptoms, but needed in order to optimize function of the primary organ (e.g. end-stage heart failure with congestive hepatopathy and cirrhosis, but preserved liver synthetic function). To accommodate waitlist candidates in need of MOTs, Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) policy dictates that when the primary organ is a heart, lung or liver, patients who receive an offer for one of these three primary organs automatically receive the second, non-primary organ from that donor, regardless of their waitlist priority for that second organ, only when the organ will be allocated to a patient in the local organ distribution unit (it is voluntary if the recipient is outside of the local organ distribution unit).⁸

Given that annual liver transplant waitlist mortality rates exceed 20% in several UNOS regions⁹, the current MOT allocation policy raises issues of equity and utility¹⁰. Prioritizing a MOT candidate for the non-primary organ may unfairly cause harm to a candidate who also has strong ethical claims to the same organ but must remain on the waitlist. Additionally, questions of utility arise as to whether allocating two organs to a MOT recipient yields greater (or fewer) quality-adjusted life-years compared with allocating each organ to a single candidate. For example, when a patient with maximum priority for a heart transplant receives the heart and liver from the same donor, the policy may be perceived as unfair to liver-transplant alone (LTA) candidates bypassed during the match run for that liver.

The problem of fairness to patients who are bypassed by an MOT depends on how much harm these patients experience. Previous MOT studies have focused on waitlist mortality for potential MOT recipients⁶ or the benefit of incremental versus simultaneous transplants, but none have focused on the outcomes of those individuals who are bypassed when organs are diverted to MOT recipients.^{10,11} Given the lack of prior work addressing the impact of MOT allocation policies on waitlist candidates bypassed by such organ diversions, there are no established methods to measure the impact of such policies. Within liver transplantation,

modeling approaches have been used to estimate the impact of broader regional and national organ sharing, but no empirical methods exist to evaluate this specific question of MOT organ allocation. Furthermore, there have been few studies utilizing recently available OPTN match run data¹², which may become a more frequent focus of research involving organ allocation and distribution. In this study, we analyze match run data from the OPTN to determine whether the current H-L allocation policy leads to greater mortality or prolonged waiting time for transplantation among LTA candidates who are bypassed by H-L recipients.

Methods

Study Population and approach

The cohort of interest included any candidate on the liver transplant waitlist who was ranked on a liver match run where the liver was allocated to a combined H-L recipient, instead of a LTA candidate. We focused specifically on H-L transplants because: 1) that is the most commonly performed combined thoracic-liver transplant⁶; 2) the number of combined H-L candidates is projected to rise due to the aging congenital heart disease population^{1,6}; and 3) in many H-L transplants, the H-L recipient has cirrhosis without overt complications of end-stage liver disease.¹

All analyses were based on OPTN/UNOS data from May 10, 2007 through May 10, 2013. The initial date was the first date for which match run data were made available for research. OPTN/UNOS data included encrypted donor and waitlist candidate variables, match run position, and match Model for End-Stage Liver Disease (MELD) for every transplant recipient, in addition to all waitlist candidates ranked higher (i.e. higher waitlist priority but turned down or were bypassed for organ) in every match run. Only match runs of combined H-L recipients 18 years of age were included given differences in organ allocation policies for adult vs. pediatric waitlist candidates.

The analyses utilized two distinct matching techniques to identify comparator groups to assess the impact of bypassing single organ candidates (Table 1). The first approach compared LTA waitlist candidates bypassed on H-L match runs to two separate cohorts of control waitlist *candidates with similar characteristics*—matched for blood type, UNOS region, and MELD score (matched candidate cohort #1 was matched by match MELD score, while matched candidate cohort #2 was matched by laboratory MELD score—taken together, these analyses are referred to as the “*matched candidate approach*”). The secondary approach utilized match runs in which *the liver allografts were of identical quality* as measured by the donor risk index (DRI;¹³ which we refer to as the “*matched allograft approach*”) to grafts of H-L recipients. These analyses were limited H-L match runs where the heart “sequestered” the liver, thereby bypassing LTA candidates with higher waitlist priority.

