The Survival Benefit of Liver Transplantation

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Demand for liver transplantation continues to exceed
donor organ supply. Comparing recipient survival to
that of comparable candidates without a transplant
can improve understanding of transplant survival ben-
efit. Waiting list and post-transplant mortality was
studied among a cohort of 12 996 adult patients placed
on the waiting list between 2001 and 2003. Time-
dependent Cox regression models were fitted to de-
termine relative mortality rates for candidates and re-
cipients. Overall, deceased donor transplant recipients
had a 79% lower mortality risk than candidates (HR =
0.21; p < 0.001). At Model for End-stage Liver Disease
(MELD) 18–20, mortality risk was 38% lower (p < 0.01)
among recipients compared to candidates. Survival
benefit increased with increasing MELD score; at the
maximum score of 40, recipient mortality risk was 96%
lower than that for candidates (p < 0.001). In contrast,
at lower MELD scores, recipient mortality risk during
the first post-transplant year was much higher than
for candidates (HR = 3.64 at MELD 6–11, HR = 2.35 at
MELD 12–14; both p < 0.001). Liver transplant survival
benefit at 1 year is concentrated among patients at
higher risk of pre-transplant death. Futile transplants
among severely ill patients are not identified under cur-
rent practice. With 1 year post-transplant follow-up,
patients at lower risk of pre-transplant death do not
have a demonstrable survival benefit from liver trans-
plant.

Key words: Donor, liver transplantation, MELD, mor-
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list

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Introduction

Liver transplantation has altered the natural history of end-
stage liver disease and is now considered the preferred
therapy for a wide range of previously fatal chronic hep-
atic diseases. Optimal timing of liver transplantation in the
course of disease is desirable to avoid harm from interven-
ing too early and futility from transplanting too late. Unfor-
tunately, little is known about the most appropriate time
in the course of chronic liver disease to offer a transplant
for the majority of patients, with the exception of primary
biliary cirrhosis and other cholestatic disorders (1–3). Ap-
propriate timing is especially important because of the un-
certain availability of a donor organ engendered by the im-
balance between the size of the pool of suitable recipients
and the number of available deceased donors (4).

Given the severe shortage of donor organs, there is a need
to identify which patients derive significant survival benefit
from transplantation and which do not. As early as 1992,
Delmonico et al. noted that assessment of outcome should
be a component of allocation policy so that futile trans-
plants could be avoided (5), and a recent report continued to
support this view (6). To date, however, only pre-transplant
mortality risk has been incorporated into liver allocation pol-
icy. The most recent change in liver allocation policy in the
United States, by which candidates are ranked according
to a more highly stratified index of pre-transplant mortality
(7), continues to offer donor livers on this basis.

Comparisons of mortality risk among transplant recipients
to mortality risk among listed transplant candidates with
chronic end-stage renal disease, matching on time since
initial listing, have been used to assess transplant survival
benefit (8). This approach avoids inappropriate compar-
isons to the entire population of patients with end-stage
disease, only a small fraction of whom are suitable candi-
dates to be listed for transplantation. Registered transplant
candidates who have already entered the transplant path-
way constitute the best comparison group to transplant
recipients.

In the field of renal transplantation, no distinctions are
drawn among candidates based on medical urgency when
allocation priority for deceased donor organs is being con-
sidered. This makes assessment of survival benefit more
straightforward (8). In contrast, liver transplant allocation is
based on the severity of the underlying disease necessitat-
ing hepatic replacement. Specifically, the current allocation

scheme for candidates with chronic end-stage liver disease utilizes a measure of each patient's pre-transplant mortality risk that is calculated based on laboratory values of serum bilirubin, international normalized ratio of prothrombin time and serum creatinine. The score is derived from published data on the Model for End-stage Liver Disease (MELD), which predicts 3-month mortality risk for adult cirrhotics undergoing transjugular intra-hepatic portosystemic shunt procedures as well as other chronic liver disease populations and liver transplant candidates (9–11). A similar system (PELD) has been developed for pediatric candidates (12).

The tacit assumption that liver transplantation provides a large differential between waiting list mortality risk and post-transplant mortality risk for candidates at all MELD levels has not been previously tested at the national level. In this article, we use data from all liver transplant centers in the United States to examine the survival benefit attributable to liver transplantation, with a focus on adult patients with chronic liver disease at the low and high ends of the pre-transplant risk spectrum.

