



# The High Risk Recipient

## You Can't Always Get What You Want: The Right Organ for the Right Recipient

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Liver transplantation is a proven, life-saving therapy for patients with end stage liver disease.<sup>1</sup> Unfortunately, today, there is simply an insufficient supply of donor livers to satisfy recipient demand. Currently, the allocation of deceased donor livers is entirely driven by the disease severity of the potential candidates with the few candidates suffering from acute liver failure preceding the majority of candidates suffering from chronic liver failure. The latter are sequenced according to Model for Endstage Liver Disease (MELD) score because it has proven to be a highly reliable predictor of a candidate's short-term mortality risk from liver disease in the absence of transplantation. This "sickest first" policy has intensified interest in understanding the impact of donor quality on transplant outcomes, particularly for those of high disease acuity. Traditional wisdom, presumably garnered from anecdotal clinical experience, has suggested that candidates of high disease severity / high MELD score should receive higher quality organs while those with low disease severity / low MELD score should receive lower quality organs. This presumably reflects a belief that critically ill candidates with minimal reserve cannot survive the additional challenge posed by a poor quality organ but healthier patients with greater reserve can tolerate the challenge. Is this traditional wisdom correct? Should the healthiest liver transplant candidates who stand to benefit the least from liver transplantation, bear the additional risk of high risk grafts? What is the interaction between recipient disease severity and donor quality? And what are the financial implications of such transplants?

Recently, analysis to better understand what organs are "appropriate" for the sick, high MELD candidate has been facilitated by the development of a quantitative measure of donor quality.<sup>2</sup> The Donor Risk Index (DRI) is a calculation of a particular liver graft's risk of failure relative to the ideal liver graft – one that comes from a young and healthy donor who died of trauma. The availability of the DRI in conjunction with MELD enables us to define historical practice patterns as to the quality of grafts used to transplant candidates of higher versus lower disease severity and explore the outcomes of these practices. Figure 1 shows that there is a strong negative correlation between MELD at transplant and median DRI. Patients with high disease severity received higher quality grafts compared to those with lower disease severity, reflective of the conventional wisdom.

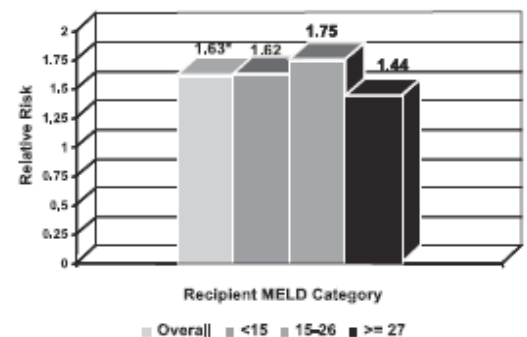


Fig 1: Liver utilization practices: Median DRI by MELD score

Several recent papers have explored the implications of inverse DRI-MELD pairing for liver transplantation. Edwards and colleagues<sup>3</sup> analyzed the outcome of transplantation with "extended donor criteria" liver allografts, defined as a DRI  $\geq 1.7$ , stratified by MELD score. They could identify no interaction between MELD and DRI. As shown in Figure 2, in increased risk of graft failure for ECD organs remained relatively constant across MELD categories. The impact of lower graft quality was not magnified by increased recipient disease severity.

Fig 2: RR of graft failure for transplantation of ECD grafts (DRI  $\geq 1.7$ ) according to MELD categories

Another approach to investigating the combined impact of graft quality and recipient disease severity on transplant outcomes is via the concept of the survival benefit of transplantation. Survival benefit of transplantation is the contrast between posttransplant and waiting list mortality. Recently, Schaubel et al. of the Scientific Registry for Transplant Recipients (SRTR) have re-visited the survival benefit of transplantation that was first derived by Merion et al. in 2005<sup>1</sup>. The updated analysis incorporated donor quality as measured by the DRI, allowed for future changes in MELD rather than considering current MELD alone, and extended post-transplant follow-up to three years.<sup>4</sup> The cohort was comprised of 28,053 non-Status 1 adult candidates first waitlisted between September 2001 and July 2005. Livers were divided into three groups: low (lowest quartile), medium (middle two quartiles) and high (highest quartile) DRI scores. Analyses showed a significant benefit of liver transplantation for candidates with MELD  $>12$  for low DRI organs, for MELD  $>15$  for medium DRI organs, and for MELD  $>18$  for high DRI organs (Figure 3). Notably, low MELD candidates (MELD  $<12$ ) suffered a negative survival benefit from transplantation. However, high MELD candidates enjoyed a substantial survival benefit from transplantation, even with lower liver quality. This analysis, consonant with