Categorization of combined heart-liver match runs

Data for all match runs for which there was a combined H-L allocation were evaluated. Match runs were categorized as “heart sequestering liver,” “liver sequestering heart,” or “equal priority.” Assignment of categories was determined by comparing the transplant

recipients' rank on the corresponding liver and heart match runs. Ranks within 2 places (i.e. 1st on heart and 3rd on liver) were considered “equal,” and differences of 3 or greater were assigned to the organ with the higher priority (i.e. 1st on heart and 9th on liver considered “heart sequestering liver”). Given that there were only eight match runs where the liver “sequestered” the heart (e.g. the candidate was ranked 1st on the liver match run, but 50th on the heart match run, thus diverting the heart from other heart-alone candidates), the primary analyses were restricted to match runs where the heart “sequestered” the liver.

The liver graft quality, measured by the DRI, was calculated for each liver graft allocated in a combined H-L transplant, and converted to a categorical variable based on predicted graft survival for the purposes of matching (1.0, 1-1.4, 1.4-1.6, and 1.6-2.0).¹³.

Selection of control liver waitlist candidates for the matched candidate analysis

This analysis compared liver waitlist candidates who were bypassed by a H-L recipient to two different sets of control liver waitlist candidates matched on UNOS region, blood type, and either: 1) laboratory MELD score; or 2) match MELD score. The utilization of these two methods tested whether the results were sensitive to the control group. Match MELD score controls served as a comparator group with similar access to transplantation based on waitlist priority, while laboratory MELD score controls functioned as a comparator group with similar expected waitlist mortality, better predicted using the laboratory MELD score.^{14,15} To account for discrepancies between laboratory and match MELD scores, we included a variable indicating whether a waitlist candidate had exception points at the time of bypass or selection as a control. The process of identifying matched candidates did not rely on match run data, but instead on candidate waitlist characteristics including most recently updated MELD score.

Selection of control liver-alone match runs for the matched allograft analysis

“Control” liver-alone match runs were compared to H-L match runs where the heart sequestered the liver. Specifically, “control” match runs were those where the liver graft was the same blood type and DRI category (graft quality) to H-L match runs where the heart sequestered the liver. Only liver waitlist candidates in the top 10 rank positions of a control or H-L match run for a given liver were evaluated because >90% of comparable livers were distributed to LTA waitlist candidate ranked 1-10.

Outcomes

The primary outcome was waitlist removal for death or clinical deterioration, defined as dying on the waitlist or within 90 days of removal from the waitlist, when the reason for waitlist removal was “too sick to transplant,” or “other.” Death within a short time from waitlist removal is reflective of severity of illness and viewed as equivalent to dying on the waitlist,^{15,16} and can be identified based by Social Security Death Master File death date.^{15,16}

Index date

The index date for bypassed waitlist candidates was the date of H-L match run from which they were bypassed. The index date for controls in the matched candidate analysis was the

date the respective waitlist candidate met matching criteria since this is the date from which the control would be expected to have similar access to transplantation (match MELD score), or waitlist mortality (laboratory MELD score) compared to the bypassed waitlist candidate. The index date for controls in the matched allograft analysis was the first date that respective waitlist candidate was ranked 1-10 on a LTA match run of comparable graft quality to the liver in a H-L match run. As many controls in the matched allograft approach were identified in more than one match run, we assigned these waitlist candidates to the first match run during the study period.¹²

Analytic methods

1. Matched candidate approach: Comparison of liver waitlist candidates bypassed by H-L allocation to control matched waitlist candidates

Waitlisted liver transplant candidates bypassed on a H-L match run were compared to control candidates matched by MELD score, blood type, and UNOS region using stratified Cox models that account for matched data. Models were stratified by match group (i.e. cohort of bypassed candidates and controls with a given combination of MELD score, region, and blood type), and incorporated a robust variance sandwich estimator to account for correlation due to matching.¹⁷ As MELD score was used for matching, it could not be a covariate; however, models included a covariate indicating whether the patient had exception points.