Methods

Data sources

This study used data from the Scientific Registry of Transplant Recipients (SRTR) regarding access to transplantation, waiting list mortality and post-transplant graft and patient survival, among all listed candidates and transplant recipients in the United States submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and supplemented by mortality information from the Social Security Death Master File (13–15).

MELD-based allocation system

The national system for liver allocation operates according to a set of nested rules (16). Donor livers are first offered to candidates with acute liver failure or immediate post-transplant graft failure (Status 1). After Status 1, organs are allocated to candidates with chronic liver disease wait-listed at transplant centers within the donor's organ procurement organization (OPO) service area in descending MELD or PELD order, next to candidates in other OPOs in the region, and finally to candidates outside the region. MELD or PELD score data must be submitted periodically, with updates at more frequent intervals required at higher MELD or PELD scores (16). Regional review boards may consider requests for assigned (rather than calculated) MELD or PELD scores.

Study population

The study population included patients 18 years of age and older with an initial date of registration for deceased donor liver transplantation between September 2001 and June 2003 (n = 12 996). The start of the study corresponded to the initial date of mandatory submission of the three components of the MELD score. Patients were followed to the earliest of death, loss to follow-up or the end of the observation period on June 30, 2003; post-transplant follow-up was a maximum of 1 year. Status 1 candidates were excluded (n = 626). Candidates with a diagnosis of hepatocellular carcinoma were excluded, since an arbitrary MELD score is assigned to such patients at listing. Patients who had MELD exception scores approved for use in lieu of calculated scores were censored at the date the exception score was granted (n = 1380). Since the study objective related to deceased

donor transplantation, patient survival was also censored at the date of living donor liver transplant (n = 242).

Changes in calculated MELD scores for patients with chronic liver disease were tracked. A total of 67 056 MELD scores was used for the analysis. Among the 12 996 patients in the study, 12 138 had more than one recorded MELD score.

Analytic approach

Patients contributed follow-up time to the candidate group before transplant and to the transplant group if and when they received a deceased donor liver transplant, and thereafter. Patients were censored at removal from the candidate pool, if removal was due to patient recovery (n = 120). Transplant recipients who experienced graft failure (with or without retransplantation) were not censored. Waiting list patients were classified based on their current MELD score. Waiting candidates contributed follow-up time at risk according to their most recent MELD score and could therefore accrue periods of follow-up time in multiple categories if their MELD score changed. Transplant recipients were classified based on their final pre-transplant MELD score.

Unadjusted mortality rates were computed as the ratio of risk category-specific deaths per 1000 patient years of follow-up. Cox regression models were used to compare mortality for waiting list candidates and transplant recipients, at equal duration since wait-listing, adjusted for age, sex, race, diagnosis, education, insurance coverage and updated (time-dependent) MELD score and ΔMELD (17). We computed ΔMELD, a measure of how rapidly the candidate's MELD is changing, as the change in MELD score divided by the length of the time interval between reported dates of change.

The covariate-adjusted hazard ratio for mortality risk of transplant compared to mortality risk on the waiting list was estimated for the study population as a whole. Separate models were also fitted for several MELD subgroups. Lastly, non-proportional (piecewise proportional hazards) Cox models were used to estimate mortality hazard ratios for post-transplant follow-up time windows of 0–7, 8–30 and 31–365 days compared to corresponding waiting list candidates.

Results

Characteristics of the study population at the time of placement on the waiting list are shown in Table 1. Just over 60% of candidates were aged 50 or older at listing. Males made up 64% of the cohort and over 87% of the candidates were white. Hispanic ethnicity was noted for 14.6% of candidates. The most common diagnosis group was non-cholestatic cirrhosis; hepatitis C cirrhosis was the most common individual diagnosis (32%).

At the time of listing, more than one-half of candidates had a MELD score less than 15 and 9% had a score above 26 (Figure 1). The distribution of MELD scores at the time of transplant showed a shift toward higher scores (more than 25% above 26), although 24% of transplants were performed at MELD scores less than 15 (Figure 2). The proportion of transplant recipients with a MELD score at transplant less than 12 was 10%.