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the Edwards et al. analysis, strongly suggest that transplantation of the sickest liver transplant candidates with lower quality livers may be justifiable and appropriate. In contrast to low MELD candidates who may suffer negative survival benefit, high MELD candidates can derive not only positive but also substantial survival benefit from transplantation with high risk livers.

**Fig 3: MELD, DRI, and the Benefit of Transplantation:** Hazard ratio expressing the mortality risk of transplant recipients by MELD and DRI scores compared to waitlisted candidates

Another potential disincentive to pair low quality livers with high disease severity recipients may be concern that there is a significant financial interaction even if there is no medical interaction. Recently, it has been reported that MELD score was, compared to other recipient factors (demographic and clinical), the strongest predictor of liver transplant cost.<sup>5</sup> Similarly, increased DRI has been reported to increase hospital transplant costs independent of recipient risk factors.<sup>6</sup> Closer look at the data shows that the largest incremental cost increase was associated with the highest DRI grafts (DRI >2.5; 1.9% of all grafts) while lower DRI categories were associated with modest increases. To directly assess the relative contribution of MELD versus DRI to transplant cost, UCSF partnered in a study with UT San Antonio, a center of similar transplant volume in a different geographical area.<sup>7</sup> Multivariate Cox models for transplant length of stay at both centers are shown in Figure 4. Notably, MELD was the only factor common to both centers and exerted a potent impact. Donor location was a significant factor for Center A while donor age and weight were significant factors for Center B.

**DRI + MELD and the Benefit of Transplantation**

MELD	DONOR RISK INDEX		
	LOW	MEDIUM	HIGH
6 - 8	1.51	1.32	3.27*
9 - 11	0.70	1.51*	1.55*
12 - 14	0.34*	0.95	0.97
15 - 17	0.42*	0.55*	0.81
18 - 20	0.24*	0.51*	0.63*
21 - 23	0.25*	0.43*	0.56*
24 - 26	0.17*	0.37*	0.44*
27 - 29	0.18*	0.30*	0.32*
30 - 39	0.17*	0.22*	0.44*
≥ 40	0.05*	0.18*	0.26*

*SRTR* \* p < 0.05

**Fig 4: Multivariate models for increased transplant length of stay for Centers A and B.** Note that MELD was the only variable common to both centers.

Therefore, in summary, several lines of evidence suggest that the traditional pairing of sick candidates with high quality livers may be more restrictive of our daily practice than either necessary or wise. Without a doubt, high risk grafts perform more poorly than low risk grafts. However, this negative impact is not magnified by recipient disease severity. In fact, candidates with high MELD scores derive substantial benefit from undergoing transplantation. In contrast, candidates with low MELD scores incur harm from such organs. In the current climate of severe organ shortage, transplant surgeons and high acuity transplant candidates must face the reality that **“you can’t always get what you want”**.

**Multivariate Models for Transplant Length of Stay Center A / Center B**

Center A			VARIABLE	Center B			
HR	95% CI	P value		HR	95% CI	P value	
			D age	per year	1.010	1.004 – 1.013	<.0001
			D weight	per lb	.99	.990 – .996	.0001
1.22	1.00 – 1.49	.048	D local				
1.012	1.003 – 1.020	<b>.0085</b>	R age	per year			
			R male		.83	1.032 – .969	.019
			R re-transplant		1.57	1.064 – 2.31	.023
			R INR	per 1.0	.92	.85 – .99	.027
<b>1.031</b>	<b>1.024 – 1.038</b>	<b>&lt;.0001</b>	<b>R MELD</b>	<b>per point</b>	<b>1.03</b>	<b>1.03 – 1.04</b>	<b>&lt;.0001</b>
			CIT	per min	1.04	1.010 – 1.071	.0090

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