2. Matched allograft approach: Comparison of heart-liver match runs to control match runs involving liver allografts of similar quality

Bypassed liver candidates from a match run where a heart sequestered the liver were compared to liver candidates in control match runs. Competing risk Cox regression models evaluating the outcome of waitlist removal for death or clinical deterioration were fit. Transplantation was modeled as a competing risk, because in evaluating pre-transplant survival, transplantation influences the probability that a waitlist candidate will be removed from the waitlist for death or clinical deterioration.¹⁸⁻²⁰ The primary covariate of interest was match run type (H-L versus LTA). Whether the liver waitlist candidate had exception points (yes/no) was modeled as an interaction term to determine if the risk of mortality for bypassed candidates was magnified whether the waitlist priority was based on a laboratory versus exception MELD score. The interaction term was considered significant at a p -value <0.10 . Covariates were reported as sub-hazard ratios (SHR), the convention for competing risk models.¹⁸⁻²⁰ Region was not a covariate as not all regions were included in the H-L match runs given the geographic distribution of H-L recipients. Time from bypass (or presence on a control match run) to transplantation was calculated, and compared between bypassed candidates and matched allograft controls to determine if the time from appearing on one match run to subsequent transplantation is longer in bypassed waitlist candidates.

Both the matched candidate and matched allograft approaches considered other potential covariates of age, gender, race/ethnicity, and primary diagnosis. The matched allograft approach also considered match MELD score at the time of ranking on a match run. While

MELD exception status (yes/no) was evaluated in both models, it was a covariate in the matched candidate models as MELD score was used for matching, but an interaction term in the matched allograft models. All final models used a stepwise variable-selection process to retain variables with p-values ≤ 0.2 .

This study was approved by the Institutional Review Board at the University of Pennsylvania. All analyses were performed using Stata 13.0 (College Station, TX).

Results

From May 10, 2007 through May 10, 2013, 59,268 LTA waitlist candidates were added to the waitlist, and there were 32,447 LTA transplants performed during this time. By contrast, there were 197 H-L waitlist candidates added during this time, with 65 H-L recipients aged 18 or older. In 2007 and 2008, there were 5 and 7 H-L recipients, respectively, compared to an average of 12 from 2009-2012. The majority of these 65 recipients were concentrated in two UNOS regions: region 2 (28, 43.1%) and 7 (19, 29.2%)—regions with above-average wait times, and match MELD scores at transplantation, for LTA recipients.⁹ The two most common causes of liver disease in H-L recipients were cardiac cirrhosis (N=31, 47.7%) and amyloidosis (N=21, 32.3%), with heart failure most commonly caused by amyloidosis (N=20, 30.8%), congenital heart disease (N=12, 18.5%), and idiopathic dilated cardiomyopathy (N=11, 16.9%; Table 2).

Among the 65 H-L recipients, the heart “sequestered” the liver in 64.6% (N=42) of match runs, the liver “sequestered” the heart in 20% (N=13) of match runs, and there was equal priority in 15.4% (N=10) of cases (Table 2). The median donor age was 28 (IQR: 21-42) and the median donor LVEF was 65% (IQR: 60-65%). The median liver DRI in these 65 transplants was 1.16 (IQR: 1.05-1.34), significantly lower ($p<0.001$) than the median DRI of all liver allografts transplanted during the same time period (median: 1.45, IQR: 1.18-1.77).

Heart-liver match runs

In the 42 match runs where the heart sequestered the liver, 69.0% (29/42) of the H-L recipients were ranked in the top three of the heart match run, while 57.1% (24/42) were ranked below the top 100 ranked candidates on the corresponding liver match run. These 42 H-L recipients bypassed a total of 268 adult waitlist candidates ranked in the top 10 positions of the liver match run.

Comparison of bypassed liver transplant candidates and controls

Table 3 demonstrates the clinical and demographic characteristics of the bypassed liver waitlist candidates and the three control groups. The median laboratory MELD score at the time of being bypassed for the 268 bypassed liver waitlist candidates was 18 (IQR: 11-30), while the median match MELD score was 29 (IQR: 27-32). A substantially greater proportion of waitlist candidates bypassed on H-L match runs had exception points accounting for their waitlist priority, and lower calculated laboratory MELD scores (Table 3; $p<0.001$).