A total of 1538 pre-transplant deaths and 255 post-transplant deaths were observed (Table 2). The unadjusted

Table 1: Characteristics of study population at wait-listing (n = 12 996)

	N	%
Age		
18-39	1161	8.9
40-49	4001	30.8
50-59	5307	40.8
≥60	2527	19.4
Sex		
Male	8291	63.8
Female	4705	36.2
Race		
Asian	468	3.6
African American	963	7.4
Caucasian	11 246	86.5
Other	319	2.5
Ethnicity		
Hispanic	1900	14.6
Non-Hispanic	11 096	85.4
Diagnosis		
Hepatitis C cirrhosis	4189	32.2
Alcoholic cirrhosis	2044	15.7
Hepatitis B cirrhosis	534	4.1
Non-cholestatic cirrhosis (other)	2644	20.3
Primary sclerosing cholangitis	586	4.5
Primary biliary cirrhosis	539	4.2
Cholestatic cirrhosis (other)	30	0.2
Others	2430	18.7
Education		
High school or less	4914	37.8
College	3982	30.6
Missing	4100	31.6
Insurance		
Medicare/Medicaid	3599	27.7
Private/self	4073	31.3
Missing/other	5324	41.0

waiting list mortality rate was 217 deaths per 1000 patient years, compared to 184 deaths per 1000 patient years among transplant recipients. There was approximately 300-fold range of waiting list mortality rates between patients with MELD scores 6–11 and those with MELD scores of 40 and higher. Patients with MELD scores 40 and higher had unadjusted post-transplant mortality rates that were more than 50% greater than that of the MELD 6–11 category.

Overall covariate-adjusted mortality risk from the Cox regression model was 79% lower for liver transplant recipients compared to candidates on the waiting list (hazard ratio = 0.21; 95% confidence interval = 0.18–0.24; p < 0.001), indicating a significant survival benefit of liver transplantation. However, the salutary effect of transplantation on survival varied across the range of MELD scores (Figure 3). With 1 year of available post-transplant follow-up, MELD category 15–17 represented a transition point. Post-transplant mortality risk was more than three times higher than waiting list mortality for MELD scores 6–11 (hazard ratio = 3.64; 95% confidence interval = 2.23–5.95; p < 0.001). The hazard ratio was also greater than 1.0 among patients with MELD 12–14 (hazard ratio = 2.35; 95% confidence interval 1.48–3.76; p < 0.001). Conversely, significant transplant survival benefit was observed at MELD scores 18 and higher, and the magnitude of transplant benefit increased with increasing MELD score (Figure 3).

The majority of patients with low MELD scores showed little to no progression over time. Among 1861 patients who were initially listed in the MELD (6–11) category and had at least 1 year of follow-up, 75.9% remained in that category 1 year later. Less than 5% progressed into a MELD score category associated with significant survival benefit.

Some patients were assigned a MELD score of 40 by the OPTN even though their calculated score was higher, because current allocation policy caps the score. Among 570 patients with a capped MELD score, 469 (82%) had an actual calculated MELD greater than 40 (range: 41–68). A separate Cox regression model for patients with MELD scores greater than or equal to 40 was fitted using the actual calculated MELD scores showed that mortality risk (and thus transplant benefit) for transplant recipients among these most ill patients remained stable (hazard ratio = 1.00; 95% confidence interval 0.89–1.11).

The observed contrast between post-transplant and waiting list mortality varied strongly across the follow-up period
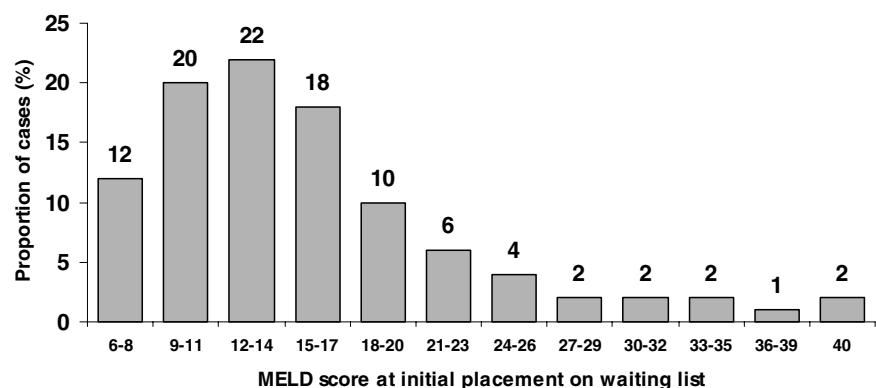