Matched candidate approach

The 268 bypassed liver waitlist candidates ranked in the top 10 of a match run where the heart sequestered the liver were matched to control waitlist candidates based on match MELD score (bypassed to control 1:8; N=2,144, as each bypassed waitlist candidate had at least 8 potential controls) or laboratory MELD score (bypassed to control 1:9; N=2,340, as each bypassed waitlist candidate had at least 9 potential controls), UNOS region, and blood type.

Significantly more bypassed candidates ($p<0.001$) had MELD exception points: 43.7% (117/268; with two-thirds for hepatocellular carcinoma) versus 19.9% (426/2,144) of match MELD score controls. From the index date, 14.6% (39/268) of bypassed liver candidates were removed from the waitlist for death or clinical deterioration, compared with 24.7% (530/2,144; $p<0.001$) of match MELD score controls; by contrast, 72.0% (193/268) of bypassed patients were ultimately transplanted, compared with 61.7% (1,323/2,144; $p=0.001$) of match MELD controls. In stratified multivariable Cox models, bypassed waitlist candidates had significantly lower risk of waitlist removal for death or clinical deterioration compared to match MELD score controls (HR: 0.56, 95% CI: 0.40-0.79; Table 4). The time from index date to either: a) transplantation or b) waitlist removal was similar between bypassed waitlist candidates and matched controls (data not shown).

By contrast, in multivariable Cox regression models of bypassed waitlist candidates and laboratory MELD score controls, there was no significant difference in the risk of subsequent mortality following bypass (HR for bypassed candidates: 0.91, 95% CI: 0.63-1.33; $p=0.64$; full model results not shown).

In the 42 transplants where the heart sequestered the liver, the median DRI was 1.24, 95% CI: 1.10-1.51. Two hundred sixty-five (98.9%) of the bypassed liver waitlist candidates received at least one subsequent liver offer, and the DRI of the next allograft offered after being bypassed was 1.65, 95% CI: 1.38-2.13; $p<0.001$ compared to the offer on the bypass match run). However, these “lower quality” offers were only accepted by nine of the bypassed waitlist candidates. Of the 193 bypassed candidates who were ultimately transplanted, the organ quality was similar to the organ transplanted during the bypass match run, with a median DRI=1.34, 95% CI: 1.14-1.59. The data did not suggest that being bypassed had adverse consequences for bypassed waitlist candidates who ultimately underwent transplant; the 1- and 3-year post-transplant patient survival was similar in bypassed candidates versus controls (data not shown). Similarly, the delays in transplantation did not lead to significantly different or clinically meaningful rates of simultaneous liver-kidney transplants (13% in bypassed candidates versus 11% in controls).

Matched allograft approach: Comparison of H-L match runs to control match runs involving liver allografts of similar quality

There were 20,962 unique control candidates who were: 1) ranked in the top 10 and 2) had higher waitlist priority than the recipient of the liver on a control match run involving a liver graft of comparable quality to that used in a H-L transplant of which the heart sequestered the liver (e.g. the waitlist candidate on the control match run turned down the organ,

allowing it to be allocated to a patient with lower waitlist priority). Among the LTA recipients from these control match runs, the median match rank was 2 (IQR: 1-5), with nearly three-quarters (75.4%) in the top five rank positions. The median laboratory MELD score was 21 (IQR: 14-30), and median match MELD was 25 (IQR: 22-31).

There was no difference in the proportion of waitlist candidates who subsequently were removed from the waitlist for death or clinical deterioration among bypassed waitlist candidates ranked in the top 10 contrasted with matched allograft controls (14.6% [39/268] vs. 15.6% [3,235/20,694]; $P=0.63$). There was also no difference in the proportion subsequently transplanted (72.0% [193/268] of bypassed candidates on H-L match runs vs. 69.3% [14,333/20,694] from matched allograft controls, $P=0.48$). The laboratory and match MELD scores at transplantation of the 193 bypassed waitlist candidates who ultimately were transplanted were similar to the values at the time of initial bypass (transplantation values: laboratory MELD: 18, IQR: 11-30, match MELD score: 31, IQR: 29-35, compared with 18 and 29, respectively).