Figure 1: Distribution of MELD scores at initial placement on waiting list.
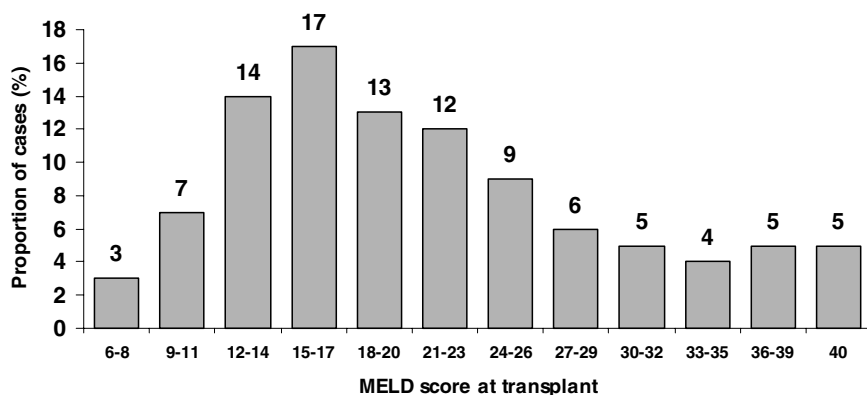
Figure 2: Distribution of MELD scores at transplant.

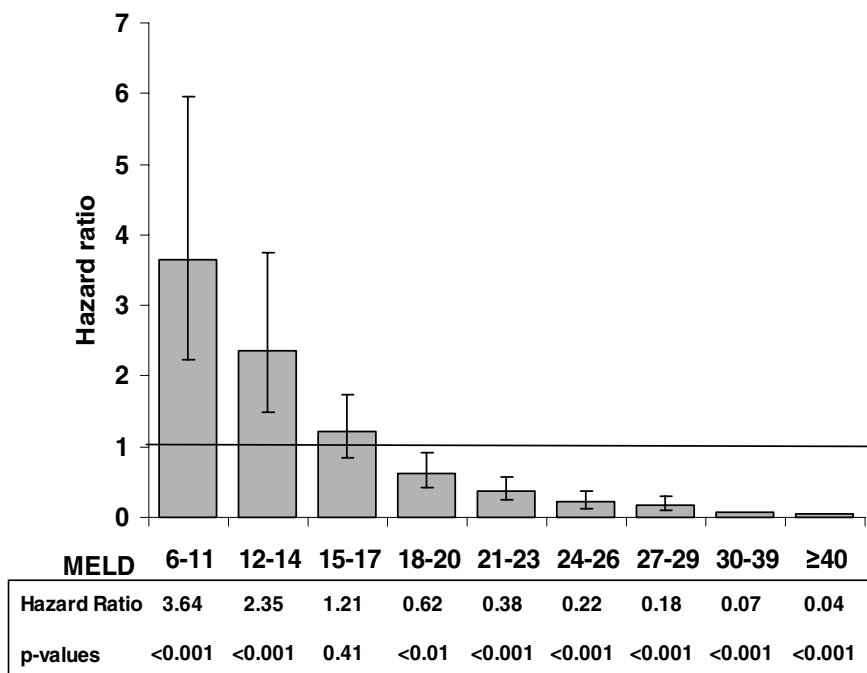| MELD	6-11	12-14	15-17	18-20	21-23	24-26	27-29	30-39	≥40
Hazard Ratio	3.64	2.35	1.21	0.62	0.38	0.22	0.18	0.07	0.04
p-values	<0.001	<0.001	0.41	<0.01	<0.001	<0.001	<0.001	<0.001	<0.001

Figure 3: Comparison of mortality risk expressed as hazard ratio by MELD score for recipients of liver transplants compared to candidates on the liver transplant waiting list.

Table 2: Unadjusted waiting list and transplant mortality rates by MELD category

MELD	Waiting list			Transplant (1 year follow-up)		
	Deaths	Patient years (PY)	Rate per 1000 PY	Deaths	Patient years (PY)	Rate per 1000 PY
6–11	130	2901	44.8	19	116	163.3
12–14	96	1830	52.5	23	180	127.4
15–17	181	1237	146.4	38	231	164.7
18–20	150	552	271.9	33	190	174.1
21–23	142	276	514.9	31	174	178.4
24–26	105	125	840.7	21	119	176.9
27–29	99	60	1663.8	18	92	195.9
30–39	348	75	4634.1	54	220	245.5
40*	287	22	13 152.7	18	68	264.6
Total	538	7078	217.3	255	1390	183.5

*Includes patients whose MELD score was capped at 40.

Table 3: Covariate-adjusted mortality hazard ratios (transplant: waiting list) by MELD score category and post-transplant follow-up time

MELD Category	Days post-transplant								
	0–7 days			8–30 days			31–365 days		
	HR*	(95% CI)†	p-value	HR*	(95% CI)†	p-value	HR*	(95% CI)†	p-value
6–11	33.03	(13.74, 79.22)	<0.001	9.26	(3.34, 25.69)	<0.001	1.79	(0.89, 3.59)	0.10
12–14	27.91	(11.81, 66.00)	<0.001	1.24	(0.17, 8.96)	0.83	1.76	(1.01, 3.06)	0.04
15–17	5.86	(2.57, 13.35)	<0.001	2.52	(1.23, 5.16)	0.01	0.82	(0.52, 1.28)	0.37
18–20	2.83	(1.04, 7.72)	0.04	1.13	(0.46, 2.78)	0.79	0.48	(0.31, 0.76)	0.002
21–29	1.65	(1.00, 2.73)	0.05	0.50	(0.29, 0.86)	0.01	0.15	(0.11, 0.22)	<0.001
30–39	0.20	(0.09, 0.43)	<0.001	0.09	(0.05, 0.17)	<0.001	0.06	(0.04, 0.08)	<0.001
40‡	0.11	(0.04, 0.26)	<0.001	0.04	(0.01, 0.10)	<0.001	0.02	(0.01, 0.03)	<0.001

*Hazard ratio for post-transplant mortality risk based on MELD score at transplant compared to wait-listing while at the same MELD score.
†95% confidence interval.
‡Includes patients whose MELD score was capped at 40.

(Table 3). Generally, post-transplant mortality within each MELD category decreased as follow-up time increased. At MELD 6–11, post-transplant mortality was significantly higher than waiting list mortality for the first post-transplant month, while recipients transplanted at MELD scores of 30 and higher had a significant survival benefit within the first post-transplant week. Recipients with MELD scores 21–29 demonstrated significant survival benefit after the first post-transplant week.

Discussion

The ability of MELD to predict mortality in patients with chronic liver disease has contributed to the evolution of liver allocation policy in the United States (9,10). It is established that MELD is an important predictor of waiting list mortality (11,17,18), and several authors have recently reported that MELD is predictive of post-transplant mortality risk (6,19). One study failed to show a significant relationship between pre-transplant MELD score and post-transplant outcome, but this report was from a single-center study with limited sample size (20). In our study, we found approximately a 300-fold range of mortality risk across the MELD spectrum for patients on the waiting list, and a 1.5-fold range for post-transplant mortality risk. The availability of serial MELD data allows detailed analyses of the survival benefit of liver transplantation to be performed, comparing waiting list and post-transplant mortality risk within MELD categories.

This study demonstrates significant overall liver transplant survival benefit for patients with chronic liver disease, and provides important validation of the procedure as life-saving therapy. Deceased donor liver transplant recipients have an overall covariate-adjusted mortality risk that is less than one-quarter that of patients on the waiting list; this finding holds with and without the inclusion of ΔMELD as a covariate.

Liver transplant survival benefit is not evenly distributed across the range of MELD scores. This is particularly use-ful in considerations of organ allocation, where relative survival benefit among a group of candidates must be determined. On the other hand, the physician and candidate faced with a decision regarding wait-listing or acceptance of an offer of a donor liver must consider whether that particular candidate's expected lifetime with a transplant, given their current medical condition as reflected by their MELD score or other factors, is predicted to exceed that expected if the transplant is not performed. Our analyses facilitate discussion of both these issues.