When evaluating waiting time, waitlist candidates bypassed on a combined H-L match run who were ultimately transplanted had significantly longer waiting times from bypass to transplantation when compared to waiting time from appearance on a match run until transplantation for matched allograft controls (median: 87 days (IQR: 27-192) versus 24 days (IQR: 5-79) for matched allograft controls; $p<0.001$).

In multivariable competing risk Cox regression models, there was no significant difference in the hazard of waitlist removal for death or clinical deterioration among bypassed waitlist candidates when the heart sequestered the liver, compared with matched allograft controls (Table 5).

Discussion

In this analysis, match run data and two complementary analytical approaches were used to evaluate the impact of combined H-L allocation on bypassed waitlist candidates. The results indicate that the impact of the H-L allocation policy on the survival of bypassed liver waitlist candidates appears to be small, despite longer waiting time to liver transplantation. Contradicting our hypothesis, we found that bypassed candidates had similar risk of waitlist removal, which may be due to the high likelihood of subsequent transplantation for patients ranked in the top 10 of a match run. Although individual waitlist candidates at the top of a match run who are bypassed may die as a consequence of being bypassed, as a group, this risk is not greater than expected. Although the sample size was small, limiting power to detect differences, this analysis is unique as it is the first to use match run data for this purpose, and applies an empirical approach to address the question of the equity of organ allocation policies from several perspectives. These analytic methods serve as a starting point to consider other potential approaches to evaluate the impact of MOT allocation policies. Furthermore, these methods can specifically be used to evaluate other liver transplant allocation policies that lead to bypassing candidates who may in fact have greater medical necessity for transplantation (i.e. liver waitlist candidates bypassed by MELD exception point recipients). If the number of simultaneous H-L transplants continues to

increase, these data will need to be reassessed, but currently, the impact on bypassed candidates is small.

The questions of fairness and equity in organ allocation are of utmost importance in dual organ allocation given the scarcity of deceased donors. At face value, by prioritizing MOT candidates above all others, the MOT allocation process may violate one interpretation of the principle of equality—that individuals who can derive similar benefit ought to have equivalent access.¹⁰ However, bioethical principles (articulated by Rawls) also state that inequalities are acceptable only if they would benefit the “worst off.”¹⁰ In this clinical setting, the identification of the “worst-off” candidates is not simple.⁶ The MELD system ranks liver transplant candidates according to probability of short-term death (one approach to identifying “worst-off candidates”), yet patients requiring both heart and liver transplants may be viewed as even worse off than single organ transplant candidates. This analysis is the first to assess the potential harm of the current allocation policy to bypassed transplant candidates and may reduce concerns about inequity.

By examining the risk of mortality or waitlist drop off to bypassed candidates, this analysis has only addressed one of many potential contentious issues surrounding the practice of dual organ transplantation. For example, other methods will be needed to assess questions of utility with separate or simultaneous organ allocation. A recent publication indicated that candidates for a H-L or a lung-liver have a greater risk of waitlist mortality compared to liver-alone candidates, suggesting that from the standpoint of minimizing mortality among patients on the waiting list for a liver transplant, the goal of liver MELD-based allocation, the current practice of allowing a second organ to bypass patients with higher waitlist priority might be justified.⁶ However with the increasing practice of dual organ transplantation, there is a need to consider a more rigorous method to adjudicate aggregate outcomes among those requiring two organs and those who require a single organ. This will require the development of new risk stratification models, especially for combined organ transplants where the basis for waiting list priority differs (e.g. liver-kidney where liver priority is based on “sickest first,” while kidney priority is largely based on waiting time). The methods we have developed can serve as a framework for measuring the impact of such multi-organ allocation.

This study has methodological limitations. First, the small sample sizes raise the potential for type II error. Second, in the matched allograft analysis, we only were able to evaluate waitlist candidates ranked higher than the recipient of that graft (e.g. if the recipient was ranked 8th, UNOS/OPTN only provides data for match run patients ranked 1-8), and not those ranked lower. While this limitation prevented a full comparison of all waitlist candidates on “control” match runs, it did allow us to evaluate outcomes among patients with similar ranks as bypassed candidates on match runs of organs of similar quality. The potential reasons that some of the waitlist candidates may have turned down an organ are diverse—due to being too sick, size mismatch, or organ quality relative to recipient status—yet such refusals could have occurred with equal frequency in the H-L match runs if the bypassed waitlist candidates had not been bypassed.