At MELD scores 18 and higher, significant and progressively increasing survival benefit was demonstrated. At the highest end of the risk spectrum, there does not appear to be a MELD score above which transplantation is clearly futile. In a supplementary analysis, a Cox model fitted to the subgroup of patients with uncapped MELD scores of 40 and greater showed that the mortality hazard ratio continued to favor transplant. However, the rate of transfer to inactive status on the waiting list increases at higher MELD scores (data not shown), suggesting that effective clinical decision making and recipient selection is at work among these sick candidates. In fact, at the highest end of the MELD scale, waiting list mortality risk is extremely high, whereas post-transplant mortality risk rises much more gradually. These relationships help to explain the progressively higher benefit of liver transplantation as MELD increases.

In contrast to the findings for patients with high MELD scores, post-transplant mortality risk for the nearly one in four recipients who received liver transplants for chronic liver disease at a MELD score less than 15 was significantly higher than for comparable candidates on the waiting list. This suggests that liver transplant is more hazardous than remaining on the waiting list in such cases, based on 1 year of post-transplant follow-up. With longer follow-up, a survival benefit for low MELD patients may eventually be demonstrated, but in relative terms that benefit is likely to be of lesser magnitude than for those with higher MELD scores. Moreover, three-quarters of patients with MELD

scores between 6 and 11 at listing continue to have MELD scores in that range 1 year later, suggesting that the risk of rapid progression is low.

On initial examination, it may be surprising that so many patients with low MELD scores receive liver transplants, as the current allocation policy is intended to direct donor livers to high MELD score candidates. Two related factors explain this finding. First, the MELD scores of the highest ranking candidate in each OPO vary considerably, reflecting the marked heterogeneity in the acuity of liver transplant candidates across the United States (21). Second, organs are offered to chronic liver disease candidates in descending MELD score order within the OPO service area where the donor is identified before they are offered to candidates outside that OPO. Thus, one-half of all livers are offered first to candidates with MELD scores less than 18 (data not shown). These factors collectively lead to the current situation in which over 40% of all liver transplants are given to patients with MELD scores below 18.

This study has implications for liver allocation policy in the United States. The current ordering of liver transplant candidates with chronic liver disease appears to be suboptimal. Distribution of donor livers to candidates with higher MELD scores in a larger initial geographic unit than the OPO, extending to the regional level, would simultaneously steer a higher proportion of scarce organs to patients likely to benefit from them and reduce the probability of transplant for those with less likelihood of benefit. The latter element is important, given that candidates with very low MELD scores cannot yet be shown to benefit from a transplant, and may even be harmed by one. The Board of Directors of the OPTN recently approved such a modification to the national allocation system for deceased donor livers in the United States (22).

Separately, establishment of a minimum MELD score for placement on the waiting list would be a more direct method of reducing the proportion of transplants given to patients with low MELD scores. Selection of a minimum listing MELD score needs to be informed by several considerations. With sufficiently long follow-up, a subset of patients with MELD scores below 18 may ultimately be shown to derive significant benefit. It may be imprudent, therefore, to suggest a minimum MELD score for listing that is too close to the currently calculated transplant benefit transition range of 15–17. On the downside, if patients were no longer able to be listed for transplant at low MELD scores, it might be more difficult for transplant physicians to study the course of end-stage liver disease. It has been suggested that transplant teams might not be permitted by third-party payers to follow patients referred for transplantation unless they are placed on the waiting list. These considerations must be weighed against the potential harm of doing a liver transplant that does not significantly prolong the life of the recipient, particularly as candidates with higher MELD scores and greater expected benefit are avail-

able on the waiting list. Reevaluation of individual benefit calculations will be useful when longer follow-up becomes available, although it will not likely change the ordering of benefit by MELD.

In summary, our analysis adds important data to the continuing evolution in organ allocation policy. These results suggest that transplants are being performed for some candidates who have a higher risk of dying from the transplant procedure than they have of dying from their underlying liver disease. Rather than relying solely on the risk of pre-transplant death, the survival benefit among candidates should be considered as a component of allocation policy in order to direct organs to those most likely to benefit from the procedure. The current practice of transplanting substantial number of patients at low MELD scores, with associated lack of demonstrable transplant benefit, should be carefully reconsidered.

Acknowledgment

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