Third, there was a higher proportion of exception point patients in the bypass cohort. Several possible mechanisms might explain the higher percentage of candidates with exception points in the H-L match lists: a) transplant centers performing the H-L transplants accepted the organs at that time because a large number of the waitlist candidates who were bypassed were from their own center, and were known to have exception points and a lower risk of subsequent waitlist removal; b) increased use of exception points over time²¹ (although the matched allograft patients had a similar distribution of match dates, and thus equal probability of having exception points based on temporal changes); or c) chance alone due to the small sample sizes. Regardless of the reasons for differences in the proportion of patients with exception points, we adjusted for exception point status in models, and the first matched candidate cohort was identified based on match MELD score. Fourth, the majority of the H-L match runs involved waitlist candidates in UNOS regions 2 and 7. Low-MELD regions, for which there is a lower risk of waitlist mortality (i.e. regions 3, 6, 10, and 11) were thus under-represented in the H-L match runs; as such, an increased risk of waitlist mortality in the H-L match runs due to clustering of patients in regions 2 and 7 might have been expected. In the matched candidate analysis, we matched by UNOS region, and demonstrated superior waitlist outcomes among bypassed candidates. Lastly, the inception of the Share 35 policy may result in sicker patients potentially being affected by heart-liver allocation policies. While current data are insufficient to assess this possibility, future work will need to examine the impact of MOT allocation policies in the Share 35 era.

In conclusion, although we did not find that current dual-organ allocation policy results in increased waitlist mortality for waitlist candidates bypassed in H-L match runs, we demonstrate methods to evaluate the impact of current and future MOT allocation policies. Given the increasing number of dual-organ waitlist candidates and recipients, the potential impact of dual-organ H-L allocation may need to be re-examined in the future. Furthermore, these analytic techniques can be employed to evaluate the impact of other organ allocation policies which may result in unintended downstream consequences on waitlist candidates (i.e. bypassing of waitlist candidates by broader geographic sharing). These data do not suggest that the current heart-liver allocation policy requires revision; however, these data should not be extrapolated to other situations where bypasses occur, such as simultaneous liver-kidney transplants, (which comprise a greater proportion of the MOT performed), without empiric data.

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Abbreviations

MOT	Multi-organ transplants
H-L	Heart-liver
OPTN	Organ Procurement and Transplantation Network
UNOS	United Network for Organ Sharing
LTA	Liver-transplant alone
MELD	Model for End-Stage Liver Disease
DRI	Donor risk index
SHR	Sub-hazard ratios

Table 1
Selection of experimental and comparator groups for analyses of waitlist outcomes of liver transplant candidates bypassed by simultaneous heart-liver recipients

Analytic approach	Experimental group	Comparator group	Rationale
Matched candidate cohort #1	268 liver candidates ranked in the top 10 positions of a match run bypassed by a H-L recipient during the years 2007-2013	2,144 liver waitlist candidates matched 8:1 based on UNOS region, blood type, and <u>match MELD score</u> to bypassed liver waitlist candidates	Compare bypassed candidates to waitlist candidates with similar access to transplantation based on <u>match MELD score</u>
Matched candidate cohort #2	268 liver candidates ranked in the top 10 positions of a match run bypassed by a H-L recipient during the years 2007-2013	2,340 liver waitlist candidates matched 9:1 based on UNOS region, blood type, and <u>laboratory MELD score</u> to bypassed liver waitlist candidates	Compare bypassed candidates to waitlist candidates with similar risk of waitlist mortality based on <u>laboratory MELD score</u>
Matched allograft approach	268 liver candidates ranked in the top 10 positions of a match run bypassed by a H-L recipient during the years 2007-2013	20,962 liver waitlist candidates who were: 1) ranked in the top 10 of a match run of a liver-alone recipient who received a graft of similar quality to a H-L recipient; and 2) ranked higher than the organ recipient on that match run	Compare bypassed candidates to waitlist candidates on match runs of similar graft quality to "simulate" the outcomes had the liver in a H-L allocation been offered to a liver-alone candidate with the highest priority

Table 2
Categorization of 65 match runs of heart-liver transplant recipients

Variable *	Heart "sequestered" liver, N=42	Liver "sequestered" heart, N=13**	Equal priority, N=10	P-value
Heart match run position	2 (1, 4)	35 (11, 52)	3 (1, 5)	<0.001
Liver match run position	138 (49, 450)	1 (1, 3)	3 (2, 6)	<0.001
Difference in heart vs. liver match run rank **	-134 (-45, -444)	33 (8, 49)	0 (-1, 1)	<0.001
Liver recipient with MELD exceptions, N (%)	4 (9.5)	12 (92.3)	6 (60.0)	<0.001
Laboratory MELD score at transplantation	15 (11,20)	10 (8,17)	13 (9,16)	0.27
Match MELD score at transplantation	15 (11,20)	29 (25,33)	26 (22,29)	<0.001
Heart status at transplant				<0.001
1a, N (%)	22 (52.4)	2 (15.4)	6 (60.0)	
1b, N (%)	18 (42.9)	3 (23.1)	3 (30.0)	
2, N (%)	2 (4.8)	8 (61.5)	1 (10.0)	
Liver diagnosis, N (%)				<0.001
Cardiac cirrhosis	28 (66.7)	1 (7.7)	2 (20.0)	
Amyloidosis	5 (11.9)	10 (76.9)	6 (60.0)	
Hepatitis C	0 (0.0)	1 (7.7)	1 (10.0)	
Cryptogenic cirrhosis/NASH	5 (11.9)	0 (0.0)	0 (0.0)	
Other	4 (9.5)	1 (7.7)	1 (10.0)	
Heart diagnosis, N (%)				0.001
Amyloidosis	5 (11.9)	9 (69.2)	6 (60.0)	
Congenital heart disease	11 (26.2)	0 (0.0)	1 (10.0)	
Idiopathic dilated cardiomyopathy	10 (23.8)	0 (0.0)	1 (10.0)	
Hypertrophic cardiomyopathy	7 (16.7)	0 (0.0)	1 (10.0)	
Other	9 (21.4)	4 (30.8)	1 (10.0)	
Age at transplant	47 (35-55)	50 (46-60)	60 (42-64)	0.09

* Median (IQR) unless otherwise specified

** Difference in heart vs. liver match run rank was the difference between an individual transplant recipient's rank on the heart match run subtracted by their rank on the liver match run

*** In 5 cases, the H-L recipient bypassed the heart match completely

Table 3
Clinical and demographic characteristics of liver waitlist candidates from bypass match runs, control match runs, and matched waitlist controls

Variable	Bypassed liver waitlist candidates, N=268	Matched candidate approach		Matched allograft approach	
		Matched by match MELD score, N=2,144	Matched by laboratory MELD score, N=2,340	Liver candidates from control match runs, N=20,694	
Male gender, N (%)	185 (69.0)	1,442 (67.3)	1,486 (63.5)	13,109 (63.4)	
Age at bypass or matching, median (IQR)	56.9 (50.7,61.5)	55.2 (49.0,60.3)	55.2 (49.4, 61.1)	55.7 (49.2,61.0)	
Race/ethnicity, N (%)					
White	189 (70.5)	1,518 (70.8)	1,796 (75.2)	14,481 (70.0)	
Black	28 (10.5)	260 (12.1)	236 (10.1)	2,139 (10.3)	
Hispanic	32 (11.9)	258 (12.0)	246 (10.6)	2,868 (13.9)	
Asian	12 (4.5)	85 (4.0)	82 (3.5)	961 (4.6)	
Other	7 (2.6)	23 (1.1)	16 (0.7)	245 (1.2)	
Primary diagnosis, N (%)					
Hepatitis C	93 (34.7)	839 (39.1)	852 (36.4)	8,948 (43.2)	
Alcohol	34 (12.7)	370 (17.3)	429 (18.4)	2,686 (13.0)	
Hepatitis B	2 (0.8)	28 (2.7)	61 (2.6)	571 (2.8)	
NASH/Cryptogenic	30 (11.2)	269 (12.6)	338 (14.4)	2,840 (13.7)	
Cholestatic	16 (6.0)	161 (7.5)	204 (8.7)	1,492 (7.2)	
Autoimmune	8 (3.0)	105 (4.9)	122 (5.2)	946 (4.6)	
Fulminant hepatic failure	18 (6.7)	64 (3.0)	313 (13.4)	1,087 (5.3)	
Other	67 (25.0)	278 (13.0)	21 (0.9)	2,124 (10.3)	
Received exception points	117 (43.7)	426 (19.9)	308 (13.2)	5,929 (28.7)	

Table 4

Matched candidate approach #1: Stratified Cox model of waitlist removal for liver waitlist candidates bypassed by H-L recipients when the heart sequestered the liver versus controls selected by match MELD score^{*}

Variable	Hazard ratio	P-value
Bypassed waitlist candidate	0.56 (0.40-0.79)	0.001
Age at waitlisting	1.02 (1.01-1.03)	0.001
Exception MELD score [†]	0.11 (0.07-0.16)	<0.001
Race/ethnicity		0.87
White	1	
Black	0.93 (0.71-1.23)	
Hispanic	0.92 (0.68-1.23)	
Asian	0.79 (0.44-1.40)	
Other	0.82 (0.25-2.70)	
Diagnosis		0.41
Hepatitis C	1	
Alcohol	0.81 (0.63-1.03)	
Hepatitis B	1.09 (0.63-1.87)	
NASH/cryptogenic	0.98 (0.76-1.27)	
Cholestatic	1.00 (0.75-1.33)	
Autoimmune	1.16 (0.71-1.91)	
Other	1.01 (0.72-1.42)	
Fulminant hepatic failure	1.52 (0.94-2.48)	

^{*} Controls were liver waitlist candidates matched 8:1 based on blood type, match MELD score, and UNOS region of bypass liver waitlist candidate. Interaction of exception points and bypass candidate versus control was not significant (p=0.8).

[†] Binary yes/no (1/0) as to whether match MELD score was based on exception points.

Table 5

Matched allograft approach: Competing risk model for risk of waitlist removal for death or clinical deterioration among liver waitlist candidates bypassed by H-L recipients when the heart sequestered the liver versus candidates from control liver-alone match runs *

Variable	Sub-hazard ratio	P-value
Control match run	0.97 (0.73-1.37)	0.99
Age at bypass	1.02 (1.02-1.03)	<0.001
Male gender	0.82 (0.77-0.89)	<0.001
Match MELD at bypass	1.05 (1.05-1.06)	<0.001
Match rank position	1.03 (1.01-1.04)	<0.001
Exception MELD score [†]	0.08 (0.06-0.09)	<0.001
Race/ethnicity		0.71
White	1	
Black	0.92 (0.82-1.04)	
Hispanic	0.97 (0.87-1.07)	
Asian	1.01 (0.83-1.23)	
Other	0.94 (0.67-1.31)	
Diagnosis		<0.001
Hepatitis C	1	
Alcohol	1.00 (0.90-1.11)	
Hepatitis B	0.93 (0.71-1.21)	
NASH/cryptogenic	0.91 (0.82-1.02)	
Cholestatic	0.89 (0.77-1.02)	
Autoimmune	0.97 (0.82-1.15)	
Other	1.44 (1.28-1.61)	
Fulminant hepatic failure	0.54 (0.44-0.66)	
Bloodtype		0.006
O	1	
A	1.06 (0.98-1.14)	
B	0.86 (0.75-0.98)	
AB	0.84 (0.68-1.03)	

* Outcome was waitlist removal for death or clinical deterioration (dying within 90 days of waitlist removal); competing risk was transplantation. Interaction of control vs bypass match run and exception point status was not significant (p=0.41).

[†] Binary yes/no (1/0) as to whether match MELD score was based on exception points.